

Compensatory Smoking of Low-Yield Cigarettes

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INTRODUCTION Most smokers are addicted to nicotine (U.S. DHHS, 1988). Nicotine addiction results in smokers seeking to take in a constant level of nicotine from smoking each day (Benowitz, 1988; U.S. DHHS, 1988). Consequently, when faced with low-yield cigarettes, smokers tend to take in more nicotine and other tobacco smoke constituents from these cigarettes than would be predicted by machine testing in order to sustain optimal levels of nicotine intake. This phenomenon of taking in similar levels of nicotine from day to day has been termed 'regulation' or 'titration' of nicotine intake. The behavior of smoking cigarettes of different machine yields more or less intensively, and/or smoking more or fewer cigarettes to achieve a particular intake of nicotine, has been called 'compensation'. If regulation of nicotine intake is precise, that is, compensation is complete, then switching to low-yield cigarettes would not be expected to reduce exposure to tobacco toxins, nor to reduce the risk of disease from smoking.

Earlier chapters have described the nature of low-yield cigarettes and the ways in which smokers can modify their smoking behaviors to take in more tobacco smoke from their cigarettes than predicted by the standard smoking-machine test. In brief review—when faced with lower yield cigarettes, smokers can smoke more cigarettes per day, can take more and deeper puffs, can puff with a faster draw rate, and/or can block ventilation holes. Using these last four techniques, a smoker can increase his or her smoke intake from a particular cigarette several fold above the machine-predicted yields.

This chapter will review nicotine addiction and the evidence that smokers regulate their intake of nicotine from cigarettes. The focus will be on primarily studies in which human exposure has been biochemically assessed. Evidence from both experimental and cross-sectional studies will be examined. The question of whether or not tar exposure might be reduced despite compensation for nicotine itself when switching to low-yield cigarettes will also be examined.

ROLE OF NICOTINE IN MAINTAINING TOBACCO ADDICTION

Nicotine is the main determinant of tobacco use and addiction. Detailed reviews of the pharmacology of nicotine and the evidence that nicotine is addictive have been published in Surgeon General's reports (for example, the 1988 Surgeon General's report, *The Health Consequences of Smoking: Nicotine Addiction*), as well as in a number of other reviews (Benowitz, 1988, 1999b; U.S. DHHS, 1988).

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Nicotine is delivered to the smoker in particulate matter and, to some extent, in the gaseous phase of tobacco smoke. It is rapidly absorbed from the lungs into the arterial circulation, from which it goes to various organs, including the brain. Rapid delivery of nicotine to the brain is particularly important to the issue of compensation because it provides rapid feedback to the smoker on the dose of nicotine absorbed, and allows minute-to-minute titration of nicotine effects.

In the brain, nicotine binds to and activates nicotinic cholinergic receptors. There are a variety of nicotinic cholinergic receptor subtypes, which are believed to mediate different actions of nicotine in different parts of the brain (Picciotto *et al.*, 2000). Nicotinic receptor activation works, at least in part, by facilitating the release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, beta endorphin, glutamate, gamma aminobutyric acid (GABA), and others. Nicotine also releases growth hormone, prolactin, and adrenocorticotrophic hormone (ACTH). Most of the behavioral effects of nicotine in people are believed to be mediated by its actions on central nervous system receptors.

Nicotine self-administration appears to be motivated both by positive and negative reinforcement. Positive reinforcement includes pleasure, arousal, relaxation, reduced stress, enhanced vigilance, improved cognitive function, mood modulation, and lower body weight. With prolonged exposure to nicotine, there is an increase in the number of nicotinic cholinergic receptors in the brain that occurs in association with the development of tolerance to the effects of nicotine (Collins *et al.*, 1994; Breese *et al.*, 1997). In the tolerant state, nicotine is necessary to maintain normal brain functioning. In the absence of nicotine, brain functioning becomes abnormal and the individual experiences nicotine withdrawal symptoms, reflecting physical dependence. Withdrawal symptoms include nervousness, restlessness, irritability, anxiety, impaired concentration, impaired cognitive function, increased appetite, and weight gain. Negative reinforcement refers to the relief of withdrawal symptoms by nicotine intake. It is difficult to separate positive reinforcement from relief of withdrawal symptoms in smokers. However, it is clear that nicotine is used by smokers to modulate their levels of arousal, mood, and performance.

The cigarette is a drug delivery system for nicotine. Smokers tend to take in similar doses of nicotine on a day-to-day basis (Benowitz, 1988; U.S. DHHS, 1988), presumably to optimize the levels of arousal and mood. A variety of experimental studies support the theory that smokers regulate daily intake of nicotine. In addition to studies of changed smoking behavior in response to different brands of cigarettes (which was discussed in detail in Chapter 2), smokers have been shown to change smoking behavior in response to other interventions that alter nicotine availability. For example, when the excretion of nicotine from the body is accelerated by acidification of the urine, smokers will increase their smoking to take in more nicotine (Benowitz and Jacob, 1985). Conversely, when nicotine is administered intravenously or by administration of nicotine patches, smokers reduce their nicotine intake from smoking (Benowitz and Jacob, 1990; Benowitz *et al.*, 1998).

In summary, cigarettes smoking can be viewed as a process of delivering nicotine to the body. Daily smoking can be viewed as a situation in which nicotine is taken initially for pleasure, for arousal, and/or for mood modulation. As the day progresses for the smoker, tolerance develops to many of the effects of nicotine, and further nicotine may be taken to primarily relieve withdrawal symptoms that emerge between cigarettes. Smokers appear to have particular desirable levels of nicotine intake throughout the day that result in optimal functioning. The need for a particular level of nicotine is central to the concept of compensation for low-yield cigarettes.

BIOMARKERS OF TOBACCO SMOKE EXPOSURE As discussed previously, there is considerable individual variability in the way smokers smoke their cigarettes. Therefore, neither the number of cigarettes smoked per day, nor the machine-determined yield, nor even a combination of the two can provide complete information on the intake by an individual smoker of tobacco smoke toxins. To determine intake most accurately, one must measure human exposure to chemicals in tobacco smoke.

The tobacco smoke constituents that have been most widely used in quantitating human exposure to smoke are nicotine and carbon monoxide (CO) (Benowitz, 1996, 1999a). Nicotine can be measured directly in blood, but more commonly nicotine intake is estimated by measuring levels of its proximate metabolite, cotinine. Cotinine has a much longer half-life than nicotine; therefore, cotinine levels in the body vary much less throughout the day than do nicotine levels. Thus, sampling time for cotinine with respect to when the last cigarette was smoked is less critical. In addition, cotinine can be readily measured in blood, saliva, and urine. Measurement of the sum of nicotine and its metabolites in urine can also be used to assess nicotine exposure from smoking.

CO is present in high concentrations in tobacco smoke and is a useful marker of exposure to the gaseous fraction of tobacco smoke, but the short half-life of CO excretion makes it a measure that is predominantly influenced by smoking within the most recent several hours. There is no reason to believe that smokers adjust their smoking to regulate CO levels in the body. Therefore, discrepancies between CO levels measured in smokers and those predicted on machine yields are most likely a result of attempts to regulate nicotine intake. Changes in CO levels in response to different smoking behaviors may differ from changes in nicotine levels, because CO absorption is more heavily influenced by depth of inhalation than is nicotine. CO is absorbed across alveolar surfaces, whereas nicotine can be absorbed across the mucosa in the upper and lower airways, as well as across the alveolar surface. Levels of CO can be measured in expired air or in the blood, the latter as carboxyhemoglobin (COHb). CO is a widely used measure of cigarette smoke exposure, although its level can be influenced by environmental exposures and the rate of its elimination is markedly influenced by the level of physical activity.

Hydrogen cyanide is another component of tobacco smoke. In the body, cyanide is metabolized to thiocyanate, which can be measured in blood or saliva. Thiocyanate has been used as a marker of tobacco smoke

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exposure in many studies. Its main limitation is that there are many dietary sources of thiocyanate, and thiocyanate levels in nonsmokers are substantial. Thus, measurement of thiocyanate yields relatively poor sensitivity and specificity for tobacco smoke exposure, particularly at low levels of cigarette smoking.

In considering smoking-related cancer risks, it would be most appropriate to measure exposure to tobacco smoke carcinogens. Such carcinogens in tobacco smoke include polycyclic aromatic hydrocarbons (PAHs), various nitrosamines, naphthylamines, polonium-210, and others. The carcinogen biomarker that has shown the most promise has been a measurement of nicotine-derived nitrosamines (Hecht, 1998). The nicotine-derived nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), is specific for tobacco smoke exposure and is metabolized to a butanol metabolite, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide (NNAL-GLUC). Urine levels of NNAL + NNAL-GLUC are elevated in smokers (Hecht *et al.*, 1993). The assay for NNAL is technically demanding. As yet, studies of NNAL levels in smokers of different yields of cigarettes have not been published.

Other potential markers of carcinogen exposure include adducts of 4-aminobiphenyl to hemoglobin in red blood cells (Bartsch *et al.*, 1990); adducts of benzo(a)pyrene and other potential carcinogens to DNA in white blood cells (Jahnke *et al.*, 1990; van Maanen *et al.*, 1994); adducts of PAHs to plasma albumin (Mooney *et al.*, 1995); and urinary hydroxyproline or N-nitrosoproline excretion (Adlkofer *et al.*, 1984). None of these markers has been used to date in studying smokers of different yields of cigarettes.

One indirect measure of carcinogen exposure that has been used is the measurement of mutagenic activity of the urine (Yamasaki and Ames, 1977). This is commonly done using the *Salmonella* histadine auxotroph reversion assay. In vitro studies indicate that the mutagenic components of cigarette smoke are found primarily in the tar rather than in the gaseous fraction (Florin *et al.*, 1980). It is known that the urine of cigarette smokers is mutagenic. For an individual smoker, mutagenic activity of the urine tends to be constant from day to day and there is a relationship between mutagenic activity and the number of cigarettes smoked per day (Sorsa *et al.*, 1984; Benowitz, 1989). The test is limited in that it is not specific for exposure to particular carcinogens, there is considerable variability in results from assay to assay and from person to person, and dietary and environmental chemical exposures can influence mutagenic activity. However, for within-subject comparisons when assays are compared for the same individual, the test provides a quantitative estimate of exposure to tar and, thus, potential carcinogen exposure.

NICOTINE ABSORPTION FROM CIGARETTE SMOKING

The intake of nicotine from a single cigarette or while smoking cigarettes throughout the day can be estimated by measuring blood levels of nicotine at frequent time intervals. If the clearance (a measure of the rate of metabolism and excretion) of nicotine is known, then blood level data can be converted to actual intake of nicotine from smoking. Nicotine clearance can be measured by

measuring blood levels during and after an intravenous infusion of a known dose. This technique has been used in the laboratory or on smokers in a research ward to determine the intake of nicotine from smoking (Benowitz and Jacob, 1984a; Feyerabend *et al.*, 1985; Benowitz *et al.*, 1991). On average, smokers take in about 1 mg of nicotine per cigarette. The intake of nicotine is quite variable from person to person, appears to be largely independent of machine-determined yield, and can increase three-fold or more in response to restricted cigarette availability (Benowitz and Jacob, 1984a; Benowitz *et al.*, 1986a).

As noted previously, cotinine can be used as a measure of nicotine intake from cigarette smoking (Benowitz, 1996). On average, 70-80 percent of nicotine is metabolized to cotinine. Cotinine has a half-life averaging 16 hours, such that levels are relatively stable throughout the day in smokers. There is some individual variation in the quantitative relationship between cotinine levels in blood, saliva, or urine, and the intake of nicotine. This is because different people convert different percentages of nicotine to cotinine (usual range is 55-92 percent) and because different people metabolize cotinine itself at different rates (Benowitz and Jacob, 1994).

The relationship between nicotine intake and cotinine levels can be expressed mathematically as:

$$\text{Intake of nicotine} = \frac{C_{ss}(\text{CL}_{\text{COT}})}{\% \text{Conv}_{\text{NIC} \rightarrow \text{COT}}}$$

where C_{ss} is the steady-state blood cotinine concentration, CL_{COT} is the clearance of cotinine, and $\% \text{Conv}_{\text{NIC} \rightarrow \text{COT}}$ is the percent conversion of nicotine to cotinine.

Rearranging the equation,

$$\text{intake of nicotine} = \left[\frac{\text{CL}_{\text{COT}}}{\% \text{Conv}_{\text{NIC} \rightarrow \text{COT}}} \right] C_{ss} = K (C_{ss})$$

In adult smokers, the conversion factor K averages 0.08 mg/24 hours/ng/ml (Benowitz and Jacob, 1994). Thus, a cotinine level of 300 ng/ml in a typical smoker corresponds to a daily nicotine intake of 24 mg. Although cotinine screening levels do not precisely predict nicotine intake for an individual because of individual variability in the conversion factor, cotinine levels in groups of smokers are expected to predict average group exposure to nicotine. Thus, the K factor can be used in population studies to relate cotinine levels to overall intake of nicotine from particular brands of cigarettes.

Another way to estimate nicotine intake from cigarette smoking is to measure urinary excretion of nicotine and its metabolites (Byrd *et al.*, 1995, 1998). Measurement of all currently known metabolites of nicotine can

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account for approximately 90 percent of a dose of nicotine (Benowitz *et al.*, 1994). Assuming a steady level of smoking from day to day, the sum of nicotine and its metabolites (as measured in 24-hour urine samples) reflects the dose of nicotine taken in each day. A related but less precise way to assess nicotine intake is to measure nicotine and its metabolites in urine using a nonspecific colorimetric assay (Peach *et al.*, 1985). This assay does not distinguish particular nicotine metabolites and is less quantitative, but allows a semi-quantitative comparison of nicotine exposure in populations of smokers.

ESTIMATING THE EXTENT OF COMPENSATION

The analysis of biochemical markers after cigarette brand switching is often expressed as degree of percentage of compensation. Complete compensation means that the same amount of nicotine or other tobacco smoke constituents is taken in before and after a switch to a cigarette with a different nominal yield. No compensation means the intake changes in direct proportion to the change in machine-determined yields relative to the new brand.

Compensation, defined as the degree to which proportional changes in a smoker's intake of a smoke constituent make up for the same proportional change in the machine-determined yield of that constituent, can be expressed mathematically in the following equation (Alison *et al.*, 1989):

$$C = 1 - \left[\frac{\log(\text{marker}_2) - \log(\text{marker}_1)}{\log(\text{yield}_2) - \log(\text{yield}_1)} \right]$$

where C = extent of compensation, marker₁ and yield₁ represent the levels of biomarker and yield before the brand change, and marker₂ and yield₂ represent the levels in the changed brand condition.

The Zacny and Stitzer (1988) data, which will be described in more detail later, were used to illustrate the use of this equation. Smokers were switched from their usual cigarettes with an average nicotine yield of 1.0 mg to cigarettes with an average nicotine yield of 0.4 mg. The average plasma cotinine concentrations were 252 ng/ml while smoking the higher yield and 188 ng/ml while smoking the lower yield cigarettes. Using the equation above,

$$C = 1 - \left[\frac{\log(188) - \log(252)}{\log(0.4) - \log(1.0)} \right]$$

where data are available, the degree of compensation will be reported for the various studies discussed in subsequent sections.

STUDIES OF SMOKING CIGARETTES WITH DIFFERENT MACHINE-DETERMINED YIELDS: METHODOLOGICAL CONSIDERATIONS

The remainder of this chapter will review studies of human exposure to tobacco smoke chemicals that have used three main types of research designs. The first

design is the experimental forced-switching study, in which smokers are asked to switch to brands of higher or lower machine-determined yield compared to their usual brand. These experimental studies have been separated into short term (up to 4 weeks) and long term (more than 4 weeks). Forced-switching studies are particularly useful in that smoking behavior and exposure can be assessed under close observation. The limitations of such studies include the fact that smokers are switching only for the purpose of the research. Motivation and cigarette acceptability are dissimilar from the natural situation of brand switching. These studies are performed over periods of time that may not provide adequate duration to adjust to the taste or puffing characteristics of the new cigarettes. Many of the short-term studies have been performed in laboratories or on research wards, environments in which individuals may not smoke cigarettes as they normally do. Longer term forced-switching studies do allow more time to become accustomed to the new cigarette and are conducted in the smoker's natural environment, but they still do not measure the effect of self-determined brand switching. Nonetheless, experimental switching studies have provided useful information on the mechanism and extent of compensation that can occur.

A second study design is one that follows smokers who smoke self-selected cigarette brands. These are cross-sectional studies of chemical exposures in smokers who have selected the brand of cigarette that they find satisfying. Data from this type of study provide the best estimate of chemical exposure in smokers smoking different brands of cigarettes, but do not address the question of what happens if a person switches brands—for example, if someone switches from high- to low-yield cigarettes.

The third type of study design is one that examines spontaneous brand switching. These are studies of smokers who have chosen to switch from higher to lower machine-determined yield cigarettes, or vice versa. In these studies, the brand of cigarettes has been selected by the smoker, not by the researchers. Such studies are more informative of smokers' exposure in the real world when switching from higher to lower yield cigarettes.

SHORT-TERM EXPERIMENTAL SWITCHING STUDIES

A number of studies have examined the effects of switching from high- to low-yield cigarettes over a short period of time, defined for the purposes of this report as up to one month. The effects of short-term switching to low-yield cigarettes on how a cigarette is puffed and on vent hole blocking are discussed elsewhere in this volume. This section will focus on switching studies in which biomarkers of tobacco smoke exposure were measured.

Russell and coworkers (1975) studied 10 smokers on different days when they were smoking their usual brand (average yield, 1.34 mg nicotine), or when they were switched to higher yield (2.3 mg nicotine) or to lower yield (0.14 mg nicotine) cigarettes. The subjects were studied in the morning while smoking their usual brands, and then again after 5 hours of smoking either their usual, high-, or low-yield brands. Plasma nicotine concentrations were measured 3 minutes after smoking a cigarette as the indicator of nicotine exposure. Plasma nicotine concentrations were similar

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while smoking the usual and high-yield cigarettes (30.1 and 29.2 ng/ml, respectively) and significantly lower (8.5 ng/ml) while smoking the low-yield cigarette. The extent of compensation is estimated to be 96 percent for the high-yield and 20 percent for the low-yield cigarettes, respectively. The number of cigarettes smoked in the 5 hours of ad libitum smoking showed a 38 percent reduction while smoking the high-yield cigarettes and an increase from an average of 10.7 to 12.5 cigarettes per day for low-yield cigarettes (the latter comparison was not statistically significant).

Benowitz and Jacob (1984b) studied 11 smokers in a hospital research ward. They were smoking their own brand of cigarettes (average yield, 16.3 mg tar, 1.1 mg nicotine), or were switched to either Camel® (15.4 mg tar, 1.0 mg nicotine) or True® (4.6 mg tar, 0.4 mg nicotine) for 4 days each. Cigarette brands were assigned in a balanced order. Nicotine intake was determined by measuring blood nicotine concentrations throughout the day. When switched from their usual brand to either Camel® or True®, the smokers showed an approximately one-third decline in nicotine exposure. However, the intakes of nicotine and CO were similar when smoking Camel® or True®. Thus, using Camel®s as a comparator, the degree of compensation when smoking True® was 100 percent. Similar findings were obtained for CO exposure (based on measurements of COHb) or mutagenic activity in a 24-hour urine collection (a measure of exposure to potentially carcinogenic chemicals).

A similarly designed study was performed where 11 subjects were switched from their usual brand (average yield, 14.7 mg tar, 1.1 mg nicotine) to Camel® (15.4 mg tar, 1.0 mg nicotine) or to ultra-low Carlton® (tar 0.8 mg, nicotine 0.1 mg) cigarettes (Benowitz *et al.*, 1986b). Compared to the high-yield Camel® cigarette, when the participants smoked the Carlton® brand, their nicotine, CO, and mutagenic activity levels were reduced by 56, 36, and 49 percent, respectively. The percent compensation based on nicotine exposure was estimated to be 74 percent.

West and associates (1984) randomized 26 smokers of high-yield cigarettes (average yield, 14.2 mg tar, 1.3 mg nicotine) who either continued their own brand or switched to an ultra-low-yield cigarette (1 mg tar, 0.1 mg nicotine) for 10 days. Subjects smoked a similar number of cigarettes in the two conditions. The trough plasma nicotine level averaged 22.8 mg/ml for the usual brand condition versus 9.4 ng/ml for the ultra-low-yield brand condition. The latter is consistent with 36 percent compensation. A similar degree of compensation was estimated based on expired CO levels.

Zacny and Stitzer (1988) studied 10 smokers of high-yield cigarettes (average, 1.0 mg nicotine) who smoked five different brands of cigarettes—their own and cigarettes with yields of 0.1, 0.4, 0.7, and 1.1 mg nicotine—each for 5 days, in random order. Subjects smoked significantly more cigarettes per day of the two brands with the lowest yields compared to the three higher yield cigarettes. When smoking low-yield cigarettes, larger and more frequent puffs were taken as well. The plasma cotinine levels at the end of each smoking period averaged 152, 188, 221, 252, and 259 ng/ml for

the 0.1, 0.4, 0.7, 1.0, and 1.1 mg nicotine brands, respectively. The cotinine levels measured when smoking the two lowest yield cigarettes were significantly lower than for the three others. Based on group average data, compensation was estimated to be 56, 58, and 60 percent for the 0.1, 0.4, and 0.7 mg nicotine brands, respectively.

A Benowitz study mentioned previously allowed a comparison of tar-to-nicotine ratios as predicted by the smoking machine and as experienced by the smoker (Benowitz *et al.*, 1986a). The machine-determined tar-to-nicotine ratios for low-yield cigarettes are generally lower than those for high-yield cigarettes. For example, the tar-to-nicotine ratios for cigarettes in this study were 15.4 for Camel®, 11.5 for True®, and 7.3 for Carlton®. Assuming that urinary mutagenicity is a quantitative measure of tar exposure (which is reasonable, since most mutagenic activity comes from tar), changes in the ratio of urinary mutagenicity to the area under the plasma nicotine concentration time curve over 24 hours can be used as an indicator of changes in the ratio of actual tar-to-nicotine exposure in the smoker. While urinary mutagenicity did decline when smokers were switched to ultra-low-yield cigarettes, the ratio of mutagenic activity to nicotine exposure did not differ for any of the cigarette types. This observation is consistent with smoking-machine studies in which vent-hole blocking and/or more intensive smoking of low-yield cigarettes resulted in increased tar-to-nicotine ratios (Rickert *et al.*, 1983). It has been suggested that low-yield cigarettes may be less hazardous, even if full compensation for nicotine occurs, because the lower tar-to-nicotine ratio would lead to less intake of tar for any given level of intake of nicotine. However, based on the urinary mutagenicity data, one must question whether predictions about lower exposure to tar based on machine-determined tar-to-nicotine ratios are valid.

In summary, these short-term switching studies demonstrated that smokers compensate for reduced nicotine deliveries, but the extent of compensation varied in different studies—from 20 percent to 100 percent. The degree of compensation is likely to be less in short-term switching studies compared to longer term switching studies, or studies in which smokers have selected their own brand of cigarettes. This is because 1) smokers have not chosen to smoke the particular brand of cigarette they are switched to, 2) they often find the low-yield cigarettes to be unsatisfying, and 3) they may not be smoking the cigarettes long enough to develop effective compensatory smoking behaviors. These short-term switching studies demonstrated that compensation occurs by a combination of smoking more cigarettes per day and by taking in more tobacco smoke per cigarette compared to smoking-machine predictions. The one study that estimated tar-to-nicotine ratios delivered to the smoker suggested that this ratio is much higher than is predicted by smoking-machine tests in smokers of low-yield cigarettes, consistent with smoking-machine studies that showed that intensive puffing increases tar-to-nicotine ratios.

LONG-TERM EXPERIMENTAL SWITCHING STUDIES

Several studies have biochemically assessed the extent of compensation after switching from higher to lower yield cigarettes for periods of more than a few weeks. Russell and associates (1982) studied 12 smokers who typically smoked an

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average of 38 'middle-tar' cigarettes per day with an average yield of 17.4 mg tar and 1.3 mg nicotine. These subjects were switched to a low-tar cigarette (yield of 10.9 mg tar and 0.7 mg nicotine) for 10 weeks. Compared to baseline, the average cigarette consumption increased by about three cigarettes per day while smoking the low-yield cigarette, although this was not statistically significant. Plasma nicotine concentration (measured 2 minutes after smoking a test cigarette) and plasma cotinine concentrations declined by an average of 30 percent. There was no change in plasma thiocyanate or blood COHb. The percentage compensation based on plasma nicotine or plasma cotinine levels was 36 percent.

Robinson and colleagues (1983) switched a group of smokers of high-nicotine cigarettes (average yield, 1.8 to 1.1 mg nicotine) to lower yield brands over two stages. Six of the subjects, who served as controls, were switched to cigarettes similar to their usual brand. Sixteen subjects were switched initially to brands with 33 percent, then to brands with 61 percent reduction of nicotine yields over 8 weeks. The average serum cotinine level did not significantly decrease in those who decreased their brand yield (284 versus 244 ng/ml). Likewise, there was no significant reduction in plasma thiocyanate or blood COHb levels. Thus, the Robinson study demonstrated nearly complete compensation when switching to lower yield cigarettes. Some smokers in this study achieved compensation by smoking more cigarettes per day, but for most smokers the main mechanism was smoking cigarettes more intensively and/or blocking ventilation holes.

Peach and associates (1986) studied 183 smokers of middle-tar cigarettes who were randomized to switch from their own brand to cigarettes of a similar yield (average, 15.5 mg tar, 1.5 mg nicotine) or a lower yield (9.0 mg tar, 0.9 mg nicotine). Test cigarettes could be purchased at a discount. The subjects were followed for 5 weeks and smoked an average of 20 cigarettes per day, a rate that did not differ between middle- and low-tar cigarettes. However, urine nicotine metabolite excretion was no different for individuals smoking the two types of cigarettes, indicating 100 percent compensation.

Guyatt and colleagues (1989) studied 29 smokers who smoked their usual brand for 4 months and then were switched to a lower tar brand for 9 months. The usual cigarette brand had an average yield of 15.6 mg tar and 1.3 mg nicotine. Subjects were switched to cigarettes of at least 3 mg lower tar than the usual brand—the average switch was to 9.3 mg tar and 0.9 mg nicotine. Smokers on average smoked a greater number of low-yield cigarettes compared to the usual brand (28.5 versus 24.9 cigarettes per day), but the difference was not statistically significant. Smokers did take more puffs and larger puff volumes when smoking the lower yield cigarettes. Plasma cotinine and COHb levels declined by 18 percent. Compensation was estimated by the authors to be 61 percent based on cotinine and 56 percent based on COHb levels. The main mechanism for compensation was judged to be more intensive puffing rather than greater cigarette consumption.

Frost and associates (1995) studied 434 smokers of high-yield cigarettes who were switched to cigarettes of approximately 50 percent lower yield compared to their usual brands. One group was switched to the cigarettes immediately, and another was switched gradually over several months. A third group, the control group, was switched to cigarettes of 10 percent lower yield than their usual cigarettes. Subjects were allowed to select the brand that they would smoke within the specified yield range. The follow-up was over 6 months. Compared to the preswitching value, levels of serum cotinine in the fast yield-reduction group declined by an average of 11 percent and COHb declined by 14 percent. In the slow yield-reduction group, there was a decrease of 6 percent in cotinine and 16 percent in COHb. For the two groups combined, the extent of compensation was estimated by the authors to be 79 percent based on cotinine and 65 percent based on COHb. There was no significant difference in the extent of compensation based on how fast the yields were reduced. On average, smokers reduced the number of cigarettes they smoked after switching, which was interpreted by the authors to reflect the desire of this group of smokers to reduce their smoking in general. The high degree of compensation despite smoking fewer cigarettes per day further demonstrates the point that cigarette yields are substantially increased by smoking lower yield cigarettes more intensively.

In summary, the data from these experimental long-term switching studies indicated that there was some reduction in smoke exposure, but that the magnitude of that reduction was small. The larger studies indicated that the extent of compensation based on nicotine intake was about 80 percent. Compensation occurred primarily by increasing the intensity with which cigarettes were smoked, in addition to the variable contribution of increased numbers of cigarettes smoked per day in the different studies. It is possible that voluntary efforts to cut down on smoking by subjects in some of these studies may have limited the increase in cigarette consumption that has been observed in response to switching to lower yield cigarettes in other studies.

STUDIES OF SMOKERS SMOKING SELF-SELECTED BRANDS

Studies of Nicotine Exposure

Cross-sectional population studies can provide data on exposure to tobacco smoke constituents in people who have selected the brand of cigarettes they find satisfying. While these studies may supply valuable data on tobacco smoke chemical exposure in smokers of different brands, there are limitations in extrapolating such data to brand switching. For example, the acceptability of nicotine delivery from a particular cigarette may influence brand selection, and a highly dependent smoker would choose only those cigarettes that would provide adequate doses of nicotine. Cross-sectional studies will also include some people who are in transition—that is, transition to regular smoking, to cessation, or in the process of relapsing from a previous cessation attempt. Health concerns may also affect brand selection. All these factors would be expected to affect the relationship between self-selected brand and measures of intensity of smoking. Therefore, self-selected brand studies are not a perfect model for studying compensation in response to brand switching.

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The biomarkers used in cross-sectional studies include markers of nicotine exposure (blood nicotine, blood or saliva cotinine, or urinary nicotine metabolites) and markers of gas-phase exposure, such as CO and thiocyanate. This section focuses on studies that measured nicotine intake. Table 3-1 summarizes a number of studies in which nicotine intake was estimated in people who smoked cigarettes with different nominal yields. Most studies found either weak or no significant correlations between nominal yields and nicotine intakes.

Three large studies, which involved general populations of smokers, warrant particular discussion. Gori and Lynch (1985) recruited 865 smokers from shopping malls in different areas of the United States. Plasma nicotine and cotinine concentrations were weakly correlated with the Federal Trade Commission (FTC) method for machine-measuring nicotine yield (see Figure 3-1). Woodward and Tunstall-Pedoe (1992) studied 2,754 smokers as part of the baseline assessment in the Scottish Heart Health Study, which was conducted between 1984 and 1986. Their main analysis presented plasma cotinine data based on categories of yield: low tar (less than 13 mg/cigarette), middle tar (14-15 mg), and high tar (greater than 14 mg). The mean cotinine values were no different across categories for males (276, 294, and 278 ng/ml for low-, middle-, and high-tar groups, respectively). For females, the cotinine level was 26 percent lower in the low-tar group (199 ng/ml) but similar for the middle- and high-tar groups (270 and 270 ng/ml, respectively). Woodward and Tunstall-Pedoe (1993) performed another analysis of the same data with comparison of the cotinine concentrations to specific yields of tar, nicotine, and CO (see Figure 3-2). Multiple regression analysis—which included tar, nicotine, and CO yields as well as cigarette consumption and gender—found that tar was the best predictor of cotinine level, with an interaction for gender as previously discussed. However, the best regression model accounted for only 19 percent of the variance in cotinine levels.

Jarvis and colleagues (2001) conducted a study of 2,031 adult smokers in the United Kingdom as part of the 1998 Health Survey for England. Smokers were defined as anyone who reported current smoking and included those who smoked only occasionally. Saliva cotinine concentrations correlated weakly with machine-determined nicotine yield ($r = 0.19$, $P < 0.001$). After controlling for confounders, machine-determined yield accounted for 0.79 percent of the variance in saliva cotinine. Using the conversion factor for estimating nicotine intake from cotinine level as described earlier, Jarvis and associates estimated a nicotine intake per cigarette of 1.17 mg in smokers of brands with machine yields of less than 0.4 mg (average, 0.14 mg), 1.22 mg nicotine for cigarettes with yields of 0.4-0.75 mg (average, 0.57 mg), and 1.31 mg for brands with yields greater than 0.75 mg (average, 0.91 mg). The authors did not find that smokers of low-yield cigarettes smoked more cigarettes than smokers of higher yield cigarettes. However, in their analysis, most of the occasional smokers fell into the low-yield cigarette group. Thus, the low-yield group contained a mixture of addicted and nonaddicted smokers, whereas the higher yield groups included a greater proportion of addicted smokers (Jarvis *et al.*, 2001).

Table 3-1

Studies of Nicotine Intake Compared with Machine Nicotine Yield

Study	Population	Nicotine Yields (mg)	Results
Russell <i>et al.</i> , 1980	330 from smokers' clinics or research volunteers	0.5-3.5	PNIC vs. Mach-N $r = 0.21^*$
Rickert and Robinson, 1981	84 during routine medical exams	0.25-1.3	PCOT vs. Mach-N $r = 0.08$
Benowitz <i>et al.</i> , 1983	272 seeking smoking cessation therapy	<0.1-1.9	BCOT vs. FTC-N $r = 0.15$ (n = 137) $r = 0.06$ (n = 123)
Ebert <i>et al.</i> , 1983	76; mix of smoking cessation, hospital employees, and ambulatory patients	0.1-1.5	PNIC vs. FTC-N $r = 0.25^*$
Gori and Lynch, 1985	865 recruited from shopping malls; 10 or more cigarettes per day	0.1-1.6	PNIC vs. FTC-N $r = 0.37^*$ PCOT vs. FTC-N $r = 0.23^*$
Benowitz <i>et al.</i> , 1986b	248 seeking smoking cessation (137 from previous study)	0.1-1.9	BCOT values similar for FTC-N 0.21 to >1.0 BCOT 2/3 of others for FTC-N < 0.20
Russell <i>et al.</i> , 1986	392 from smokers' clinics	—	BCOT vs. Mach-N $r = 0.13^*$ BNIC vs. Mach-N $r = 0.26^*$
Rosa <i>et al.</i> , 1992	125 attending military medical center	0.38-1.38	BCOT vs. Mach-N $r = 0.30$
Coultas <i>et al.</i> , 1993	298 from Hispanic household survey	—	SCOT vs. FTC-N $r = 0.12$
Woodward and Tunstall-Pedoe, 1993	2,754 from Scottish Heart Health Study (1984-1986)	0.1-1.7	BCOT vs. Mach Tar, N, and CO and gender (multiple regression); accounted for 19% variance
Byrd <i>et al.</i> , 1995	33 volunteers	0.13-1.3	UNIC + metabolites vs. FTC-N N/24 hr: $r = 0.68^*$ N/cig: $r = 0.79^*$

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Table 3-1 (continued)

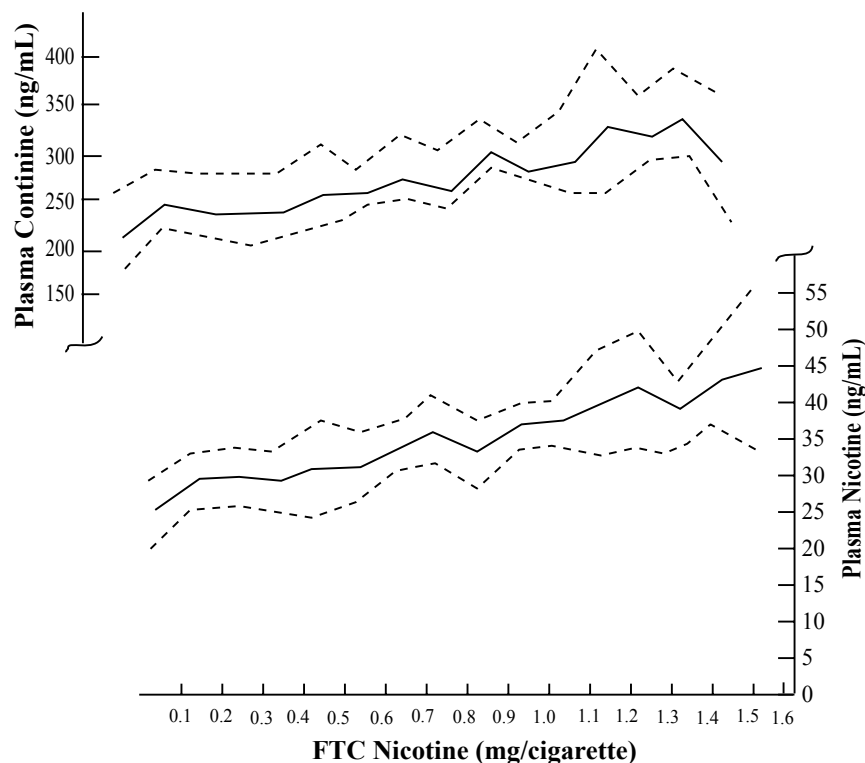
Study	Population	Nicotine Yields (mg)	Results
Hee <i>et al.</i> , 1995	108 volunteers; 5 or more cigarettes per day	0.09-1.19	UNIC, UCOT vs. Mach-N; NS
Byrd <i>et al.</i> , 1998	72 volunteers	0.1-1.4	UNIC + metabolites vs. FTC-N N/24 hr: $r = 0.19$ N/cig: $r = 0.31^*$ SCOT vs. FTC-N $r = 0.15$
Jarvis <i>et al.</i> , 2001	2,031 from 1998 Health Survey for England	0.04-1.06	SCOT vs. Mach-N $r = 0.19^*$

* $P < 0.05$.

Key: PCOT = plasma cotinine concentration; Mach-N = smoking-machine-determined nicotine yield; PNIC = plasma nicotine concentration; BCOT = blood cotinine concentration; FTC-N = machine yield by Federal Trade Commission method; BNIC = blood nicotine concentration; SCOT = saliva cotinine concentration; UNIC = urine nicotine concentration; UCOT = urine cotinine concentration; N = nicotine; CO = carbon monoxide.

Figure 3-1

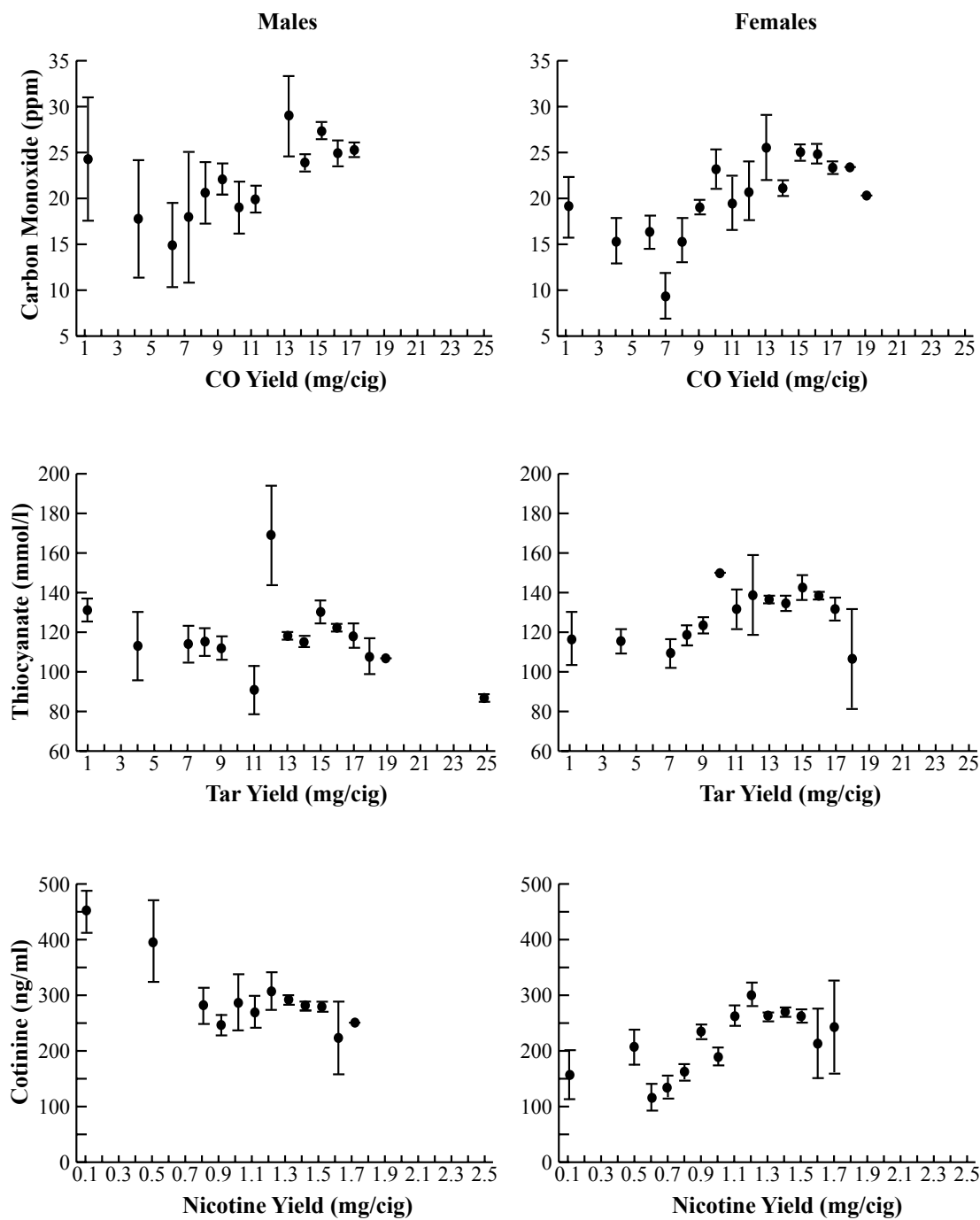
Plasma Cotinine and Nicotine Concentrations in Cigarette Smokers According to the FTC Nicotine Yield



Note: Solid line indicates mean; dashed line indicates 95% confidence intervals (from Gori and Lynch, 1985).

Figure 3-2

Mean Values for Expired Carbon Monoxide v. CO Yield, Serum Thiocyanate v. Tar Yield, and Serum Cotinine Against Machine-Determined Yields for Men and Women



Note: Bars indicate one standard error (from Woodward and Tunstall-Pedoe, 1993).

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Another study by Gori and Lynch (1983) warrants particular discussion with respect to ultra-low-yield brands of cigarettes. They studied 288 smokers of two ultra-low-yield cigarette brands (1 mg tar). The subjects were recruited in shopping malls, and plasma cotinine levels were measured. The cotinine concentrations in smokers averaged 322 and 195 ng/ml for brands with yields of 0.18 and 0.10 mg nicotine, respectively. The cotinine values of the second brand were about 30 percent lower than the typical smoker population value of 300 mg/ml. Smokers of the first ultra-low brand had cotinine concentrations similar to the smoker population average. These findings were similar to those of a short-term experimental study, by Benowitz and associates, in which smokers were switched from regular to ultra-low-yield cigarettes (Benowitz *et al.*, 1986b). In that study, the intake of nicotine fell by about 30 percent when switching to ultra-low-yield cigarettes compared to the usual brand.

In summary, most studies of nicotine intake in populations smoking self-selected brands of cigarettes showed some differences in nicotine exposure when high- and low-yield brands were compared. However, the differences were quite small and not nearly quantitatively proportional to the changes in nominal yield. Thus, nicotine ratings of cigarettes are poor predictors of actual nicotine intake and of the intake of other toxins as well. The FTC method generally underestimates human exposure to nicotine, particularly in smokers who are smoking low-yield cigarettes.

Studies of Carbon Monoxide Exposure

Studies on CO exposure in populations of self-determined brand smokers are summarized in Table 3-2. An example of CO data from a large group of smokers recruited from shopping centers is shown in Figure 3-3 (Gori and Lynch, 1985). Similar data were reported by Woodward and Tunstall-Pedoe (1992) in the Scottish Heart Health Study (see Figure 3-2). Most other studies likewise found no relationship between machine-determined CO yield and CO exposure, although a few studies did report weak correlations. The conclusions for CO were similar to those discussed above for nicotine; that is, machine-determined yields are poor predictors of human exposure to CO, and presumably to other gaseous components of tobacco smoke as well.

Studies of Other Tobacco Smoke Biomarkers

Several studies have measured plasma or saliva thiocyanate concentrations, and one study measured urinary mutagenic activity. In most studies, thiocyanate concentrations were no different in smokers of cigarettes with different nominal yields. The Woodward and Tunstall-Pedoe study (1993) found a weak relationship between serum thiocyanate and cigarette yield. Benowitz and colleagues (1986b) found that smokers of ultra-low-yield cigarettes had about 25 percent lower thiocyanate levels compared to other brands, but Maron and Fortmann (1987) found no difference in thiocyanate concentration comparing smokers of ultra-low and other brands.

Hee and coworkers (1995) measured urinary mutagenicity in 108 smokers of different yield cigarettes. They found a weak relationship between urinary mutagenicity and nicotine yield ($r = 0.22$, $P > 0.05$).

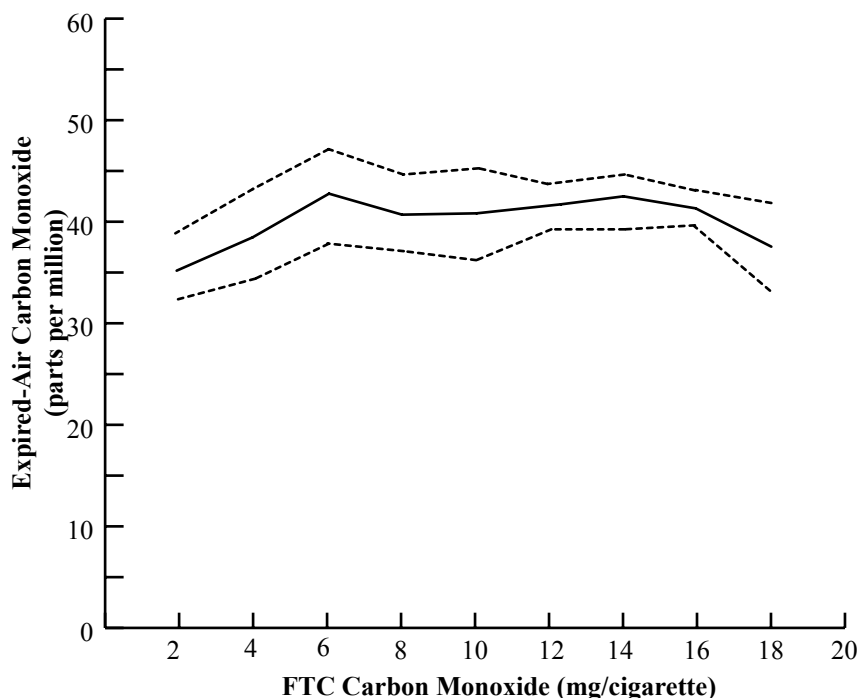
Table 3-2

Studies of Carbon Monoxide Intake Compared with Machine Yield

Study	Population	Machine Yields (mg)	Results
Jaffe <i>et al.</i> , 1981	200 recruited from urban workplaces	0.2 - >1.0 mg nicotine	ECO vs. FTC-N $r = 0.028$
Rickert and Robinson, 1981	159 during routine medical exams	4-22 mg CO	COHb vs. Mach-CO $r = 0.10$
Sutton <i>et al.</i> , 1982	55 volunteers	11-20 mg CO	COHb vs. Mach-CO $r = 0.03$
Ebert <i>et al.</i> , 1983	76; mix of smoking cessation, hospital employees, and ambulatory patients	1-22 mg CO	ECO vs. Mach-CO $r = 0.03$
Wald <i>et al.</i> , 1984	2,455 males during health screening exams in London	0.8-28.1 mg CO	CO remained relatively constant regardless of cigarette yield
Gori and Lynch, 1985	865 recruited from shopping malls; 10 or more cigarettes per day	2-18 mg CO	ECO vs. FTC-CO; virtually no correlation
Maron and Fortmann, 1987	713 in a community-based survey	<0.2 - >1.0 mg NIC	ECO vs. FTC-N Analysis of variance revealed NSD
Woodward and Tunstall-Pedoe, 1992	2,754 from Scottish Heart Health Study (1984–1986)	1-19 mg CO	ECO vs. Mach Tar, N, and CO and gender (multiple regression) accounted for 19% of variance
Coultas <i>et al.</i> , 1993	298 in a population survey, primarily Hispanic	—	ECO vs. FTC-CO $r = 0.03$
Hee <i>et al.</i> , 1995	108 volunteers, 5 or more cigarettes per day	1.1-15.0 mg	COHb vs. Mach $r = 0.24$

Key: CO = carbon monoxide; FTC-N = machine yield of nicotine by Federal Trade Commission method; ECO = expired CO; COHb = blood carboxyhemoglobin; Mach-CO = smoking-machine-measured CO.

Figure 3-3

Expired Carbon Monoxide Concentrations in Smokers According to FTC CO Yields of Cigarettes Smoked

Note: Solid line indicates mean; dashed line indicates 95% confidence intervals (from Gori and Lynch, 1985).

Thus, the data on other biomarkers support the overall conclusions of studies that measured nicotine and CO—that there is very little difference in tobacco smoke exposure in people smoking cigarettes of different machine-determined yields. For the general population of smokers who select their own brand of cigarettes, the extent of nicotine compensation appears to be almost complete.

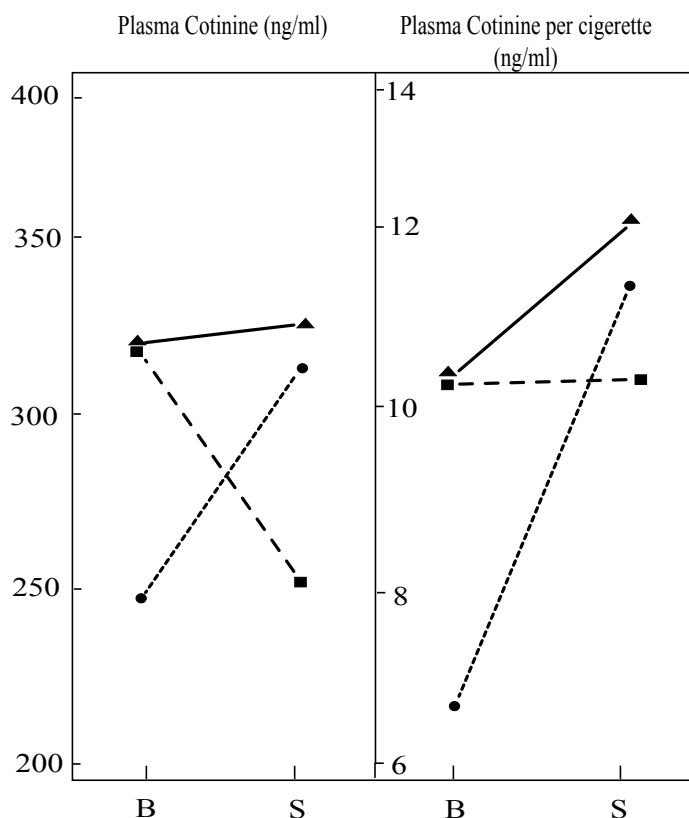
SPONTANEOUS BRAND SWITCHING Smokers in their natural environment have chosen the brand of cigarettes they smoke. A smoker's choice of cigarette brand is influenced by a variety of factors, including the brand smoked by peers, the influence of advertising and promotional materials, a desire to reduce the health risks of smoking (which is, in turn, influenced by advertising and promotion), and the characteristics of the cigarette (*i.e.*, adequacy of nicotine dose, taste, etc.). Experimental studies of brand switching are, to some extent, artificial in that the researchers select the brand. Spontaneous brand switching studies are more informative of smokers' exposures in the real world when they switch to lower yield cigarettes.

Two studies of spontaneous brand switching were reviewed for this chapter. Lynch and Benowitz (1987) reported on 197 smokers who had measurements of plasma cotinine and COHb while smoking self-selected brands on 2 occasions, 6 years apart. Of these smokers, 104 were smoking cigarettes of the same or similar machine-determined yields as before, 62 had switched to a lower yield (0.2 mg or more reduction in nicotine delivery), and 31 had switched to higher yields (0.2 mg or more increase in nicotine delivery). Plasma samples and expired CO were measured on approximately the same day at baseline and on retesting. Smokers who did not change the nicotine yield showed a slight decrease in the numbers of cigarettes smoked per day, but there was no change in cotinine or CO levels (see Figure 3-4). Smokers who switched to lower yield cigarettes initially smoked cigarettes with higher nicotine yields (average 1.09 mg) and then switched to cigarettes with an average yield of 0.68 mg, a 38 percent reduction. Brand switching was associated with a reduction in cotinine and expired CO of about 20 percent. However, these smokers had also decreased their cigarette consumption by about 20 percent. Analysis of cotinine concentration or CO per cigarette showed no change despite reduction in yield. Thus, the smokers obtained the same dose of nicotine and CO from each cigarette even though the yield was lower. This observation is consistent with findings described previously showing that when switching from high- to low-yield cigarettes, full compensation from each cigarette is easily achieved. Reduction in daily exposure to tobacco smoke occurred primarily because certain smokers who switched to low-yield cigarettes smoked fewer cigarettes. Possibly, switching was part of an attempt by these individuals to reduce their health risks by smoking both lower yields and fewer cigarettes per day.

Switchers to high-yield cigarettes had smoked a low-yield cigarette at the initial study (average, 0.42 mg nicotine) and switched to cigarettes with an average yield of 0.85 mg, a 102 percent increase. After switching, cotinine levels increased by 23 percent and expired CO by 5 percent (see Figure 3-5). In this case, smokers did take in more nicotine and CO per cigarette, although much less than predicted by the relative increase in machine yield. Because these subjects were smoking lower yield cigarettes and had lower cotinine levels at baseline compared to subjects who switched to cigarettes of similar or lower yields, it is likely that this group was composed of smokers in an escalating phase of developing tobacco dependence. This idea was supported by the observation that, after switching, cotinine levels rose to levels similar to those of the other two groups at baseline.

Peach and coworkers studied 599 males over 13 years (from 1971 to 1984) in a study of the effects of brand switching on phlegm production on pulmonary function tests (Peach *et al.*, 1986a). Average cigarette consumption decreased in all smokers, but less so in those smokers who switched to lower yield cigarettes. Nicotine intake was estimated by a colorimetric assay of total nicotine plus metabolite excretion in the urine. At the 1984 assessment, no difference in nicotine metabolite excretion was observed in individuals who had or had not switched from higher to lower yield cigarettes. This suggests full compensation when switching to lower yield cigarettes.

Figure 3-4

Spontaneous Brand Switching Study: Plasma Concentrations of Cotinine and Cotinine Concentration Normalized for Cigarettes Smoked per Day

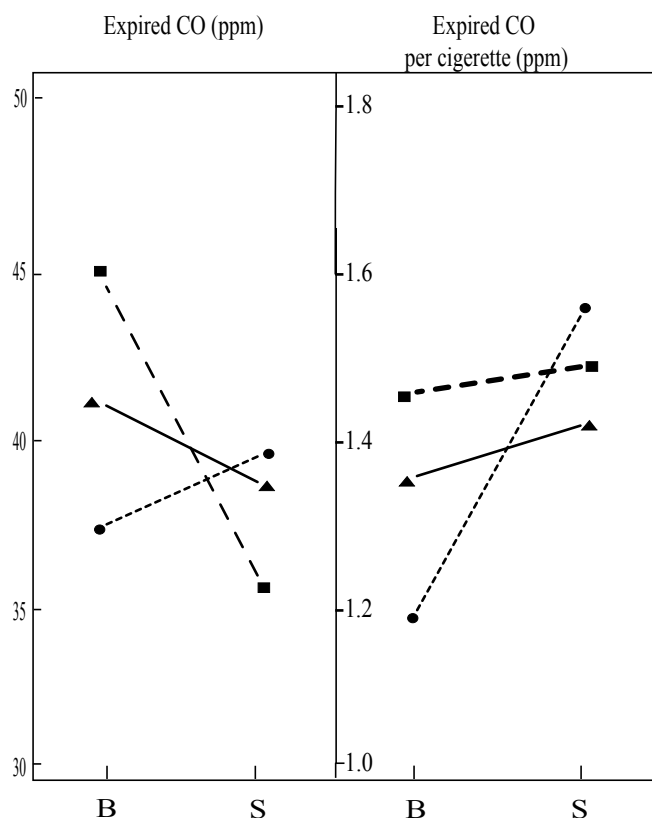
Note: B indicates baseline and S indicates follow-up study.

Symbols: Triangles=subjects who did not switch brands (n=109); solid squares=decreaseers (n=62); solid circles=increaseers (n=32); asterisks indicate significant change from baseline to follow-up study (from Lynch and Benowitz, 1987).

In summary, these two spontaneous brand-switching studies indicated that when smokers choose to switch to low-yield cigarettes, their intake of nicotine and CO (and presumably other smoke constituents) per cigarette does not significantly change. Thus, for spontaneous brand switchers, there appears to be a complete compensation for each cigarette smoked, reflecting more intensive smoking. These observations suggest, at least when considering modern cigarettes, that switching from higher to lower yield cigarettes per se is not likely to reduce disease risk.

SUMMARY Studies of subjects who smoked cigarettes with lower machine-determined yields support the idea that smokers regulate their intake of nicotine to take in the amount of nicotine that they need to sustain their addiction. Experimental switching studies show varying degrees of compensation. Variability from study to study probably reflects the characteristics of the smokers and the types of cigarettes to which they were switched. Experimental studies in which smokers were switched from regular to ultra-

Figure 3-5
Spontaneous Brand Switching Study: Expired Air CO Concentration and CO
Concentration Normalized for Cigarettes Smoked per Day



Note: B indicates baseline and S indicates follow-up study.

Symbols: Triangles=subjects who did not switch brands (n=109); solid squares=decreaseers (n=62); solid circles=increaseers (n=32); asteriks indicate significant change from baseline to follow-up study (from Lynch and Benowitz, 1987).

low-yield cigarettes suggest a significant but modest reduction in nicotine exposure. Spontaneous brand-switching studies suggest that there is no reduction in smoke intake per cigarette, and that any reductions that were seen in brand switchers depended upon whether or not those individuals also cut down their cigarette consumption.

Studies of smokers smoking self-selected brands assessed exposure in individuals who smoked as many of their cigarettes as they wish. These studies convincingly showed a weak relationship between nicotine yield and nicotine, CO, or thiocyanate exposure. An exception may be smokers of ultra-low-yield cigarettes, for whom in some studies there was an approximately 30 percent reduction of cotinine levels. However, the market share for ultra-low-yield cigarettes is extremely small.

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Considering the overall exposure data in individuals selecting their own brands, there is little reason to expect that smokers of low-yield cigarettes will have a lower risk of disease than those smoking higher yield cigarettes. Lower tar-to-nicotine ratios could result in reduced risk, in theory, even if there is full compensation for nicotine, but the few human exposure data available to date suggest that exposure to tar compared to nicotine is not different in smokers smoking low-yield cigarettes.

The majority of smokers appear to compensate by smoking their cigarettes more intensively and/or by blocking ventilation holes. Some studies show that smokers of low-yield cigarettes smoke more cigarettes per day. Other studies indicate that occasional smokers are more likely to be in the low-yield category, which may result in estimates of smoking similar or even fewer cigarettes in the low-yield group compared to higher yield groups. Recent data from California suggest that if one looks at addicted smokers who have been smoking at a stable level for some time, smokers of low-yield cigarettes do smoke more cigarettes. This type of analysis has not been performed on other data sets, where cigarette consumption was simply taken for all smokers of a particular yield regardless of level of dependence or the stability of smoking behavior.

CONCLUSIONS

1. Smokers regulate their intake of nicotine to obtain the amount of nicotine that they need to sustain their addiction.
2. Spontaneous brand-switching studies suggest that there is no reduction in smoke intake per cigarette, and that any reductions that are seen in brand switchers depend upon whether or not those individuals also reduce their cigarette consumption.
3. Studies of smokers smoking self-selected brands showed a weak relationship between machine-measured nicotine yield and a smoker's nicotine, CO, or thiocyanate exposure.
4. Considering the overall exposure data for individuals selecting their own brands, there is little reason to expect that smokers of low-yield cigarettes will have a lower risk of disease than those who smoke higher yield cigarettes.

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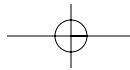
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