Biomarkers of Cigarette Smoking

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INTRODUCTION   This chapter addresses the following question: To what extent do smoking-machine-derived tar, nicotine, and carbon monoxide ratings of cigarettes predict how much of those substances smokers actually absorb into their bodies?

Two issues need to be clarified. First is the difference between delivery and content: What a cigarette delivers to the smoker is not the same as what is present in the cigarette tobacco. Second is the issue of compensation vs. regulation or titration: Kozlowski and Pillitterri (this volume) focus on compensation—the individual's smoking behavioral response to a change in a cigarette brand; this chapter focuses on cigarettes that people have self-selected to smoke. Whether behavioral adjustment to nicotine yields indicates regulation or titration or compensation is not important. What is important is the relationship between what people choose to smoke and their intake of various tobacco-derived toxins.

USE OF VARIOUS BIOMARKERS   The biomarkers most widely used to quantitate exposure to tobacco smoke include nicotine, its metabolite cotinine, carbon monoxide, and with less success, thiocyanate. Recent investigation has focused on various hemoglobin and DNA (deoxyribonucleic acid) adducts and excretion of nitrosamines in the urine. These latter measures represent important future directions, but there are inadequate data in large enough populations to make conclusions about the relationship between these measures and U.S. Federal Trade Commission (FTC) yields. The use of mutagenic activity of the urine is discussed to address the utility of the tar-to-nicotine ratio that is computed from the "FTC method" in predicting relative human exposure to tar and nicotine. This is an important consideration in estimating human risks from different types of cigarettes.

NICOTINE ABSORPTION FROM CIGARETTES   Nicotine is rapidly absorbed from cigarettes. It enters arterial circulation first, then venous circulation; nicotine levels then fall relatively quickly as it is redistributed from the bloodstream to various body tissues. Subsequently, nicotine levels fall off with an elimination half-life of about 2 hours (Benowitz, 1988).

The intake of nicotine from a single cigarette can be approximated by measuring the nicotine blood concentration profile after a person smokes a single cigarette. The area under the plasma concentration-time curve is a reflection of systemic dose. The 24-hour nicotine consumption also can be estimated. Volunteer smokers have been studied smoking cigarettes on a research ward, where blood levels could be sampled frequently. Blood levels rise with smoking in the morning, more or less plateau through the latter part of the day, and then fall overnight (Benowitz and Jacob, 1984a). Carbon monoxide levels also build up during the day, plateau, and then

fall overnight. By sampling blood periodically throughout the day for measurement of nicotine levels, it is possible to estimate daily exposure to nicotine in human smokers.

The metabolic disposition of nicotine in humans has been determined based on urine-recovery studies plus infusion studies of nicotine and cotinine (Figure 1) (Benowitz et al., 1994). On average, about 70 to 80 percent of nicotine is converted to cotinine, which is the main proximate metabolite. Most studies of nicotine intake from cigarettes producing different yields have used cotinine as the marker of nicotine intake. Cotinine is extensively metabolized, primarily to *trans*-3'-hydroxycotinine. Nicotine, cotinine, and hydroxycotinine also are conjugated as glucuronides. In the urine, a relatively small amount of cotinine is excreted unchanged compared with the total amount generated. However, in general, urine cotinine is well correlated with plasma cotinine so that urine cotinine can be used as a surrogate for plasma cotinine concentration (Jarvis et al., 1984). Saliva cotinine also is highly correlated with plasma cotinine and has been used in the same way.

Plasma cotinine levels fluctuate somewhat throughout the day. There is about a 15-percent change in cotinine levels from morning to night,

Figure 1

Quantitative scheme of nicotine metabolism, based on average excretion of metabolites as percentage of systemic dose during transdermal nicotine application
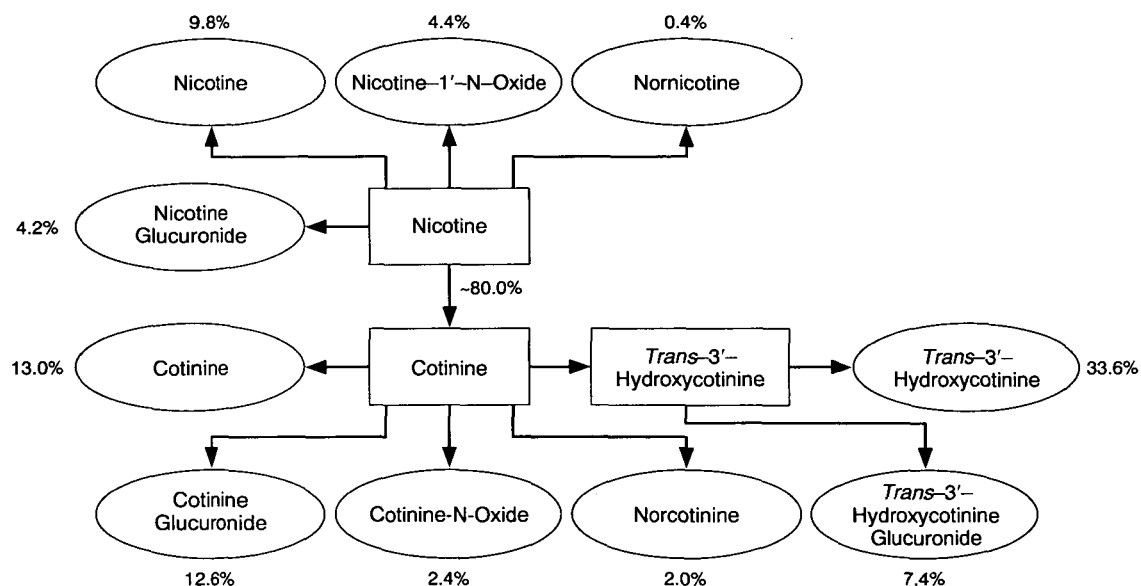
Note: Compounds in ovals indicate excretion in urine, and associated numbers indicate percentage of systemic dose of nicotine.

Source: Benowitz et al., 1994.

reflecting the approximately 16-hour half-life of cotinine (Benowitz et al., 1983a). Because of the relatively small circadian variation, cotinine levels can be measured at various times of the day, and this value can be used as representative of the average daily cotinine level.

It is possible, by measuring all the metabolites in the urine, to account for an average of 90 percent of the nicotine dose (Benowitz et al., 1994). An approach to estimating nicotine consumption is to measure all the metabolites in the urine and sum them up. At steady state (where the rates of intake of drug and generation of metabolism are the same as rates of elimination of drug and metabolites), this sum of all metabolites in a 24-hour urine excretion reflects the amount of nicotine that a person takes in each day.

NICOTINE CONTENT OF TOBACCO VS. FTC YIELD   As noted earlier, cigarette content is not the same as cigarette yield or delivery. Figure 2 shows data from a 1983 study (Benowitz et al., 1983b) that investigated the nicotine content of tobacco. The nicotine concentration of tobacco averaged 1.6 percent. There was no relationship between nicotine content in the whole tobacco rod and the FTC-predicted nicotine yield. There was a significant inverse relationship between the concentration of nicotine and the FTC nicotine yield. Thus, the yield as measured by smoking machine gives no information whatsoever about the content of nicotine or other potential toxins in the tobacco. The content of nicotine in the tobacco simply represents the ultimate limit of the nicotine dose. The FTC method provides no information about the amount of nicotine that could be obtained from the tobacco if a person smoked it in a way to optimize intake.

QUANTITATING NICOTINE INTAKE IN SMOKERS   There are four general methods for quantitating the intake of nicotine from tobacco: (1) In circadian fashion, measure blood nicotine levels during cigarette smoking (Benowitz and Jacob, 1984a and 1984b). If the clearance of nicotine also is measured by intravenous infusion of nicotine, blood levels during smoking can be converted to an absolute daily dose of nicotine. (2) The same can be done with blood level data after a person has smoked one or two cigarettes (Benowitz et al., 1991). (3) Blood cotinine levels during ad libitum cigarette smoking have been used widely to estimate nicotine intake, which is discussed below. (4) Finally, as mentioned by Byrd and colleagues (1995), measuring urine nicotine and metabolites during ad libitum smoking can be used to estimate nicotine intake. These four ways can be used to address the question of how much nicotine is being taken into the body from smoking.

Table 1 presents a summary of data on the dose per cigarette from the first three methods. The first method was used to study 44 smokers, measuring blood levels during 24 hours of smoking, at steady state (Benowitz and Jacob, 1984a, 1984b, and 1985). The dose was estimated to be about 1 mg per cigarette, with a range of 0.37 to 1.60 mg per cigarette.

Figure 2
**Nicotine content of cigarettes as compared with FTC-determined values
(regression analysis)**
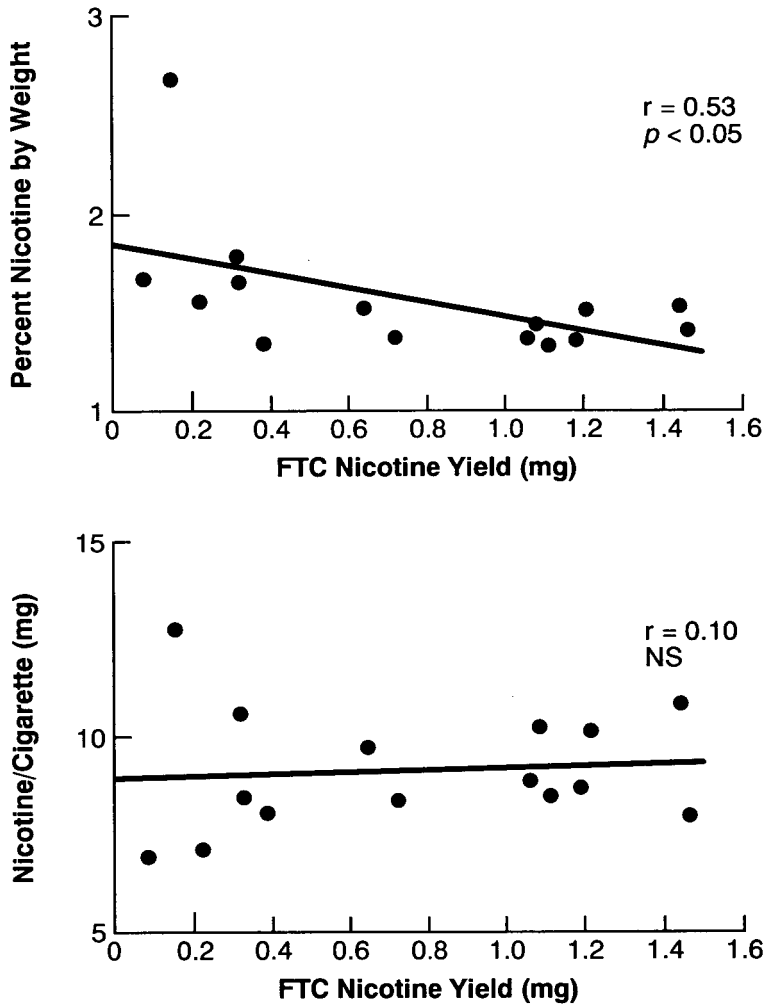
Note: *"Nicotine intake per cigarette (mg)" indicates total amount of nicotine in the length of cigarette
tobacco rod smoked in the standard FTC smoking machine assay.*

Key: *NS = not significant.*

Source: *Benowitz et al., 1983b.*

The second method is based on studies of persons smoking one or two
cigarettes (Benowitz et al., 1994). This method produced an average dose of
2.3 mg per cigarette, with a range of 0.37 to 3.47 mg. The study paradigm
was one in which smokers were deprived overnight and given only one or
two cigarettes to smoke in the morning. These were the only cigarettes
allowed all day. The unusually high dose per cigarette most likely reflected

Table 1
Summary of absolute bioavailability of nicotine from cigarette smoking studies

Method	N	Systemic Dose (mg/cigarette)			Reference
		Average	Standard Deviation	Range	
1	22	1.04	0.36	0.37-1.60	Benowitz and Jacob, 1984a
	11	1.00	0.15	0.87-1.48	Benowitz and Jacob, 1984b
	11	0.90	0.15	—	Benowitz and Jacob, 1985
2	10	2.29	1.00	0.37-3.47	Benowitz et al., 1991
3	20	0.87	0.41	0.22-1.92	Benowitz and Jacob, 1994

the smokers' anticipation of no more cigarettes becoming available that day. This finding illustrates the tremendous range of nicotine intake a smoker has when there is a need, or an anticipated need, for nicotine. The intake of nicotine per cigarette in this study was double that typically consumed from ad libitum daily smoking. Consistent with this observation was another study in which subjects tripled their intake of nicotine per cigarette by smoking more intensely when the number of cigarettes allowed to be smoked per day was limited (Benowitz et al., 1986a).

The third method, that is, measuring blood cotinine concentrations, resulted in an estimated dose of about 0.9 mg of nicotine per cigarette, with a range of 0.22 to 1.92 mg per cigarette (Benowitz and Jacob, 1994). What is the quantitative relationship between nicotine intake and yield? Figure 3 shows nicotine intake data from volunteer smokers studied whose plasma nicotine levels were measured while they smoked their usual brand of cigarettes ad libitum while in a research ward (Benowitz and Jacob, 1984a). There was no correlation between the FTC-measured nicotine yield and study-measured intake of nicotine. The only yield that turned out to be accurate was 1 mg, which is fortuitous because it represents the average consumption. Also, most smokers of nonfiltered cigarettes took in less nicotine than predicted from the FTC yield. People who smoked low-yield cigarettes took in, on average, more nicotine than predicted by FTC yield. It is possible that in the 1940's and 1950's, when people smoked cigarettes with a nominal yield of 2.5 mg or higher of nicotine, they may in fact have been undersmoking those cigarettes and taking in considerably less smoke per cigarette than they do now. That behavior might explain the change in lung cancer pathology over the years. That is, a change in depth of inhaling and intensity of smoking may affect the location of the lung tumor.

Figure 3

Regression analysis of relationship between nicotine intake per cigarette and machine-determined nicotine yield
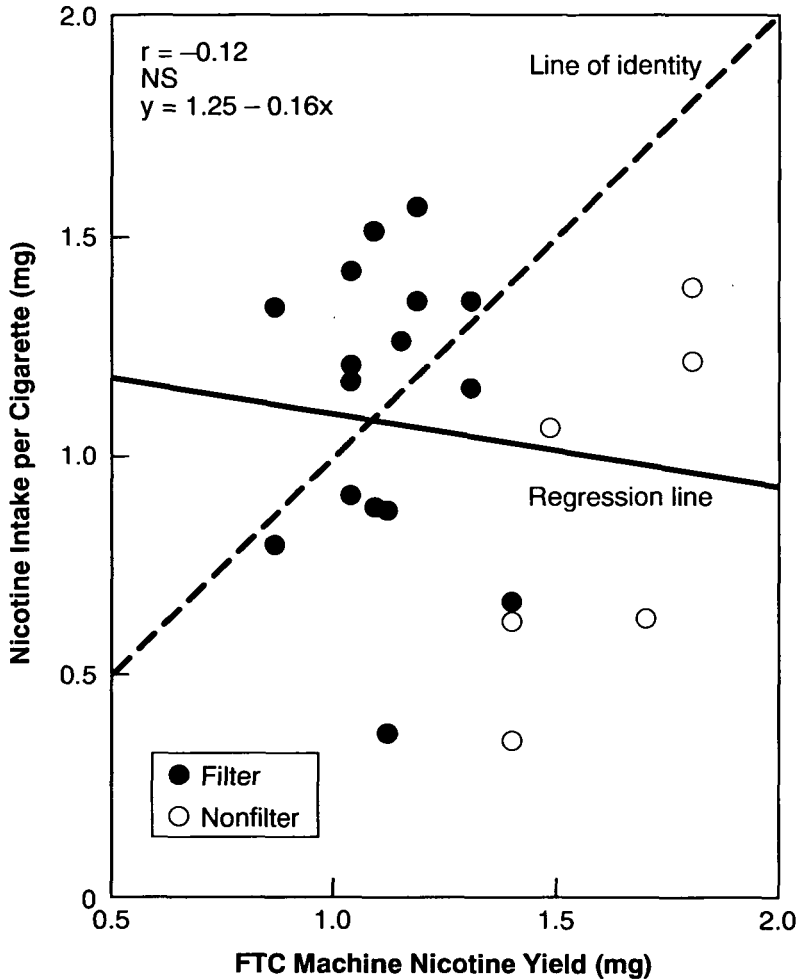
Key: *solid line = regression line; broken line = line of identity, which indicates points at which measured nicotine intake per cigarette equals machine-determined nicotine yield; NS = not significant.*

Source: *Benowitz and Jacob, 1984a.*

COTININE
**LEVELS AND**
NICOTINE
INTAKE

What is the quantitative relationship between cotinine levels and the intake of nicotine from smoking? To address this question, dual infusions of deuterium-labeled nicotine and cotinine were given to smokers (Benowitz and Jacob, 1994). From resultant blood level data, it was possible to calculate the percentage of nicotine that is converted to cotinine and the clearance of cotinine per se. From these parameters can be derived a factor (K) that relates a given blood level of cotinine at steady state

to a given daily intake of nicotine, a factor that averages 0.08. Thus, for a typical smoker with a level of 300 ng/mL, nicotine intake is estimated to be 24 mg per day. Based on average cigarette consumption, that represents an intake of about 1 mg of nicotine per cigarette. This K factor did not vary as a function of whether a person was a smoker or nonsmoker, brands of cigarette smoked, or gender. Thus, the author is aware of no bias in using this K factor to estimate the dose of nicotine based on a plasma cotinine concentration.

Data from a study of 136 smokers entering a smoking cessation program are shown in Figure 4 (Benowitz et al., 1983b). There was a weak relationship between FTC yield and cotinine level. The slope of this relationship was shallow and, in this study, not significant. From the lowest to the highest yield of cigarettes, there was only a 5- to 10-percent change in cotinine level, reflecting a 5- to 10-percent change in nicotine intake. There was a much stronger correlation between cigarettes per day and cotinine level (or nicotine intake). Thus, the greater the number of cigarettes a person smokes, the more nicotine is taken in. This is important because some studies, such as that of Rosa and colleagues (1992), purport to show a strong relationship between

Figure 4

Afternoon blood cotinine concentrations (Group 1) as compared by regression analysis with the number of cigarettes smoked per day (Panel A) and with the FTC-determined nicotine values (Panel B)
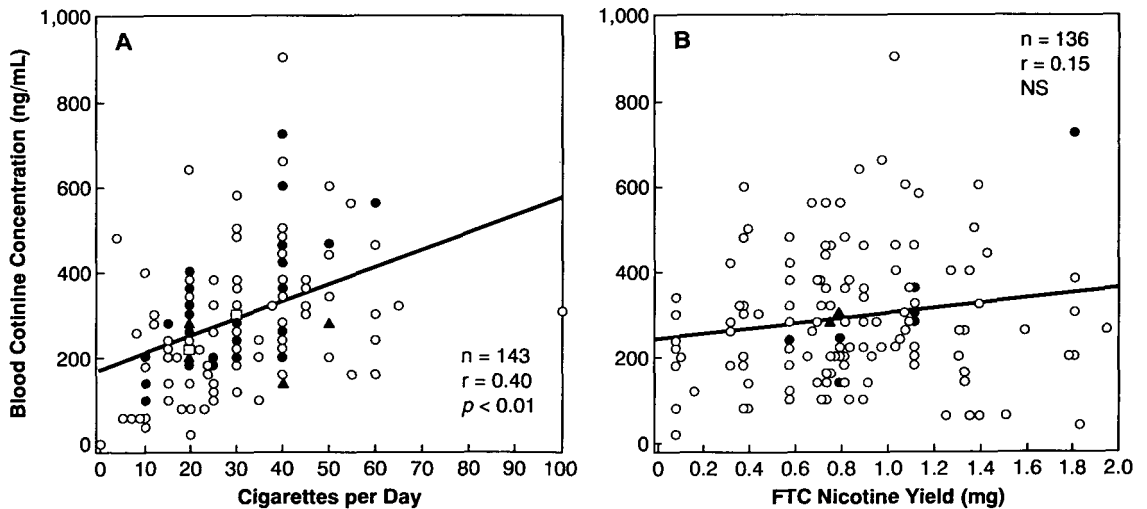
Note: *These smokers' values were so similar that plots of individual values overlapped. The total number of subjects shown in Panel B is lower because data for a few subjects were incomplete. Morning blood cotinine concentrations (Group 2, not shown) were on average slightly lower but had similar correlations with the number of cigarettes (r = 0.45) and the FTC yield (r = 0.06).*

Key: *NS = not significant; O = 1 observation; ● = 2 observations; ▲ = 3 observations; □ = 4 observations.*

Source: *Benowitz et al., 1983b.*

predicted nicotine intake and cotinine levels. But nicotine intake was calculated by Rosa and colleagues as the multiple of cigarettes per day times FTC yield. The strength of the relationship between this hybrid parameter and FTC yield derives primarily from the cigarettes-per-day term rather than from the FTC-yield term.

Figure 5 presents data by Gori and Lynch (1985) based on a population of more than 800 smokers recruited at shopping malls. These were not smokers who were trying to stop smoking. Plasma cotinine and nicotine concentrations were measured. The average cotinine concentration was about 300 ng/mL. Again, there was only a shallow slope in the relationship between FTC nicotine and cotinine level, with little difference in cotinine level comparing the lowest and the highest FTC nicotine yields.

Figure 5

Mean plasma nicotine and cotinine concentrations as a fraction of FTC nicotine yield of cigarettes smoked: n = 865
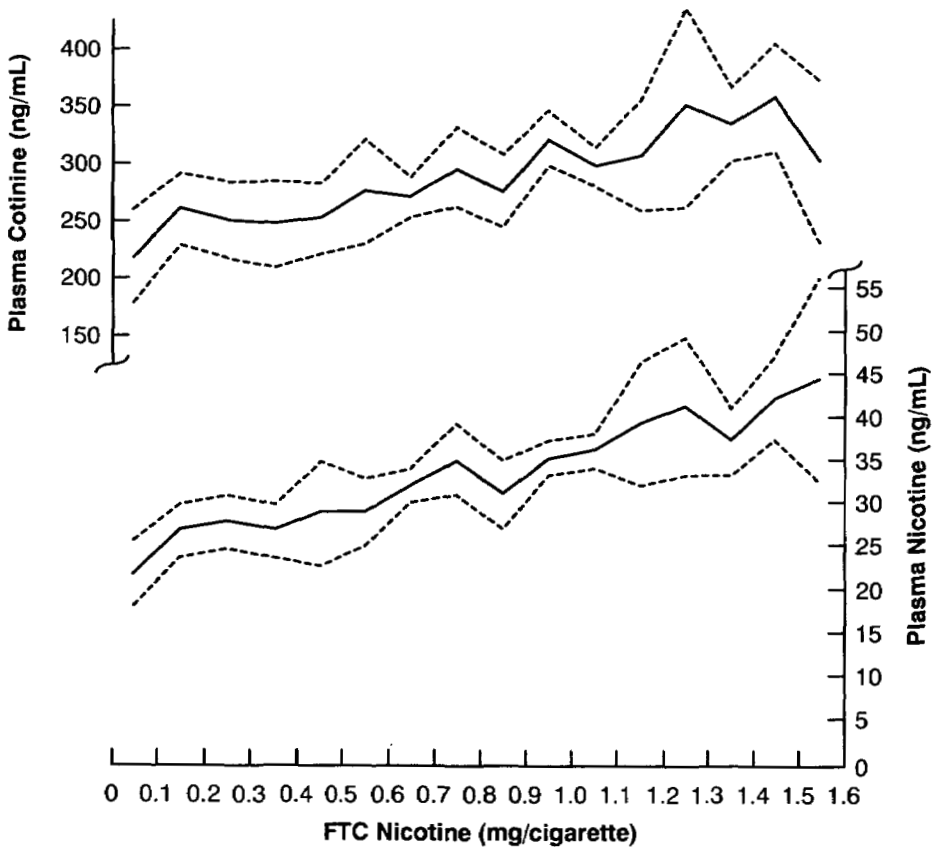
Key: *solid line = mean; broken line = 95-percent confidence intervals.*

Source: *Gori and Lynch, 1985.*

ULTRALOW-YIELD   Yields from the ultralow cigarette may differ from yields from
CIGARETTES   other cigarettes. Figure 6 shows data from another study of
smokers of cigarettes of different yields compared by category of FTC nicotine
(Benowitz et al., 1986b). The high-yield category was 1.0 mg of nicotine or
higher; the low was 0.60 to 0.99 mg; the very low was 0.20 to 0.59 mg; and
the ultralow was less than 0.20 mg nicotine per cigarette by FTC method.

Figure 6
**Expired carbon monoxide, plasma thiocyanate, blood nicotine, and cotinine
concentrations in 248 habitual smokers of cigarettes according to FTC yield**
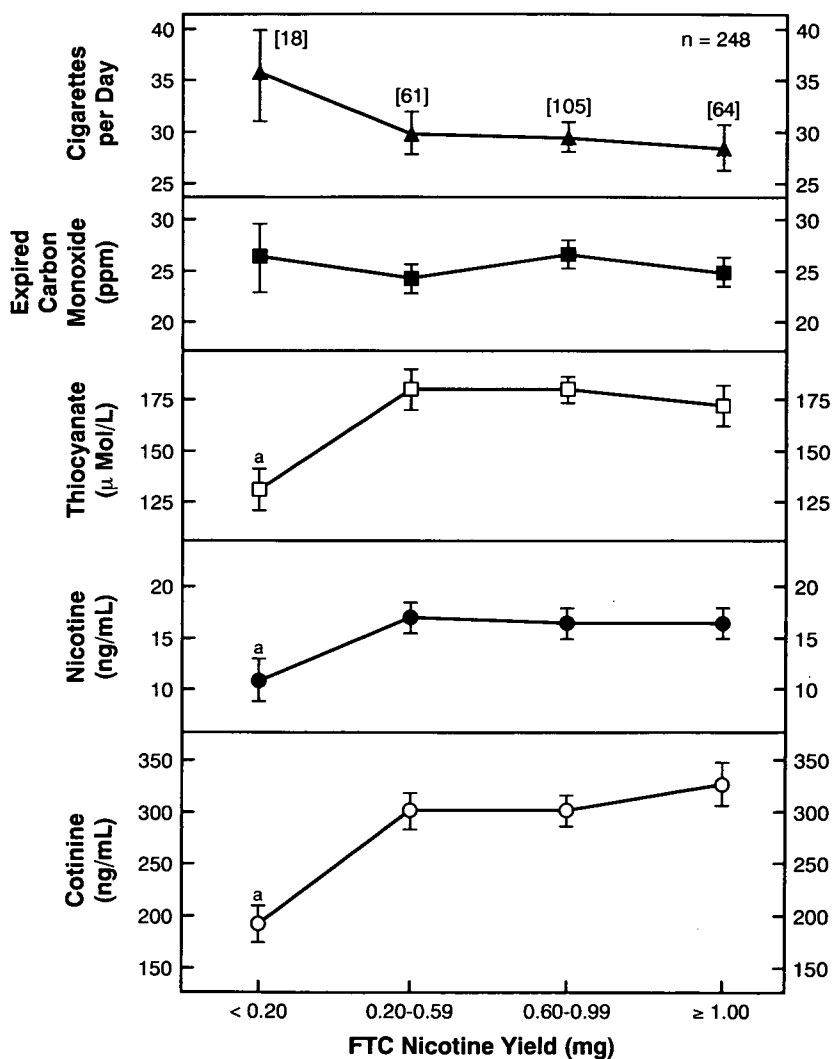
[a] *Significant difference compared with other yields.*

Key: ppm = parts per million.

Source: Benowitz et al., 1986b.

The ultralow cigarettes are typically rated 1 mg of tar or less. Smokers of ultralow-yield cigarettes smoked on average a few more cigarettes per day than other smokers. This appears to be one way in which these smokers are compensating for lower nicotine yields. Of note, carbon monoxide levels were similar for all yields. Thiocyanate, nicotine, and cotinine levels were the same for smokers of cigarettes with nicotine yields of 0.20 mg and higher. Only in the ultralow group was there any reduction in nicotine exposure, about 30 percent. Thus, cotinine levels produced by smoking ultralow-yield cigarettes, instead of averaging 300 ng/mL, averaged about 200 ng/mL. Gori and Lynch (1983) presented similar findings in a larger group of smokers. Smokers of the low-yield cigarette brand had the same mean cotinine levels as smokers of all other cigarette brands. In contrast, smokers of ultralow-yield cigarettes had lower cotinine levels, averaging about 200 ng/mL. Note that 200 ng/mL still corresponds to a daily intake of 16 mg of nicotine per day. If the FTC yield of 0.1 mg nicotine per cigarette were correct, one would need to smoke 160 cigarettes per day to achieve an intake of 16 mg. These smokers were not smoking 160 cigarettes per day. Thus, the FTC information on the ultralow-yield cigarette does not provide meaningful quantitative information, although there may be a difference between the ultralow- and higher yield cigarettes.

NICOTINE INTAKE AND MACHINE-DETERMINED YIELD
Table 2 provides a summary of several studies of nicotine intake vs. machine-derived yields. These are studies that have examined the relationship between FTC machine yield and nicotine intake measured either by cotinine concentrations or by nicotine concentration. Rickert and Robinson (1981) reported plasma cotinine concentrations vs. machine nicotine yield and found no relationship. Russell and coworkers (1980) studied 330 subjects and found a weak relationship between plasma nicotine concentration and yield. Benowitz and colleagues (1983b) studied 272 smokers interested in smoking cessation and found no significant relationship between plasma cotinine and yield. Ebert and coworkers (1983) found a shallow relationship between plasma nicotine and yield. Gori and Lynch (1985) found a very shallow slope with 865 subjects but also found significant relationships because of the large number of subjects. In a study by Benowitz and colleagues (1986b), cotinine concentrations were virtually the same for any cigarette with a yield of 0.2 mg and more and were a third less for the ultralow cigarettes. In a study by Russell and coworkers (1986), the 392 smokers studied showed a shallow relationship between cotinine level and nicotine yield. Rosa and colleagues (1992) found a shallow slope relating cotinine level vs. FTC yield, similar to that of other studies. However, when Rosa and coworkers (1992) combined cigarettes per day times FTC yield, they found a strong relationship, which they interpreted as supporting the utility of the machine test method. In 298 Hispanics, Coultas and coworkers (1993) showed findings similar to those of the other studies.

The Byrd and colleagues study (1995) was the only study with different results: thirty-three volunteers were asked to provide 24-hour urine samples in which nicotine and metabolites were measured. The nicotine intake was

Table 2
Studies of nicotine intake compared with machine nicotine yield

Study	Population	Nicotine Yields (mg)	Results
Rickert and Robinson, 1981	84 during routine medical exams	0.25-1.3	PCOT vs. Mach-N r = 0.08
Russell et al., 1980	330 from smokers' clinics or research volunteers	0.5-3.5	PNIC vs. Mach-N r = 0.21[a]
Benowitz et al., 1983b	272 seeking smoking cessation therapy	<0.1-1.9	BCOT vs. FTC-N r = 0.15 (n = 137) r = 0.06 (n = 123)
Ebert et al., 1983	76—mix of smoking cessation, hospital employees, ambulatory patients	0.1-1.5	PNIC vs. FTC-N r = 0.25[a]
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[a] PCOT vs. FTC-N r = 0.23[a]
Benowitz et al., 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 et al., 1986	392 from smokers' clinics	—	BCOT vs. Mach-N r = 0.13[a] BNIC vs. Mach-N r = 0.26[a]
Rosa et al., 1992	125 attending military medical center	0.38-1.38	BCOT vs. Mach-N r = 0.30
Coultas et al., 1993	298 from Hispanic household survey	—	SCOT vs. FTC-N r = 0.12
Byrd et al., 1995	33 volunteers	0.13-1.3	Urine N + metabolites vs. FTC-N N/24 hr: r = 0.68[a] N/cig: r = 0.79[a]

[a] $p < 0.05$.

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 FTC method; BNIC = blood nicotine concentration; SCOT = saliva cotinine concentration; N = nicotine.

taken on the basis of total recovery. This study found a strong relationship between yield and nicotine intake per cigarette per day that was totally different from any other study's findings. There are serious methodological concerns that might affect these conclusions. First, there were only 33 subjects, and recruitment procedures were unclear. In contrast, data already presented involving 2,000 individuals have shown a weak or no relationship between cotinine and FTC nicotine yields, so there is a problem of generalizability of the Byrd data. Second, an examination of particular data in the 1-mg tar group results in an average intake of 9 mg nicotine. However, the studies of Gori and Lynch (1985) and Benowitz and colleagues (1986b) showed an average cotinine concentration of 200 ng/mL for large groups of smokers of the same ultralow-yield cigarettes. A cotinine level of 200 ng/mL would correspond to an average daily intake of 15 or 16 mg, not the 9 mg reported by Byrd and colleagues (1995). Thus, even if only one group is studied, the subjects are not representative of the much larger numbers of subjects that have been studied by other investigators.

CARBON MONOXIDE AND FTC YIELD
Gori and Lynch (1985) have provided data on carbon monoxide levels in a large group of smokers of cigarettes of different yields (Figure 7). Their study and other studies have found virtually no relationship between carbon monoxide levels and FTC yields, even for the ultralow group. Thus, FTC carbon monoxide yield appears to be of no value in predicting human carbon monoxide exposure.

TAR-TO-NICOTINE RATIO
The tar-to-nicotine ratio also must be considered. Some authors have argued that even if there is only a small reduction of nicotine, because the machine tar-to-nicotine ratios are lower for low-yield cigarettes, there is a disproportionately greater overall health benefit due to reduced tar exposure (Russell et al., 1986). The question is whether machine-determined tar-to-nicotine ratios predict ratios of exposure in human smokers.

The author attempted to examine this question by studying mutagenic activity of urine by Ames test. This test involves culturing salmonella bacteria that are unable to generate histidine and therefore cannot grow. However, if the bacteria are mutated so that they can make histidine, they can grow. Growth can be quantitated by the number of colonies on a culture plate, and the number of colonies can be used as a measure of mutagenic activity of chemicals that were added to the salmonella culture before incubation. It is well known that the urine of cigarette smokers is mutagenic, presumably reflecting exposure to chemicals found primarily in cigarette smoke tar (Yamasaki and Ames, 1977).

Figure 8 shows urine mutagenicity data from one individual smoking his or her own brand of cigarettes who switched to a Camel (1 mg nicotine) cigarette, then switched to a True (0.4 mg nicotine) cigarette, and followed with a period of no smoking (abstinence). Urine mutagenicity was fairly stable for the individual, and there was no difference between smoking the Camel and True cigarettes.

Figure 7

Mean expired air carbon monoxide values as a function of FTC carbon monoxide yield of cigarettes smoked
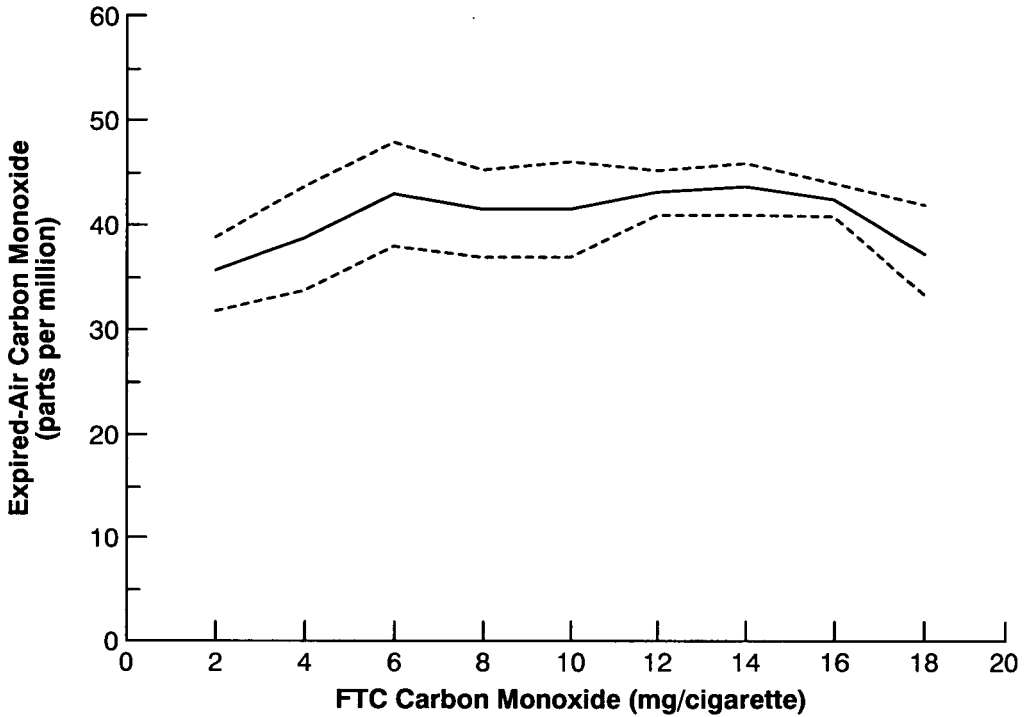

Key: *solid line = mean; broken line = 95-percent confidence intervals.*

Source: *Gori and Lynch, 1985.*

Figure 9 shows data from a crossover study of urine mutagenicity and nicotine intake from smokers smoking their own brand, high-yield (Camel), and low-yield cigarettes (True) (Benowitz et al., 1986b). The mutagenic activity of the urine was lower for both Camel and True compared with the usual brand, most likely because smokers did not like these other brands of cigarettes as much as they liked their own. However, the mutagenicity values for Camel and True were similar. The ratio of mutagenic activity over the 24-hour period under the nicotine plasma concentration-time curve (the latter being an estimate of daily nicotine intake) was used as a surrogate for tar-to-nicotine ratio and was the same in all conditions, although the machine-predicted ratios were 14.8 for smoker's own, 15.1 for Camel, and 11.5 for True. Thus, the in vivo tar-to-nicotine ratio did not correspond to differences in the machine-determined tar-to-nicotine ratios for different brands.

Figure 9 also shows similar data when switching to Carlton, which is an ultralow-yield cigarette. There was a small difference in the ratio of mutagenic

Figure 8
Urinary mutagenicity based on 24-hour urine collections in a habitual smoker smoking his or her own brand, Camel (high-yield), and True (low-yield) cigarettes
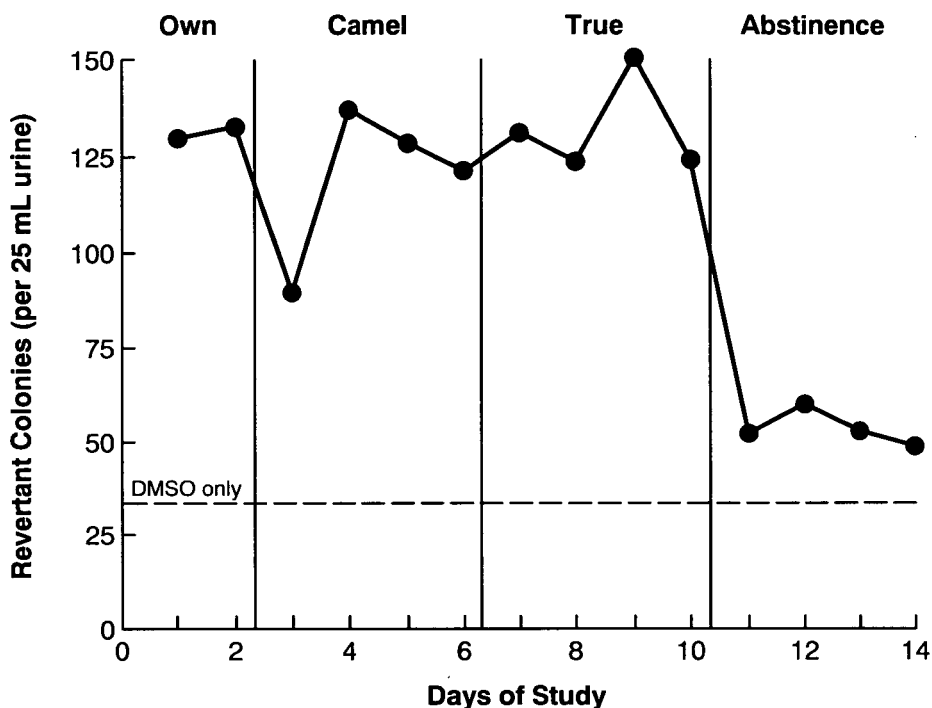
Note: *Mutagenic activity tends to be constant from day to day and falls to the DMSO control value (similar to that of nonsmokers) rapidly after stopping smoking.*

Key: *DMSO = dimethyl sulphoxide.*

Source: *Benowitz, 1989.*

activity to tar for Carlton compared with other cigarettes, but the difference was not near the values of 13.5, 15.4, and 7.3, which were predicted by FTC values.

The data of Rickert and Robinson (1981) shown in Table 3 explain the discrepancy between measured and predicted tar-to-nicotine ratios. These data, based on smoking machine tests, show that when cigarettes are smoked more intensely, the tar-to-nicotine ratio of low-yield cigarettes increases substantially. Thus, when smokers compensate for low-yield cigarettes by smoking them more intensely, the tar-to-nicotine ratio increases. Therefore, tar-to-nicotine ratios published by the FTC method cannot be used to make estimates of what the overall tar exposure will be for actual smokers.

CONCLUSIONS   The suggestion that there is a meaningful quantitative relationship between FTC-measured yields and actual intake is misleading. There do appear to be differences in nicotine exposure comparing high- vs. low-yield

Figure 9

Average urine mutagenicity and ratio of mutagenic activity to nicotine exposure for subjects in high-low yield (Group 1) and high-ultralow yield (Group 2) studies
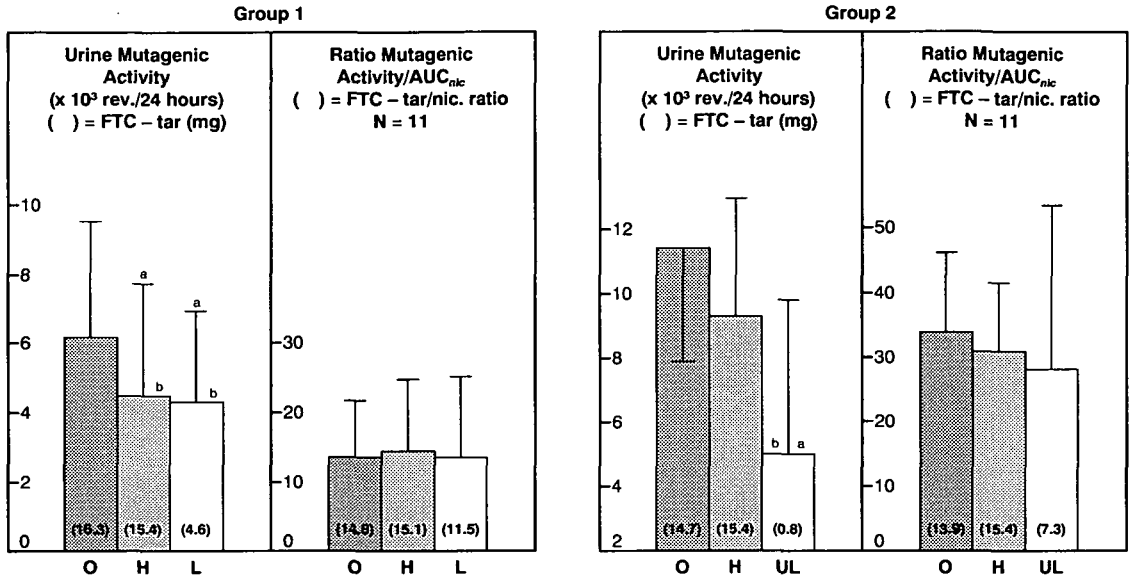
[a]Indicates significant difference (p < .05, repeated measures analysis of variance) compared with own brand.
[b]Indicates significant difference compared with high-yield cigarettes.

Note: Despite lower ratios of tar and nicotine based on FTC testing for low- and ultralow-yield cigarettes, ratios of mutagenic activity to nicotine exposure were not different while subjects smoked high-, low-, or ultralow-yield cigarettes. Also, bars indicate standard error of the mean.

Key: AUC_{nic} = ratio of mutagenic activity to nicotine exposure; rev = revertant colonies; nic = nicotine; O = smoker's own brand; H = high-yield cigarettes (Camel); L = low-yield cigarettes (True); UL = ultralow-yield cigarettes (Cambridge or Carlton).

Source: Benowitz et al., 1986b.

Table 3

Influence of intensity of smoking on tar-to-nicotine ratio, based on smoking machine studies

		Standard Yield (mg)		Tar-to-Nicotine Ratio Under Different Smoking Conditions		
Group	N	Tar	Nicotine	Standard	Moderate	Intensive
I	4	< 2	< 2	9.2	9.9	11.1[a]
II	10	2 - 5	0.2 - 0.5	10.3	11.7[a]	12.2[a]
III	8	5 - 10	0.5 - 0.9	11.3	11.9	12.6[a]
IV	9	10 - 14	0.8 - 1.0	12.7	13.3[a]	12.4
V	5	14 - 17	0.9 - 1.0	15.7	16.5[a]	14.7

[a] p < 0.05 compared with standard smoking machine conditions.

Key: N = number of brands tested.

Source: Rickert et al., 1983.

cigarettes, but the differences are small and not quantitatively proportional to nominal yield. Tar and nicotine ratings are poor predictors of human intake, except for those cigarettes that happen to be rated by smoking machines as 1 mg nicotine per cigarette, in which case that rating fortuitously fits the population average. Tobacco manufacturers have stated that the FTC method was never intended to measure intake in any individual. The author agrees. However, data for 2,000 people summarized here indicate that the FTC method does not work for the general population of smokers either.

In general, the FTC method underestimates human exposure. Smoking-machine-derived tar-to-nicotine ratios, which have been used to argue the benefit of switching to low-yield cigarettes, are not of value because these ratios change with changes in smoking behavior. On the other hand, because there is some relationship between yields and nicotine, and although the slope of that relationship is shallow, it is not recommended that smokers regress to smoking higher yield cigarettes.

QUESTION-AND-ANSWER SESSION

DR. RICKERT: When we first looked at this back in 1981, there was absolutely no relationship between yields and uptake as measured by cotinine. And then, as you follow the studies from 1981 through to 1994, there seems to be a growing tendency toward an association of some sort, and at the end you pointed out there was a shallow slope. Is this just a spurious change with time, or do you feel this may be related to changes in product characteristic because, obviously, the product that was smoked in 1981 is not the product that is smoked in 1994.

DR. BENOWITZ: Yes, when you look at the earlier studies, they show basically the same slope that studies that were done in 1989 and 1990 are showing. So, I think when we have a large enough population, we are probably seeing it even back in the 1980's. Prior to that, I have no idea.

DR. BOCK: Dr. Benowitz, you were quoted as saying something to the effect that compensation over the long term does not appear to be persistent. Is that your opinion?

DR. BENOWITZ: That statement was made in dealing with the question of when people are shifting from one cigarette to a lower yield cigarette, will there be permanent overcompensation? And the only studies that I found (I think Dr. Kozlowski is going to talk about these) looked at carbon monoxide levels and the amount of compensation. At least in one study, carbon monoxide levels went up and then went down again.

But if you look at the issue of compensation broadly, how do you interpret the fact that people smoke a cigarette with an FTC yield of .2 the same as the one that has the FTC nicotine yield of 1.5, and they have the same nicotine cotinine levels? If you do not call it compensation, you have to think of something to call it.

At some point in time, I do think people will be limited by how much smoke they take into their lungs. I do not think it is relevant to modern cigarettes as currently marketed, but it could be relevant to a low-nicotine cigarette.

DR. BOCK: You made a distinction just now and said "overcompensation." Is that what you intend to imply?

DR. BENOWITZ: Yes.

DR. BOCK: Because there is a little bit of a difference between overcompensation and compensation.

DR. BENOWITZ: Yes, I know. It is a good point.

DR. HATSUKAMI: In the studies where you looked at the FTC yield and the actual intake, have any of the studies differentiated people who actually initiated with low-tar and low-nicotine cigarettes and those who switched? Are there any differences in terms of slopes between those two groups of people?

DR. BENOWITZ: I have never seen that, but obviously that is a very interesting question in terms of initiation. The earlier data that we heard from Dr. Giovino suggest that most low-yield cigarette smokers are people who switched from higher yield, which I think is quite interesting. But I do not know the percentage of people who start with low-yield cigarettes. It would be a good question.

DR. DEBETHIZY: Would you say that, on average, the people who smoke lower yielding cigarettes absorb less nicotine?

DR. BENOWITZ: Yes, but the slope is very shallow.

DR. DEBETHIZY: So, if people are smoking very low-yielding cigarettes, they are absorbing less nicotine and the data do speak to that. So, compensation is incomplete; there is not a flat line.

One of the studies that you pointed out up there said that people absorbed, on average, 1 mg of nicotine from cigarettes. And I think that it is important to point out that people who smoke lower yielding cigarettes do absorb less nicotine.

DR. BENOWITZ: Yes, although it is unclear where the break is. Some of our data have suggested that the break is actually with the very, very low-yield cigarettes, rather than the cigarettes most people smoke. But I would accept the fact that there is a shallow relationship. Understand, however, that you are talking about a 10-percent variation in nicotine intake, going across yields from 0.1 to 1.6. So, there is some reduction in nicotine intake per cigarette on average, but it is very small.

DR. DEBETHIZY: The other point I want to make is, you do rightfully point out that I will discuss a little later why our study, which is the Byrd study, may be unique from the plasma cotinine studies, in the fact that it is done

with a completely different method and what we think is a more precise method.

DR. WOOSLEY: I think the point you make is that the predictive accuracy of any yield numbers, except at the low end of the scale, is useless, and I think that is the most important message that I got out of your presentation.

The other message I have gotten out of the presentation was that this indicates that the differences in mortality that we saw earlier, which had the potential to be confounded, are very likely to be confounded because of the lack of a difference in exposure that your data indicate.

DR. BENOWITZ: I would certainly agree with that. On the coronary heart disease data, for example, with the low-yield cigarettes, I think you can virtually assume that their exposure to everything was substantially the same. It is no surprise that there is no protective effect of smoking low-yield cigarettes for heart disease.

DR. RICKERT: How relevant do you feel the absorption of nicotine is to the levels of other harmful constituents, such as benzo(*a*)pyrene and biphenyl, which are probably more related to disease processes than nicotine per se?

DR. BENOWITZ: I think there is considerable variability, and one has to look at that issue. I don't think there are enough data to know for the range of products.

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