Reconciling Human Smoking Behavior and Machine Smoking Patterns: Implications for Understanding Smoking Behavior and the Impact on Laboratory Studies

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Abstract

Background: Recent Food and Drug Administration legislation enables the mandating of product performance standards for cigarette smoke and the evaluation of manufacturers’ health claims for modified tobacco products. Laboratory studies used for these evaluations and also for understanding tobacco smoke toxicology use machines to generate smoke. The goal of this review is to critically evaluate methods to assess human smoking behavior and replicate this in the laboratory. Methods: Smoking behavior and smoking machine studies were identified using PubMed and publicly available databases for internal tobacco company documents. Results: The smoking machine was developed to generate smoke to allow for comparing cigarette tar and nicotine yields. The intent was to infer relative human disease risk, but this concept was flawed because humans tailor their smoking to the product, and chemical yields and toxicologic effects change with different smoking profiles. Although smoking machines also allow for mechanistic assessments of smoking-related diseases, the interpretations also are limited. However, available methods to assess how humans puff could be used to provide better laboratory assessments, but these need to be validated. Separately, the contribution of smoke mouth-holding and inhalation to dose need to be assessed, because these parts of smoking are not captured by the smoking machine. Better comparisons of cigarettes might be done by tailoring human puff profiles to the product based on human studies and comparing results across regimens. Conclusions: There are major research gaps that limit the use of smoking machine studies for informing tobacco control regulation and mechanistic studies. (Cancer Epidemiol Biomarkers Prev 2009;18(12):3305–20)

Introduction

In June 2009, the Food and Drug Administration (FDA) received regulatory authority over tobacco products. The FDA is now empowered to develop product performance standards and evaluate manufacturers’ health claims for modified tobacco products. Laboratory studies used for these evaluations and also for understanding tobacco smoke toxicology use machines to generate smoke. The goal of this review is to critically evaluate methods to assess human smoking behavior and replicate this in the laboratory. Smoking behavior and smoking machine studies were identified using PubMed and publicly available databases for internal tobacco company documents. The smoking machine was developed to generate smoke to allow for comparing cigarette tar and nicotine yields. The intent was to infer relative human disease risk, but this concept was flawed because humans tailor their smoking to the product, and chemical yields and toxicologic effects change with different smoking profiles. Although smoking machines also allow for mechanistic assessments of smoking-related diseases, the interpretations also are limited. However, available methods to assess how humans puff could be used to provide better laboratory assessments, but these need to be validated. Separately, the contribution of smoke mouth-holding and inhalation to dose need to be assessed, because these parts of smoking are not captured by the smoking machine. Better comparisons of cigarettes might be done by tailoring human puff profiles to the product based on human studies and comparing results across regimens. There are major research gaps that limit the use of smoking machine studies for informing tobacco control regulation and mechanistic studies. (Cancer Epidemiol Biomarkers Prev 2009;18(12):3305–20)
methods preclude an estimation of human exposure and toxicologic effects, challenging new regulatory processes. The best example of the flawed use of the smoking machine relates to the earlier assumptions that reduced tar and nicotine yield cigarettes (as ranked based on data obtained by standard FTC/ISO machine-smoking method), the so-called “lights,” were less harmful than higher yield cigarettes (13). Almost 3 decades ago, the public health community advocated that for smokers who could not or would not quit to switch to lower tar yield cigarettes, for example as recommended by the Surgeon General (14-16). Advertising and marketing by the tobacco industry reinforced the perceptions that lower tar was less harmful. We now know that smoking machine yields were misunderstood in relation to human exposure and tobacco companies intentionally misrepresented the impact of lowering tar yields on smokers’ health (13, 17, 18). Development of smoking behavior measurements revealed that compensatory mechanisms for adjusting to the reduced nicotine yields of reduced yield cigarettes led smokers to increase their nicotine exposure by increasing cigarette puffing intensity and smoking more cigarettes per day (19-23). Moreover, human biomarker studies have shown that smokers’ exposures were not different when smoking cigarettes with different tar yields (24-26). Separately, although early epidemiology data supported the hypothesis for reduced risk in relation to tar yields, a recent reanalysis of the data established that the early interpretations were wrong (13, 27). As the realization for the limitations of smoking machine studies became clear, and how the uses for public health recommendations were based on flawed interpretations, the Federal Trade Commission (FTC) in November 2008 officially rescinded its widely used guidance for reporting smoking machine determined tar and nicotine yields.7 Thus, today, there are no recommended smoking machine protocols in the United States that the FDA can use to inform their decision making processes regarding performance standards and health claims, although the WHO has made recommendations (see below; refs. 10, 28).

To develop and validate new smoking machine methods, a better understanding of how to assess human smoking behavior is needed. Currently, smoking behavior is assessed by smoking topography devices that record puff profiles (e.g., puff volume, interpuff interval, puff duration, and air flow) and methods to assess inhalation. However, there are limitations to these methods for estimating human exposure, and very few studies combine these research tools to cover all the components of smoking. Conceptually, these methods could be validated by human biomarker studies, and some studies have been done.

The goal of this review is to critically evaluate methods to assess human smoking behavior and how best to replicate this on smoking machines. Although there will always be limitations to such studies, certain limitations can be mitigated, and the context for other limitations can be better understood. This review will summarize the state of the art in smoking machine protocols and human smoking behavior measurement, identifying what is and is not captured by smoking machine replication of human smoking. These data will be synthesized to identify research gaps related to laboratory research on cigarette smoke and regulation of tobacco products. This review is organized into three major sections, followed by a discussion. The first section provides a review of the technical aspects of machine smoking and the early development of the standardized smoking machine. This will set the stage to contrast this early work with what we know about human smoking behavior and how well we measure that. The third section reviews methods where researchers have tried to apply what we know about human smoking behavior for smoking machine studies. Last, the discussion provides an overall summary of the most important points and identifies the research gaps that lead from earlier work.

Materials and Methods

Smoking behavior and smoking machine studies were identified using PubMed search strategies. The search keyword strings included “human smoking behavior, smoking topography, human puff profiles, smoking machines, smoke exposure, and PREPs,” and combinations of these. All identified studies were reviewed that have been published since 1980, and citation lists were cross-referenced to ensure that the most complete list of publications was identified. Articles published before 1980 with high relevance to the study of PREPs or low-yield cigarettes also were identified and reviewed. Separately, internal tobacco company documents were reviewed, as identified by searches using TobaccoDocuments.org8 and the Legacy Tobacco Documents Library.9

Studies were identified that investigated methodologic, descriptive, validation, and application aspects related to the assessment of human smoking behavior, human puff and respiration patterns, biomarkers of acute smoke exposure, and smoking machine regimens and yields as they relate to exposure. Research publications were compiled to examine the following: (a) the goals of the study; (b) the methods for assessing human smoking behavior or machine smoking protocols; (c) the experimental designs that were used; and (d) the effects of smoking behavior in relation to the effects of smoking machine protocols on smoke yields. The information was synthesized to provide usefulness for the study of cigarettes and identify research gaps. Although others have reviewed the origins and limitations of smoking machine yield testing (29-31), the focus of this article is to identify how to better replicate human smoking in the laboratory through understanding both the design of smoking machine and human behavior studies, and identify the research gaps associated with this.

Results

Technical Aspects of Machine Smoking. Smoking machines are intended to generate smoke in a systematic
Puffing parameters, are manufactured by var-

alytic smoking machines, which have flexibility for
et al. in the 1930s (33, 34). Today, commercially available

recently, puff shape.

the length of cigarette smoked (butt length), and more

parameters are puff volume, puff frequency, puff duration,

that can be adjusted, typically, the programmable pa-

ies. Although smoking machines have several variables

although it is sometimes used for

chemical constituents. Whole smoke is used to determine

for animal skin painting studies, and for assessing the

assayed as whole smoke. Total particulate matter and

trap (termed cigarette smoke condensate) or directly

and vapor phase passes through the Cambridge filter

particulate matter minus water and nicotine. The gas

vapor phase passes through the Cambridge filter

pad and can be collected or tested directly. Alternatively,

smoke can be collected as a condensate usually in a liquid

trap (termed cigarette smoke condensate) or directly

assayed as whole smoke. Total particulate matter and

cigarette smoke condensate are typically used in studies

assessing the toxicology of tobacco smoke

in vitro

condensate. Therefore, they suggest that the

sources produced mainly unsaturated hydrocarbons,

whereas the electric lighting device produced oxygen-

containing compounds. Therefore, they suggest that the

use of electric lighters in smoking machines be reconsidered,
because human smokers generally use open flame

lighters. Some smoking machines have sensors to deter-
mine if the cigarette is lit and they are programmed to
stop smoking once the cigarette is smoke down to a
specified distance from the end of the filter (e.g., by us-
ing a laser detector). Less sophisticated machines rely on
a string to mark the stopping point — when the ciga-

rette burns through the string, the puffing mechanism is
deactivated.

The Early Development of Standardized Smoking
Regimens. The development of smoking machine regi-

ments has been extensively reviewed elsewhere (36-38).
In 1936, Bradford et al. (34), who worked for the American

Tobacco Company, described the need for standardized

smoking parameters that would aid in the characteriza-
tion and reproducibility of cigarette smoke experiments

in the laboratory. However, machine-measured emissions

were not widely publicized until the early 1950s (39, 40),

Table 1. Overview of smoking regimens (from ref. 149)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>FTC</th>
<th>Massachusetts</th>
<th>Canadian</th>
<th>ISO</th>
<th>ISO A</th>
<th>ISO B</th>
<th>ISO C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puff volume</td>
<td>35 ± 0.5 mL</td>
<td>45 ± 0.5 mL</td>
<td>55 ± 0.5 mL</td>
<td>35 ± 0.3 mL</td>
<td>55</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>Puff duration</td>
<td>2 ± 0.05 s</td>
<td>2 ± 0.05 s</td>
<td>2 ± 0.05 s</td>
<td>30</td>
<td>50% blocked</td>
<td>50% blocked</td>
<td>100% blocked</td>
</tr>
<tr>
<td>Puff frequency</td>
<td>60 ± 0.5 s</td>
<td>30 ± 0.5 s</td>
<td>30 ± 0.5 s</td>
<td>60 ± 0.5 s</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Ventilation holes</td>
<td>Open</td>
<td>50% blocked</td>
<td>100% blocked</td>
<td>Open</td>
<td>50% blocked</td>
<td>50% blocked</td>
<td>100% blocked</td>
</tr>
<tr>
<td>Conditioning atmosphere</td>
<td>60% RH ± 2% RH</td>
<td>23°C ± 1°C min 1, max 14 d</td>
<td>60% RH ± 3% RH</td>
<td>22°C ± 1°C min 2, max 10 d</td>
<td>60% RH ± 3% RH</td>
<td>22°C ± 1°C min 2, max 10 d</td>
<td></td>
</tr>
<tr>
<td>Smoking environment</td>
<td>60% RH ± 3% RH</td>
<td>23.9°C ± 2°C</td>
<td>60% RH ± 5% RH</td>
<td>22°C ± 2°C</td>
<td>60% RH ± 5% RH</td>
<td>22°C ± 2°C</td>
<td></td>
</tr>
<tr>
<td>Air flow linear ind.</td>
<td>200 ± 50 mL/min</td>
<td>200 ± 30 mL/min</td>
<td>200 ± 30 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>port linear avg. rotary</td>
<td>200 ± 50 mL/min</td>
<td>200 ± 30 mL/min</td>
<td>200 ± 30 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butt length (whichever is the highest value)</td>
<td>Tipping + 3 or 23 mm from butt</td>
<td>Tipping + 3 mm or filter + 8 or 23 mm from butt</td>
<td>Tipping + 3 mm or filter + 8 or 23 mm from butt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: FTC and Massachusetts protocols have air flow sufficient to exhaust the smoke, about 20 mL/min.
Abbreviation: RH, relative humidity.
when studies became available linking smoking and lung cancer, and as cigarette manufacturers were racing to produce lower smoking machine tar yield products (commonly called a “tar derby”), making a multitude of inconsistent, noncomparable claims about tar yields to consumers (31). The tar derby ended in 1960 with a voluntary agreement by the FTC and the manufacturers to end tar and nicotine yield claims. The FTC later retracted this agreement and decided to develop a standardized testing method. The initial protocol was largely based on the work of U.S. Department of Agriculture chemist C.L. Ogg in 1964 (31, 41). It seems, however, that this protocol was based on one person’s observations about how people smoked, was not determined with some systematic method, and it actually was very similar to the 1936 method of Bradford and coworkers (34). It should be noted that the protocol was not intended to represent the typical smoker, but rather to offer a common basis for a comparison among brands. It should not be inferred that the FTC protocol represents how any person might smoke.

The FTC puffing protocol prescribes drawing a 35-mL puff of 2-second duration every minute until the length of the cigarette is no less than 23 mm for nonfiltered cigarettes or filter overwrap plus 3 mm for filtered cigarettes. Table 1 describes this protocol and others that have been developed over time. The original protocol developed by Ogg et al. (42), also consisted of conditioning of cigarettes at 23.9°C and 60% relative humidity for 24 hours. At the outset, the FTC method was intended only to compare tar and nicotine yields across brands, although carbon monoxide (CO) was added to the protocol in 1980. The analysis of other smoke constituents have never been specified by the FTC, but the FTC protocol has been widely adopted in analyses of other constituents for product testing and research. It also has been widely used for toxicology studies.

Following the work of the FTC, virtually identical standardized smoking regimes were developed by the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), and later the International Organization for Standardization (ISO). CORESTA’s initial standardized smoking method was published in 1969 (43). The ISO protocol uses the same puffing regimen as the FTC method, except that it specifies an air flow of 200 mL/minute. Additionally, CORESTA and ISO stipulate standards for physical components of the machine: the cigarette holders, smoke traps, ports, channels, and ashtray specifications (43). It should be noted that the tobacco companies heavily influenced CORESTA to motivate ISO to set standards and generate research results in an attempt to preempt regulations (37). Although ISO and CORESTA were seemingly independent, ISO essentially adopted CORESTA’s recommended methods, as the ISO committees overseeing standards development for tobacco products have been composed mostly of persons affiliated with the tobacco industry (37, 44).

**Human Smoking Behavior**

*Physical Processes Involved in Smoking.* To understand the limitations and misuse of the smoking machine measuements, it is important to understand how smokers smoke their cigarettes. The physical process of smoking a cigarette is continuous, but can be divided into three phases: puffing, mouth-holding, and inhalation. The smoking cycle is shown in a diagram reproduced from the British American Tobacco Company (BATCo) research in 1986 (Fig. 1). This figure defines different parameters that can be measured during smoking. Puffing refers to the act of drawing smoke from the cigarette into the mouth. The act of puffing draws air through the burning rod that causes an increase in temperature that in turn burns some amount of tobacco and the cigarette paper wrap. During puffing, the tongue contracts down creating a negative pressure to aid the puffing process and the soft palate contracts, essentially blocking airflow into the nasopharynx and lungs. Puffing is then followed by a period of mouth-holding before air moves into the lungs, as typically smoke is not directly inhaled from the cigarette through the mouth into the lungs. Following puffing, as reported via the BATCo documents, the smoke is either

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12 [http://www.time.com/time/magazine/article/0,9171,871506,00.html](http://www.time.com/time/magazine/article/0,9171,871506,00.html)

13 [http://tobaccodocuments.org/bat_cdc/8652.html](http://tobaccodocuments.org/bat_cdc/8652.html)
immediately inhaled via nose inhalation into the lungs, paused in the mouth before nose inhalation (perhaps to enhance the sensation and taste), or paused in the mouth with some exhalation of smoke before nose inhalation. According to BATCo, nose inhalation allows the soft palate to relax, providing an easy path for the smoke to be drawn into the pharynx and nasopharynx.14 The mouth is closed so that the air pressure sucking the smoke into the lung is such that it moves from the nose into the lungs. Following nose inhalation, exhalation occurs after some period of time. Puffing resumes after an interpuff interval, and in at least 80% of smokers, this takes place during the exhalation phase of a breath, which can occur at any point during exhalation, e.g., at the onset, in the middle, or at the end of exhalation (45). An example of the various parameters for puffing and inhalation is shown in Fig. 2. Thus, it is the combination of puffing, mouth-holding, nose inhalation, and inhalation time that determines a smoker’s internal dose of smoke toxicants and nicotine. These studies only had a few subjects (n = 8), measurement was confined to one setting, and this study has not been replicated; a systematic study might show different or more patterns of inhalation, e.g., mouth inhalation in addition to nose inhalation.

Measuring Puff Topography. Puff profiles are measured by assessing smoking topography, namely puff volume, puff duration, interpuff interval, flow rate (sometimes also termed puff velocity), the number of puffs per cigarette, and total puff volume (46-55). These correspond to parameters that can be programmed on a smoking machine. Most commonly, puff topography is measured by having the cigarette smoked through a small tube that can measure air flow via a transducer, and the analog signal is converted to a digital signal for recording and interpretation. Initially, various research groups used their own puff profile recording devices, such as the “tobacco smoke inhalation testing system” originally developed by Puustinen and coworkers in 1986, and then manufactured by the College of Engineering at the University of Kentucky (56-58). Other early techniques included flow meters (59, 60), pneumotachographs (61), pressure transducers and Grass polygraphs (62), and puff analyzers (63). Tobacco industry scientists developed devices in the late 60s and early 70s, such as the cigarette-holder flow meter described by Adams and Creighton (64-66). Portable devices that can be used for at-home monitoring also have been developed (49, 66-69).

Although custom-built apparatuses are still used (70), commercially available topography devices, such as the CreSS units from Plowshare Technologies, Inc.15 and the SODIM SPA/D and SPA/M smoking topography units16 have largely superseded them. To our knowledge, there are no published studies using the SODIM topography units and the majority of studies assessing human smoking topography have used the Plowshare.

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14 http://legacy.library.ucsf.edu/tid/zll13f00
16 http://www.sodim.com/English.htm
CReSS and CReSSMicro units (25, 53, 71-80). CReSS desktop topography units are capable of real-time recording of individual puffs, including shape and flow rates, for later replication of human puff profiles on smoking machines (portable devices at the present time cannot do this and only provide statistical means of the parameters). The desktop units also contain the ability to cue the smoker for controlled smoking conditions, for example cueing them when to puff, puff duration, and puff volume. These systems also can integrate subjective, performance, and physiologic measures.

Validation of Puffing Topography Recording Devices. Although there are numerous studies about puffing topography, there are few studies that have validated the available methods. Validation would be done in several ways, namely by assessing intraindividual, intralaboratory, and interlaboratory variation, as well as by comparing different methods to assess topography. Published validation studies for intraindividual and intralaboratory methods are limited to the CReSS devices. These studies have conducted repeated measures on different days, which assesses both intralaboratory and intraindividual variation measured in the laboratory, and these have generally shown good reproducibility (53, 76, 81). For example, Lee and coworkers (53) found good reliability by intraclass correlation coefficients computed for puff volume (0.66), puff duration (0.75), and maximum puff velocity (0.68). Hammond et al. (82) investigated the smoking topography characteristics with the portable CReSSMicro device on 59 subjects smoking an average of 19 cigarettes per day, reporting similar measures of smoking topography for the same subject over time. For a biomarker assessment, in a study of 180 smokers measuring CO and nicotine boosts for two cigarettes 1 hour apart, the use of the topography device did not affect the CO or nicotine levels, because these were measured with and without the topography device in place, although the correlation coefficient with and without the device for CO was only 0.31 (P < 0.001).17

Similar results have been reported in a small study by Lee and coworkers (53). Blank and colleagues (83) recently reported head-to-head comparisons of the desktop and portable CReSS devices versus observed smoking using a video tape. The authors found that measured puff duration and interpuff interval on both devices, as well as the video were well correlated (r's > 0.70), although there were quantitative differences among the devices for puff volume and duration, indicating that comparisons of data across devices might not be reliable. Separately, it has been shown that topography assessments in the laboratory provide similar assessment in the naturalistic environment, e.g., at home (79, 84). Thus, these studies support the reliability and validity of the CReSS devices for topography measurement.

What Is Known about Human Puffing Patterns? There is wide interindividual variation for smoking behavior, but a low intraindividual variability because smokers in general show a stable smoking pattern over time, or at least a short period of time (23, 54, 55, 82, 85-88). A clear and consistent finding is that human smoking behavior differs substantially from the commonly used FTC and ISO parameters, a fact recognized early by the tobacco companies (82, 89-91). Several factors have been documented to influence smoking behavior, such as gender, race, psychological factors, and genetic background. In general, men smoke more cigarettes per day than women and have higher serum cotinine levels (92-96). Although the data are less consistent for smoking topography, men tend to have larger puffs of longer duration, but women may smoke more puffs per cigarettes (52, 70, 71, 97, 98). Differences in smoking topography have been observed between Whites and African-Americans: the latter group generally reflecting greater exposure to smoke toxicants (60, 70, 96, 99). Psychological factors, concurrent use of psychoactive drugs, time of the day and place where a cigarette is smoked also can have an effect on the smoking topography (80, 88, 100, 101, 102).

Generally, there is a high correlation for various puff parameters, e.g., interpuff interval, puff duration, and puff volume; all of these directly impact total puff volume per cigarette (85, 97, 103, 104). However, these parameters are not sufficient proxies for each other and so all need to be recorded when measuring smoking topography (97). Other studies indicate that topography results are not kept constant during the course of smoking a cigarette, where puff volume decreases and interpuff interval initially increases and then decreases (58, 85, 105).

The number of cigarettes smoked per day generally do not relate to puffing topography, or sometimes only is positively correlated with longer interpuff intervals (49, 62, 82, 104, 106). Published studies also are inconsistent for relating puff topography to various biomarkers such as CO and nicotine/cotinine levels, where different parameters affect these biomarkers differently (61, 104, 107-117). For example, puff number and to a lesser extent the puff volume and duration affect nicotine levels, whereas CO levels are mostly influenced by puff volume and less by puff number (112). Zacny and coworkers (61) reported that both nicotine and CO increase proportionally with an increase in puff volume. In a study of 180 subjects, there was a statistically significant correlation for CO boost and puff volume, but not the interpuff interval.17

Product Design Effects on Smoking Topography. Cigarette design characteristics affect puffing topography when smokers first switch, for example by changes in the draw resistance, sensation, and taste (23, 30, 82, 89). Numerous studies indicate that switching from higher to lower yield cigarettes increase topography parameters such as puff volume and puffs per cigarette (61, 82, 86, 110, 118-126), whereas a decrease in puffing intensity or longer time spent on smoking a cigarette takes place when smokers switch to a higher overall yield cigarette, or cigarettes with constant tar but increased nicotine content (56, 110, 127-132). In a 1986 British American Tobacco study,13 19 subjects who were “low” tar (<10 mg tar yields) and

http://legacy.library.ucsf.edu/tid/sp600h0.pdf; http://legacy.library.ucsf.edu/tid/cyz24000; http://legacy.library.ucsf.edu/tid/yct0699/pdf; http://legacy.library.ucsf.edu/tobacco/bacto/html/13200/13274/index.html; http://legacy.library.ucsf.edu/tid/sgz00h00; http://legacy.library.ucsf.edu/tid/syj51f00; http://www.library.ucsf.edu/tobacco/bacto/html/6900/6922/index.htm

17 Shields, Lerman, Pickworth, and Loffredo, unpublished data.
Table 2. Smoking parameters, 1986 BAT study (means ± SD)

<table>
<thead>
<tr>
<th>Cigarette type</th>
<th>Puff number</th>
<th>Puff volume (mL)</th>
<th>Mouth hold (s)</th>
<th>Inhaled volume (mL)</th>
<th>Exhaled volume (mL)</th>
<th>Inhalation time (s)</th>
<th>Exhalation time (s)</th>
<th>Breath hold (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 mg tar yield (n = 11)</td>
<td>9.4 ± 2.9</td>
<td>44.9 ± 12.3</td>
<td>0.49 ± 0.27</td>
<td>702 ± 437</td>
<td>577 ± 329</td>
<td>1.19 ± 0.29</td>
<td>2.01 ± 0.76</td>
<td>0.45 ± 0.48</td>
</tr>
<tr>
<td>&lt;10 mg tar yield (n = 8)</td>
<td>12.1 ± 5.6</td>
<td>44.5 ± 10.9</td>
<td>0.65 ± 0.39</td>
<td>636 ± 138</td>
<td>655 ± 195</td>
<td>1.22 ± 0.37</td>
<td>2.89 ± 0.72</td>
<td>0.45 ± 0.57</td>
</tr>
</tbody>
</table>

NOTE: http://tobaccodocuments.org/bat_cdc/8652.html. Similar smoking parameters were observed in subjects grouped according to cigarette tar yields with a cutoff of 10-mg tar.

“middle” tar (>10 mg tar yields) smokers had similar puff topography and inhalation parameters, as shown in Table 2. The investigators found that puff volume increased when their subjects who were middle tar yield smokers were switched to a low-tar cigarette, but decreased for the opposite test scenario. The investigators concluded that the increased puff volume was due to decreased draw resistance. In this study, inhalation parameters did not change with switching. Studies by Benowitz et al. (133) suggest that during short-term switching studies, smokers that switch to lower yield cigarettes tend to compensate by changing their behavior by smoking more vigorously or by increasing cigarettes per day (13).

An important design feature of lower yield cigarettes is ventilation via holes punched on the filter paper that allow smoke to be diluted with air during puffing. However, some smokers block these ventilation holes by their fingers or lips, which would then result in yields different than predicted by a smoking machine. In a study of smokers who were trained to uniformly smoke with a particular puff profile that restricted the puffs per cigarette and puff frequency, Strasser and coworkers (117) showed that hole blocking resulted in an increase of CO boost, implying an increase of other tobacco smoke constituents. Puff volumes decreased for both cigarettes with 50% hole blocking. Other switching studies reported similar results but differed in the magnitude of the CO response depending on the cigarette type that was smoked, namely the effects are greatest for ultralight smokers (116, 134). One explanation for the difference in results might be the lack of controlling for puff number and puff interval; in the latter two studies, there were many more puffs per cigarette that might have obscured a difference. Regardless, it is clear that smoking machine studies that compare cigarettes with different physical design characteristics using the same puffing profile fail to accommodate for what happens to smokers who switch or naturally adopt one product versus another.

Filter efficiency is affected by puffing. Increasing smoke flow through the filter, such as with greater puff volumes and decreasing filter ventilation, but not so much decreasing puff frequency, will tend to decrease filter efficiency, leading to a narrower range of yields across brands. For example, Marlboro UltraSmooth (MUS) with a novel carbon filter is much less effective in reducing toxic smoke constituents when smoked under the HC regimen compared with the FTC method (135).

For many PREPs, design features are varied and switching studies show that smoking behavior changes (summarized in Table 3). For example, smokers who switched to the Advance cigarette that has a modified filter took fewer puffs and had higher nicotine levels, whereas the rest of puffing characteristics remained unchanged (136, 137). Two studies investigating the Accord electronic smoking system found that subjects had shorter puff intervals and fewer puffs per cigarette, because this is electronically controlled, and higher puff volume and duration compared with smoking own brand cigarettes (72, 74). Eclipse smokers, which is a product designed to heat tobacco rather than burn it, substantially increased their puff volumes, and decreased the interpuff interval (138-140). For Eclipse, CO levels also increased, and for some smokers, the levels were quite high (141). Acrolein also is increased. For Quest cigarettes that vary in nicotine yields, there is compensatory smoking with an increase in the total puff volume and CO boost (115). Another study reported that switching to Omnic cigarettes that had a modified filter resulted in fewer puffs compared with the usual brand, but there also was an increase in CO boost and not a significant decrease in carcinogen exposure when compared with conventional cigarettes (75). When comparing MUS that had a modified filter with charcoal particles embedded in cellulose acetate, with two conventional cigarettes (Marlboro Lights and Ultralights), investigators observed a decrease in number of puffs, but higher puff volumes (79). The overall conclusion of the study was that there is no significant change in smoking topography between the MUS and conventional cigarettes; therefore, there will be no reduced exposure among smokers that switch from a conventional brand. Thus, smoking machine studies that compare PREPs to conventional products using the same puffing profile could be misleading in terms of relative effects.

Measuring Inhalation and Exhalation. Smoking behavior also involves not only assessing puffing behavior, but also inhalation, which more closely relates to biological dose. Several techniques have been developed for measuring times and volumes for inhalation and exhalation. Some early methods were reviewed in a report from Imperial Tobacco Ltd. These techniques are summarized in Table 4. The main conclusion was that these devices were not completely accurate in measuring the physical mechanics of inhalation and exhalation, but they did not permit studies in the naturalistic setting and they imposed restrictions on free smoking behavior. Tobin and coworkers (142) used chest plethysmography, to assess the pattern of inhalation in smokers and then compared this with the smokers’ subjective reports for inhalation. They found that smokers inaccurately perceived their inhalation patterns. In another

19 http://legacy.library.ucsf.edu/tid/cbi31d00 and http://legacy.library.ucsf.edu/tid/buaf1e80

20 http://legacy.library.ucsf.edu/tid/kjn70f00
Table 3. Selected smoking topography characteristics among PREP studies

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Products</th>
<th>Participants (n)</th>
<th>Puff numbers</th>
<th>Puff volume (mL)</th>
<th>Total puff volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breland AB 2003 (136)</td>
<td>Advance</td>
<td>12 (8F, 4M)</td>
<td>9.6 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breland AB 2002 (137)</td>
<td>Advance</td>
<td>20 (10F, 10M)</td>
<td>34.5 (21.9)</td>
<td>51.6 (9.4)</td>
<td>384.1</td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>33.9 (23.6)</td>
<td>56.5 (11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>17.2 (14.2)</td>
<td>66.5 (43.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buchhalter R 2000 (72)</td>
<td>Accord</td>
<td>10 (7F, 3M)</td>
<td>24.0 (12.1)</td>
<td>7.8 (0.7)</td>
<td>55.4 (17.0)</td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>35.0 (17.9)</td>
<td>10.3 (2.1)</td>
<td>38.4 (11.7)</td>
<td>395.52</td>
</tr>
<tr>
<td>Breland AB 2006 (138)</td>
<td>Eclipse</td>
<td>35 (8F, 27M)</td>
<td>21.38</td>
<td>17.03</td>
<td>65.01</td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>30.74</td>
<td>10.03</td>
<td>50.97</td>
<td>511.22</td>
</tr>
<tr>
<td>Slade J 2002 (139)</td>
<td>Eclipse</td>
<td>19.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>67</td>
<td></td>
<td>1371</td>
<td></td>
</tr>
<tr>
<td>Breland AB 2002 (74)</td>
<td>Eclipse</td>
<td>20 (10F, 10M)</td>
<td>53.3 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>61.8 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49.8 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strasser AA 2007 (115)</td>
<td>Quest 0.05</td>
<td>50</td>
<td>18.6</td>
<td>10</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>Quest 0.3</td>
<td>19.6</td>
<td>9.9</td>
<td>55.9</td>
<td>518.1 (145.6)</td>
</tr>
<tr>
<td></td>
<td>Quest 0.6</td>
<td>21.6</td>
<td>9.8</td>
<td>58.1</td>
<td>540.3 (144.9)</td>
</tr>
<tr>
<td>Rees VW 2008 (79)</td>
<td>ML</td>
<td>32 (21F, 11M)</td>
<td>32.1 (11.9)</td>
<td>11.4 (3)</td>
<td>50.7 (19.6)</td>
</tr>
<tr>
<td></td>
<td>MUS</td>
<td>Tampa</td>
<td>28.4 (8.4)</td>
<td>10.2 (2.9)</td>
<td>54.2 (19.4)</td>
</tr>
<tr>
<td></td>
<td>MUL</td>
<td>35.0 (14.9)</td>
<td>11.3 (2.6)</td>
<td>51.4 (19)</td>
<td>580.82</td>
</tr>
<tr>
<td></td>
<td>ML</td>
<td>24.8 (11.45)</td>
<td>13.1 (4.8)</td>
<td>47.4 (16.9)</td>
<td>630.94</td>
</tr>
<tr>
<td></td>
<td>MUS</td>
<td>Salt Lake City</td>
<td>23.9 (9.2)</td>
<td>12.5 (5)</td>
<td>56.7 (15.2)</td>
</tr>
<tr>
<td></td>
<td>MUL</td>
<td>21.8 (10.4)</td>
<td>13.9 (5.6)</td>
<td>50.1 (15.6)</td>
<td>696.39</td>
</tr>
<tr>
<td>Lee EM 2004 (140)</td>
<td>Eclipse</td>
<td>10</td>
<td>16.1 (2.1)</td>
<td>89.3 (10.8)</td>
<td>1,437.73</td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>11.5 (0.7)</td>
<td>60.1 (4.0)</td>
<td>691.15</td>
<td></td>
</tr>
<tr>
<td>Hughes JR 2004 (75)</td>
<td>Omni</td>
<td>34</td>
<td>11.6 (0.5)</td>
<td>49 (2)</td>
<td>547 (25)</td>
</tr>
<tr>
<td></td>
<td>Own</td>
<td>12.7 (0.7)</td>
<td>50 (2)</td>
<td>612 (34)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Data presented as mean (SD) or mean only as available in the original paper. Empty cells mean no value exists in the paper for that parameter. Calculated values are presented in italic.

Abbreviations: ML, Marlboro Light; MUL, Marlboro Ultra Light; MUS, Marlboro UltraSmooth; IPI, Interpuff interval; F, Females; M, Males.

study, Tobin and Sackner (128) used the same system to assess switching from high to low-tar cigarettes, showing that there was no change in the inhalation characteristics.

The most widely used device by the tobacco industry to assess smoke inhalation by inductive respiratory plethysmography has been the RespiTrace, developed for assessing respiratory function and disease (NonInvasive Monitoring Systems, Inc.; ref. 143). The system consists of insulated coils enclosed in elastic bands applied on the rib cage and abdomen of the subject, registering the changes in respiratory movements that alter the self-inductance of the coils. The device must be calibrated for tidal volume with the use of a spirometer (144). BATCo used the RespiTrace system in the studies discussed above to discern the physical process of smoking. Rees et al. (145) showed that postpuff inhalation volume and duration unaltered in smoking machine regimen. However, the various aspects of smoking also affect smoking machine yields and smoke toxicant effects, as indicated below. Some parts of human smoking are not captured at all by the smoking machine, and the amount of the chemical constituent on the pad was considered retained in the smoker.

In summary, smoking behavior is complex and many of the individual components covary, so that affecting one might affect each other. These are directly affected by cigarette designs. However, the various aspects of smoking also affect smoking machine yields and smoke toxicant effects, as indicated below. Some parts of human smoking are not captured at all by the smoking machine, whereas some variables such as puff velocity and puff shape are usually not considered. Smokers vary their puffing behavior during the course of their cigarette, by day, and by who they are. These added variables make it impossible to replicate a typical smoker using one smoking machine regimen.

21 http://legacy.library.ucsf.edu/tid/zll13f00; http://tobaccodocuments.org/bat_cdc/8652.html
Smoking Machine Profiles and Mimicking Human Smoking Behavior

As evidence accumulated that smokers’ behaviors and exposures were distinct from machine-measured yields, increased interest was placed on altering machine smoking methods to better reflect smoker practices. The 1981 Surgeon General Report, for example, acknowledged that the FTC testing method needed to account for compensatory smoking (via larger and more frequent puffs) and ventilation holes (10). A National Cancer Institute ad hoc expert committee convened in 1994 came to similar conclusions (88). Research on alternative testing regimens was ongoing in the public health/regulatory community. For example, Rickert and coworkers (148) tested smoke yields under ISO conditions and reported that the tested smoke yields under ISO conditions and with ventilation hole blocking (16). A National Cancer Institute concluded that more resemble human smoking. Initially, two sets of smoking regimens were chosen, derived from 32 studies on ad libitum smoking topography presented in the 1988 Surgeon General’s report (149). One was termed the “average smoker” protocol and the other a more intense “heavy smoker” protocol. The former had a 45-mL puff volume every 30 seconds, with a puff duration of 2 seconds and taping closed 50% of the ventilation holes. The MDPH 50% hole blocking in particular was recommended in the context that smokers will block ventilation holes when they smoke, for example with their fingers or

Table 4. Summary of inhalation/exhalation monitoring methods used for assessing human smoking behavior (excerpted from internal company documents)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Method</th>
<th>Variables measured</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinkota F. F. 1967*</td>
<td>Partial body plethysmography</td>
<td>Volume of the puff</td>
<td>Discomfort leading to high puff by puff variation observed in the breathing patterns of individual smokers and abnormal tidal breathing caused by stress</td>
</tr>
<tr>
<td>Creighton D.E. 1978 (66)</td>
<td>Impedance pneumography</td>
<td>Holding time of the puff</td>
<td>Needs calibration against a partial body plethysmograph before each use. Nonlinear response and day-to-day variations for individual and variation between subjects.</td>
</tr>
<tr>
<td>Guillerm R. and Radziszewski E. 1975 (170)</td>
<td>Mercury strain gauge chest pneumograph</td>
<td>Lung volume at the beginning of the puff</td>
<td>The puff volume recorded did not always correspond to the true inhaled puff volume and the technique imposed some physical restrictions on the subject, particularly concerning the cigarette holder.</td>
</tr>
<tr>
<td>Rawbone R.G. 1978 (171)</td>
<td>Respiratory inductive plethysmography</td>
<td>Location of the puff in the ventilatory cycle</td>
<td>Calibration was required before each study.</td>
</tr>
<tr>
<td>Sackner M.A. 1980 (172)</td>
<td>No. of puffs</td>
<td>Accuracy of the results depended on the initial calibration and the stability of the calibration during changes in body positions and lung volumes.</td>
<td></td>
</tr>
<tr>
<td>Tobin M.J. 1982 (128, 142)</td>
<td>Consisting in two coils of Teflon-insulated wire, which were sown into elastic bands encircling the rib cage and the abdomen and connected to an oscillating module.</td>
<td>Tidal volume measured by spirometry.</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: http://legacy.library.ucsf.edu/tid/zll13f00; http://legacy.library.ucsf.edu/tid/kjn70f00.

*http://legacy.library.ucsf.edu/tid/hwo00000


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affect smoke yields. For example, decreasing puff volume, increasing puff frequency (decrease interpuff interval), and increasing filter ventilation decrease tar and chemical yields on a per cigarette basis (155).24 In smokers, though, using higher ventilated cigarettes generally results in larger puff volumes. Toxicology studies also show the influence of puff volume, ventilation, and ventilation hole blocking (156).25 The ISO/FTC, MDPH, and HC methods use different puff volumes, puff frequency, and ventilation hole blocking, and increases in these variables result in increased tar, nicotine, and other constituent yields on a per cigarette basis (109, 148, 157, 158).

The data indicate that the relative rankings of different products, on a per cigarette basis, will generally be preserved across regimens although the gap in toxicant emissions with more intense protocol is reduced. Counts and colleagues from Philip Morris (157) published a large survey of emissions from international brands tested under ISO, MDPH, and HC conditions, showing that the ratios of constituents to total tar were dependent on the puffing profile, and mostly driven by filter ventilation. For example, when cigarettes were grouped broadly by filter ventilation, the yields of individual constituents relative to tar changed differently as the different profiles were compared. This effect was greater for vapor phase compared with particulate phase constituents. However, the effect was least for the cigarettes with lower ventilation and higher tar yields. Separately, Hammond and O’Connor (155) examined the relationships between yields under the ISO and HC regimens for the 2004 Canadian market and showed that the increased intensity of the HC system changes the absolute concentrations of constituents, but also their concentrations relative to nicotine (157).

Both Philip Morris and RJ Reynolds Tobacco companies, as early as 1974, developed the capability to capture human topography data and mimic this on a smoking machine, and it was shown that the yields predicted for different smokers substantially varied among them, and higher than the FTC predicted yields.26 In a 1982 report by RJ Reynolds’ scientists, an analysis indicated that using five variables within the puff for flow velocity at different times of the puff and the time to reach \( V_{\text{max}} \), six types of profiles could be described.27 Although, each smoker would vary their shape within a cigarette, it was reported that 12 patterns would characterize all 550 smokers.

Whether changing the shape of the puff affects yields is unclear, and there are no recently published studies. A 1968 report from Brown and Williamson showed that when air flow peaked (early versus late), different yields were obtained.28 The parameters that affect the shape of the puff or the variability for the puff-by-puff profile are unknown, but it seems that filter ventilation does not affect the latter.29 None of the above studies, however, measured specific chemical constituents. New commercial topography devices have the capability to record puff-by-puff data, including the change of airflow within a puff. Today, smoking machines also can be programmed with the use of specialized pumps and software to better replicate the human-type puff on a puff-by-puff basis. However, whether this new technology affects the smoke yields and provides for a better replication of human smoking remains to be determined.

A more meaningful comparison might come from an assessment using different puff profiles tailored to the product as it might be used by smokers. For example, a method has been proposed based on nicotine yields by Kozlowski and O’Connor (91). They proposed a two-step system where the first step would use the traditional ISO/FTC yield on a per cigarette basis, whereas a second step would use puff parameters adjusted to yield the same nicotine levels, for example by adjusting the puff volume. Later, Hammond and colleagues revised this recommendation to propose a system whereby puffing profiles would be iteratively adjusted so that all brands yielded a specific nicotine level. In both cases, the goal would be to better simulate compensatory smoking by humans within the limitations of machines. However, little work has been done to operationalize these methods. It should be noted that the above methods adjust smoking machine parameters based on total cigarette yields and not on a per milligram of tar basis and assumes that the chemical composition of tars are similar; however, this is known not to be true (157–159).

Hammond and coworkers (30) compared the smoke yields produced under ISO, MDPH, HC, and the two-stage compensatory regimen described above to the average of actual topography measures for 51 smokers using their usual brand and 21 who switched to ultralights (human mimic profiles). Ventilation hole blocking was 50% for the MDPH and compensatory and human mimic profiles, whereas it was 100% for the HC method. None of the yields for the four smoking regimens replicated the human mimic profiles. Tar, nicotine, and CO yields obtained for the regular tar smokers under the mimic protocol were double of those obtained with the ISO and compensatory regimens, but slightly lower than the HC regimen and similar to the compensatory regimen. Importantly, none of the standardized machine determined nicotine yields predicted levels of salivary cotinine, except for the human mimic regimen. Thus, it is likely that no single smoking regimen can adequately characterize smoking.

Philip Morris has proposed another method for comparing products, which is to characterize human smoking behavior on a smoking machine based on several regimens statistically modeled based on topography data and urinary nicotine metabolites (160). The method uses the determined 10th percentile, mean, and the 90th percentile of the puff volumes, and the other parameters...
were modeled. Thus, they proposed testing cigarettes with a low (25-mL puff volume, 0.8-second puff duration, 2.4/minute puff frequency), a medium (48-mL puff volume, 1.3-second puff duration, 1.8/minute puff frequency), and a high (65-mL puff volume, 1.6-second puff duration, 1.9/minute puff frequency) puffing profile. However, we are unaware of any actual implementation of this proposal.

Data on comparative emissions for PREPs are rare. A specific example of a PREP for the utility of testing under multiple smoking machine methods is the Eclipse cigarette, which is claimed to heat rather than burn tobacco under the FTC conditions. When smoked on a machine in a way more similar to what smokers do, the tobacco becomes significantly charred and the smoke chemistry differences compared with conventional cigarettes become much less.30

Discussion

The need for validated laboratory methods to assess tobacco smoke for chemical constituents and toxic effects has recently been underscored by the new FDA authority to enact product performance standards and evaluate manufacturer health claims for modified tobacco products. Prior uses of smoking machine results led to miscomparisons about product design. This would lead to smoking machine regimens are sufficiently mimicking human exposure.

Although there are some data demonstrating the replicability of smoking behavior using these devices (53, 76, 81, 82), additional studies are needed to compare different commercial units and to validate them. It is unknown if these devices are measuring accurately air flow and volumes, and so a major limitation for validating topography measurements is the comparison to some “gold standard.” But none exists. Validation of topography as an indicator of exposure requires statistically significant and consistent correlations with biomarkers that have been validated for smoking (141), but the data thus far for comparing topography to biomarkers have produced conflicting results. Biomarkers of exposure reflect not only puff topography but also mouth-holding and inhalation, and so it may be that a biomarker comparison is not valid, assuming that varying mouth-holding and inhalation affect the dose to smokers. Thus, additional studies are needed to assess mouth-holding and inhalation to determine how much, if any, these components of smoking affect exposure. However, methods to assess mouth-holding and inhalation are poorly developed, and so better technologies are needed that can be applied to human studies. Once developed, controlled smoking and cross-sectional studies can be conducted with biomarkers to determine how much puffing, mouth-holding, and inhalation contribute to variance in human smoke exposure. The current designs for smoking machine puffing profiles have been developed considering each parameter as independent effects, but changing one actually influences the others (58, 85, 105). So a better understanding of the impact of changing one parameter on others is needed, both for topography and for smoking machine studies.

It is known that many of the various topography parameters covary (85, 97, 103, 104), but a systematic study has not been done to identify the extent of this. Another parameter that is only partially characterized is blocking ventilation holes (54, 116, 117, 134). To determine how people block holes, how much, and how often has been insufficiently studied. However, filter ventilation affects smoke dilution and puff volume, and so is critical for determining smoking yields. Thus, better technologies are needed to determine ventilation hole blocking and incorporate them into human studies that assess topography.

There is sufficient data to know that different machine puff profiles cause cigarettes to burn differently and have different chemical yields and biological activity, and that this would also result in different exposures in humans (157, 158).31 Thus, smoking machines need to better mimic human smoking, including methods to replicate puff-by-puff parameters, and studies need to be done to determine if the shape of the puff significantly affects yields. How to model the diversity of human smoking behavior needs to be developed. Then, better methods to compare cigarettes

30 http://legacy.library.ucsf.edu/tid/kqm60a99; http://legacy.library.ucsf.edu/tid/pkd56a00
and product design changes through cross-regimen comparisons are needed. Whether this is done using topography data or by standardizing for nicotine yields needs to be developed, and there is sufficient rationale to indicate that both methods might have utility.

Since the passing of the FDA legislation and the Institute of Medicine report conclusion that risk reduction through PREPs is a feasible approach (11), a comprehensive framework for studying tobacco products, including PREPs, is needed. This would include studies ranging from premarket assessments using laboratory studies to population surveillance. It would use integrative approaches by examining individual smoking behavior for new products and establish their relationship with actual delivered dosages of nicotine and a select panel of toxic and carcinogenic agents. An iterative process would therefore be used, where product design changes are tested first in the laboratory for increases in smoking yields and toxicity, followed by human use in short-term studies, and then replication of human use in the laboratory to confirm the yield and toxicity changes. Central to this process is the understanding of human smoking behavior and how to replicate this in the laboratory, but current knowledge and methods are insufficient to do this. Additional research, however, can fill in the research gaps to improve tobacco product assessment. Having validated methods for assessing tobacco products in the laboratory is vital for the fulfillment of the promise of regulatory oversight to protect the public health.

Disclosure of Potential Conflicts of Interest
P.G. Shields serves as an expert witness in tobacco litigation cases on behalf of plaintiffs. D.K. Hatazaki has received grants from NabiBiopharmaceuticals to undertake clinical trials on the nicotine vaccine.

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Mimicking Smoking Behavior in the Laboratory


Reconciling Human Smoking Behavior and Machine Smoking Patterns: Implications for Understanding Smoking Behavior and the Impact on Laboratory Studies


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