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Establishing a Nicotine Threshold for Addiction -- The Implications for Tobacco Regulation

On February 25, 1994, the Food and Drug Administration (FDA) released a letter to the Coalition on Smoking or Health announcing its intention to consider regulating cigarettes. The agency's premises were that the vast majority of tobacco users self-administer the product for the drug effects of nicotine and to sustain addiction and that cigarette manufacturers control the levels of nicotine in cigarettes to maintain this addiction. The FDA further raised the possibility of regulating cigarettes on the basis of their nicotine content to prevent addiction.

On February 28, 1994, the ABC news program Day One presented evidence that tobacco manufacturers manipulate the nicotine content of cigarettes. One way they do this is by removing nicotine from tobacco and then adding it back in controlled amounts, using tobacco extracts containing nicotine. It was suggested on the news program that the amount of nicotine in tobacco was controlled to ensure that the level was adequate to maintain nicotine addiction. In support of this idea the program quoted an internal memorandum from a Philip Morris Tobacco Company scientist that had been discovered in recent litigation: "The cigarette should be conceived not as a product but as a package. The product is nicotine. . . . Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke."¹ That the pharmacologic actions of nicotine are important determinants of why people smoke is supported by studies conducted by the tobacco industry^{2,3} and by nonindustry researchers⁴.

That nicotine addiction sustains tobacco use for most smokers is well established⁴. Once a person is addicted to nicotine, quitting smoking is difficult, and more than 90 percent of the smokers who try to quit each year fail⁵. An important, if not the most important, component of a policy to reduce tobacco use in the population is to prevent the development of nicotine addiction in young people⁶. Young people do not start to smoke because they are addicted, but rather because of psychosocial and environmental influences, particularly peer influences, psychological factors, and advertising.

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Young people generally underestimate the addictiveness of nicotine, and most of them at first intend to smoke only for a few years⁶. However, once they begin to smoke, many become addicted to nicotine, and this addiction sustains the self-injurious behavior into adulthood. The result of nicotine addiction is a 40 percent probability of premature death from illness caused by tobacco⁷. It is difficult to prevent adolescents from experimenting with cigarettes. However, by regulating the availability of nicotine in tobacco products, it may be possible to prevent the transition from experimental or occasional smoking to addiction. This paper examines the proposition that the level of nicotine likely to produce addiction can be estimated and that mandating a nicotine content below that level is a feasible approach to tobacco regulation.

Is There a Threshold Level of Nicotine Intake Associated with Addiction?

We define addiction according to the Surgeon General's 1988 Report on Nicotine Addiction: it is the compulsive use of a drug that has psychoactivity and that may be associated with tolerance and physical dependence (i.e., may be associated with withdrawal symptoms after the cessation of drug use)⁴. For smokers, addiction is assumed to involve daily smoking of cigarettes, difficulty in not smoking every day, and a high likelihood of withdrawal symptoms after cessation of smoking.

Most American smokers are believed to be addicted according to these criteria⁸. However, approximately 10 percent of current smokers (a group sometimes called tobacco "chippers") regularly smoke five or fewer cigarettes per day and appear not to be addicted⁹. Most do not have withdrawal symptoms when they stop. Typically, such people smoke in specific situations, can skip smoking for one or more days, and can quit smoking without great personal distress.

The daily intake of nicotine from tobacco can be estimated from the level of cotinine, the principal metabolite of nicotine, in blood or saliva¹⁰. The average blood cotinine concentration in addicted smokers is about 300 ng per milliliter^{11,12}. Smokers of 5 or fewer cigarettes per day have average serum cotinine levels of 54 ng per milliliter and an average consumption of 3.9 cigarettes per day¹³. The cotinine level normalized for cigarette consumption is 14 ng per milliliter per cigarette, or 70 ng per milliliter for a person who smokes five cigarettes per day. Thus, it is reasonable to estimate a level of 50 to 70 ng of cotinine per milliliter as a cutoff point for the addictive threshold. Of course, there is no sharply demarcated threshold level, and there are some people who smoke fewer than five cigarettes per day and have great difficulty in quitting and others who can smoke more than five cigarettes per day and quit with ease.

Studies involving the infusion of nicotine and cotinine into smokers indicate that the daily intake of nicotine can be estimated as 0.08 times the blood cotinine concentration¹⁰. A level of 50 to 70 ng of cotinine per milliliter corresponds to a daily intake of 4 to 6 mg of nicotine. Thus, 5 mg of nicotine per day is proposed as a threshold level that can readily establish and sustain addiction.

Delivery of Nicotine from Cigarettes

On average, an American cigarette contains 8 to 9 mg of nicotine¹¹. The concentration of nicotine in tobacco ranges from 1.5 to 2.5 percent.

Typically, the cigarette delivers about 1 mg of nicotine to the circulation of the smoker,¹⁴

representing an absolute bioavailability of about 12 percent. The variation in intake per cigarette is considerable, however, ranging from 0.3 to 3.2 mg, representing a bioavailability of 3 to 40 percent, depending on how the cigarette is smoked^{14,15}. The daily intake of nicotine is poorly correlated with machine-determined yields^{11,12,16}. This is because smoking machines smoke cigarettes in a standardized way, whereas people can take more puffs, puff more intensively, and occlude ventilation holes in the filter or on the cigarette in order to obtain the desired dose of nicotine from most cigarettes. 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,¹⁷ a figure consistent with the maximal absolute bioavailability cited, 40 percent. We emphasize that this absolute bioavailability is the percentage of the nicotine contained in the cigarette that can be absorbed systemically by the smoker; it is unrelated to the smoking-machine yield. If the design of cigarettes were to change, bioavailability would need to be reassessed in people smoking the redesigned cigarettes.

Threshold Levels of Nicotine in Cigarettes as a Way to Avert Addiction

Although machine-measured cigarette yields are not useful in predicting a smoker's intake of nicotine, the absolute level of nicotine in a cigarette could be regulated to limit the maximal obtainable dose. Studies using cigarettes developed for research purposes to be low in nicotine have demonstrated that intake can be limited by restricting the amount of nicotine in the tobacco^{2,18}.

Assuming 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 addiction in most young people. At the same time, it may provide enough nicotine for taste and sensory stimulation.

A Possible Strategy for Regulation

The rationale behind the strategy for regulating the nicotine content of cigarettes is to prevent the development of nicotine addiction in young people. To minimize the hardship to already addicted adult smokers, the level of nicotine in tobacco could be reduced gradually, with a goal of reaching a target nicotine level over perhaps 10 to 15 years. The intended result of such a strategy would be that cigarettes could still be sold, but the number of addicted smokers would be markedly reduced. In the absence of addiction, levels of tobacco consumption should decline sharply, causing a substantial reduction in the rates of tobacco-caused illnesses.

There are, of course, a number of caveats. A threshold level for nicotine addiction is a theoretical concept based on observations in current smokers and studies of the bioavailability of nicotine during smoking restriction. That restricting levels of nicotine would prevent addiction needs to be verified empirically. There is concern that for already addicted adult smokers, reducing the nicotine level in tobacco might result in more intensive compensatory smoking, with increased exposure to toxic combustion products such as carbon monoxide and tar. Switching from higher-yield to lower-yield cigarettes has been shown to result in smoking more cigarettes or smoking more intensively, both of

which are associated with increased exposure to carbon monoxide and other toxins^{18,19}. Overcompensation (i.e., inhaling more smoke from low-nicotine cigarettes than from higher-yield brands) appears, however, to persist only for days or weeks. In long-term studies of carbon monoxide exposure after subjects switched to low-yield cigarettes, compensatory oversmoking appears not to persist^{20,21}. It is also conceivable that cigarettes could be manufactured to reduce the delivery of tar and carbon monoxide as well as the nicotine content. Even if there is some element of overcompensation and smokers are exposed to increased levels of toxins, their short-term (10 year) risk may be offset by the long-term benefit of a greater likelihood that they will stop smoking (as cigarettes become less satisfying) and by the enormous benefit of preventing nicotine addiction in future generations.

It should be noted that other researchers have proposed the introduction of "safer" cigarettes that are enriched with nicotine in order to reduce the ratio of tar to nicotine²². The rationale for such cigarettes is that smokers would need to inhale less smoke to obtain the desired dose of nicotine, and exposure to toxins would thus be reduced. A strategy involving nicotine-enriched cigarettes might reduce morbidity and mortality from cigarette smoking, but the reduction would probably be limited, because even at reduced doses, tobacco smoke is highly toxic. The goal of that approach -- producing a safer cigarette for those who cannot stop smoking -- is the diametric opposite of ours. Our goal is the prevention of nicotine addiction and a reduction in the prevalence of cigarette smoking, which in the long term would eliminate exposure to the toxins in tobacco smoke and reduce tobacco-induced morbidity and mortality much more.

The measures described in this proposal may seem drastic to some. However, the problem of one quarter of a billion premature deaths caused by tobacco use in developed countries⁷ calls for drastic action. Tobacco use is motivated by nicotine addiction. We offer a strategy for the prevention of nicotine addiction based on recent scientific data. This approach deserves study by the regulatory authorities.

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