Doses of Nicotine and Lung Carcinogens Delivered to Cigarette Smokers

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Background: Cigarette smoke yields of tar and nicotine obtained under the Federal Trade Commission (FTC)-specified machine-smoking protocol (35-mL puff volume drawn for 2 seconds once per minute) may not accurately reflect the delivery of toxins and carcinogens to the smoker. We conducted this study to obtain more realistic estimates of exposure to components of cigarette smoke that affect lung cancer risk. Methods: We used a pressure transducer system to evaluate puffing characteristics for 133 smokers of cigarettes rated by the FTC at 1.2 mg of nicotine or less (56 smokers of low-yield cigarettes [≤0.8 mg of nicotine per cigarette] and 77 smokers of medium-yield cigarettes [0.9–1.2 mg of nicotine per cigarette]). We programmed measurements from a randomly chosen subset of 72 of these smokers into a piston-type machine to generate smoke from each smoker’s usual brand of cigarettes for assays of nicotine, carbon monoxide, tar, and the lung cancer-causing agents 4-(methylamino)-1-(3-pyridyl)-1-butanone and benzo[a]pyrene. The FTC protocol was also used to assess levels of targeted components in the 11 brands most frequently smoked by study subjects. Results: Compared with the FTC protocol values, smokers of low- and medium-yield brands took in statistically significantly larger puffs (48.6 and 44.1 mL, respectively) at statistically significantly shorter intervals (21.3 and 18.5 seconds, respectively), and they drew larger total smoke volumes than specified in the FTC parameters. They received, respectively, 2.5 and 2.2 times more nicotine and 2.6 and 1.9 times more tar than FTC-derived amounts, as well as about twofold higher levels of benzo[a]pyrene and 4-(methylamino)-1-(3-pyridyl)-1-butanone. Smokers of medium-yield cigarettes compared with smokers of low-yield cigarettes received higher doses of all components. Conclusions: The FTC protocol underestimates nicotine and carcinogen doses to smokers and overestimates the proportional benefit of low-yield cigarettes. Thus, FTC-based nicotine medication doses prescribed/recommended for smoking cessation may need to be reassessed. [J Natl Cancer Inst 2000;92:106–11]
The effect of these behavioral adaptations on lung cancer risk is not readily evaluated because of the difficulty in measuring the doses of the carcinogens in cigarette smoke actually inhaled by the smoker and because of the necessity of relating those doses to metabolic biomarkers of carcinogen uptake. Few such dose measurements have been reported. The amount of tar and nicotine in cigarette smoke is commonly reported on the basis of standardized laboratory procedures that conform to the FTC machine-smoking protocol. This protocol specifies that each cigarette be machine smoked to a standard butt length by use of a 35-mL puff volume drawn over 2 seconds at a rate of one puff per minute (21,22). This smoking pattern may have approximated the habits of consumers who smoked nonfilter, nicotine-rich (>2 mg) cigarettes in the 1930s when machine-smoking methods were first standardized (23–25). However, studies in our own (26–29) and in other (29,30) laboratories have shown that, on average, smokers of contemporary cigarettes with an average yield of 0.9 mg of nicotine per cigarette (from the FTC method) are more likely to draw 50-mL puffs at the rate of two to three puffs per minute. The total volume of smoke thus generated and, consequently, the body burden of smoke toxins and carcinogens may differ substantially from the amounts produced under the FTC protocol.

This study was undertaken to determine how the dose delivered to the smoker relates to the nominal FTC yield and whether this delivered dose differs meaningfully between smokers of low- and medium-yield cigarettes. These low- and medium-yield cigarettes now account for more than 80% of all brands consumed in the United States. Our secondary goal was to assess whether intake of BaP and NNK differed between smokers of low-yield and medium-yield cigarettes. These data should help in the evaluation of proposed revisions to the existing FTC protocol for generating tar, nicotine, and carbon monoxide yields in cigarette smoke (31).

METHODS

Study Population and Procedures

One hundred thirty-three current smokers, between 18 and 59 years of age, were recruited in Westchester County, NY, through advertisements in local newspapers. Eligibility was determined in a brief telephone interview. Subjects had to have smoked only cigarettes with FTC-rated nicotine yields of less than 1.2 mg for at least 3 years and to have smoked their current brand for at least 1 year before enrollment. They had to be in good health, with no history of any tobacco-related disease, and could not be taking any medication for depression or cardiovascular diseases.

Each volunteer signed an informed consent form that was approved by the Institutional Review Board of the American Health Foundation (Valhalla, NY) and was paid for participation in the study. Eligible subjects were interviewed in our laboratories by a trained interviewer who used a structured questionnaire to obtain a detailed smoking history and data on occupational exposures, diet, family medical history, and other lifestyle factors. The smoking history included the age at onset of smoking, the brand name and type of cigarettes (length and whether filter-tipped, menthol, hard pack, or soft pack), and, for every brand smoked, the quantity of cigarettes and the number of years of smoking. Detailed brand information was needed to assign the correct FTC smoke yield because several cigarette varieties with different FTC yields are marketed under the same brand name. Subjects were asked to demonstrate how they hold the cigarette while puffing to determine whether they block filter-tip vents with fingers or lips. Questions required for calculation of the Fagerstrom index for nicotine dependence were also asked (14,32). Height and weight were measured to permit calculation of body mass index (weight in kilograms divided by the square of the height in meters). Each participant was given a 4-day supply of his or her own cigarette brand and instructions on how to collect cigarette butts that were to be brought back to the laboratory. The returned butts were used to validate the subject’s self-reported number of cigarettes smoked per day, to estimate the average length of cigarette usually smoked, and to evaluate whether or not air vents on the filter tips were blocked during smoking. The number of self-reported and actual cigarettes per day, as determined by the number of cigarette butts, correlated well (r = .95), indicating reasonably accurate reporting by study participants. Filter blocking is important because some smokers of low-yield cigarettes block the air flow through the ventilation holes on the filter tips by lips or fingers to increase uptake of nicotine to a desired level (17,33). The degree of blocking filter vents was determined by observation using the so-called “bull’s-eye” method (33), whereby blocking is determined by observing the circular pattern of the “tar” stain at the filter tip when viewed end-on. A completely stained surface indicates complete blocking, a smaller circular stain at the center of the tip with white on the periphery (the bull’s-eye) indicates no blocking, and incomplete staining of the bull’s-eye indicates partial blocking.

The length of cigarette smoke was used to assess smoking topography, defined as the physical characteristics of smoke inhalation including puff volume, duration, frequency, and interval between puffs. Each smoker was asked to extinguish the cigarette when it reached a mark that corresponded to the usual butt length, as determined by averaging the lengths of the cigarette butts collected from that individual. This average length also served to guide the machine smoking of cigarettes that corresponded to the parameters of the same individual.

Assessment of Smoking Topography

Smoking topography was ascertained with the Tobacco Smoke Inhalation Testing System (26,27), a microcomputer-assisted flow transducer that determines the flow of smoke from a lit cigarette as it is smoked by measuring the pressure difference between two sites within an orifice flow meter (34). We used this apparatus to evaluate 56 smokers of low-yield cigarettes (25 men and 31 women) and 77 smokers of medium-yield cigarettes (38 men and 39 women). Each subject smoked his or her regular cigarette brand twice with the Tobacco Smoke Inhalation Testing System, which records the foregoing topographic parameters for each puff, their average values per cigarette, and the total volume of smoke delivered per cigarette. Before smoking, each individual’s cigarette was inserted in the holder with open or covered ventilation holes on the filter tip according to the smoker’s usual habit. Smoking was halted when the cigarette glow reached a mark that was determined from the average measured butt length for that individual. After smoking a cigarette with the Tobacco Smoke Inhalation Testing System, the smoker was asked to exhale into a carbon monoxide breath analyzer (Vitalograph BreathCO; Vitalograph Inc., Lenexa, KS). Ten minutes later, the breath analysis was repeated. When the subject indicated readiness to smoke a second cigarette, the Tobacco Smoke Inhalation Testing System was again used to record all parameters. Carbon monoxide in exhaled breath was measured immediately after taking the last puff of the second cigarette and again 10 minutes later. The subject later smoked a third cigarette normally, without using the Tobacco Smoke Inhalation Testing System. The correlation between carbon monoxide levels obtained with the two modes of smoking was very high (r = .98). This suggests that the smoking parameters determined by the Tobacco Smoke Inhalation Testing System truly reflect human smoking and are not artifacts attributable to the laboratory smoking environment. To minimize diurnal variation in smoking habits, appointments were scheduled for early afternoon (usually between 1 and 2 PM). Reproducibility of the Tobacco Smoke Inhalation Testing System data was assessed by evaluating the coefficient of variation in the smoking topography measurements for three smokers. By use of the Tobacco Smoke Inhalation Testing System, subject E21/4 smoked his customary low-yield cigarette four times on the same day, subject E26/69 smoked his customary medium-yield cigarette five different days over a 4-month period, and subject E21/1 smoked his medium-yield cigarette on different days over a 9-month period. The coefficient of variation for the puff volume was not greater than 10% for any of these individuals, and the coefficient of variation for the number of puffs per cigarette ranged from zero for one smoker to 14.0% and 15.6% for the two other smokers. The frequency with which puffs were drawn during smoking showed a greater degree of variation, i.e., between 14.0% and 21.4%. However, intra-subject variation of the total volume of smoke inhaled did not exceed 10.1%, indicating that the assessment of smoking patterns by the Tobacco Smoke Inhalation Testing System reliably reflected the behavior of smokers of low-yield filter cigarettes (27,28).

Machine Smoking of Cigarettes

The average smoking parameters per cigarette from two recordings with the Tobacco Smoke Inhalation Testing System for each individual were pro-
grammed into a one-channel, piston-type smoking machine, and then cigarettes were smoked under conditions simulating the smoking habits of each subject for his or her customary cigarette brand. Special attention was paid to open or blocked filter vents during machine smoking. Before machine smoking, cigarettes were inserted into the holder with the vent holes open or inserted with the vents that were blocked fully or partially with invisible tape. Cigarettes were smoked to the butt length that was determined for each individual from the 4-day collection of butts.

Mainstream Smoke Assays

The mainstream smoke generated via the smoking machine programmed with topographic smoking parameters from individual study participants was analyzed for tar, nicotine, carbon monoxide, BaP, and NNK, as described elsewhere (35–45). Each compound of interest was assayed in triplicate in the smoke collected from the smoking of four cigarettes under parameters obtained for each participant studied. For these assays, a group of 72 study participants, consisting of 30 smokers of low-yield cigarettes and 42 smokers of medium-yield cigarettes, was chosen at random from the pool of 133 smokers (56 smokers of low-yield cigarettes [≤0.8 mg of nicotine per cigarette] and 77 smokers of medium-yield cigarettes [0.9–1.2 mg of nicotine per cigarette]). We also measured smoke yields under FTC conditions of the 11 brands of cigarettes most frequently smoked by study subjects to obtain yields of BaP and NNK, which are not reported by the FTC.

Statistical Evaluation

Our primary hypotheses for this study were as follows: 1) that the actual amount of tar and nicotine taken in by smokers statistically significantly exceeded the measured levels based on FTC machine smoking of cigarettes and 2) that the actual volume, duration, and frequency of smoke inhalation differed statistically significantly from the values obtained by use of the protocol prescribed by the FTC for machine smoking.

We tested the first hypothesis by comparing FTC mainstream smoke yields of tar and nicotine with amounts derived from machine smoking of identical cigarettes according to the topographic parameters determined for each smoker. Comparisons were restricted to those participants for whom both sets of measurements were available and are reported separately for smokers of low- and medium-yield cigarettes. The statistical significance of the difference between levels of smoke components measured by use of human versus FTC-prescribed smoking topographies was evaluated with paired two-tailed Student’s t tests, after the logarithmic transformation of the dependent variables.

We tested the second hypothesis with one-sample, two-tailed Student’s t tests to evaluate the differences between the observed values and the values from the FTC protocol for puff volume, puff duration, and puff interval. The statistical significance of the differences was evaluated with a Student’s t distribution, and the analyses were carried out separately for smokers of low- and medium-yield cigarettes after logarithmic transformation of the data.

All P values were subsequently adjusted for 10 multiple comparisons through a Bonferroni’s adjustment. In addition, secondary hypotheses were explored only through summary statistics. Data for carbon monoxide are shown for comparative purposes because carbon monoxide is the only other mainstream smoke component that is routinely reported by the FTC. However, independent statistical comparisons were not performed for carbon monoxide, which is highly correlated with levels of tar and nicotine. Because the majority of the variables originally were not normally distributed, all data were subjected to logarithmic transformation and, therefore, are presented as the geometric mean and its 95% confidence interval (CI). The majority of all variables examined and all measures included in the primary hypothesis testing were normalized by logarithmic transformation. All P values are two-sided.

RESULTS

Age and smoking habits of study participants are presented separately for smokers of low- and medium-yield cigarettes in Table 1. The two groups were similar in current age, age at smoking onset, duration of smoking, number of cigarettes smoked per day, and Fagerström index but differed (by design) in the average FTC-rated amounts of nicotine, tar, and carbon monoxide from the cigarettes usually smoked (0.7, 8.5, and 9.7 mg in the low-yield group and 1.1, 15.4, and 14.6 mg in the medium-yield group, respectively).

In Table 2, the smoking patterns of smokers of FTC-rated low- and medium-yield cigarettes are compared. Furthermore, these patterns are contrasted with the values obtained from the FTC machine-smoking protocol itself. These variables did not differ substantially between the two groups of smokers, except that total volume of smoke per cigarette was 18% greater for

### Table 1. Characteristics of smokers by type of cigarette as defined by Federal Trade Commission (FTC) ratings of current cigarettes

<table>
<thead>
<tr>
<th>Characteristic of smoker or cigarette</th>
<th>Low-yield cigarettes (n = 56 smokers; ≤0.8 mg of nicotine/cigarette)</th>
<th>Medium-yield cigarettes (n = 77 smokers; 0.9–1.2 mg of nicotine/cigarette)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC nicotine, mg/cigarette</td>
<td>0.7 (0.6–0.8)</td>
<td>1.11 (1.09–1.13)</td>
</tr>
<tr>
<td>FTC tar, mg/cigarette</td>
<td>8.5 (7.7–9.5)</td>
<td>15.4 (15.0–15.8)</td>
</tr>
<tr>
<td>FTC carbon monoxide, mg/cigarette</td>
<td>9.7 (9.0–10.4)</td>
<td>14.6 (14.2–14.9)</td>
</tr>
<tr>
<td>Age, y</td>
<td>34.1 (31.3–37.2)</td>
<td>34.7 (32.5–37.1)</td>
</tr>
<tr>
<td>Age at onset of smoking, y</td>
<td>15.9 (15.1–16.8)</td>
<td>15.4 (14.6–16.3)</td>
</tr>
<tr>
<td>Total years of smoking</td>
<td>15.7 (13.0–19.1)</td>
<td>17.1 (14.8–19.8)</td>
</tr>
<tr>
<td>Current No. of cigarettes smoked/day</td>
<td>14.9 (13.1–16.9)</td>
<td>15.9 (14.3–17.8)</td>
</tr>
<tr>
<td>Fagerström index*</td>
<td>3.3 (2.3–4.8)</td>
<td>3.8 (2.7–5.3)</td>
</tr>
</tbody>
</table>

*Data for low- and medium-yield cigarettes are the geometric mean (95% confidence interval). The FTC protocol specifies a 35-mL 2-second puff once per minute.

†Fagerström index (32) is a test of nicotine dependence.

### Table 2. Smoking characteristics observed in 133 smokers and values from the Federal Trade Commission (FTC) protocol for machine smoking of cigarettes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Observed value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-yield cigarettes (n = 56 smokers; ≤0.8 mg of nicotine/cigarette)</td>
</tr>
<tr>
<td>Puff volume, mL†</td>
<td>48.6 (45.2–52.3)</td>
</tr>
<tr>
<td>Puff duration, sec</td>
<td>1.5 (1.4–1.7)</td>
</tr>
<tr>
<td>Puff interval, sec</td>
<td>21.3 (19.0–23.8)</td>
</tr>
<tr>
<td>Puff No.</td>
<td>12.7 (11.8–13.6)</td>
</tr>
<tr>
<td>Total volume, mL/cigarette</td>
<td>615 (566–668)</td>
</tr>
<tr>
<td>Total volume, L/day</td>
<td>9.5 (8.0–11.2)</td>
</tr>
<tr>
<td>Blocked filter vents, %</td>
<td>21</td>
</tr>
</tbody>
</table>

*Data for low- and medium-yield cigarettes are the geometric mean (95% confidence interval). The FTC protocol specifies a 35-mL 2-second puff once per minute.

†Puff volume measurements were from 47 smokers of low-yield cigarettes and 71 smokers of medium-yield cigarettes.

‡Varies with length of cigarette smoked.
smokers of low-yield cigarettes than for the total volume from medium-yield cigarettes. However, this was partially compensated by a slightly greater average number of cigarettes smoked per day by individuals in the latter group, resulting in a similar daily total smoke volume for both groups. Similar proportions of low- and medium-yield smokers blocked the vents of their cigarette filters.

Table 2 also shows that the values of topographic parameters prescribed by the FTC for machine smoking differed markedly from the values measured in smokers of both types of cigarettes. For example, the average volume of smoke taken in with each puff by smokers of low- and medium-yield cigarettes differed very little (48.6 versus 44.1 mL, respectively). However, both were statistically significantly higher than the FTC puff volume of 35.0 mL ($P<.001$). More than three fourths of the smokers of both types of cigarettes drew puffs greater than 35.0 mL. Furthermore, more than two thirds of the smokers puffed more frequently. Compared with the values specified by the FTC protocol, our subjects had shorter puff durations (1.5 versus 2 seconds), puffed at much more frequent intervals (19–21 versus 58 seconds), took more puffs per cigarette (12 or 13 versus 8–10 puffs), and inhaled a considerably greater total volume of smoke per cigarette (523–615 mL versus 280–350 mL, respectively). None of the FTC values fell within the 95% CIs of the corresponding smoking parameters that we measured in smokers of either cigarette type.

In Table 3, we compare the “delivered doses” per cigarette of nicotine, tar, and carbon monoxide measured in smokers of low- and medium-yield cigarettes with the corresponding FTC values. The FTC values for nicotine, tar, and carbon monoxide were from the annual FTC listings published for each cigarette variety used by our subjects. Average yields are shown per cigarette and per day; the per-day amount for each smoker was obtained by multiplying the per-cigarette yield by the number of cigarettes smoked per day, as observed from a 4-day collection of butts.

Table 3 also shows that, on a per-cigarette basis, the ratio of measured values to FTC values ranged from 2.2 to 2.5 for nicotine and from 1.9 to 2.6 for tar.

In Table 4, we show delivered doses of BaP and NNK delivered to smokers in this study. We also measured BaP and NNK concentrations in mainstream smoke with the FTC protocol by machine smoking the six most popular low-yield brands and the five most popular medium-yield brands. The delivered dose ranged from 60% to 80% higher than the FTC dose. There was no overlap between the 95% CIs of delivered dose and the FTC dose for NNK in smokers of either type of cigarette or for BaP intake in low-yield smokers. There was, however, a small overlap of 95% CIs for BaP intake in medium-yield smokers.

The average delivered dose of BaP was slightly higher to smokers of medium-yield cigarettes than to smokers of low-yield cigarettes, but the doses of NNK were far higher.

**DISCUSSION**

Our data show that low- and medium-yield cigarettes deliver to the smoker, respectively, between 2.6 and 1.9 times the amount of tar and 2.5 and 2.2 times the amount of nicotine obtained by smoking these cigarettes under FTC machine-smoking conditions. Although the brands smoked by study participants are not necessarily representative of all low- and medium-yield cigarettes, they encompass a range of nicotine that accounts for about 80% of all cigarettes smoked in the United States. The absence of meaningful differences between the way smokers of low- and medium-yield cigarettes smoke suggests that the differences in delivered doses between these two groups must be related to the differences in the cigarettes themselves, such as tobacco blends or physical properties of materials used in manufacturing [e.g., cigarette paper porosity and filter-tip ventilation (7–10)].

On a per-cigarette basis, smokers of medium-yield cigarettes received higher doses of nicotine and tar and, more important,
also BaP and NNK than did smokers of low-yield cigarettes. When administered to rodents, NNK elicits adenocarcinoma and BaP evokes squamous cell carcinoma of the lung (46); these are the two most common histologic types of lung cancer in humans (11). Per-cigarette dose is important, especially for nicotine, because it strongly affects the smoker’s behavior and, therefore, intake of carcinogens. However, the daily dose received by smokers may be a more relevant indicator of cancer risk. The measured daily amounts of nicotine, tar, and carbon monoxide were 1.7–2.7 times as great as the corresponding FTC method-based daily dose. (Nicotine nasal spray differs from other recently marketed nicotine medications in that nicotine is absorbed rapidly per day. (Nicotine nasal spray differs from other recently marketed nicotine medications in that nicotine is absorbed rapidly per day, respectively). This supports a finding by Benowitz et al. (47) who showed that individuals who smoked 16 cigarettes per day had twice as much nicotine and cotinine in plasma as individuals who received 24 1-mg doses of nicotine in nasal spray per day. (Nicotine nasal spray differs from other recently marketed nicotine medications in that nicotine is absorbed rapidly from the nose and produces psychologic effects that resemble effects of an equal dose of inhaled cigarette smoke.) Our observations suggest a need to re-evaluate the doses of nicotine that are recommended in smoking cessation programs and of nicotine-based medications for the treatment of nicotine addiction (14).

Our data strongly support the conclusion of the Expert Committee from the National Cancer Institute (48) that FTC listings of tar and nicotine, which have been published since 1967, do not offer the public sound information on which to base critical decisions with regard to health risks. This conclusion was based in part on the recognition that human smoking conditions differ considerably from the parameters of the FTC smoking-machine protocol. Although nothing in the listings themselves encourages smokers to engage in “comparison shopping” for lower risk cigarettes, such comparisons by unwary smokers are inevitable. The FTC recently proposed a major revision to the protocol (31) that specifies more intense puffing conditions (56-mL puff volume, 2-second puff duration, 26-second puff interval, and blocking air vents on the filter tips of cigarettes), conditions that reflect human smoking more realistically than the current protocol. The FTC proposal needs to be evaluated by use of realistic human smoking data generated by methods such as those used in this study. Although low-yield cigarettes delivered lower levels of carcinogens to the smoker than did medium-yield cigarettes, the proportional reductions expected of the former were less than would be predicted by the FTC ratings. In other words, a smoker who uses the FTC ratings to choose a brand of cigarettes with lower amounts of carcinogenic agents will not achieve the reduction anticipated. It is, therefore, somewhat misleading to use published FTC tar and nicotine ratings as a guide for risk assessment of the potential carcinogenicity of low-yield cigarettes.

Finally, regulation of the levels of nicotine, tar, and other harmful constituents in tobacco smoke frequently figures in broader proposals for regulation of tobacco products. Any proposal that would regulate the concentrations of constituents in mainstream cigarette smoke needs to be cognizant of their strong dependence on the measurement protocol used.

**REFERENCES**
