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From the US Food and Drug Administration

Statement on nicotine-containing cigarettes

David A Kessler

On 25 March 1994 the Commissioner of the US Food and Drug Administration (FDA), Dr David Kessler, presented testimony to the Subcommittee on Health and the Environment, Committee on Energy and Commerce, US House of Representatives. In his statement Dr Kessler commented on the addictive nature of cigarette smoking. He also presented evidence which, in his view, suggests that the cigarette industry has manipulated the level of nicotine in cigarettes with the intent to create and sustain addiction in smokers. We consider this testimony, because of both its content and the position of the person who gave it, to be an historic event in the history of tobacco control. Therefore, despite its length, we are reproducing the statement below.

We have used bold type to highlight some of the more noteworthy statements made by Dr Kessler. Eight figures have been omitted (such omissions are noted in brackets), and some of the references have been modified to conform to the journal's style. Otherwise, the testimony is reproduced in its original form.

An editorial by Dr John Slade commenting on this testimony appears on page 99. A cover essay by Dr Edythe London, which addresses nicotine action in the brain, appears on page 101. – ED

Mr Chairman, the cigarette industry has attempted to frame the debate on smoking as the right of each American to choose. The question we must ask is whether smokers really have that choice.

Consider these facts:

- Two-thirds of adults who smoke say they wish they could quit.[1]
- Seventeen million try to quit each year, but fewer than one out of 10 succeed.[2] For every smoker who quits, nine try and fail.
- Three out of four adult smokers say that they are addicted.[1] By some estimates, as many as 74% to 90% are addicted.[3]
- Eight out of 10 smokers say they wish they had never started smoking.[1]

Accumulating evidence suggests that cigarette manufacturers may intend this result – that they may be controlling smokers' choice by controlling the levels of nicotine in their products in a manner that creates and sustains an addiction in the vast majority of smokers.

That is the issue I am here to address. Whether it is a choice by cigarette companies to maintain addictive levels of nicotine in their cigarettes, rather than a choice by consumers to continue smoking, that in the end is driving the demand for cigarettes in this country.

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DA Kessler

Although the FDA has long recognised that the nicotine in tobacco produces drug-like effects, we never stepped in to regulate most tobacco products as drugs. One of the obstacles has been a legal one. A product is subject to regulation as a drug based primarily on its intended use. Generally, there must be an intent that the product be used either in relation to a disease or to affect the structure or function of the body. With certain exceptions,[4,5] we have not had sufficient evidence of such intent with regard to nicotine in tobacco products. Most people assume that the nicotine in cigarettes is present solely because it is a natural and unavoidable component of tobacco.

Mr Chairman, we now have cause to reconsider this historical view. The question now before us all is whether nicotine-containing cigarettes should be regulated as drugs. We seek guidance from the Congress on the public health and social issues that arise once the question is posed. This question arises today because of an accumulation of information in recent months and years. In my testimony today, I will describe some of that information.

The first body of information concerns the highly addictive nature of nicotine. The second body of information I will be talking about – in some detail – concerns the apparent ability of cigarette companies to control nicotine levels in cigarettes. We have information strongly suggesting that the amount of nicotine in a cigarette is there by design. Cigarette companies must answer the question: what is the real intent of this design?

Nicotine is a highly addictive substance

Let me turn then to my first point about the addictive nature of nicotine. The nicotine delivered by tobacco products is highly addictive. This was carefully documented in the 1988 US Surgeon General's report. You can find nicotine's addictive properties described in numerous scientific papers.[6–12]

As with any addictive substance, some people can break their addiction to nicotine. But I doubt there is a person in this room who hasn't either gone to great pains to quit smoking, or watched a friend or relative struggle to extricate himself or herself from a dependence on cigarettes.

Remarkably, we see the grip of nicotine even among patients for whom the dangers of smoking could not be starker. After surgery for lung cancer, almost half of smokers resume

smoking.[13] Among smokers who suffer a heart attack, 38% resume smoking while they are still in the hospital.[14] Even when a smoker has his or her larynx removed, 40% try smoking again.[15]

When a smoker sleeps, blood levels of nicotine decrease significantly. But the smoker doesn't need to be an expert on the concept of nicotine blood levels to know full well what that means. More than one-third of smokers reach for their first cigarette within 10 minutes of awakening; nearly two-thirds smoke within the first half hour.[16] Experts in the field tell us that smoking the first cigarette of the day within 30 minutes of waking is a meaningful measure of addiction.[17]

I am struck especially by the statistics about our young people. A majority of adult smokers begin smoking as teenagers.[6] Unfortunately, 70% of young people aged 12–18 who smoke say that they believe that they are already dependent on cigarettes.[6] About 40% of high school seniors who smoke regularly have tried to quit and failed.[6]

It is fair to argue that the decision to start smoking may be a matter of choice. But once they have started smoking regularly, most smokers are in effect deprived of the choice to stop smoking. Recall one of the statistics I recited earlier. Seventeen million Americans try to quit smoking each year. But more than 15 million individuals are unable to exercise that choice because they cannot break their addiction to cigarettes. My concern is that the choice that they are making at a young age quickly becomes little or no choice at all and will be very difficult to undo for the rest of their lives.

Mr Chairman, nicotine is recognized as an addictive substance by such major medical organisations as the Office of the US Surgeon General,[18] the World Health Organisation,[19,20] the American Medical Association,[21] the American Psychiatric Association,[22] the American Psychological Association,[23] the American Society of Addiction Medicine,[24] and the Medical Research Council in the United Kingdom.[25] All of these organisations acknowledge tobacco use as a form of drug dependence or addiction with severe adverse health consequences.

Definitions of an addictive substance may vary slightly, but they all embody some key criteria: first, compulsive use, often despite knowing the substance is harmful; second, a psychoactive effect – that is, a direct chemical effect in the brain; third, what researchers call reinforcing behaviour that conditions continued use (figure 1).[18] In addition, withdrawal symptoms occur with many drugs and occur in many cigarette smokers who try to quit. These are hallmarks of an addictive substance and nicotine meets them all.

When a smoker inhales, once absorbed in the bloodstream, nicotine is carried to the brain in only 7–9 seconds,[26] setting off a biological chain reaction that is critical in establishing and reinforcing addiction.

Over the past few years, scientists have generated a tremendous amount of information

Criteria for drug dependence

Primary criteria
- highly controlled or compulsive use
- psychoactive effects
- drug-reinforced behaviour

Additional criteria

Addictive behaviour often involves:
- stereotypic patterns of use
- use despite harmul effects
- relapse following abstinence
- recurrent drug cravings

Dependence-producing drugs often produce:
- tolerance
- physical dependence
- pleasant (euphoric) effects

Figure 1 Source: US Surgeon General's report, 1988[18]

on the similarities among different addictive substances. Some crucial information has come from the fact that, in a laboratory setting, animals will self-administer addictive substances. This self-administration may involve the animal pushing a lever or engaging in other actions to get repeated doses of the addictive substance. With very few exceptions, animals will self-administer those drugs that are considered highly addictive in humans, including morphine and cocaine, and will not self-administer those drugs that are not considered addictive.[27,28]

Understanding that animals will self-administer addictive substances has fundamentally changed the way that scientists view addiction in humans.[27] It has turned attention away from the concept of an "addictive personality" to a realisation that addictive drugs share common chemical effects in the brain.[27]

Despite the wide chemical diversity among different addictive substances, a property that most of them share is the ability to affect the regulation of a chemical called dopamine in parts of the brain that are important to emotion and motivation.[29] It is now believed that it is the effect of addictive substances on dopamine that is responsible for driving animals to self-administer these substances and for causing humans to develop addictions.[27]

Regulation of dopamine rewards the activity, and causes the animal or person to repeat the activity that produced that reward.[27,29] The process by which the regulation of dopamine leads an animal or a human to repeat the behaviour is known as "reinforcement".[27] Drugs that have the ability to directly modify dopamine levels can produce powerfully ingrained addictive behaviour.[27]

One of the ways that researchers now test the addictive properties of drugs is to determine whether animals will self-administer that substance and then to determine whether the animals will stop self-administering if the chemical action of the substance is blocked by

the simultaneous administration of another drug that prevents the first substance from acting in the brain. Data gathered over the past 15 years have documented that laboratory animals will voluntarily self-administer nicotine;[18,28,29] that nicotine stimulates the release of dopamine;[30] and that laboratory animals will decrease self-administration of nicotine if the action of nicotine, or the release of dopamine, in the brain is blocked.[31,32]

A number of top tobacco industry officials have stated that they do not believe that tobacco is addictive.[33,34] They may tell you that smokers smoke for "pleasure", not to satisfy a nicotine craving. Experts tell us that their patients report that only a small minority of the cigarettes they smoke in a day are highly pleasurable.[35] Experts believe that the remainder are smoked primarily to sustain nicotine blood levels and to avoid withdrawal symptoms.[35]

The industry couches nicotine's effects in euphemisms such as "satisfaction" or "impact" or "strength". Listen to what they say in one company's patent:

> It also has been generally recognised that the smoker's perception of the "strength" of the cigarette is directly related to the amount of nicotine contained in the cigarette smoke during each puff.[36]

But these terms only sidestep the fact that the companies are marketing a powerfully addictive agent. **Despite the buzzwords used by industry, what smokers are addicted to is not "rich aroma" or "pleasure" or "satisfaction". What they are addicted to is nicotine, pure and simple, because of its psychoactive effects and its drug dependence qualities.**

To smokers who know that they are addicted, to those who have buried a loved one who was addicted, it is simply no longer credible to deny the highly addictive nature of nicotine.

Controlling the level of nicotine in cigarettes

My second point today involves a growing body of information about the control of nicotine levels exercised by the tobacco industry. Mr Chairman, I do not have all the facts or all the answers today. The picture is still incomplete. But from a number of pieces of information, from a number of sources, a picture of tobacco company practices is beginning to emerge.

The public thinks of cigarettes as simply blended tobacco rolled in paper. But they are much more than that. **Some of today's cigarettes may, in fact, qualify as high technology nicotine delivery systems that deliver nicotine in precisely calculated quantities – quantities that are more than sufficient to create and to sustain addiction in the vast majority of individuals who smoke regularly.**

But you don't have to take it from me. Consider how people in the tobacco industry itself view cigarettes.

Just take a moment to look at the excerpts from an internal memorandum written by a supervisor of research that circulated in the Philip Morris Company in 1972:

> Think of the cigarette pack as a storage container for a day's supply of nicotine... Think of the cigarette as a dispenser for a dose unit of nicotine... Think of a puff of smoke as the vehicle for nicotine... Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke.[37]

"Dispensers of smoke... [which is] a vehicle for delivering nicotine." This quote is a revealing self-portrait. Or listen to the words in one tobacco company patent:

> Medical research has established that nicotine is the active ingredient in tobacco. Small doses of nicotine provide the user with certain pleasurable effects resulting in the desire for additional doses.[38]

THE DESIGN OF CIGARETTES

How does this industry design cigarettes?

The history of the tobacco industry is a story of how a product that may at one time have been a simple agricultural commodity appears to have become a nicotine delivery system. Prior to the 1940s, the waste products from cigarettes – the stems, the scraps, and the dust – were discarded. The tobacco industry had identified no use for these materials in the cigarette manufacturing process.

Then, in the 1940s and '50s, the industry created reconstituted tobacco from the previously unusable tobacco stems, scraps, and dust. This gave cigarette makers the ability to reduce the cost of producing cigarettes by using fewer tobacco leaves and making up the difference by using reconstituted tobacco. While the motive appeared to be purely economic, the reconstitution process was nevertheless a critical development that started the industry down the path toward controlling and manipulating nicotine levels. The ability to control and manipulate nicotine levels becomes important in light of another key realization. Industry patents show that the industry recognized that nicotine is the active ingredient in tobacco smoke. It is what produces the psychoactive effects that lead smokers to crave cigarettes.

Numerous patents illustrate how the industry has been working to sustain the psychoactive effects of nicotine in cigarettes. These charts [omitted here] show samples from several categories of patents: eight patents to increase nicotine content by adding nicotine to the tobacco rod (patents 3,109,436; 4,215,706; 4,830,028; 4,836,224; 5,031,646; 3,861,400; 4,715,389; 4,595,024); five patents to increase nicotine content by adding nicotine to filters, wrappers and other parts of the cigarette (patents 3,280,823; 3,584,630; 5,105,834; 4,676,259; 4,236,532); three patents that use advanced technology to manipulate the levels of nicotine in tobacco (patents 0,280,817; 4,898,188; 5,018,540); eight patents on extraction of nicotine from tobacco (patents 3,046,997; 4,068,671; 4,557,280; 3,139,435;

4,150,677; 5,065,775; 4,967,771; 5,018,540); and nine patents to develop new chemical variants of nicotine (patents 5,138,062; 5,015,741; 4,590,278; 4,155,909; 4,321,387; 4,220,781; 4,442,292; 4,452,984; 4,332,945).

Patents not only describe a specific invention. They also speak to the industry's capabilities, to its research, and provide insight into what it may be attempting to achieve with its products.

It is prudent to keep in mind that patents do not necessarily tell us what processes are currently being used in manufacturing cigarettes. Nevertheless, the number and pattern of these patents leave little doubt that the cigarette industry has developed enormously sophisticated methods for manipulating nicotine levels in cigarettes. Today, a cigarette company can add or subtract nicotine from tobacco. It can set nicotine levels. In many cigarettes today, the amount of nicotine present is a result of choice, not chance.

Let me show you the language in some of these patents. This is in the industry's own words. Listen to what industry says it *wants* to be able to do with nicotine.

First, the industry wants precise *control* of the amount of nicotine in cigarettes to provide desired physiological effects:

Maintaining the nicotine content at a sufficiently high level to provide the desired physiological activity, taste, and odor ... can thus be seen to be a significant problem in the tobacco art.[39]

Second, the industry wants to *increase* the amount of nicotine in some cigarettes.

... the perceived taste or strength of the cigarettes classified as having lower levels of "tar" and nicotine are progressively less than that of the cigarettes which are classified as approaching the characteristics of the "full flavor" cigarettes. It has been proposed to add nicotine and other flavorants to the cut filler of the lower "tar" cigarettes to enhance the taste, strength, and satisfaction of such cigarettes.[40]

This invention ... concerns the problem of maintaining or increasing the nicotine content of the smoke whilst avoiding an undesirable level of particulate matter in the smoke ...[41]

Now listen to what the industry says it *can* do, right now, at least for patent purposes, with the nicotine in cigarettes. It can precisely *manipulate nicotine levels* in cigarettes:

This invention permits the release into tobacco smoke, in controlled amounts, of desirable flavorants, as well as the release, in controlled amounts and when desired, of nicotine into tobacco smoke.[39]

It is another object of the invention to provide an agent for the treatment of tobacco smoke whereby nicotine is easily released thereinto in controlled amounts.[42]

[I]t can be seen that the process ... enables the manipulation of the nicotine content of tobacco material, such as cut leaf and reconstituted leaf, by removal of nicotine from a suitable nicotine tobacco source or by the addition of nicotine to a low nicotine tobacco material.[43]

... processed tobaccos can be manufactured under conditions suitable to provide products having various nicotine levels.[44]

Examples of suitable tobacco materials include ... processed tobacco materials such as expanded tobaccos, processed tobacco stems, reconstituted tobacco materials or reconstituted tobacco materials having varying levels of endogenous and exogenous nicotine ...[44]

... the present invention ... is particularly useful for the maintenance of the proper amount of nicotine in tobacco smoke.

... previous efforts have been made to add nicotine to tobacco products wherein the nicotine level in the tobacco was undesirably low.[42]

It can precisely *manipulate the rate* at which the nicotine is delivered in the cigarette:

It is a further object of this invention to provide a cigarette which delivers a larger amount of nicotine in the first few puffs of the cigarette than in the last few puffs.[36]

It can *transfer nicotine from one material to another* at will:

Moreover, the process is useful for transferring naturally occurring nicotine from tobacco having a generally high nicotine content to a nicotine deficient tobacco, tobacco filler materials, or RL (reconstituted leaf) which are used in the production of cigarettes and other smoking products ... [A] low nicotine tobacco ... can also be used as the nicotine donor ...[43]

It is another object of this invention to provide a process for the migration of nicotine from one tobacco substrate (leaf material or reconstituted leaf) to a second tobacco substrate (leaf material, reconstituted leaf material or tobacco stems) or to a non-tobacco substrate.[45]

It can *increase* the amount of nicotine in cigarettes:

If desired, nicotine can be incorporated into the expansion solvents used to provide a volume expanded processed tobacco material having a high nicotine content.[44]

The present invention provides a nicotine-enhanced smoking device with a high nicotine release efficiency ... Thus, the smoker is provided with more nicotine from the nicotine-enhanced device than from a similar smoking device which does not contain the nicotine solution or from a comparable cigarette.[38]

The present invention is concerned with the application of additives, such as ... physiologically active agents such as nicotine components to the smoking rod, in order to improve or help to improve the satisfaction provided to the smoker.[46]

It can *add nicotine to any part* of the cigarette:

The salts [nicotine levulinate] can be incorporated into the smoking article in a variety of places or sites. For example, the salt can be applied to the filler material, incorporated within some or all of the filler material, applied to the wrapper of the tobacco rod, applied within the glue line of the wrapper of the tobacco rod, applied within a region (eg, a cavity) ...[40]

It can use a variety of methods to add nicotine to tobacco:

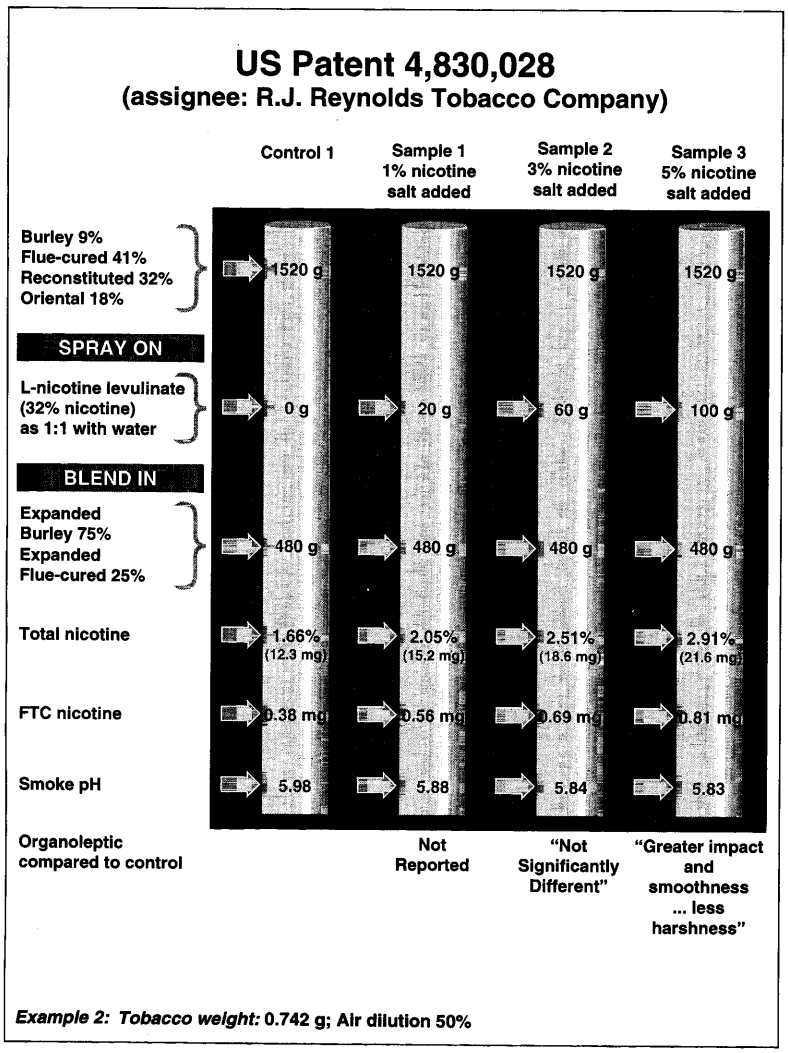


Figure 2

... [T]he additive [nicotine levulinate] can be applied using syringes or techniques such as spraying, electrostatic deposition, impregnation, garniture injection, spray drying, inclusion and encapsulation technologies, and the like.[40]

Let me describe in some detail how some of the technologies can be used to increase or control the nicotine level of tobacco.

The industry had to tackle a new problem beginning in the 1960s as public concern about the health consequences of smoking intensified. The industry began to market cigarettes it described as low yield. It faced a major challenge, however, because in the words of Patent No 4,830,028 (RJ Reynolds Tobacco Company), "the perceived taste or strength of the cigarettes classified as having lower levels of 'tar' and nicotine are progressively less than that of the cigarettes which are classified as approaching the characteristics of the 'full flavor' cigarettes."

The patent then describes a way to add nicotine to the "low-yield" cigarettes. If nicotine alone is sprayed on a blend of tobacco, the patent states that the smoke that results will be unacceptably harsh or irritating to the user. So, instead of just spraying nicotine on the tobacco blend, the patent combines nicotine with another compound, an organic acid called levulinic acid, to form a salt that masks the irritating qualities of nicotine (figure 2) [one figure omitted]. The patent demonstrates that different percentages of the nicotine salt can be added to blends of tobacco to produce different nicotine concentrations. The control cigarette, the one without any added nicotine, contains 1.66% nicotine. Adding 1% nicotine salt results in a cigarette with 2.05% nicotine. As one increases the amount of nicotine salt sprayed on the tobacco blend, the nicotine content of the tobacco increases.

In this process, great care is paid to the pH of the smoke because pH affects the bioavailability of nicotine – that is, how much the body absorbs. The patent demonstrates the technology to increase nicotine content in tobacco by up to 76%.

US Patent No 5,065,775 (Col 3: 55–63) (RJ Reynolds Tobacco Company) describes another technology that can control the nicotine content of tobacco filler (figure 3). This involves a process for "modifying the alkaloid content of a tobacco material and, in particular, for providing a processed tobacco material having a controlled nicotine content". In the words of the patent "[t]he process of the present invention provides a skilled artisan with an efficient and effective method for changing the character of a tobacco material (eg, rearranging components of a tobacco material or altering the chemical nature or composition of a tobacco material) in a controlled manner. That is, the process ... can be employed in a way such that changes in the chemical composition of tobacco can be monitored as to occur to a desired degree."

The patent allows for the removal of selected substances from tobacco, and incorporating controlled amounts of substances into tobacco. Example 4 within this patent shows how a tobacco blend that starts off with a 2.3% nicotine content can end up with a 5.2%

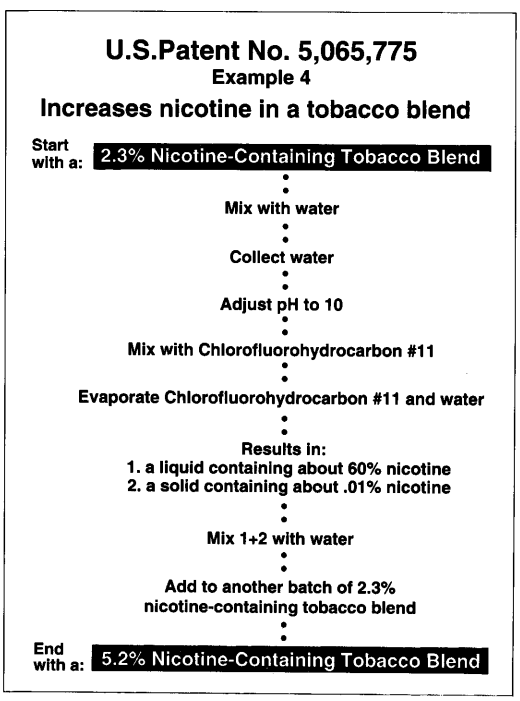


Figure 3

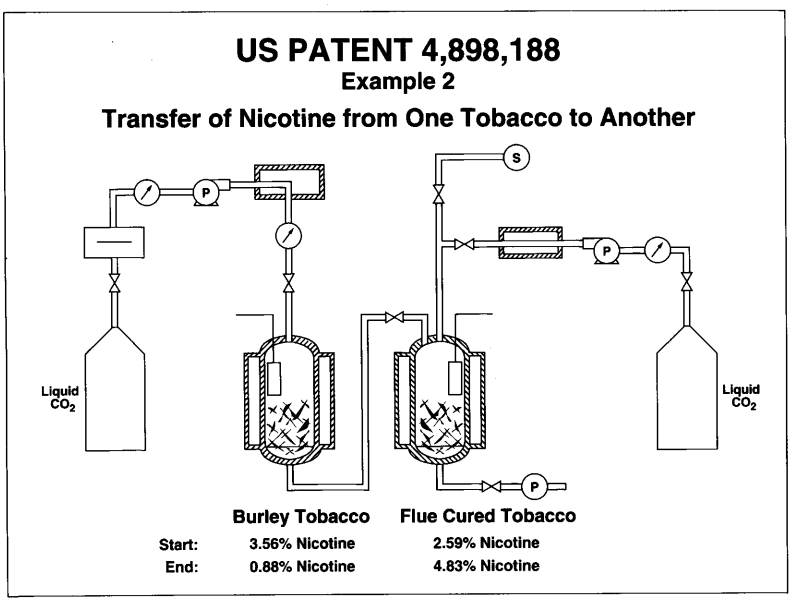


Figure 4

nicotine content. A highly concentrated nicotine solution is created by subjecting a tobacco blend to a series of chemical steps, including adding water, removing solids, increasing the pH, and mixing this substance with chlorofluorocarbon (CFC) 11 and then evaporating off that CFC 11. This concentrate is then added to water-washed tobacco to increase its nicotine content. This patent demonstrates the technology to increase the nicotine content in tobacco by more than 100%.

A third example of sophisticated technology involves the direct transfer of nicotine from one type of tobacco to another type of tobacco (figure 4). US Patent No 4,898,188 (RJ Reynolds Tobacco Company) utilizes supercritical fluid extraction. In example 2 in the patent, liquid carbon dioxide is used to transfer nicotine from Burley cut tobacco filler to flue-cured cut tobacco. The flue-cured cut filler starts off with a nicotine content of 2.59% and ends up with a nicotine content of 4.83%. The Burley cut filler starts off with a nicotine content of 3.56% and ends with a nicotine content of 0.88%. This patent demonstrates that nicotine can be transferred in significant amounts from one type of tobacco filler to another.

Additional information about the ability to set nicotine content at varying levels comes from the following advertisement, headlined "MORE OR LESS NICOTINE", which appeared in an international tobacco trade publication (figure 5):

Nicotine levels are becoming a growing concern to the designers of modern cigarettes, particularly those with lower "tar" deliveries. The Kimberly-Clark tobacco reconstitution process used by LTR Industries permits adjustments of nicotine to your exact requirements. These adjustments will not affect the other important properties of customized reconstituted tobacco produced at LTR Industries: low tar delivery, high filling power, high yield, and the flexibility to convey organoleptic modifications. We can help you control your tobacco.

In fact the process described in this advertisement can raise the level of nicotine beyond what is naturally found in tobacco materials, especially the stems and scraps. A 1985 tobacco [industry] journal article describing the LTR process states:

Though standard reconstituted tobacco products contain 0.7–1.0 percent nicotine, LTR Industries offers the possibility of increasing the nicotine content of the final sheet to a maximum of 3.5 percent...

A dramatic increase in tobacco taste and smoke body is noted in the nicotine-fortified reconstituted tobacco.[47]

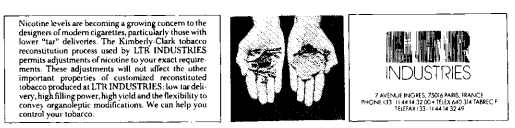
All of this apparent technology for manipulating nicotine in tobacco products raises the question of how the industry determines how much nicotine should be in various products. More importantly, **since the technology apparently exists to reduce nicotine in cigarettes to insignificant levels,[48,49] why, one is led to ask, does the industry keep nicotine in cigarettes at all?**

The tobacco industry would like you to believe that all it is doing is returning the nicotine that is removed during the process of producing reconstituted tobacco. It should be clear from what I have described thus far that the technology the industry may have available goes beyond such modest efforts.

The industry may also tell you that it is adjusting nicotine levels to be consistent with established "FTC yields" – these are the amounts of tar, nicotine, and carbon monoxide that are measured for each cigarette product by smoking machines, and disclosed under a voluntary agreement with the Federal Trade

A likeness of Jean Nicot, French diplomat, after whom "nicotine" and "Nicotiana Tabacum" were named

MORE OR LESS NICOTINE



Get more tobacco from all your tobacco

LTR INDUSTRIES, a subsidiary in France of
Kimberly-Clark Corporation

Figure 5

Commission (FTC). In fact, the control of nicotine levels in cigarettes, dating back at least to patents granted in 1966 for adjusting nicotine levels, preceded the first rules adopted by the FTC on disclosing tar and nicotine yields. Moreover, there is nothing about the FTC yields that would require tobacco companies to increase nicotine in low-tar cigarettes, as the industry patents suggest they do. There are no FTC restrictions on nicotine levels, and the FTC guidelines take into account crop variability by sampling completed cigarettes from 50 retail outlets across the country. Indeed, there is no FTC restriction that would prevent the industry from reducing nicotine below addicting levels or eliminating it altogether.

In fact, the technology reflected in the cigarette industry's patents appears to be intended to allow the industry to set the nicotine content of tobacco products at defined levels that have little to do with either the amount of nicotine that was removed during the processing of the tobacco, or with the simple goal of maintaining consistency with established FTC yields. **The technology may exist to allow the industry to set nicotine levels wherever it wants, or, in fact to remove nicotine entirely. With all the apparent advances in technology, why do the nicotine levels found in the vast majority of cigarettes remain at addictive levels?**

Nicotine levels may be dictated in part by marketing strategies and demographics. A blatant example comes from information on the marketing of smokeless tobacco. **There is evidence that smokeless tobacco products with lower amounts of nicotine are marketed as "starter" products for new users, and that advertising is used to encourage users to "graduate" to products with higher levels of nicotine** (figure 6). The evidence was developed in lawsuits brought against one manufacturer of smokeless tobacco.

The tobacco industry may tell you that nicotine is important in cigarettes solely for "flavour". There is a great deal of information that suggests otherwise. Some of the patents specifically distinguish nicotine from flavourants.[42] An RJ Reynolds book on flavouring tobacco, while listing around a thousand flavourants, fails to list nicotine as a flavouring agent.[50] Even research scientists from the same company acknowledge that the nicotine in cigarettes provides pharmacological and psychological effects in smokers in addition to any mere sensory effects.[33]

Moreover, the available information shows that the industry has gone to significant lengths to develop technologies to mask the flavour of increased levels in cigarettes. As I have already noted, the industry's own patents reveal that increasing nicotine in fact usually produces an unacceptably harsh and irritating product, and that the industry has had to take special steps to mask the flavour of increased nicotine in low-tar cigarettes.

This should not come as a surprise. The

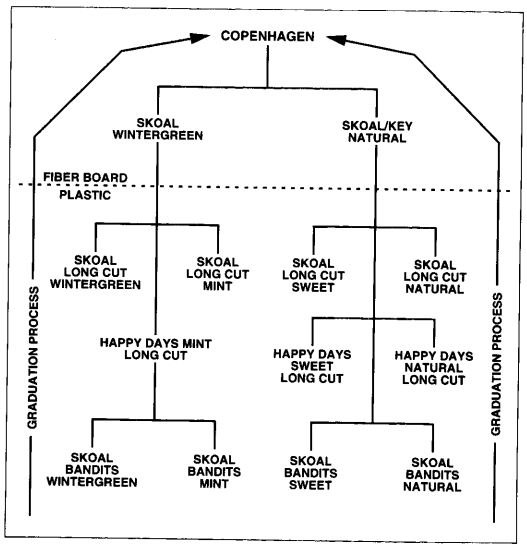


Figure 6 Source: Marsee *vs* US Tobacco Co, *plaintiff's exhibit 100 (provided by plaintiff's attorney)*

Merck Index, the authoritative encyclopaedia of chemicals, describes nicotine as having "an acrid, burning taste". *Webster's 7th New Collegiate Dictionary* defines acrid as "sharp and harsh or unpleasantly pungent in taste or odor; irritating, corrosive." In fact, US patent 4,620,554 uses the word "hazardous" to describe the taste of nicotine.

What appears to be true is that smokers become accustomed to the sensory impact of nicotine (burning in the throat) and associate it with the resulting psychoactive effects of nicotine, and thus look for those sensory signals in a cigarette; this is called "conditioned reinforcement".[51]

Moreover, **if nicotine is just another flavourant in tobacco, why not use a substitute ingredient with comparable flavour, but without the addictive potential?** For example, it has been repeatedly shown that substitute ingredients, such as hot pepper (capsaicin)[52] and citric acid,[53] have similar irritating sensory effects.

Similarities to the pharmaceutical industry

Mr Chairman, **this kind of sophistication in setting levels of a physiologically active substance suggests that what we are seeing in the cigarette industry more and more resembles the actions of a pharmaceutical manufacturer.** Besides controlling the amount of a physiologically active ingredient, there are a number of other similarities.

One similarity between the cigarette industry and the pharmaceutical industry is the focus on bioavailability. Bioavailability is the rate and extent that pharmacologically active substances get into the bloodstream. For example, the pH of tobacco smoke affects the bioavailability of nicotine.[54] The tobacco industry has conducted research on the pH of smoke[55] and has undertaken to control the pH in tobacco smoke. In patent examples,

chemicals have been added to tobacco to affect the pH of tobacco smoke.[40] The industry has even performed bioavailability and pharmacokinetic studies on conventional and novel cigarettes.[56]

The cigarette industry has undertaken research to look at the specific activity of added versus naturally occurring nicotine.[57] Additional research looked at the differences between spiking, spraying, and blending compounds into cigarettes.[58]

Development of an "express" cigarette, a shorter, faster burning cigarette with the same amount of tar and nicotine, has been reported in the lay press recently.[59,60] This is another example of how cigarette companies appear to be controlling the amounts of nicotine to deliver set levels.

The cigarette industry has also undertaken a significant amount of research looking at the potential "beneficial" effects of nicotine. It has studied the effects of nicotine on anxiety, heart rate, electroencephalograms, and behavioural performance tasks.[61–68] Such research on the physiological effects of an active ingredient is a common part of pharmaceutical drug development.

Psychotherapeutic Agents

(Patent 5,138,062)

Nicotine Analogues	Dose (IP) mg/kg	Sedation	Body Tone	Tranquilization (IVC) 50 ug
❶ R $-(CH_2)_2-N(CH_3)_2$	10	+	+	++++
	20	++	++	
❷ R $-(CH_2)_3-N(CH_3)_2$	5	+	+	++++
	10	++	+	
	20	+++	++	
❸ R $-(CH_2)_4-N(CH_3)_2$	10	+	+	+++
	20	+	+	
❹ R $-(CH_2)_5-N(CH_3)_2$	40	++	++	+++
❻ R $-(CH_2)_3-NH_2$	10	0	0	+++
	20	+	0	
❼ R $-(CH_2)_4-NH_2$	10	0	0	+++
	20	+	0	
❽ R $-(CH_2)_3-$ N-pyrrolidine	10	+	0	+++
	20	++	++	
❾ R $-(CH_2)_3-$ N-piperidine	10	0	0	++
	20	++	+	
❿ R $-(CH_2)_2-$ N-morpholine	10	0	0	+
	20	+	+	
⓫ R $-(CH^2)-$ N-piperazine $-N-CH_3$	20	++	+	++++
	40	+++	++	

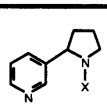
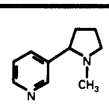
R =  NICOTINE =  (Data from rats)

Figure 7

Perhaps the most striking aspect of the research undertaken by the tobacco industry is its search for, and its patenting of, new nicotine-like chemicals that exhibit pharmacological properties which, in their own words, "are indicated for utility as potential psychotherapeutic agents".[69] One patent describes nicotine-like chemicals which

> exhibit tranquilizing and muscle-relaxing properties when administered to mammals. The nicotine analogs do not exhibit nicotine-like properties, such as tachycardia, hypertension, gastrointestinal effects, emesis in dogs, and the like.[69]

Example XXIX in the patent illustrates the pharmacological properties of nicotine analogues...

> The tranquilizing effects of invention nicotine compounds are measured after intraperitoneal (IP) and intraventricular (IVC) administration in the form of hydrochloride salts.
>
> Sedation is determined by measuring locomotion in an open field maze, and the response to noxious (air blast) stimuli. Body tone is estimated by handling rats and by the ability to hang from a rotating rod.
>
> Tranquilization after intraventricular (IVC) injection is estimated from muscle weakness in all four limbs, body tone and general activity.[69]

Figure 7 illustrates the results.

The problem of the low-yield cigarette

We at the FDA are concerned not only about the control over nicotine levels exercised by the cigarette industry, but also that the problems associated with nicotine are aggravated by significant limitations in the consumer's ability to reduce their exposure to nicotine by selecting "low"-nicotine cigarettes.

Most people who smoke low-yield or "light" cigarettes believe that they are getting less nicotine and tar by smoking these cigarettes. For the last 25 years the American public has relied on FTC ratings of tar and nicotine in advertising to tell them what they will be consuming. The "FTC method" utilizes a machine that tests cigarettes in a process involving a two-second, 35 ml puff each minute until a predetermined butt length is reached.[70]

Most people don't realise that low-yield cigarettes, as determined by the FTC method, do not usually result in proportionally less nicotine being absorbed when compared to high-yield cigarettes.[71,72] Furthermore, there is little correlation between low-yield FTC ratings and the total amount of nicotine in cigarettes.[71]

It is a myth that people who smoke low-nicotine cigarettes are necessarily going to get less nicotine than people who smoke high-nicotine cigarettes. There are several reasons for this. One reason is that there are differences between the smoking habits of a machine and a human. The way in which a cigarette is smoked is probably the most important determinant of how much tar and

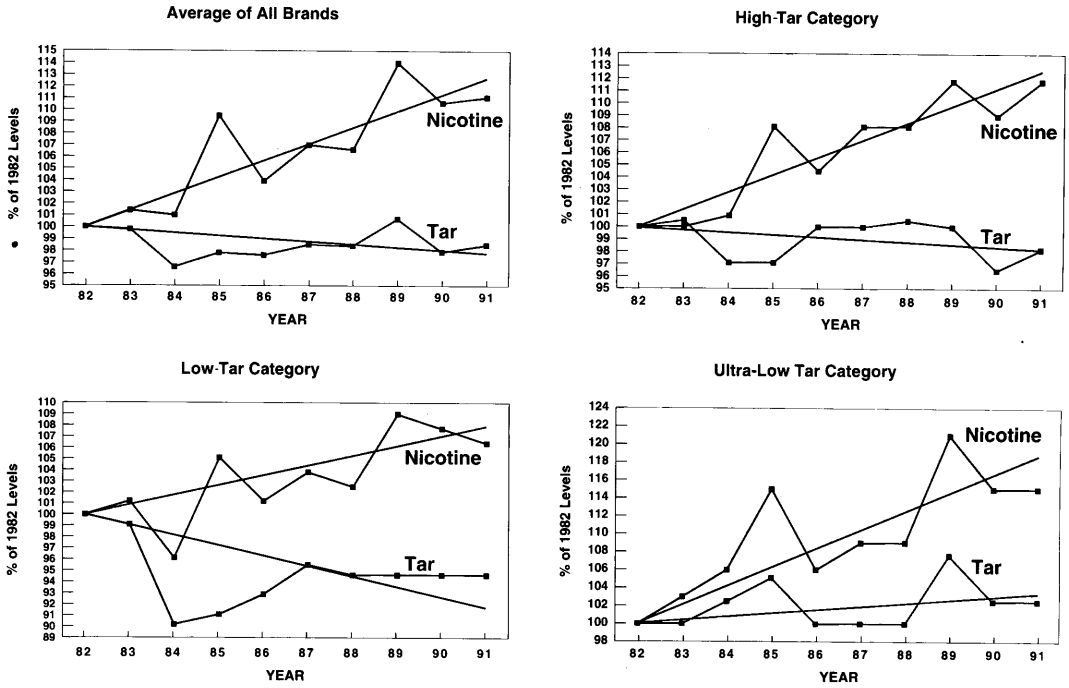


Figure 8 Sales-weighted nicotine and tar yields in smoke as a percentage of 1982 levels, for all brands and for specific tar categories. High tar: > 15 mg tar by the FTC method; low tar: 6–15 mg tar; ultra-low tar: < 6 mg tar. Source: FTC annual data

nicotine are inhaled. Humans can and do compensate when smoking low-yield cigarettes, by altering puff volume, puff duration, inhalation frequency, depth of inhalation, and the number of cigarettes smoked.[73–79] As a result of these compensatory mechanisms, a low-yield cigarette can actually result in a relatively high intake of nicotine.[72]

Beyond the human compensatory mechanisms, several other factors under manufacturers' control contribute to a lowering of machine ratings. These factors include the positioning of ventilation holes, how fast the cigarette paper burns, and the length of the filter paper overwrap.[80]

To understand how the position of ventilation holes in a cigarette can confound the FTC ratings, it is important to recognise that the main determinants of whether a cigarette has a high or low yield in machine testing are the cigarette's ventilation and burning characteristics.[71] Most low-yield cigarettes achieve their low ratings because of filter characteristics and also because the smoke is diluted with air. The air dilution is accomplished in part by placing ventilation holes in the filter. What scientists have demonstrated is that "although smoking machines which measure tar and nicotine do not occlude the perforations", 32 % to 69 % of low-tar smokers have blocked the holes with their fingers or lips, resulting in larger nicotine yields.[81] The ventilation holes are sometimes laser generated and can be hard for the smoker to see. Not all smokers are aware of the existence of these holes or that the smoker may be blocking them [figure omitted].

Two other factors that are under manufacturers' control can also confound the usefulness of the FTC ratings. The FTC method smokes a cigarette down to within 3 mm of the tipping paper overwrap. According to one study, "between 1967 and 1978, 18 brands of filter cigarettes underwent increases in overwrap width that reduced the amount of tobacco smoked in the cigarettes on the machine, even though the remaining tobacco is still smokeable" [figure omitted].[80] Another way that the FTC numbers can be confounded is by "increasing the rate at which cigarettes burn." A faster burning cigarette lowers the puff count. Manufacturers can increase the rate at which a cigarette burns by controlling the porosity of the cigarette paper. The machine takes a puff every minute, but humans can adjust their smoking rate*.[80]

Because of all these confounding factors we are concerned that consumers may assume that low-yield cigarettes in fact deliver low tar and nicotine when in reality they do not.

ACTUAL NICOTINE LEVELS IN CIGARETTES

To assess the levels of nicotine in cigarettes, we did two things. First, FDA laboratories measured the amount of nicotine actually in several types of cigarettes. We analysed three varieties of one brand family of cigarettes; one regular, one low tar, and one ultra low tar. What surprised us was that the variety advertised as having the lowest yield in fact had the highest concentration of nicotine in the cigarette (table).

Second, we formally requested from our colleagues at the FTC summary information derived from their data base on the levels of

* According to data reviewed in the 1988 Surgeon General's report (pp 156–7),[18] smokers take a puff on average every 34 seconds. — ED

Table % Nicotine in one brand family

Variety	% Nicotine (mg/g)
Regular 100s	1.46
Low tar 100s	1.67
Ultra low tar 100s	1.99

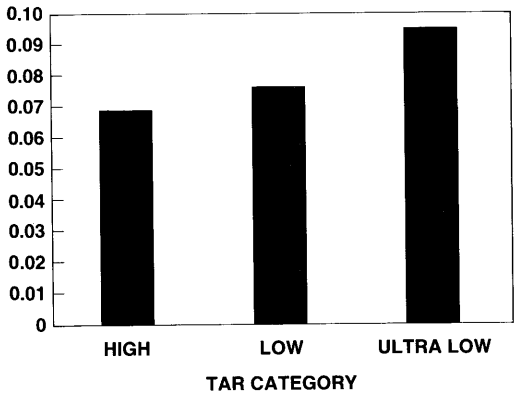


Figure 9 Sales-weighted nicotine: tar ratios, 10-year average 1982–91. Source: FTC annual data weighted by sales

nicotine in cigarettes. What we found was that since 1982 (the earliest year for which the computer data base is available), the sales-weighted levels of FTC nicotine in cigarettes appear to increase (figure 8). What was equally striking was that when we segmented sales into high-tar, low-tar, and ultra-low-tar cigarettes, the nicotine: tar ratio was higher in the ultra-low-tar group (figure 9). We would not have expected to see these differences because high tar has usually been associated with high nicotine, and low tar with low nicotine. It has often been said that tar and nicotine travel together in the cigarette smoke. The disparities in the nicotine: tar ratios among these varieties raise the question as to how this can occur.

FDA regulation of nicotine in cigarettes

The next task facing the FDA is to determine whether nicotine-containing cigarettes are "drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act.

Our inquiry is necessarily shaped by the definition of "drug" in the Act. It is a definition that focuses on "vendor intent". More specifically, it focuses primarily on whether the vendor intends the product to "affect the structure or any function of the body".

Mr Chairman, the evidence we have presented today suggests that cigarette manufacturers may intend that most smokers buy cigarettes to satisfy their nicotine addiction.

We do not yet have all the evidence necessary to establish cigarette manufacturers' intent. It should be clear, however, that in determining intent, what cigarette manufacturers say can be less important than what they do. The fact that the technology may be available to reduce the nicotine to less than addictive levels is relevant in determining manufacturer intent.

It is important to note that the possibility of FDA exerting jurisdiction over cigarettes raises many broader public health and social issues for Congress to contemplate. There is the possibility that regulation of the nicotine in cigarettes as drugs would result in the removal of nicotine-containing cigarettes from the market, limiting the amount of nicotine in cigarettes to levels that are not addictive, or otherwise restricting access to them, unless the industry could show that nicotine-containing cigarettes are safe and effective. If nicotine were removed, the nation would face a host of issues involving the withdrawal from addiction that would be experienced by millions of Americans who smoke.

There is, of course, the issue of black market cigarettes. With nicotine, as with other powerfully addicting substances, a black market could develop.

In these issues, we seek guidance from Congress.

The one thing that I think is certain is that it is time for all of us – for the FDA, for the Congress, for the American public – to learn more about the way cigarettes are designed today and the results of the tobacco industry's own research on the addictive properties of nicotine.

1 Thomas RM, Larsen MD. Smoking prevalence, beliefs, and activities by gender and other demographic indicators. Princeton, New Jersey: *The Gallup Organization, Inc*, 1993.
2 US Centers for Disease Control and Prevention. Smoking cessation during previous years among adults – United States. *MMWR* 1993; **42**: 504–7.
3 Hughes JR, Gust SW, Pechacek TF. Prevalence of tobacco dependence and withdrawal. *Am J Psychiatry* 1987; **144**: 205–8.
4 United States *vs* 46 Cartons ... Fairfax Cigarettes, 113 F. Supp. 336 (DNJ 1953).
5 United States *vs* 354 Bulk Cartons Trim Reducing-Aid Cigarettes, 178 F. Supp. 847 (DNJ 1959).
6 US Department of Health and Human Services. *Preventing tobacco use among young people. A report of the Surgeon General, 1994.* Atlanta, Georgia: Centers for Disease Control and Prevention, Office on Smoking and Health, 1994. (Publication No S/N 017–001–00491–0.)
7 Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. *N Engl J Med* 1988; **17**: 1318–30.
8 Benowitz NL. Cigarette smoking and nicotine addiction. *Med Clin North Am* 1992; **76**: 2.
9 Henningfield JE, Nemeth-Coslett R. Nicotine dependence: interface between tobacco and tobacco-related disease. *Chest* 1988; **93**: 37S-55S.
10 US Department of Health and Human Services. *Drug abuse and drug abuse research: the third triennial report to Congress from the Secretary.* US Department of Health and Human Services, 1991: 213–42.
11 Schelling TC. Addictive drugs: the cigarette experience. *Science* 1992; **255**: 430–3.
12 Jones RT. Tobacco dependence. In: *Psychopharmacology: the third generation of progress.* New York: Raven Press, 1987. p1589.
13 Davison AG, Duffy M. Smoking habits of long-term survivors of surgery for lung cancer. *Thorax* 1982; **37**: 331–3.
14 Bigelow GE, Rand CS, Gross J, Burling TA, Gottlieb SH. Smoking cessation and relapse among cardiac patients. In: *Relapse and recovery in drug abuse*, NIDA Research Monograph 72. US Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, 1986: 167–71.
15 Himbury S, West R. Smoking habits after laryngectomy. *BMJ* 1985; **291**: 514–5.
16 Giovino G. Unpublished report to the US Food and Drug Administration from the US Centers for Disease Control and Prevention, Office on Smoking and Health, based on the 1987 National Health Interview Survey.
17 Giovino G. US Food and Drug Administration interview

with the US Centers for Disease Control and Prevention, Office on Smoking and Health, March 1994.
18 US Department of Health and Human Services. *The health consequences of smoking: nicotine addiction. A report of the Surgeon General, 1988*. Rockville, Maryland: Centers for Disease Control, Office on Smoking and Health, 1988. (DHHS Publication No (CDC) 88–8406.)
19 World Health Organisation. *Smokeless tobacco control*. Geneva: World Health Organisation, 1988. (Technical Report Series 773.)
20 Chollat-Traquet C. *Women and tobacco*. Geneva: World Health Organisation, 1992: 33–4.
21 American Medical Association. *AMA Policy Compendium*. Policy No 30.958. Chicago: American Medical Association, 1993: 35.
22 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 3rd rev edn (DSM-IIIR). Washington, DC: American Psychiatric Association, 1987: 150–1, 181–2.
23 American Psychological Association. *Statement before the US House of Representatives Committee on Energy and Commerce Subcommittee on Health and the Environment*, 29 July 1988.
24 The Royal Society of Canada. *Tobacco, Nicotine and Addiction*. Ottawa, Ontario: Health Protection Branch, Health and Welfare Canada, 31 August 1989.
25 The basis of drug dependence. *Medical Research Council Field Review* (United Kingdom), January 1994: 1–13.
26 Henningfield JE, Stapleton JM, Benowitz NL, *et al*. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend* 1993; **33**: 23–9.
27 Gardner EL. Brain reward mechanisms. *Substance abuse: A comprehensive textbook*, 2nd edn, Baltimore: William and Wilkins, 1992.
28 Yokel RA. Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preference. In: *Methods of assessing the reinforcing properties of abused drugs*. New York: Verlag, 1987: 1–33.
29 DiChiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci* 1988; **85**: 5274–8.
30 Imperato A, Mulas A, DiChiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. *Eur J Pharmacol* 1986; **132**: 337–8.
31 Corrigall WA, Franklin KBJ, Coen KM, Clarke PBS. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology* 1992; **107**: 285–9.
32 Corrigall WA, Coen KM. Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology* 1991; **104**: 171–6.
33 Robinson JH, Pritchard WS. The role of nicotine in tobacco use. *Psychopharmacology* 1992; **108**: 397–407.
34 Rosenblatt R. How do tobacco executives live with themselves? *New York Times Magazine*, 20 March 1994: 34–41, 55, 73–6.
35 Henningfield JE, Schiffman S. Personal communications to the US Food and Drug Administration, March 1994.
36 US Patent No 4,595,024, Col 1: 33–6. RJ Reynolds Tobacco Company. 17 June 1986.
37 Dunn WL. Motives and incentives in cigarette smoking. Richmond, Virginia: Philip Morris Research Center, 1972. (Plaintiff's exhibit 5171, *Cipollone vs Liggett Group Inc*, USDC NJ.)
38 US Patent No 4,676,259, Col 1: 21–4, Col 2: 30–3, 53–6. Advanced Tobacco Products, Inc. 30 June 1987.
39 US Patent No 3,280,823, Col 1: 43–8, Col 2: 37–40. Philip Morris, Inc. 25 October 1966.
40 US Patent No 4,830,028, Col 1: 40–7, Col 5: 59–65, Col 6: 4–7. RJ Reynolds Tobacco Company. 16 May 1989.
41 US Patent No 3,861,400, Col 1: 1–10. Imperial Tobacco Group Ltd. 21 January 1975.
42 US Patent No 3,584,630, Col 1: 57–8, Col 2: 5–15, 69–71. Philip Morris, Inc. 15 June 1971.
43 US Patent No 4,215,706, Col 1: 40–8, Col 3: 61–6. Loew's Theatres, Inc. 5 August 1980.
44 US Patent No 5,031,646 Col 5: 21–7, 63–8. RJ Reynolds Tobacco Company. 16 July 1991.
45 US Patent No 5,018,540, Col 2: 39–43. Philip Morris, Inc. 28 May 1991.
46 US Patent No 4,236,532, Col 1: 35–40. Gallaher, Ltd. 2 December 1980.
47 Silberstein DA. Flavouring reconstituted tobacco. *Tobacco J Int* 1985; 1: 26–9.
48 US Patent No 3,046,997 (Method of removing nicotine from tobacco using organic solvent). Philip Morris, Inc, 31 July 1962.
49 US Patent No 4,068,671 (Denicotinize tobacco by rapid drying of an alkaline aqueous dispersion of tobacco). AMF Inc. 17 January 1978.
50 Leffingwell JC, Young HJ, Bernasek E. *Tobacco flavoring for smoking products*. Winston-Salem, North Carolina: RJ Reynolds Tobacco Company, 1972.
51 Rose JE, Levin ED. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *Br J Addict* 1991; **86**: 605–9.
52 Blanc P, Liu D, Juarez C, Boushey HA. Cough in hot pepper workers. *Chest* 1991; **99**: 27.
53 Levin ED, Behm FM, Schur C, Tashkin DP, Rose JE. Clinical evaluation of a citric acid inhaler for smoking cessation. *Drug Alcohol Depend* 1993; **31**: 131–8.
54 Gori GB, Benowitz NL, Lynch CJ. Mouth versus deep airways absorption of nicotine in cigarette smoker. *Pharmacol Biochem Behav* 1986; **24**: 1181–4.
55 Harris J, Hayes L. A method for measuring the pH value of whole smoke. *Tobacco Sci* 1977; **XXI**: 58.
56 RJ Reynolds Tobacco Company. *Chemical and biological studies: new cigarette prototypes that heat instead of burn tobacco*. Winston-Salem, North Carolina: RJ Reynolds Tobacco Company, 1988: 455–557.
57 Jenkins RW, Comes RA. Exogenous vs endogenous transfer of nicotine during smoking. *Int J Appl Radiat Phys* 1976; **27**: 323–4.
58 Jenkins RW, Bass RT, Newell GC Jr, Segura G, Newman RH. Recommendations for the standardized preparation of carbon-14 labeled cigarets. *Tobacco* 1975; **177(20)**: 35–8.
59 *Newsweek*, 21 March 1994: 52–3.
60 Victor P. Smokers may get a quick fix cigarette. *Sunday Times (London)*, 19 September 1993.
61 Gelbert DG, Robinson JH, Chamberlin CL, Speilberger CD. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. *Psychophysiology* 1989; **26**: 311–20.
62 Pritchard WS. Electroencephalographic effects of cigarette smoking. *Psychopharmacology* 1991; **104**: 485–90.
63 Pritchard WS, Duke DW, Coburn KL, Robinson JH. Nonlinear dynamical electroencephalographic analysis applied to nicotine psychopharmacology and Alzheimer's disease. In: Lippiello PM, Collins AC, Gray JA, Robinson JH, eds. *The biology of nicotine*. New York: Raven Press, 1992;195–214.
64 Pritchard WS, Duke DW. Modulation of EEG dimensional complexity by smoking. *J Psychophysiol* 1992; **6**: 1–10.
65 Pritchard WS, Robinson JH, Guy TD. Enhancement of continuous performance task reaction time by smoking in nondeprived smokers. *Psychopharmacology* 1992; **108**: 437–42.
66 Pritchard WS, Robinson JH. The meaning of addiction: reply to West. *Psychopharmacology* 1992; **108**: 411–6.
67 Robinson JH, Pritchard WS, Davis RA. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. *Psychopharmacology* 1992; **108**: 466–72.
68 Pritchard WS, Gilbert DG, Duke DW. Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity. *Psychopharmacology* 1993; **113**: 95–102.
69 US Patent No 5,138,062 (Nicotine analogs), Col 4: 41–48, Philip Morris, Inc. 11 August 1992.
70 Pillsbury C, Bright K, O'Connor J, Irish FW. Tobacco: tar and nicotine in cigarette smoke. *J Assoc Off Anal Chem* 1969; **52**: 458–62.
71 Benowitz NL, Hall SM, Herning RI, Jacob P III, Jones RT, Osman AL. Smokers of low-yield cigarettes do not consume less nicotine. *N Engl J Med* 1983; **309**: 139–42.
72 Benowitz NL, Jacob P. Daily intake of nicotine during cigarette smoking. *Clin Pharmacol Ther* 1984; **35**: 499–504.
73 Gust SW, Pickens RW. Does cigarette nicotine yield affect puff volume? *Clin Pharmacol Ther* 1982; **32**: 418–22.
74 Herning RI, Jones RT, Bachman J, Mines AH. Puff volume increase when low-nicotine cigarettes are smoked. *BMJ* 1981; **283**: 187–9.
75 Sutton SR, Russell MA, Iyer R, Feyerabend C, Saloojee Y. Relationship between cigarette yield, puffing patterns, and smoke intake: evidence for tar compensation? *BMJ* 1982; **285**: 600–3.
76 Wald NJ, Boreham J, Bailey A. Relative intakes of tar, nicotine, and carbon monoxide from cigarettes of different yields. *Thorax* 1984; **39**: 361–4.
77 Goldfarb T, Gritz ER, Jarvik ME, Stolerman IP. Reactions to cigarettes as a function of nicotine and "tar". *Clin Pharmacol Ther* 1976; **19**: 767–72.
78 Maron DJ, Fortmann SP. Nicotine yield and measures of cigarette smoke exposure in a large population: are lower-yield cigarettes safer? *Am J Public Health* 1987; **77**: 546–9.
79 Stepney R. Consumption of cigarettes of reduced tar and nicotine delivery. *Br J Addict* 1980; **75**: 81–8.
80 Grunberg NE, Morse DE, Maycock VA, Kozlowski LT. Changes in overwrap and butt length of American filter cigarettes. *NY State J Med* 1985; **7**: 310–2.
81 Kozlowski LT, Frecker RC, Khouw V, Pope MA. The misuse of "less-hazardous" cigarettes and its detection: hole-blocking of ventilated filters. *Am J Public Health* 1980; **70**: 1202–3.