# Pharmacology and Markers: Nicotine Pharmacology and Addictive Effects

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**INTRODUCTION** Dosing characteristics of cigarette brands are estimated using machines that smoke representative cigarettes from each brand according to a protocol termed the Federal Trade Commission (FTC) method (Peeler, this volume; Pillsbury, this volume). This technology and methodology provide tar- and nicotine-dosing estimates of cigarettes that are misleading to consumers and do not accurately predict what level of tar and nicotine intake consumers will obtain by smoking a given brand of cigarettes (Henningfield et al., 1994). An understanding of the dependence-producing and other behavior-modifying effects of cigarette smoke is necessary to understand why the FTC method is a poor predictor of the nicotine, tar, and carbon monoxide levels people obtain from cigarettes. Cigarette smoking behavior is influenced by nicotine dose, and smokers tend to maintain nicotine intake within upper and lower boundaries (Kozlowski, 1989). In brief, nicotine produces dose-related tolerance, physical dependence, and discriminative effects (i.e., effects that people can feel, which modify mood and physiology), and smokers change their behavior in response to these effects. Unlike human smokers, machines are not nicotine dependent, nor do they modify their behavior based on the flavor of the smoke.

The FTC method was developed in the 1960's to provide a relative ranking of nicotine, tar, and carbon monoxide yields from various cigarettes (Peeler, this volume; Pillsbury, this volume). This ranking has provided consumers with the false sense that they can tell precisely the amount of these substances they will obtain from a given cigarette. Since the 1960's there have been many advances in the understanding of nicotine and smoking behavior that can be useful in reforming this methodology. This chapter provides an overview of relevant research, including (1) physiological and behavioral pressures to sustain nicotine intake; (2) the relationship between smoking and nicotine dose; (3) determinants of compensatory behavior, including the role of nicotine and other factors, such as flavor; and (4) measurement of smoking and nicotine intake.

## CIGARETTE SMOKING AS DRUG DEPENDENCE

### Addiction Severity

Several findings bear on the issue of the strength of dependence on cigarettes. Although 70 to 90 percent of smokers are interested in quitting, only one in three succeeds before age 65 (Fiore, 1992). There is good and bad news about coronary bypass surgery and even a lung removal. The good news is that these traumatic events are among the most powerful incentives to quit smoking. If one intervenes with patients who undergo these procedures, about one-half of them quit. However, the bad news is that the other half

or more soon return to smoking (U.S. Department of Health and Human Services, 1988). There are two lessons here. First, incentives and motivation are important factors in the treatment of nicotine and other drug dependencies. Second, incentives and motivation have limitations; even the threat of death is not sufficient for half these smokers to stop smoking.

This is a tenacious addiction in which, despite so many people wanting and trying to quit, fewer than 1 in 10 has a 1-year success, and this means that only 2 to 3 percent of smokers stop smoking each year (Fiore, 1992). Indeed, as Kozlowski and colleagues (1989) show, more than half of heroin and cocaine users and alcoholics rate smoking cigarettes as harder to give up than these other drugs. Thus, there are strong biological pressures in nicotine-dependent humans that do not exist in machines to sustain addictive levels of nicotine intake.

**Clinical Characteristics**

As with dependence on other drugs, cigarette smoking tends to be a progressive, chronic, relapsing disorder (U.S. Department of Health and Human Services, 1988). The most notable distinction between cigarette smoking and other drug dependencies is that a much higher percentage of people who start smoking escalate and graduate to dependent levels than with other addictive drugs. About 1 in 10 smokers in this country is a low-level smoker, termed a "chipper," who smokes 5 or fewer cigarettes per day (U.S. Department of Health and Human Services, 1988); most of the rest show evidence of dependence. This is in contrast to alcohol use, where 10 to 15 percent of alcohol drinkers are problem drinkers; the rest generally drink in moderation and at times of their own choosing (U.S. Department of Health and Human Services, 1988).

People do not start smoking a pack of cigarettes per day. They likely would become ill at that level of nicotine intake. Rather, they start out with low levels. Over months and years, most people progress to higher and higher nicotine intake. They become tolerant; that is, nicotine loses effectiveness with its continued presence in the body, and it is necessary to increase the dose to maintain its effectiveness after repeated administrations. Eventually, smokers do more than simply tolerate high nicotine doses; they need continued nicotine to feel normal and function satisfactorily. At this point, smokers may go to great lengths to continue smoking and sustain their nicotine intake within upper and lower boundaries so that their intake does not fall low enough that they experience withdrawal symptoms or high enough to produce adverse effects (Kozlowski, 1989).

An important aspect of the chronic nature of tobacco dependence is related to daily patterns of nicotine blood levels. When smokers wake up in the morning, some residual nicotine remains in their blood from smoking on the previous day. Blood concentrations rise as they smoke until, by midafternoon, most smokers' intake equals metabolism and excretion, and nicotine level stabilizes. Levels fall rapidly overnight, and the cycle resumes the next day. Thus, blood concentrations never reach zero unless the person quits smoking for more than a few days. Moreover, cotinine, an active

nicotine metabolite, has a half-life of about 20 hours (Cummings and Richard, 1988; Jarvis, 1989; Jarvis et al., 1987) and therefore persists in the body even longer.

It is difficult to disrupt these patterns when people have access to cigarettes. In a study by Benowitz and colleagues (1986a), people switched from 30 to 5 cigarettes per day. Because they tended to smoke these 5 cigarettes much more intensely, they reduced carbon monoxide levels by only one-half and nicotine levels by only about one-third. Thus, nicotine intake remained high enough to sustain dependence.

After quitting smoking, most people relapse quickly, and about one-third of the people who have quit smoking and remained abstinent for 1 year relapse (Fiore, 1992). As with alcohol and heroin, most nicotine relapses occur during the first 3 months of abstinence (Hunt et al., 1971). In fact, the determinants of relapse (e.g., degree of dependence and negative emotional states) and remission (e.g., substance-associated health problems and learning to manage cravings) are also similar across these three classes of drug dependence (U.S. Department of Health and Human Services, 1988).

Relapse to nicotine dependence has been studied in greater detail than relapse to heroin, cocaine, and alcohol dependence. Data from a Mayo Clinic study showed that, with minimal treatment intervention, one-quarter of the people relapsed in 2 days and about one-half in the first week (Kottke et al., 1989). More recent data on people who quit on their own showed that about two-thirds relapse within 3 days (Hughes et al., 1992). The withdrawal syndrome can be debilitating in its own right, but in the long run, its worst health consequences may be that most efforts to quit smoking never survive the withdrawal phase (Hughes et al., 1992), thereby dooming one-half of persistent smokers to die prematurely because of their tobacco use (Peto et al., 1994). Much of the benefit of current nicotine medications is providing adequate nicotine replacement for that formerly provided by cigarettes to help more people remain nonsmokers during the important first few weeks of tobacco abstinence.

## NICOTINE DELIVERY SYSTEMS

Tobacco products come in many different forms. All have toxicities and dependence potential, and there is variation related to the type of tobacco product and route of administration. Although the focus here is on cigarettes, at some point similar issues must be addressed with other tobacco products that currently have no dosage labeling. For example, moist snuff products vary widely in their nicotine-dosing capabilities, and there is evidence that the variation is accomplished primarily by manipulation of the pH level of the products by tobacco manufacturers (Henningfield et al., 1995; Djordjevic et al., 1995), but neither tobacco companies nor governmental agencies provide any form of nicotine dosage information to consumers except in cigarette advertising.

The cigarette, which may be conceived of as a nicotine dispenser with smoke as the vehicle, is the most toxic and dependence-producing form of nicotine delivery. Nicotine is volatilized at the tip of a burning cigarette from

which it is carried by particulate matter (tar droplets) deep into the lungs with inspired air. The nearly 2,000 °F microblast at the cigarette's tip is also the source of carbon monoxide and many other toxicologically significant pyrolysis products. Nicotine is rapidly absorbed in the alveoli of the lungs, concentrated in the pulmonary veins as a bolus, and pumped by the left ventricle of the heart throughout the body. Absorption characteristics are similar to those of gases, such as oxygen, that are exchanged in the lung from inspired air to venous blood (Henningfield et al., 1993). Thus, smoke inhalation produces arterial boli that may be 10 times more concentrated than the levels measured in venous blood (Henningfield et al., 1990 and 1993).

Psychoactive effects have rapid onset and short duration, dissipating within a few minutes. This short duration requires the user to self-administer the drug repeatedly, perhaps taking hundreds of puffs per day. The cigarette allows the smoker very fine, "fingertip," dose control. The powerful engulfing sensory effects are also important in dependence. It is not just the drug but the conditions and the cues that become associated with the drug that make nicotine dependence so tenacious. Finally, the cigarette is a convenient, portable system that permits easily repeated dosing.

Benowitz (this volume) reviewed the pharmacokinetics of various nicotine delivery systems. Briefly, a cigarette produces a rapid spike of nicotine in the arterial blood. Smokeless tobacco products are also rapid, especially the higher pH tobacco products, and they require little practice for the user to achieve high nicotine levels. Whereas the nicotine dose obtained from a cigarette is largely determined by the behavior of the user, the nicotine dose obtained from a "chew" of smokeless tobacco is largely controlled by the product (Henningfield et al., 1995). In contrast to delivery from tobacco products, delivery of nicotine from polacrilex (nicotine gum) is slower and takes a great deal of practice and work to achieve even modest nicotine plasma levels. Transdermal nicotine medications (patches) provide slow absorption—so slow that users cannot reliably detect nicotine's effects. The speed of delivery is clearly an important determinant of addictive effects, and the cigarette, like crack cocaine, provides an explosive dose of nicotine.

## NICOTINE'S EFFECTS

Nicotine is a fascinating psychoactive drug. It was used to help map the cholinergic nervous system early in the 20th century. Much of receptor theory and many of the methods used to study competitive agonists and antagonists were developed at the turn of the century using nicotine (Langley, 1905).

Nicotine has diverse effects, not only in the brain but also in the adrenals and skeletal muscles. These diverse effects may explain why a smoker reports that on some occasions cigarettes have relaxing effects and on other occasions, stimulating effects. This has been referred to as a paradoxical effect, but it is not paradoxical at all; other drugs generally referred to either as sedatives or stimulants also produce both sedating and stimulating effects (Gilman et al., 1990). Like the effects of these other drugs, nicotine's effects are complicated; they depend on the dose, the time since dosing, how the

drug was administered, which responses are being measured, and other factors (Henningfield and Keenan, 1993; Pomerleau and Rosecrans, 1989).

If people with histories of drug abuse are given nicotine, they like the nicotine; that is, liking scale scores increase with greater doses within a certain range of parameters (Henningfield et al., 1985). Among drug abusers, similar findings are reported for morphine and amphetamines but not for drugs that have little psychoactivity (Fischman and Mello, 1989). Such psychoactive effects are predictive of addiction potential and are correlated with the ability of a drug to serve as a reinforcer for animals and humans (Griffiths et al., 1980). Nicotine is psychoactive in humans and is readily discriminated by animals; several forms of nicotine delivery have been shown to serve as reinforcers for animals and humans (U.S. Department of Health and Human Services, 1988).

**Physical Dependence and Withdrawal**

The cellular and neurological changes that lead to tolerance also lead to physical dependence so that when people abruptly discontinue tobacco use, withdrawal occurs (U.S. Department of Health and Human Services, 1988). Withdrawal onset begins within a few hours of the last cigarette; symptoms include decreased cognitive capabilities and heart rate and increased dysphoria or depressed mood, insomnia, craving, anxiety, irritability, restlessness, appetite, and tendency to smoke (American Psychiatric Association, 1994; Hughes and Hatsukami, 1992). Altered brain electrical potentials and hormonal output are generally opposite in direction of those produced by acute nicotine administration, and decrements in evoked electrical potentials of the brain indicate impaired information processing capabilities (Pickworth et al., 1989; U.S. Department of Health and Human Services, 1988).

Nicotine dependence seems to be mediated primarily by the activation of nicotinic cholinergic receptors in the brain (U.S. Department of Health and Human Services, 1988) and secondarily through the cascading effects of nicotinic systems to modulate levels of hormones such as epinephrine (adrenaline) and cortisol (Pomerleau and Pomerleau, 1984; U.S. Department of Health and Human Services, 1988). The mesolimbic dopaminergic reward system, which mediates the ability of cocaine to produce dependence, also has been implicated in nicotine dependence (Corrigall, 1991; U.S. Department of Health and Human Services, 1988). The cells of this system are located in the ventral tegmental area of the midbrain. Axons project to the limbic system—specifically, to the nucleus accumbens, olfactory tubercle, nuclei of the stria terminalis, and parts of the amygdala. Behaviors followed by such neural activation can become extremely persistent. Cortical effects of nicotine administration include changes in local cerebral metabolism (London and Morgan, 1993) and electroencephalogram results (Jones, 1987). Prominent endocrine effects include release of catecholamines, serotonin, prolactin, growth hormone, arginine vasopressin, beta-endorphin, and adrenocorticotropic hormone (Pomerleau and Pomerleau, 1984; U.S. Department of Health and Human Services, 1988). These effects mediate both the positive nicotine reinforcement sought by smokers and even

animals (Corrigall, 1991; Henningfield and Goldberg, 1983; Pomerleau, 1992; U.S. Department of Health and Human Services, 1988) and the negative reinforcement of withdrawal symptoms that also fuel the compulsion to smoke (Hughes and Hatsukami, 1992; Pomerleau and Pomerleau, 1984). Nicotine also produces increased expression of brain nicotinic receptors in humans and animals (U.S. Department of Health and Human Services, 1988). Taken together, these physiologic effects confirm that nicotine exposure alters the structure and function of the nervous system and leads to modification of behavior. Thus, there are physiological factors that drive smokers to sustain continued nicotine intake across changing delivery systems.

Smokers may report that they feel impaired and distracted after only a few hours of abstinence, and their performance on various cognitive and psychomotor tasks can decline within approximately 4 hours (Heishman et al., 1994). Symptoms are rapidly reversed with resumed smoking or nicotine replacement, thus providing a potentially powerful source of reinforcement for continued smoking. The degree of reversal is generally proportional to the percentage of plasma nicotine that is replaced (Pickworth et al., 1989; U.S. Department of Health and Human Services, 1988).

Data from a performance study indicated that when patients abstained from cigarettes and used placebo gum, they made more errors and took longer to complete a task than during their smoking baseline. When they were given 2 mg gum, their performance returned to baseline. With 4 mg gum, they did not do significantly better than at baseline, but 4 mg appeared to produce somewhat more reliable clinical effects than 2 mg (Snyder and Henningfield, 1989).

The same pattern of effects occurs with theta power, a measure of brain function (Pickworth et al., 1989). This nicotine-withdrawal-induced deficit can be completely reversed with nicotine replacement. When other volunteers resumed smoking, electrocortical potentials recovered quickly in all volunteers. Interestingly, these people did not like the gum, and they were not trying to quit smoking. The lesson is that nicotine replacement can maintain physiological function and cognitive performance. The conclusion relating to performance is not that nicotine makes the user perform better, faster, or more intelligently but that nicotine deprivation results in impairments that are quickly and dose-dependently reversed by nicotine readministration (Heishman et al., 1994).

The nicotine-withdrawal-induced decline in performance has practical ramifications in policy decisions. Currently, the Federal Aviation Administration is examining its policies on smoking by pilots in the flight decks of commercial airlines. Because of the time course of nicotine withdrawal, if smoking were eliminated in the flight deck, acutely deprived pilots might suffer withdrawal-induced performance declines on flights longer than approximately 4 hours. Thus, the nicotine withdrawal syndrome poses a potential safety hazard if it is not rationally addressed by appropriate strategies to detoxify pilots safely and treat their withdrawal symptoms with nicotine replacement medications.

The duration of the nicotine withdrawal syndrome varies across individuals, but on average, the acute physical syndrome is worst during the first month. Gross and Stitzer (1989) studied the time course of the nicotine withdrawal syndrome in detail. In their study, people quit smoking and received either active or placebo nicotine gum. People who received active gum chewed an average of 6.9 pieces of 2 mg gum per day, which provided less nicotine than they were obtaining by smoking cigarettes. People given placebo gum gradually decreased their intake from 6.8 pieces per day during the first week of treatment to 4.9 pieces per day by the 10th week. The nicotine gum substantially reduced withdrawal symptom severity relative to that observed in placebo subjects.

**Nicotine's Beneficial Effects**

Nicotine provides many effects that cigarette smokers may consider useful. These include weight control, mood control, and preventing withdrawal symptoms (U.S. Department of Health and Human Services, 1988). The issue of whether nicotine would provide substantial cognitive enhancement in healthy persons who had never been nicotine dependent is controversial. In nonsmokers, nicotine administration can increase finger-tapping rate and slightly (but significantly in some studies) attenuate the deterioration in attention that occurs during protracted testing (Heishman et al., 1994). However, complex cognitive performance may be impaired by nicotine in cigarette smokers as well as nonsmokers (Heishman et al., 1994). On the other hand, there is no question that nicotine intake restores withdrawal-induced deficits (Snyder and Henningfield, 1989). Nicotine intake also may provide some level of cognitive enhancement in persons who are cognitively impaired by Alzheimer's disease (Heishman et al., 1994; Sahakian et al., 1989; Newhouse and Hughes, 1991).

One of the Brown and Williamson Tobacco Corporation (B&W) documents made available for the National Cancer Institute conference on the FTC cigarette test method also supported the conclusion that nicotine's central nervous system effects contribute to the strong motivation to use tobacco products. The document concluded that

> to understand smoking, just as any other behavior, it is necessary to consider it as a process embedded within everyday life . . . . It is apparent that nicotine largely underpins these contributions through its role as a generator of central physiological arousal effects which express themselves as changes in human performance and psychological well being. (Brown and Williamson, 1984)

**SMOKING AND NICOTINE DOSE**

Nicotine dosage is an important factor in smoking behavior. Currently available cigarettes allow people to fairly easily administer the nicotine dose they need or desire (Henningfield et al., 1994). This was true of a low-content cigarette, NEXT, that was marketed a few years ago and removed from the market following poor sales, even though taste and draw characteristics were similar to conventional cigarettes. With that cigarette, the nicotine content was so low that no amount of compensatory puffing

and inhaling could result in the extraction of substantial amounts of nicotine (Butschky et al., 1995).

**Compensatory Behavior**

Compensation is nicely described in the B&W documents (Brown and Williamson, 1984) as "the tendency for a smoker to obtain similar delivery, intake and uptake of smoke constituents on a daily basis from a variety of products with different standard (machine-smoked) deliveries."

As the B&W researchers noted, if smokers are dependent, then the nicotine they receive from cigarettes can be supplemented by other forms, and this will reduce smoking. Likewise, cigarettes of different strengths are smoked differently; that is, smokers given low-delivery cigarettes smoke them more intensively and vice versa.

In fact, this is what has been found in many studies (U.S. Department of Health and Human Services, 1988). Cigarette consumption increases in response to reduced nicotine, and most compensation occurs at the individual cigarette level, not by cigarettes per day. Whereas people given cigarettes of lower nicotine yield also may smoke a few more cigarettes per day, they smoke each of the cigarettes more intensely to obtain proportionately more nicotine than the rating of nicotine yield would suggest (Hill and Marquardt, 1980; Russell et al., 1980; Benowitz et al., 1983; Robinson et al., 1983).

When people are given nicotine gum and their smoking is measured, smoking decreases as the nicotine gum dose increases (Nemeth-Coslett and Henningfield, 1986). When mecamylamine is administered to antagonize nicotine's effects, people smoke more cigarettes, take more puffs per cigarette, and take in more total smoke, as can be seen by increased carbon monoxide level (Nemeth-Coslett et al., 1986; Rose et al., 1989). Taste and other sensory factors are also important modulators of human smoking behavior (Butschky et al., 1995; Rose and Behm, 1987; U.S. Department of Health and Human Services, 1988).

This finding addresses why the nicotine dependence issue is relevant to why the FTC method of measuring tobacco smoke constituents is seriously flawed. Simply put, the FTC method uses machines that do not change their behavior to self-administer a preferred nicotine dose or in response to the taste of the smoke, as human smokers do. It may be an accurate predictor of what smoking machines obtain under specifically programmed conditions, but it is not an accurate predictor of what people get from cigarettes.

The dose-response relationship between FTC ratings and plasma nicotine levels is weak, except at low doses (Russell et al., 1980 and 1986; Rickert and Robinson, 1981; Benowitz et al., 1983 and 1986b; Robinson et al., 1983; Gori and Lynch, 1985; Maron and Fortmann, 1987; Coultas et al., 1993). The relationship between cigarette dosage ratings and plasma nicotine levels may be better in studies using research cigarettes where nicotine content

varies. With other drugs, compensation can be diminished when the cost of compensation increases. That is, if a drug becomes too costly in terms of expense or physical difficulty in sustaining intake, users may not compensate as effectively and will not administer as much of the drug as they did when the cost was lower (U.S. Department of Health and Human Services, 1988; Lemaire and Meisch, 1985; Bickel et al., 1993). Thus, if cigarettes have low enough nicotine contents, smokers would be expected to adjust over time to lower nicotine levels rather than spend the time and money necessary to maintain constant dose intake. Conversely, most smokers probably would not smoke 160 to 200 low-nicotine-content cigarettes per day to continue to receive the intake that they previously obtained from conventional cigarettes.

**Measurement of Smoking and Nicotine Intake**

The role of dependence is assumed by the authors and the tobacco industry to be important determinants of nicotine intake. Brown and Williamson (1983) noted

> the basic assumption is that nicotine, which is almost certainly the key smoke component for satisfaction, is fully released to the body system before exhalation takes place. It is essential, therefore, to quantify the change in chemical composition between inhaled and exhaled smoke under different smoking conditions.

Cigarette dose determination is indeed complicated, and some may suggest that it is so complex that use of the flawed FTC method might as well continue simply because it has been used for nearly 30 years. However, such a conclusion contradicts the enormous research advances made over the past 30 years. This research can be used to devise a better method. Furthermore, the complexity of dose determination is not unique to cigarettes. The Food and Drug Administration (FDA) faces this issue routinely whenever a manufacturer submits a new drug. Unless the drug is injected into a vein, determination of dosing is complicated. If the drug is delivered by an inhaler or oral capsule, many factors must be and are considered so that consumers are provided with realistic estimates of what they will get. In particular, they are provided with information relevant to the maximal doses that they are likely to receive from a drug-delivering product.

To provide accurate dosing information for drug delivery systems, FDA uses different methods as indicated by the chemical and its delivery system; moreover, verification of dosing estimates is accomplished in human bioavailability testing studies because, in the final analysis, we care about the dose that people receive, not the machine-derived dose. Also, if there are factors that produce major changes in bioavailability, such as whether the drug is taken with food or on an empty stomach, this can be indicated in the labeling.

**A PROPOSAL FOR MORE MEANINGFUL CIGARETTE LABELING**

One approach to more meaningful cigarette labeling is that described by Henningfield and colleagues (1994). This approach was adapted from that used by FDA to label food products with constituents of health-related relevance. One issue that FDA addressed in food labeling was serving size. In the case of cigarettes, research has indicated the need for larger and more intense puffs from the machine to more closely parallel smokers' behavior (U.S. Department of Health and Human Services, 1988). A second issue for cigarette labeling is the need to use biologically meaningful categories. For example, labels might specify "no nicotine" or "low nicotine" instead of including numerical values that imply that differences of a few percentage points have practical meaning and provide the consumer with the illusion that she or he will obtain different doses from different cigarettes. Similarly, terms such as "light" should be banned altogether because they imply health benefits; these terms are permitted with foods only if the food type provides a health benefit relative to the conventional type of food in a given category. Actual nicotine content of the cigarettes also should be provided to consumers because the content determines the absolute limit of nicotine that could be extracted.

Nicotine delivery ratings also could be linked to other factors having health effects, for example, tar. Thus, a low-nicotine-delivering cigarette could not be labeled "low nicotine" unless it was also low in tar and carbon monoxide delivery. A comparable situation in food labeling is that a label may not use the phrase "fat free" if a product contains cholesterol. Finally, nicotine yield estimates from standardized machine tests should be validated with bioavailability testing, as is done with other drugs, because what is of interest is the dose obtained by smokers.

This approach would not in itself solve the health problem posed by tobacco use, but it would at least provide consumers with what they have come to expect in the United States, namely, honest labeling that gives them the information on which to make decisions about the products they use. Three decades of research on cigarette smoking, nicotine dependence, and measurement of tobacco constituent intake have provided the means to give consumers such information.

**QUESTION-AND-ANSWER SESSION**

DR. DEBETHIZY: Dr. Henningfield, you really did not speak very much to the FTC method, but I think it is important to point out that the FTC method was never intended to measure nicotine uptake.

I also agree with you. I think we can do better in terms of measuring nicotine uptake when we want to do that. I think the methods that have been used in the past are estimates. I think the study that I will tell you about a little bit later is a step in that direction, and I will be looking forward to sharing that with you.

I would like to make a point about your proposal to measure content. I have heard that a number of times today, and we have to remember that people do not eat cigarettes; they smoke cigarettes. And there is no indication that people obtain the amount of nicotine that is contained in a cigarette.

DR. HENNINGFIELD: On content, I think that the most important thing is bioavailability tests. Again, that is the gold standard: what people are likely to get and generally under maximum conditions. The importance of content, though, is that content limits the amount of nicotine that you can get. If it is not there, you cannot get it.

DR. DEBETHIZY: I think the important thing is the FTC method is set up to provide relative ranking, so that consumers can get an idea of what different cigarettes will yield. It was not intended to measure uptake.

Now, if you want to measure uptake and evaluate the FTC method, that is a different activity, and I think that we need to make sure that we distinguish those two activities. One is to provide a relative ranking. The FTC method has done an excellent job of that over the years.

DR. HENNINGFIELD: I am not addressing the method, but I think it is pretty clear that it has not done a good job of telling people what they will have in their bloodstream. And that is what I am addressing: that what people get in their bloodstream does not bear much relation to the FTC yields. So, I am not sure how much use that has been.

DR. HARRIS: I see the dispute as distinguishing between an ordinal ranking and a cardinal ranking. An ordinal ranking merely says one brand, to some degree, delivers more or less nicotine than another; whereas, a cardinal ranking would say, this brand delivers one-fifth as much or five times as much.

And what I understand the dispute to be about is that the FTC ranking actually may preserve an ordinal ranking in the roughest sense, but it does not preserve the cardinal ranking. From what I can gather, a 10-percent increase in FTC nicotine corresponds with, at most, about a 2-percent increase in blood nicotine, roughly speaking, and that that is where the problem lies.

DR. HENNINGFIELD: It is not even that good, because if the slope were constant, you could maybe say there is an ordinal ranking. That still may not tell you if it is meaningful if it was so trivial. But what Dr. Benowitz showed was if there is a break.

In other words, at the ultralow end, those cigarettes are in a slightly different category. From the data I have seen, it is not even a meaningful ordinal ranking. It is a pretty flat ranking. The slope is, I would contend until proven otherwise, biologically trivial.

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