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Could Science-Based Regulation Make Tobacco Products Less Addictive?

Jack E. Henningfield, Ph.D.* and Mitch Zeller, J.D. †

The marketplace for all tobacco products centers on creating and sustaining an addiction to nicotine. This addiction ensures a lifetime of tobacco use by millions of customers. It was with this notion in mind that a top executive for Brown & Williamson Tobacco Corporation wrote, in 1963, that cigarette companies were not in the business of selling tobacco products but, rather, were "in the business of selling nicotine, an addictive drug."

Thirty-three years later, in the 1996 United States presidential campaign, candidate Bob Dole stated, "Some people who have tried [tobacco] can quit easily. Others don’t quit. So I guess it's addictive to some and not to others." Mr. Dole’s conclusions that some people can quit and that not all become addicted are true at face value. His statements may not have seemed so remarkable had he not been supporting tobacco company interests, arguing against the general conclusion that tobacco is addictive. The idea that not all users of addictive drugs become addicted was acknowledged by the U.S. Surgeon General in 1988. In fact, it is true

* Jack E. Henningfield is Vice President of Research and Health Policy for Pinney Associates, Inc. and an Adjunct Professor in the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine.
† Mitch Zeller is Vice President for Policy and Strategic Communications for Pinney Associates, Inc. and is former Associate Commissioner and Director of the Office of Tobacco Programs of the U.S. Food and Drug Administration.
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Jacob Sullum, Give Dole a Break, N.Y. TIMES, July 12, 1996, at A27.

Nonetheless, some characteristics are unique to cigarettes. First, there is a higher risk of addiction to nicotine in cigarettes than to any other addictive drug. Second, there is a higher risk of premature death associated with cigarette smoking than with other addictive drugs.

The Food and Drug Administration (FDA) concluded that seventy-seven to ninety-two percent of adult cigarette smokers meet the criteria for dependence. In contrast, pure nicotine products used to treat tobacco dependence vary in addictiveness, with very low levels associated with nicotine patches and gum and somewhat higher levels with nasal nicotine spray. Overall, however, the risk of addiction to these pharmaceuticals is very low compared to that of cigarettes.5

What is it about cigarettes that make them so addictive? Are they designed with the intent to create and sustain addiction? Could product regulation contribute to tobacco disease reduction by reducing the addictiveness of the products? One argument in favor of pursuing such an approach is the inescapable reality that the toxicity of tobacco products makes it extremely unlikely they can be rendered safe. Since cigarette smoke contains a toxic cocktail of more than four thousand chemicals, the most we can hope for is a reduction in the level of toxicity by setting standards for allowable contents and design features.6

While efforts to make tobacco products less deadly are worthwhile and should be pursued, we propose that it may be feasible to reduce the addictiveness of cigarettes and thereby lessen the risk that experimenters would become addicted. This may also make it easier for addicted persons to quit.7 The following Commentary will examine the scientific foundation and implications for such a regulatory approach. Although our focus will be on cigarettes, similar principles appear applicable to smokeless tobacco and other tobacco products.

4 See Gary A. Giovino et al., Epidemiology of Tobacco Use and Dependence, 17 EPIDEMIOLOGIC REV. 48, 60 (1995).
5 SURGEON GENERAL, supra note 3, at 213-14.
7 But see Neal L. Benowitz & Jack E. Henningfield, Establishing a Nicotine Threshold for Addiction—The Implications for Tobacco Regulation, 331 NEW ENG. J. MED. 123 (1994) (offering an earlier proposal to render cigarettes pharmacologically non-addictive by removing their nicotine); Jack E. Henningfield et al., Reducing the Addictiveness of Cigarettes, 7 TOBACCO CONTROL 281 (1998).
CASE STUDY—HENNINGFIELD

ESSENTIAL TERMS AND CONCEPTS

The risk of tobacco-caused disease is directly related to the amount (e.g., cigarettes per day) and duration (e.g., years) of tobacco use. Addiction is the biological force that drives most tobacco users to patterns of persistent daily exposure to high levels of deadly tobacco toxins. The cornerstone of the FDA’s evaluation of whether or not nicotine in tobacco met criteria for classification as a drug hinged on the finding that use of cigarettes and smokeless tobacco was largely driven by addiction to nicotine. Nicotine is a powerful and potent drug (about five to ten times more potent than cocaine in the alteration of mood and behavior) that naturally occurs in the tobacco plant. It has been used as a pharmacological tool to explore the workings of the nervous system. It has also been used as a pesticide at high dosages. In small doses, nicotine and nicotine analogues have potential medical uses such as the treatment of Alzheimer’s disease and ulcerative colitis.

Addiction is the general term that is used synonymously with the more technical term dependence to label regular, compulsive, and maladaptive self-administration of a psychoactive drug such as morphine, cocaine, alcohol, or nicotine. If an addicted person uses a drug regularly and persistently, his or her body may develop physiological dependence, such that a withdrawal syndrome may emerge within several hours to one day after drug administration is terminated. Dependence and withdrawal can be diagnosed according to objective criteria outlined by both the American Psychiatric Association and the World Health Organization. The strongest reactions, desired and undesired, that are often experienced upon initial drug exposure tend to diminish over time as a person develops tolerance for the drug. Tolerance is typically accompanied by an increase in dosage until a stable level develops. Higher levels of tolerance and drug intake are associated with higher levels of addiction, and in turn, a higher risk of

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9 See David J.K. Balfour & Karl O. Fagertrom, Pharmacology of Nicotine and Its Therapeutic Use in Smoking Cessation and Neurodegenerative Disorders, 72 PHARMACOLOGY & THERAPEUTICS 51 (1996); Paul A. Newhouse et al., Nicotinic System Involvement in Alzheimer’s and Parkinson’s Diseases—Implications for Therapeutics, 11 DRUGS & AGING 206 (1997).
10 Bridgette E. Garrett et al., Tobacco Addiction and Pharmacologic Interventions, 2 EXPERT OPINION ON PHARMACOTHERAPY 1545, 1546 (2002).
11 For example, smoking a pack-per-day for a month or more is assumed sufficient to lead to abstinence-associated withdrawal in many people.
adverse health consequences.

The effects of psychoactive drugs are strongly determined by the amount or dose that reaches the brain, as well as its speed of absorption into the bloodstream. The amount of a drug that is absorbed into the bloodstream from a given formulation is referred to as its bioavailability. For example, only about ten to thirty percent of the 10 milligrams of nicotine contained in a conventional cigarette is typically absorbed, while about fifty percent of the nicotine from a 2-milligram piece of nicotine gum is typically absorbed. The speed of absorption through the lining of the mouth is enhanced when the molecules of the drug have been liberated of their electrical charges (i.e., convert to their free base or un-ionized form), which is accomplished for many psychoactive drugs by use of substances to increase the alkalinity or pH.

**DESIGNED TO ADDICT**

The FDA’s nicotine investigation hinged on the determination of whether tobacco product manufacturers intentionally controlled the nicotine dosing characteristics of their products to facilitate the development and maintenance of nicotine addiction. The FDA found that cigarettes and smokeless tobacco products were highly controlled with respect to their nicotine content, their bioavailable nicotine, and the rate at which the delivered nicotine could be absorbed into the bloodstream.

The FDA also found that many aspects of cigarette design and manufacture, including the use of reconstituted tobacco and various chemical ingredients, were routinely employed to control nicotine delivery. Its analysis suggests that cigarette design could be employed either to increase or decrease the addictive effects of cigarettes by, for example, increasing what was variously referred to as the nicotine “kick” or “impact” of cigarettes. In other words, it is evident that addictiveness is not an all-or-nothing attribute of a product. Rather, a product can apparently be engineered to become more or less addictive by controlling its physical properties. With respect to drug products, this concept is well understood, and drug manufacturers are required to design their products so as to achieve desired effects while minimizing addictive ones.

Addictiveness is measured in animal and human studies estimating the level of risk that substance use will lead to addiction according to objective

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These studies are used by the FDA and the Drug Enforcement Administration (DEA) to determine whether or not a drug is addictive and, if so, its level of addictiveness. This information in turn helps the FDA and the DEA determine product labeling and marketing restrictions.

Because addictiveness can be affected by increases in drug dosage and the speed of delivery, drug manufacturers design formulations, or drug delivery systems, to maximize desired effects while minimizing undesired effects such as addiction. In fact, despite the increasingly widespread availability of nicotine delivering medications, these products have not emerged as gateways to nicotine addiction. Although a small fraction of users continue taking the products for a year or more (apparently out of the justifiable fear that they will relapse into smoking), the vast majority use them for less than three months and find them far easier to discontinue than cigarettes.

These examples are not presented to imply that the addictiveness of cigarettes can be reduced to the level of nicotine gum, but rather to illustrate that drug design can increase or decrease psychoactive effects by controlling the speed of drug delivery and other characteristics. If nicotine medications and other drug products can be designed to minimize their addictive effects, and if tobacco products are designed to increase their addictive effects, could tobacco products be designed with the opposite intent?

It's the Dose

In the course of the FDA’s investigation of tobacco products, it became apparent that major elements in product design related to nicotine dose control, i.e., providing consumers with the most palatable and addictive forms of nicotine possible. The FDA learned that tobacco companies faced a great challenge in ensuring adequate nicotine delivery in the years following the 1964 Surgeon General’s report amidst the increasing health concerns of smokers. Smokers wanted less tar and nicotine. The industry, however, understood what it was hiding from consumers—nicotine at dosages high enough to readily sustain addiction is critical to smoking


17 Although nearly any vehicle for drug delivery might, in principle, be considered a drug delivery system, whether a substance is regulated as a drug, drug delivery system, or combination drug and delivery system depends on many factors. World Health Org., Advancing Knowledge on Regulating Tobacco Products, supra note 6.
satisfaction and cigarette preference. Truly low-nicotine cigarettes were shown as far back as 1945—in a study funded by the American Tobacco Company—to be unsatisfactory for many smokers. Subsequent internal research shows that, to make smoking satisfying, most smokers require cigarettes that can readily deliver more than approximately 0.8 milligrams of nicotine per cigarette.

**PRODUCT DESIGN FEATURES THAT SUBVERT THE FEDERAL TRADE COMMISSION METHOD**

To provide a standardized method for determining tar and nicotine yields, the Federal Trade Commission (FTC) adopted a machine test developed by the American Tobacco Company in the 1930s. Although the FTC recognized that intake from individual smokers could vary, it assumed that the method would provide consumers with a fair means of differentiating among cigarette brands on the basis of their expected, relative deliveries of tar and nicotine. This testing method was also intended to provide cigarette manufacturers an incentive to design their cigarettes so that tar and nicotine deliveries would be reduced. Instead, the industry deliberately designed cigarettes to yield tar and nicotine deliveries on the machine test that they knew were substantially lower than the levels delivered in “real world” smoking by actual smokers.

The FTC testing method essentially involves the use of smoking machines programmed to take 35-milliliter puffs every minute until the cigarette has burned to 3 millimeters below the filter paper overwrap, which holds the filter to the tobacco tube portion of the cigarette (typically leaving two to four puffs worth of tobacco unsmoked). By contrast, humans take puffs at a rate nearly double that of the machines—at intervals of thirty to forty seconds—and can smoke beyond the point that machines stop. Since each puff becomes more concentrated in tar and

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18 J.K. Finnegan et al., *The Role of Nicotine in the Cigarette Habit*, 102 SCI. 94 (1945).
23 James C. Zacny & Maxine L. Stitzer, *Human Smoking Patterns: The FTC Cigarette Test for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes*, in NAT'L CANCER INST.,
nicotine, just a few extra puffs can result in a substantially greater intake.

Cigarette manufacturers could have designed their cigarettes so that tar and nicotine intake by smokers would generally correspond to FTC test ratings. In fact, such cigarettes have been used by researchers.\(^\text{24}\) Alternatively, they could have suggested to the FTC how to conduct tests that would measure maximal exposures and not substantially under-represent what humans would receive (this is the standard for food and drug labeling).

However, cigarette companies were faced with a dilemma. Consumers increasingly expressed the desire for reduced-tar and nicotine-rated cigarettes, but the flavor and satisfaction derived from smoking was strongly related to the amount of tar and nicotine delivered. Diminished levels of nicotine resulted in unsatisfying cigarettes and withdrawal symptoms, fostering growing concern in the tobacco industry that substantial reductions in nicotine delivery could lead to the erosion of the entire cigarette market.\(^\text{25}\) Therefore, cigarette companies used creative designs to beat the FTC test method, allowing them to advertise their cigarettes with lower tar and nicotine ratings while still delivering full doses of both. In practice, this meant there was virtually no relation at all between cigarette ratings and actual human nicotine blood levels.\(^\text{26}\) One study showed that tar deliveries from typical smoking are approximately two to three times greater than FTC-rated levels.\(^\text{26}\)

One tobacco company document bluntly stated its challenge as follows: “Irrespective of the ethics involved, we should develop alternative designs (that do not invite obvious criticism) which will allow the smoker to obtain significantly enhanced deliveries should he so wish.”\(^\text{27}\) Another document raised the following questions before approving cigarettes that tested low on machine tests yet provided no demonstrated safety benefit:

Should we market cigarettes intended to reassure the smoker that they are safer without assuring ourselves that they are indeed so or are not less

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safe? For example, should we “cheat” smokers by “cheating” League Tables (the British equivalent of the FTC test)? Should we use our superior knowledge of our products to design them so that they give low League Table positions but higher deliveries on human smoking? In essence, the FTC test came to the rescue of the tobacco industry and proved to be among its most powerful marketing tools because it gave manufacturers a course to follow and a credible “government-endorsed” communication. It enabled the industry to achieve its dual goal of marketing cigarettes for their reduced nicotine (and tar) while actually sustaining addictive nicotine dosage levels. Manufacturers cited the FTC test to support their claims of reduced tar and nicotine even as they designed cigarettes to nimbly dodge the test and give smokers all the tar and nicotine they desired—for a satisfying smoking experience that maintained their addiction.

The following design features allow cigarettes to provide several times higher levels of exposure to tar and nicotine than their FTC ratings:

- Whether advertised as “ultra-low” or “full-strength,” all cigarettes contain several times more nicotine than consumers “need” per cigarette.
- Cigarettes can “hide” more nicotine under the filter overwrap, thus making more tobacco available to a smoker than to the FTC machine.
- Ventilation holes in the filter allow up to ninety percent ambient air to be collected with each puff on the machine, but the holes are frequently covered by the fingers and/or lips of human smokers because they are typically hidden and there is no direction not to cover them.
- Increased use of burn accelerants make cigarettes burn faster between puffs and, therefore, send more “sidestream” smoke into the ambient air that is not collected by the machine. Human smokers inhale some of this sidestream smoke and also puff more frequently, so a larger fraction of the tobacco is inhaled.

In the course of beating the FTC method, tobacco companies simultaneously developed techniques to provide more “kick” per milligram of delivered nicotine. Several design features undoubtedly contributed to

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28 Id. at 1178.
50 “Kick” is a tobacco industry term often used to describe the pharmacological effect of
both the subversion of the FTC method and the enhancement of addictive effects. This enabled the industry to produce cigarettes that were even more addictive, and, at the same time, claim lower nicotine yields in its advertising.

The following techniques could have plausibly increased the kick per milligram of delivered nicotine:

- Chemically control the pH of the tobacco to increase the transfer of nicotine from tobacco to smoke aerosol in a free base gas form that is not detected by the FTC machine but that may have a strong impact on upper airway receptors and be more readily absorbed.
- Engineer the cigarette so that the smoke will be at an optimal pH to increase the fraction of nicotine in the smoke that is quickly absorbed.
- Employ aerosol-engineering techniques to increase the fraction of smoke particles that can be inhaled deep into the lung and thus enable more complete absorption of nicotine (and probably carcinogenic lung toxins as a side effect).
- Increase acetaldehyde in the smoke as shown by Philip Morris researchers to enhance the addictive effects of nicotine.
- Add menthol and / or other ingredients to enable larger and more deeply inhaled puffs, thereby increasing nicotine doses.

Based on our understanding of pharmacology and drug design, and on information in tobacco industry documents, the following design features and ingredients may have made smoking more pleasant, even though they may have also made cigarettes more toxic:

- Cigarette ventilation dilutes the smoke, requiring larger volumes to obtain the same nicotine doses. (This is analogous to diluting vodka with water, thereby producing a milder beverage but one that is no less intoxicating than the undiluted version.)
- Leuvenalic acid appears to have been used to smooth the smoke a user inhales.
- Menthol provides a throat-soothing effect, which could make highly toxic smoke feel smoother and lighter.
- Glycerin can carry nicotine particles deep into the lung as well as provide a “smoother” smoke.
It is important to note that there has been little systematic evaluation of these pleasure-enhancing modifications by experts outside the tobacco industry. These features are presented as examples of cigarette characteristics that may have the intended effects that we postulate. In principle, the FDA could require the tobacco industry to disclose the effects of such alterations and to justify their application.

**Using Regulatory Authority to Alter Product Characteristics and Reduce Addictiveness**

So far, we have examined *controllable* ingredients and design features that plausibly enhance the addictiveness of cigarettes, increase their toxicity, and/or contribute to misleading estimates of human exposure to nicotine and tar. To protect the public, Congress could grant the FDA authority to prohibit their use or set performance standards. For example, if particle size can be controlled to decrease the fraction of particles that can be absorbed in the lungs, the FDA might set an allowable absorption percentage. Similarly, if ammonia increases the addictive kick of nicotine doses, and if menthol enhances the rapid absorption of nicotine deep into the lungs and increases carcinogenicity, such compounds might be prohibited. Finally, if pH manipulations increase the speed of nicotine absorption, standards might be set to diminish the rate of absorption.

In general, performance standards can be based on allowable ingredient levels, design and manufacturing techniques, or empirical tests of actual performance. There are precedents from food and drug regulation that can be adapted to many aspects of tobacco product regulation. This does not imply the need to tell manufacturers how to make their products; it merely ensures that public health considerations drive the FDA’s scrutiny of product design and manufacture. Such oversight stands in stark contrast to the current unregulated environment in which tobacco companies are free to use any methods at their disposal, including techniques that maximize rather than minimize addictiveness. In principle, a wide range of standards could be set that would not render cigarettes unacceptable, incapable of delivering nicotine, or even non-addictive. However, if such strategies could contribute to incrementally reduced cigarette addictiveness, then they warrant exploration. The idea is similar to striving for incremental reductions in cigarette toxicity through performance standards such as allowable maximums for nitrosamines, pesticide residues, arsenic, carbon monoxide, and other substances. Such

*21 C.F.R. §§ 1, 801 et seq. (2002); Jack E. Henningfield et al., *A Proposal To Develop Meaningful Labeling for Cigarettes*, 272 JAMA 312 (1994).*

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performance standards are unlikely to lead to safe and non-addictive cigarettes in the near future, but if they reduce disease prevalence and morbidity, their exploration is justifiable.

We are well aware of the potential unintended consequences of what we propose. For instance, non-smokers may initiate tobacco use under the mistaken impression that cigarettes have been made non-addictive, rather than merely less addictive. There is also the possibility that being a little bit addictive is no different than being a little bit pregnant. Such broad, population-based concerns should be at the forefront of the FDA's examination of whether regulatory powers should be used to make tobacco products less addictive.

**IMPLICATIONS FOR OTHER TOBACCO PRODUCTS**

Available data and documents indicate that it is also possible to reduce the addictiveness of smokeless tobacco products by setting ceiling levels on the use of buffering compounds. In addition, it is possible to determine product characteristics that are particularly appealing to and effective in establishing smokeless tobacco use among children. Such appealing designs and ingredients could be restricted.

Cigars and pipes pose a separate dilemma. It is important not to leave any category out of a regulatory framework lest we send the implicit message that there is less concern about that product category. However, the challenge is greater with cigars and pipes because there are far fewer data on these products.

**IMPLICATIONS FOR LABELING AND ADVERTISING**

The major tobacco companies do not label or advertise their tobacco products as addictive. This is a major flaw in the existing consumer warning system. There has been extensive theoretical discussion on how much nicotine would render a cigarette addictive. Until such values are empirically established, all tobacco products should include a strong addiction warning.

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32 The fact that there is no regulatory barrier to such warnings has been demonstrated by several small companies, which provide some form of addiction warning on their tobacco products. See, e.g., Star Scientific, Inc., Stonewall™ brand snuff, at http://www.starscientific.com; Vector Tobacco, Omni™ cigarettes, at http://www.omnicigs.com.

33 All nicotine-containing tobacco products should include a strong warning that they are addictive. Such warnings provide vitally important consumer information but should in no way relieve manufacturers of responsibility, or any accompanying legal liability, for creating and sustaining addiction among consumers.
As for how to appropriately label a cigarette with sub-biologically active levels of nicotine, we leave the question for another day. The challenges involved are extraordinarily complex; they comprise a whole other category of issues that require comprehensive regulatory oversight. For now, however, it bears mentioning that non-alcoholic beer typically contains small amounts of alcohol. Similarly, "fat-free" foods may contain trace levels of fats but their labels may say that there is "not a significant source of calories from fat." Perhaps a label such as "may promote nicotine addiction" should be considered for "nicotine-free" or "de-nicotinized" cigarettes, given the uncertainty of 1) what nicotine content might qualify as "nicotine-free" or "de-nicotinized," and 2) whether exempting "nicotine-free" or "de-nicotinized" cigarettes from bearing an addiction warning will actually lead to nicotine addiction through a graduation process.

CONCLUSION

Considering the extent to which determinants of addiction risk for cigarettes and other forms of tobacco are controllable, it is plausible that a regulatory approach can reduce the addiction risk of tobacco products. Regulation could reduce tobacco use and tobacco-caused disease without banning tobacco products and without rendering them nicotine-free. This approach is worth exploring, especially if it is simply not possible to make tobacco products substantially less toxic.

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34 Beer can be labeled as "non-alcoholic" if it contains less than 0.5% alcohol by volume, provided that the label includes the statement "contains less than 0.5 percent alcohol by volume." 27 C.F.R. § 7.71e (2002).

35 "Fat-free" food contains less than 0.5 grams of fat per serving (considered a "trivial level" of fat). A 0-gram standard is analytically impossible to measure. See Food Labeling; General Requirements for Health Claims for Food, 58 Fed. Reg. 2478-2536 (Jan. 6, 1993) (to be codified at 21 C.F.R. pt. 101).