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Delivery of Smoke Toxicants from Cigarettes Made in Developed and Developing Countries: a comparison of U.S. full flavor and ultra light brands with Syrian cigarettes

Lynn M. Anderson
Virginia Commonwealth University

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Delivery of Smoke Toxicants from Cigarettes Made in Developed and Developing Countries: a Comparison of U.S. Full Flavor and Ultra Light Brands with Syrian Cigarettes.

A thesis defense submitted in fulfillment of the requirements for the degree of Masters of Science at Virginia Commonwealth University

By Lynn M. Anderson
B.A., Salisbury University, 2001

Director: Thomas E. Eissenberg, Ph.D.
Associate Professor
Department of Psychology and
Institute for Drug and Alcohol Studies

Virginia Commonwealth University
Richmond, Va.
August 2, 2005
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Abstract

DELIBERATION OF SMOKE TOXICANTS FROM CIGARETTES MADE IN DEVELOPED AND DEVELOPING COUNTRIES: A COMPARISON OF U.S. FULL FLAVOR AND ULTRA LIGHT BRANDS WITH SYRIAN CIGARETTES.

By Lynn M. Anderson, B.A.

A thesis defense submitted in fulfillment of the requirements for the degree of Masters of Science at Virginia Commonwealth University

Virginia Commonwealth University, 2005

Major Director: Thomas E. Eissenberg, Ph.D., Associate Professor, Department of Psychology and Institute for Drug and Alcohol Studies

Clinical research is needed to understand how cigarette toxicant yield affects smoker toxicant exposure. While there is much clinical research on yield and exposure in developed countries, there is little in developing countries.

Forty smokers completed one, 4-hour session to compare yield and exposure of different cigarettes. Participants smoked three cigarettes under controlled topography conditions: one U.S. full flavor, one U.S. ultra light, and one Syrian cigarette, with 90 minutes between cigarettes. Sessions differed by Syrian brand; 21 participants smoked
Alhamraa while 19 smoked Al Sham cigarettes. Blood nicotine and breath CO samples were obtained, HR was monitored and subjective withdrawal and cigarette effect questions were asked.

Results suggest that Syrian Alhamraa and U.S. full flavor were similar in exposure while Syrian Al Sham and U.S. ultra light were similar. Though U.S. full flavor and ultra light cigarettes differed in toxicant yield and exposure, subjective ratings of withdrawal were similar.
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- Informed consent and in-person screening.
- Practice session.
- Evaluation session.

# Procedure

- Telephone screening.
- Informed consent and in-person screening.
- Practice session.
- Evaluation session.

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- Expired air CO

# Secondary Outcome Measures
- Heart rate
- Puff topography measures
- Subjective measures of the direct effects of smoking and withdrawal

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- Secondary Outcome Measures
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<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td><em>ad lib</em></td>
<td><em>ad libitum</em></td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychological Association</td>
</tr>
<tr>
<td>BaP</td>
<td>benzo[a]pyrene</td>
</tr>
<tr>
<td>bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
</tr>
<tr>
<td>cig</td>
<td>cigarette(s)</td>
</tr>
<tr>
<td>cig/day</td>
<td>cigarettes per day</td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td>ES</td>
<td>effect size</td>
</tr>
<tr>
<td>FTC</td>
<td>Federal Trade Commission</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>HSD</td>
<td>honestly significant difference (Tukey)</td>
</tr>
<tr>
<td>IPI</td>
<td>inter-puff-interval</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>mg</td>
<td>milligrams</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>mg/cig</td>
<td>milligrams per cigarette</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>ml</td>
<td>milliliters</td>
</tr>
<tr>
<td>mm</td>
<td>millimeters</td>
</tr>
<tr>
<td>ms</td>
<td>millisecond</td>
</tr>
<tr>
<td>NAT</td>
<td>N-nitrosoanatabine</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NFDPM</td>
<td>nicotine-free dry particulate matter</td>
</tr>
<tr>
<td>ng/ml</td>
<td>nanograms per milliliter</td>
</tr>
<tr>
<td>NNK</td>
<td>4-(methylnitramino)-1-(3-pyridyl)-1-butanone</td>
</tr>
<tr>
<td>NNN</td>
<td>N-nitrosonornicotine</td>
</tr>
<tr>
<td>PAH</td>
<td>polycyclic aromatic hydrocarbons</td>
</tr>
<tr>
<td>ppm</td>
<td>concentration in parts per million</td>
</tr>
<tr>
<td>QSU</td>
<td>Questionnaire on Smoking Urges</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>sec</td>
<td>second(s)</td>
</tr>
<tr>
<td>USDHHS</td>
<td>United States Department of Health and Human Services</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analog scale</td>
</tr>
<tr>
<td>VCU</td>
<td>Virginia Commonwealth University</td>
</tr>
<tr>
<td>vs.</td>
<td>versus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Delivery of Smoke Toxicants from Cigarettes Made in Developed and Developing Countries: a Comparison of U.S. Full Flavor and Ultra Light Brands with Syrian Cigarettes.

Chapter 1

Introduction

Overview

The leading cause of preventable death in the world is tobacco smoking. Roughly 13,500 deaths occur every day from tobacco-related diseases, with a total of 4.9 million tobacco-related deaths occurring globally each year (World Health Organization [WHO], 2004). These deaths have several causes, including cancer, cardiovascular disease, and lung disease (WHO, 1997; Taylor & Bettcher, 2000; Centers for Disease Control [CDC], 2004). The number of tobacco-related deaths worldwide is projected to increase to 10 million per year by the year 2030 (WHO, 2004). If changes are not made, these trends are expected to continue, with 1 billion people across the globe dying from tobacco-related diseases by the end of the twenty-first century (Peto & Lopez, 2000). Thus, cigarette smoking is an increasingly important global health threat.

The detrimental effects of smoking on global health are likely to be particularly devastating in developing countries. In the year 2000, 2.43 million smoking-related deaths occurred in developed countries, and 2.41 million occurred in developing
countries (Ezzati & Lopez, 2003). By 2030, 70% of smoking-related deaths worldwide will likely occur in developing countries (WHO, 2004). Unfortunately, despite the lethality of the tobacco epidemic, and the expectation that developing countries will soon bear the brunt of it, most tobacco science has been limited to developed nations.

The high mortality rates for tobacco smokers are due to the many toxic smoke constituents they inhale: cigarette smoke contains over 4,000 constituents, 60 of which are known or suspected carcinogens, including polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines (United States Department of Health and Human Services [USDHHS], 1988; Hoffmann, Djordjevic, & Hoffman, 1997). Many of these carcinogens and other constituents are grouped under the heading “tar” (Federal Trade Commission [FTC], 2000). Carcinogen doses per cigarette are small, but they accumulate over a lifetime, thus increasing smokers’ cancer risk dramatically (Hecht, 2002).

Another component of cigarette smoke that causes adverse health effects is carbon monoxide (CO). CO has been implicated in cardiovascular disease, with smokers being twice as likely to die of coronary heart disease relative to non-smokers (Epstein & Perkins, 1988). Despite knowledge of these well known health risks, about 23% of the U.S. population (CDC, 2003), and 59% of the global population (WHO, 1997) smoke tobacco cigarettes. Continued smoking despite known health risks may be the result of dependence upon one or more tobacco smoke constituents.

Nicotine is a tobacco smoke constituent and mild psychomotor stimulant that supports physical dependence in non-human animals (USDHHS, 1988; Malin, Lake, Newlin-Maulsby, Roberts, Lanier, Carter, et al., 1992) and humans (USDHHS, 1988;
Benowitz, 1999). In humans, nicotine dependence is revealed during periods of tobacco abstinence, when a withdrawal syndrome produces somatic signs (e.g., bradycardia, increased food intake) and affective symptoms (e.g., anxiety, restlessness, depressed mood; Hughes, Gust, Skoog, Keenan, & Fenwick 1991; American Psychological Association [APA], 1994). Not surprisingly, 77-92% of tobacco smokers are dependent upon nicotine (Douglas, 1997). Nicotine dependence can contribute to smoking-related death and disease because it makes quitting difficult. For example, 70% of American smokers report that they want to quit, and 30% will attempt to quit each year. However, only 3% of those who attempt to quit will be successful after one year (Benowitz, 1999). In samples of smokers in other countries, the percentage able to maintain long-term abstinence is similar (e.g., 5% in India, China, and Syria; Gupta, 1996; Yang, Ma, Chen, Zhang, Samet, Taylor, et al., 2001; Maziak, 2002). The aversive withdrawal symptoms that accompany a quit attempt likely contribute to these relatively low cessation rates, especially considering that relapse to cigarette use is an effective method for suppressing these symptoms (USDHHS, 1988).

Overall, tobacco smoking is a global issue that produces serious adverse health effects via carcinogen and CO intake and that is maintained, at least in part, by nicotine dependence. One step in addressing this health problem involves gaining an understanding of the levels of nicotine and other smoke toxicants that cigarettes yield and to which smokers are exposed. A great deal of this research has been conducted in the U.S. and other developed countries, though the extent to which these results generalize to cigarettes and smokers in developing countries is unknown. This research from the U.S.
and developed countries is reviewed below, with a primary emphasis on CO and nicotine. A similar review is then conducted with research from developing countries.

Smoke Toxicants that Cigarettes in Developed Countries Yield and to Which Smokers in Developed Countries are Exposed

There is much research on the constituent yield of tobacco smoke that is produced by cigarettes manufactured and marketed in developed countries like the U.S., Canada, and the United Kingdom [U.K.]. The constituents most often measured in cigarettes that are marketed in these countries include carcinogens, CO, and nicotine. One method of measuring smoke toxicant yield was developed by the U.S. Federal Trade Commission (FTC) and involves the use of smoking machines to “smoke” cigarettes in a prescribed manner so that different brands can be compared (Pillsbury, Bright, O’Connor, & Irish, 1969). Using the FTC method, a cigarette is placed in one of several smoking machine ports. The cigarette is lit and the machine draws 35 ml, 2 sec duration “puffs” with an inter-puff-interval (IPI = time between puffs) of 58 sec until one of two conditions is met (whichever takes more time): either a butt length of 23 mm is reached or the cigarette has burned to within 3 mm of the edge of the tipping paper (Pillsbury et al., 1969). As the puffs are drawn, particulate matter from the smoke is collected onto a filter pad, and gases that pass through the pad are also collected. Thus, the FTC method allows for measurement of smoke toxicant yield in terms of milligrams of nicotine-free dry particulate matter (NFDPM; found in the pad), CO (measured in the gases that pass through the pad), and nicotine (found in the pad). One disadvantage of the FTC method is that smoke toxicant yields do not always predict smoke toxicant exposure in smokers,
as measured in exhaled breath and/or body fluids (saliva, urine, or blood; Kozlowski, Rickert, Pope, Robinson, & Frecker, 1982; Herning, Jones, Benowitz, & Mines, 1983).

Thus the sections below discuss the smoke toxicant yield of cigarettes marketed in the U.S. and the smoke toxicant exposure of U.S. smokers. Subsequent sections will discuss yield and exposure from cigarettes and smokers in developing countries.

**Carcinogens that cigarettes in developed countries yield and to which smokers in developed countries are exposed.** Cigarette smoke contains over 60 carcinogens (Hoffman et al., 1997). Some of these carcinogens are tobacco specific nitrosamines (TSNAs) such as N-nitrosonornicotine (NNN), N-nitrosoanatabine (NAT), and 4-(methylnitramino)-1-(3-pyridyl)-1-butanone (NNK) (Swauger, Steichen, Murphy, & Kinsler, 2002) and others are polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene (BaP), dibenz[a,h]anthracene, and 5-methylchrysene (Zevin, Gourlay, & Benowitz, 1998; Hecht, 1999). Because carcinogens are so numerous in cigarette smoke, they are seldom measured individually, and the carcinogenic compounds in cigarette smoke are reported as either NFDPM or, more commonly, as “tar”.

As can be seen in Table 1, the tar levels of U.S. cigarettes differ by brand type, with so-called “full flavor” brands yielding significantly more tar than so-called “light” brands, which, in turn, yield significantly more tar than so-called “ultra-light” brands (full flavor, light, and ultra light are defined by FTC yields). Light and ultra light cigarettes are made by using specific tobacco blends, differing filter tips, and porous filter paper and/or filter ventilation holes that dilute the smoke. By the 1990’s, over 90% of U.S. cigarettes were filtered, and 50% of these filters had ventilation holes (National Cancer
The resulting difference in tar yield of light and ultra light brands, often noted in cigarette advertisements, led many U.S. smokers to believe that these brands reduced carcinogen exposure, relative to full flavor brands (NCI, 1996). Not surprisingly then, smokers purchased cigarettes with lower tar yields: the sales-weighted average tar yield decreased from 38 mg in 1954 to 12 mg in 1993 (Hoffman et al., 1997; NCI, 1996). Interestingly, many smokers chose these cigarettes with the belief that they would inhale smoke with lower toxicant levels (Giovino et al., 1996). Also, smokers who were not able to quit smoking were urged to smoke these brands as a means of reducing their carcinogen exposure (Kozlowski et al., 1982). Thus, there was some expectation that reductions in the tar yield of cigarettes purchased and smoked by U.S. smokers might have been associated with reduced rates of smoking-related cancer.

Though 63% of men and 84% of women smokers in the U.S. smoke light/ultra light cigarette brands, cancer rates have not decreased accordingly (NCI, 1996, 2001). This failure of low tar cigarette use to lower cancer rates was highlighted in one study in which data were analyzed from studies that followed smokers in two cohorts (cohort I enrolled in 1959 and cohort II enrolled in 1982) and observed their lung cancer rates. Results indicate that despite the decrease in FTC tar yields, lung cancer rates have increased since the 1950’s, and the increase in lung cancer rates across cohorts suggest that reducing tar yield reduces neither carcinogen exposure nor lung cancer rates (Thun & Heath, 1997). Thus, epidemiological data suggest that analysis of cigarette smoke produced by smoking machines (as in the FTC method) is insufficient for understanding smokers’ exposure to cigarette-delivered toxicants.
Several exposure studies support the notion that smokers' carcinogen exposure cannot be predicted by smoke toxicant yield (Russel, Jarvis, Iyer, & Feyerband, 1980; Kozlowski et al., 1982; Djordjevic, Hoffman, & Hoffman, 1997; Djordjevic, Stellman, & Zang, 2000; NCI, 2001; Woodward & Tunstall-Pedoe, 1992). One of the reasons that FTC yield is a poor predictor of exposure is that smokers do not adhere to the FTC method. Indeed, in most studies of smokers, variables such as puff volume and IPI are different from the FTC method, and show considerable variability across subjects. In yield and exposure studies, puff topography assessment (i.e., measurement of puff volume, puff duration, puff number, and IPI) reveals that puff parameters determine the tar, nicotine, and CO yield and exposure.

For example, when low tar cigarettes are “smoked” by machines using FTC parameters versus using human parameters, the estimated tar deliveries do not match. One study addressing this point measured the puff topography (puff volume and IPI) of smokers of low tar yield cigarettes and then set a smoking machine to these parameters (Djordjevic et al., 2000). As compared to FTC parameters, humans took larger puffs (average puff volume of 48.6 ml low-yield vs. 35 ml FTC) and had shorter IPIs (21.3 sec low-yield vs. 58 sec FTC). As a result, the mean tar yield for human parameters was 22.3 mg/cig (geometric mean; 95% confidence interval = 18.8 – 26.5), a full 13.8 mg/cig higher, on average, than the tar yields derived from the FTC parameters (geometric mean = 8.5 mg/cig; 95% confidence interval = 7.7-9.5; Djordjevic et al., 2000). These differences in tar yield observed using the FTC method and more realistic smoking parameters reflect differences in the yield of specific carcinogens. For example, the
yields of the carcinogens BaP and NNK from low yield cigarettes can increase relative to FTC yields when smoking parameters are more realistic. The yield of BaP was 7.9 mg/cig higher under human parameters than the yield derived from FTC methods (geometric mean = 17.9 mg/cig; 95% confidence interval = 15.3-20.9). NNK yield was 73.6 mg/cig higher under human parameters than the yield derived from FTC methods (geometric mean = 186.5 mg/cig; 95% confidence interval = 158.3-219.7; Djordjevic et al., 2000).

The FTC method also underestimates tar and carcinogen yield across medium-yield cigarettes (Djordjevic et al. 2000). The yield of BaP was 7.4 mg/cig higher under human parameters (geometric mean = 21.4 mg/cig; 95% confidence interval = 19.2-23.7) than the yield derived from FTC methods (geometric mean = 14.0 mg/cig; 95% confidence interval = 10.1-19.4). NNK yield was 104.7 mg/cig higher under more realistic parameters (geometric mean = 250.9 mg/cig; 95% confidence interval = 222.7-282.7) than the yield derived from FTC methods (geometric mean = 146.2 mg/cig; 95% confidence interval = 132.5-161.3; Djordjevic et al. 2000). Thus, tar yield may communicate some information regarding carcinogen yield, although the FTC method clearly does not communicate real-world values. Human puffing parameters may convey more realistic values.

However, puff topography values can vary considerably and systematically between subjects. Indeed, smokers' gender is an important factor: men take significantly larger (mean=54.8 ml, SEM=2.5) and longer puffs (mean=1.53 sec, SEM=0.08) than women (mean=41.61 ml, SEM=2.8, mean=1.19 sec, SEM=0.09) (Eissenberg, Adams,
Riggins, & Likness, 1999). These differences need to be taken into account when studying cigarette yields.

Another reason that FTC yield is a poor predictor of exposure is that smokers cover some or all of the ventilation holes in a cigarette filter with lips or fingers when they smoke (e.g., Kozlowski et al., 1982). Covering ventilation holes does not allow the smoke that is inhaled by the smoker to be diluted with the surrounding air, as it is using the FTC method. In one study that examined this issue, smoke constituent levels of eleven low yield brands were determined using standard FTC machine smoking and non-standard machine smoking where the parameters were set to the sample population’s average puff volume (47 ml), duration (2.4 sec) and IPI (44 sec) with filter ventilation holes occluded with tape. Relative to FTC methods (mean tar yield = 0.7 mg/cig; SD = 0.2), tar yields obtained from cigarettes smoked under non-standard parameters and with blocked ventilation holes were higher (mean tar yield = 17.5 mg/cig; SD = 6.7). Thus, the combined influence of realistic smoking parameters and blocked ventilation holes results in a dramatic increase in tar yield (i.e., mean difference in tar yield = 16.8 mg/cig; SD = 6.6; Kozlowski et al., 1982).

As the above studies have shown, smokers of low yield cigarettes may be exposed to higher levels of carcinogens than predicted by the FTC. Another way to observe this apparent increase in exposure is to measure biomarkers of exposure (blood, saliva, or urine). In a study that used these methods, daily smokers smoked ten cigarettes from each of three brand types: low tar yield, medium tar yield, and high tar yield (Mohtashamipur, Norpoth, & Lieder, 1987). Urine samples were collected and examined
for mutagenic activity (causing genetic mutation). Mutagenic activity levels in the urine were higher when smokers smoked the low tar yield cigarettes than when they smoked medium or high tar yield cigarettes. Unfortunately, puff topography was not controlled, thus the influence of changes in smoking behavior on these increases in urine mutagenic levels after smoking low yield cigarettes is uncertain (Mohtashamipur et al., 1987). Regardless of the mechanism, these results do not support the notion that carcinogen exposure is lowered when smokers smoke low-yield cigarettes.

Another study collected and analyzed urine samples from smokers of regular, light, and ultra light cigarettes to determine if smokers of these different types of cigarettes are exposed to different levels of 1-HOP and NNAL (biomarkers for lung cancer). Published tar levels for these cigarettes were compared with the biomarkers to examine possible tar delivery differences between the different types of cigarettes. Urinary cotinine levels were also compared. No significant differences were found in either the 1-HOP or NNAL levels found in the smokers of different types of cigarettes and no correlation was found between published tar levels and corresponding biomarker delivery. Also, the urinary cotinine levels that the different smokers were exposed to were not significantly different (Hecht, Murphy, Carmella, Li, Jensen, Le, et al., 2005). The results do not support the notion that light cigarettes expose smokers to lower levels of carcinogens than regular cigarettes.

Another study observed biomarkers of exposure in order to estimate tar delivery in smokers of cigarettes with differing tar levels (Woodward & Tunstall-Pedoe, 1992). Smokers were classified into three categories based on the machine-smoking tar yields of
the cigarettes that they usually smoked: high tar (mean = 15.7 mg/cig), middle tar (13.3 mg/cig), and low tar (7.77 mg/cig). Blood samples were obtained from smokers of cigarettes within each tar level group to examine cotinine and thiocyanate (a metabolite of hydrogen cyanide) levels and breath samples were obtained to determine CO levels. These levels were used to calculate the estimated tar exposure. Number of cigarettes smoked per day was not controlled for. Results indicated that smokers of relatively low tar cigarettes do indeed consume less tar for the same number of cigarettes smoked, but the decrease is much less than the official yields would suggest. The consumption of other smoke components may not be less amongst those smoking relatively low tar cigarettes, and may even be higher when we compare a middle tar smoker with a high tar smoker (Woodward & Tunstall-Pedoe, 1992; p. 927).

Thus, although smokers of lower tar cigarettes may receive less tar, this reduction is not proportional to machine smoking yields.

In summary, in developed countries, tar yield (and thus carcinogen yield) is measured by the FTC or other machine smoked method, and is related to cigarette brand (i.e., full flavor, light, ultra light). Few studies have investigated carcinogen exposure in smokers directly (i.e., by measuring carcinogens or carcinogen metabolites in smokers blood or urine). However, epidemiological and laboratory data suggest that carcinogen exposure is high in this population, and that exposure is not predicted accurately by FTC yield. FTC yield is not a good predictor for several reasons, including the fact that smokers do not smoke according to FTC smoking parameters and block filter ventilation holes when smoking. As Woodward & Tunstall-Pedoe (1992) conclude, differences
between machine smoking tar yields and actual tar exposure are "likely to be extremely important in diseases related to tar intake, such as lung cancer" (p. 925). Generally, then, assessment of smoke constituent yield must be complemented by an assessment of smoke constituent exposure in smokers, in order to attain a realistic estimate of disease rates. As discussed below, this same general message is relevant to CO and nicotine yield and exposure.

Table 1
*Mean FTC yields of popular full flavor, light, and ultra light cigarette brands manufactured and sold in the U.S.*

<table>
<thead>
<tr>
<th>Cigarette type</th>
<th>Tar</th>
<th>Nicotine</th>
<th>CO</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Flavor</td>
<td>15.3(1.5)</td>
<td>1.0(0.15)</td>
<td>15.3(1.5)</td>
<td>8</td>
</tr>
<tr>
<td>Light</td>
<td>9.2(1.0)**</td>
<td>0.7(0.1)**</td>
<td>11.0(1.2)**</td>
<td>8</td>
</tr>
<tr>
<td>Ultra light</td>
<td>5.6(1.5)†</td>
<td>0.5(0.12)†</td>
<td>7.6(1.5)†</td>
<td>7*</td>
</tr>
</tbody>
</table>

*Note.* The average tar, nicotine, and CO levels (mg) for eight popular brands of U.S. cigarettes. Six of the eight brands of cigarettes chosen for this analysis were listed as the most popular in the U.S. by the Centers for Disease Control (CDC, 2004).

*The n of the ultra light cigarette type is less than the n of the full flavor and light cigarette types because one brand is not produced in an ultra light version. ** Indicates a significant difference from full flavor cigarettes at p < .001. † Indicates a significant difference from light cigarettes at p < .001.

**CO levels that cigarettes from developed countries yield and to which smokers in developed countries are exposed.** CO is a gas that is produced when a material, such as tobacco, is burned. CO is rapidly absorbed from the lungs into the blood stream where it
binds with hemoglobin which would normally carry oxygen. Hemoglobin’s affinity for CO is over 200 times greater than it’s affinity for oxygen. Therefore, CO binding to hemoglobin reduces the amount of oxygen that is delivered to tissues throughout the smokers’ body, including the heart (Stewart, 1975; Lakier, 1992). This reduction in oxygen delivery, in turn, causes the heart to pump harder to provide the body with oxygen. Also, the majority of inhaled CO is eliminated, unchanged, from the lungs, with less than 1% being metabolized to carbon dioxide in the body. CO has a half-life of 4-5 hours in a sedentary adult (Stewart, 1975).

In the U.S., the FTC method is used to determine a cigarette’s CO yield and Table 1 shows that CO yield for U.S. cigarettes differ by cigarette type. As with tar yields, light cigarettes deliver significantly less CO than full flavor cigarettes, and ultra light cigarettes deliver significantly less CO than light cigarettes. Also as with tar yields, CO yield does not predict CO exposure in smokers. As discussed previously, the difference between FTC yield and smoker exposure is due, in part, to the fact that smokers do not adhere to FTC smoking parameters (e.g. Djordjevic et al., 2000). As discussed below, filter ventilation blocking and brand-induced changes in smoking behavior are also relevant.

Cigarette brands have varying degrees of filter ventilation: full flavor cigarettes generally have no ventilation and ultra light cigarettes generally have the greatest amount of ventilation. Frequently, filter ventilation is accomplished with vents or holes that are approximately 11-15 mm away from the end of the filter (NCI, 2001). Ventilation holes allow air to mix with and dilute the smoke of a cigarette decreasing the amount of smoke
that is inhaled (NCI, 1996). For example, a cigarette that has 60% ventilation will generate a puff that is 60% air and 40% smoke (NCI, 2001). In one study of the influence of ventilation hole blocking, smokers used brands of cigarettes which varied in percent ventilation, ranging from 40% ventilation, (FTC CO yield = 9 mg) to 83% ventilation (FTC CO yield = 1 mg; Sweeney, Kozlowski, & Parsa, 1999). Using ad lib smoking, the cigarettes were either smoked with no ventilation holes covered or as many ventilation holes as possible covered by the participants’ fingers. Filter ventilation hole blocking clearly influenced CO exposure in cigarettes with more ventilation. For example, a significant increase was found in the mean CO boost (post-smoking CO minus pre-smoking CO) of cigarettes with 66% ventilation after ventilation holes were blocked (unblocked mean = 2.0 ppm; SEM = 0.57 versus blocked mean = 3.7 ppm; SEM = 0.49). Results of this study suggest that the more ventilation a cigarette filter has, the higher the increase in CO delivery if the smoker engages in ventilation hole blocking (Sweeney et al., 1999).

Similar results were found in another study which examined the effects of ventilation hole covering of ultra low yield cigarettes (FTC 1 mg CO) on CO levels in smokers of medium to high yield cigarettes (Zacny, Stitzer, & Yingling, 1986). In two experiments, ultra low yield cigarettes were smoked, each with a varying degree of occluded ventilation holes: 0% occluded, 50% occluded, or 100% occluded. In experiment one, eight cigarettes were smoked in the lab in each of three sessions under controlled puffing parameters (i.e., 8 puffs, 1 puff every 50 sec, 60 ml puff volume, with a breath hold duration of 3.5 sec) with a 20 min inter-cigarette interval. CO was
measured immediately before and 2 min after smoking, in order to determine CO boost. Results indicated that CO boost increased significantly as a function of percent of ventilation holes covered with mean CO boost of 0.83 ppm, 2.87 ppm, and 7.07 ppm for 0%, 50%, and 100% ventilation holes covered, respectively (Zacny et al., 1986).

In experiment two, one cigarette from each of the ventilation occlusion conditions was smoked in the lab under ad lib puffing conditions for a total of three cigarettes every day for five days. Results indicated that CO boost increased significantly from pretrial CO with mean CO boost of 4.32 ppm, 6.44 ppm, and 8.96 ppm for 0%, 50%, and 100% ventilation holes covered, respectively. Mean puff volume increased as ventilation occlusion decreased from 42.8 ml at 100% occlusion to 63.3 ml at 0% occlusion. Results from these experiments suggest that smokers will increase the amount of smoke they inhale when smoking cigarettes with ventilation holes. These smokers will therefore be exposed to higher levels of CO than the FTC yields predict (Zacny et al., 1986).

Another study observed CO exposure in smokers of high-, medium-, and low-yield cigarettes (Woodward & Tunstall-Pedoe, 1992). Breath samples were obtained from smokers of cigarettes within each tar level group to determine CO levels. Smokers of low tar cigarettes were exposed to less CO than smokers of medium or high tar cigarettes. Smokers of medium tar cigarettes (mean = 24.5; SD = 13.9), however, may be exposed to higher CO levels than those who smoke high tar cigarettes (mean = 23.5; SD = 13.1). These differences may be due to changes in smoking topography, but as no topography measures were examined, it is difficult to explain these differences with any certainty.
In summary, much is known in developed countries about CO yield and delivery. Brands that have low CO yield as determined using machine smoking methods do not necessarily expose smokers to lower levels of CO. This failure to reduce exposure is likely due to blockage of filter ventilation holes and/or changes in smoking topography. Thus, an accurate assessment of a cigarette’s ability to deliver CO to a smoker involves measuring CO exposure in humans who are smoking.

Nicotine levels that cigarettes in developed countries yield and to which smokers in developed countries are exposed. Nicotine is an agonist, a drug that triggers an action, and it binds to nicotinic cholinergic receptors (Kilaru, Frangos, Chen, Gortler, Dhadwal, Arai, et al., 2001; Rosenzweig, Breedlove & Leiman, 2002). These receptors are found in the brain and the peripheral nervous system (Watkins, Koob & Markou, 2000). Nicotine produces many effects such as mild euphoria (Pomerleau & Pomerleau, 1992), heightened arousal, appetite suppression, reduction of stress (Benowitz, 1996), body weight regulation, and mood (e.g., anxiety and tension; Palfai & Jankiewicz, 1997). Once in the brain, nicotine binds to acetylcholine receptors triggering the release of serotonin, acetylcholine, norepinephrine, and dopamine neurotransmitters. The release of serotonin in the brain reduces negative affect and anxiety (Benowitz, 1999; Royal College of Physicians, 2000). Acetylcholine release affects memory and performance. Nicotine-induced release of norepinephrine (and epinephrine) from the adrenal glands results in increased heart rate and blood pressure. Dopamine release creates feelings of pleasure and the effects of this neurotransmitter may be one of the main reasons for the
positive reinforcing effects of cigarettes (Pomerleau & Pomerleau, 1984; Royal College of Physicians, 2000).

Nicotine is believed to be the tobacco smoke constituent that is responsible for maintaining tobacco use in humans, primarily because nicotine administration is reinforcing and repeated nicotine administration can produce physical dependence (USDHHS, 1988; Stolerman & Jarvis, 1995; Benowitz, 1999; Eissenberg, 2004). The most efficient delivery device of nicotine is the cigarette (Benowitz, 1996), and a majority of cigarette smokers eventually become nicotine dependent (Balfour, 1994; Stolerman, 1991). Nicotine dependence can be revealed by an aversive withdrawal syndrome experienced during periods of tobacco abstinence (Hughes & Hatsukami, 1986). Withdrawal symptoms can begin within minutes after cessation (Schuh & Stitzer, 1995), peak within 1 – 4 days after cessation (Hatsukami, Hughes, Pickens, & Svikis, 1984; Buchhalter, 2002) and may include headache, irritability, sleep disturbances, an inability to concentrate, and hunger (Hughes & Hatsukami, 1986). The maintenance of regular tobacco smoking is thought to be facilitated by the avoidance or suppression of withdrawal symptoms through nicotine administration (Watkins et al., 2000; USDHHS, 1988; Eissenberg, 2004).

As with tar and CO, Table 1 shows that, in the U.S., FTC cigarette nicotine yields differ by brand: full flavor cigarettes have higher average nicotine yields than light cigarettes which have higher nicotine yields than ultra light cigarettes. And, as with CO, FTC yields are poor predictors of smokers’ nicotine exposure (Herning et al., 1983; Russell et al., 1980). For example, in one study eleven daily smokers (≥ 40 cig/day) were
asked to smoke two cigarettes during each laboratory visit for a total of 40 cigarettes smoked over a total of 20 days (Herning et al., 1983). The smoking sessions occurred in the laboratory setting and puff topography was measured. The first cigarette of a session was always a standardized research cigarette that contained more (2.5 mg) or less (0.4 mg) nicotine, as measured by the FTC method, than the smoker’s usual brand (mean = 1.0 mg; SD = 0.2). The other brand was the smoker’s own brand and was smoked at the request of the smoker (mean ± SD = 18.5 ± 8.2 min inter-cigarette-interval). Blood was sampled 60-120 sec before and 30-120 sec after smoking. Results indicated that machine predicted nicotine yield and actual nicotine delivery were only moderately correlated (r = 0.50) and the remaining variability in blood nicotine level was accounted for largely by individual differences in smoking behavior (Herning et al., 1983).

One factor that contributes to the poor predictive relationship between FTC nicotine yield and smokers’ nicotine exposure is the fact that smokers regulate their daily intake of nicotine (NCI, 2001): smokers of low and medium nicotine yield cigarettes smoke with more intensity by increasing their puff volume than smokers of high nicotine cigarettes (Djordjevic et al., 1997). This effect is most readily observed in the laboratory when smokers are provided with cigarettes that have lower FTC nicotine yields than their usual brand. For example, in one study of 26 daily, full flavor brand smokers (mean of 24 cig/day), twelve participants were given ultra low yield cigarettes (0.1 mg nicotine) and were asked to smoke only these cigarettes for ten days (West & Gossop, 1994). The other fourteen participants smoked their usual brand of full flavor cigarettes (1.3 mg nicotine) for ten days. Blood samples were taken to measure nicotine levels in both
groups. All participants reported smoking the same number of cigarettes per day (mean of 23.8 cig/day in the low yield condition vs. 22.3 in the full flavor condition). While nicotine levels were lower in the ultra low yield condition (mean of 3 days = 10.5 ng/ml) than in the full flavor condition (mean of 3 days = 33.2 ng/ml), the levels were not as low as might be predicted using FTC nicotine levels (e.g., smoking a 0.1 mg nicotine cigarette instead of a 1 mg nicotine cigarette is a tenfold reduction in nicotine yield). Nicotine exposure that differs from that predicted using FTC yield could be due to changes in smoking behavior. In other words, these smokers may have increased their puff volume, duration, and/or IPI when using ultra low yield cigarettes in an attempt to maintain their usual nicotine exposure (West & Gossop, 1994).

Another study (Zacny & Stitzer, 1988) revealed similar results. Ten daily smokers (mean 30.5 cig/day) who normally smoked full flavor brand cigarettes were given four brands of cigarettes of differing nicotine yields, as well as their own brand, over a period of five weeks. In each five-day period, the participants smoked a different yield brand: ultra low yield (0.1 mg), low yield (0.4 mg), medium yield (0.7 mg), high yield (1.1 mg), and own brand (1.0 mg). They smoked cigarettes ad lib and returned all butts and unused cigarettes to the laboratory each week. Topography measures and blood samples were obtained when participants smoked in the laboratory on the first and last day of each week. Results indicated that daily cigarette consumption (own brand mean = 30.5 cpd vs. ultra low yield = 34.3 cpd), puff volume (own brand mean = 53.4 ml vs. ultra low yield = 64.7 ml), and number of puffs (own brand mean = 6.8 vs. ultra low yield = 11.3 puffs/cigarette) increased from own brand when participants smoked ultra low yield.
yield cigarettes. Blood nicotine level reductions were not well predicted by FTC yields (e.g., a 90% reduction would be predicted when smoking 0.1 mg nicotine yield cigarettes, as compared to an observed reduction of 67%) which may be due to the observed changes in number of cigarettes smoked and/or smoking topography. These full flavor smokers may have changed their smoking behavior in order to maintain their exposure to nicotine when smoking lower nicotine yield cigarettes (Zacny & Stitzer, 1988).

_Cigarettes in developed countries: summary of carcinogen, CO, and nicotine yield and exposure._ There is a large body of evidence in the U.S. and other developed countries that smoke from cigarettes contains many toxic constituents and that the machine derived yields of these constituents do not reveal the actual constituent exposure in smokers. This discrepancy is almost certainly due to changes in smoking topography and ventilation hole blocking. In essence, people do not smoke according to the FTC method, but instead alter their smoking behavior in ways that negate cigarette design changes and that produce smoke constituent yields that differ from those produced using the FTC method. These alterations in smoking behavior may be due to a failure of some cigarette types (i.e., low yield cigarettes) to suppress withdrawal effectively (e.g., West & Gossop, 1994). Interestingly, FTC yield might be a better predictor of exposure under conditions where smokers’ topography is held constant and where filter ventilation holes cannot be blocked, though this hypothesis has not been tested.
Smoke toxicants that cigarettes in developing countries yield and to which smokers in developing countries are exposed

In developing countries, there is less literature available regarding yield and exposure of smoke toxicants. A developing country is defined as a low- or middle-income country in which most people have a lower standard of living than most people in high-income countries (The World Bank Group, 2004). Of the few studies that have been conducted on cigarette constituent yields in developing countries, some were conducted many years ago (e.g., studies on African cigarette constituent levels; Seftel, 1979; Awotedu, Higenbottam, & Onadeko, 1983). However, cigarettes and smokers may have changed in the intervening 25 years. Of the more recent studies, all have focused primarily on the cigarette constituent yields as determined by machine methods (e.g., Mitacek, Brunnerman, & Polednak, 1990; Hamadeh, Dphil, McPherson, & Doll, 1994; Pakhale & Maru, 1998; Ashley, Beeson, Johnson, McCraw, Richter, Pirkle et al., 2003). Some results are consistent with the hypothesis that toxicant yields from cigarettes sold in developing countries are higher than those from cigarettes made and sold in developed countries (Mitacek et al., 1990; Firat, 1996; Ashley et al., 2003). One study showed no difference in machine-smoked constituent yields of Marlboro brand cigarettes manufactured in or exported to 35 different countries. In this case only the local manufactured, non-Marlboro brands varied in yield, with Eastern Mediterranean and Southeastern Asian regions having higher deliveries than those made in Europe and the Americas (Calafat, Polzin, Saylor, Richter, Ashley, & Watson, 2004). A limitation of
this study is that these yields were determined by machine smoking methods and cannot predict actual exposure to the smoker.

Of the studies examining differing brands of cigarettes in developing countries, no clinical research could be found that examined the exposure of smokers to cigarette toxicants such as CO and nicotine.

*Carcinogens that cigarettes in developing countries yield.* Generally, smoke toxicant yields can vary from country to country, even within the same brand (Seftel, 1979; Firat, 1996; Kozlowski, Mehta, Sweeney, Schwartz, Vogler, Jarvis, et al., 1998; Ashley et al., 2003). In Thailand, six brands of locally made cigarettes, several of which were unfiltered, were analyzed to determine their FTC tar yields and these were compared with the FTC yields of two normally-marketed U.S. brands (Mitacek et al., 1990). The locally made, filtered brands yielded higher tar levels (21.3-28.1 mg) than the U.S. filtered brands (10.3-26.4 mg) and the non-filtered brands yielded on average 8 mg/cig more tar (24.0 mg/cig ± 14.8) than the U.S. non-filtered brand (16.0 mg/cig). As 23% of the Thai population smokes cigarettes, higher tar levels could increase the rates of tobacco-related disease in a country where 467,668 people died from such diseases in 1994 alone (Mitacek et al., 1990; WHO, 2003). Tar yields are also high in cigarettes made and sold in Turkey (Firat, 1996). Several local and imported brands were measured using International Organization for Standardization [ISO] methods, which are similar to FTC methods, (one 35 ml puff, 2 sec in duration every 60 sec; NCI, 1996) to determine the tar yield. The locally produced brands had a higher tar yield (11.8-29.2 mg) as compared to the imported brands (7.23-17.1 mg). In addition, two of the fourteen locally
produced brands were the only brands to have tar yields below 12 mg (the European standard). When examining brands exported to both Turkey and the U.K., tar yields were found to be higher by up to 4 mg in five of the seven brands that were exported to Turkey (Firat, 1996). Though Turkey and the U.K. are importing the same brands, smokers in Turkey may have a higher risk of developing tobacco-related cancer due to the higher tar yields (to the extent that greater tar yields increase cancer risk).

A more recent study compared the machine-smoked yields of locally made cigarette brands with Marlboro brand cigarettes either manufactured in or exported to various countries (Calafat et al., 2004). Seventy-seven cigarette brands were obtained from 35 countries, of which 97% of the brands were filtered and 95% were non-mentholated. The cigarettes were machine-smoked according to FTC methods. The average 13.4 mg (SD = 1.7) tar yield of Marlboro brand cigarettes was similar to the 14.4 mg (SD = 3.8) average of local brands. Results for cigarettes from 29 other developing countries represented in this study are displayed in Table 2, which shows that the individual and mean tar yields of these cigarettes approximate that of U.S. full flavor brands (see Table 1 for U.S. brand tar yields). However, as noted in the report’s conclusion: “... an important limitation of this study is that people do not smoke cigarettes as machines smoke them” (Calafat et al., 2004, p. 50). Thus, understanding the carcinogen exposure of smokers in developing countries likely will involve clinical evaluation.
Table 2  
Toxicant yields of twenty-nine cigarette brands sold in developing countries.

<table>
<thead>
<tr>
<th>Developing Country</th>
<th>Tar</th>
<th>Nicotine</th>
<th>CO</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>10.9(2.5)</td>
<td>0.9(0.2)</td>
<td>11.1(2.4)</td>
<td>4</td>
</tr>
<tr>
<td>China</td>
<td>13.7(1.9)</td>
<td>1.2(0.1)</td>
<td>12.3(0.8)</td>
<td>2</td>
</tr>
<tr>
<td>Cyprus</td>
<td>13.5(1.2)</td>
<td>0.9(0.1)</td>
<td>13.4(0.4)</td>
<td>1</td>
</tr>
<tr>
<td>Egypt</td>
<td>16.7(0.8)</td>
<td>0.8(0.1)</td>
<td>14.7(1.0)</td>
<td>2</td>
</tr>
<tr>
<td>Fiji</td>
<td>11.3(3.1)</td>
<td>0.9(0.1)</td>
<td>11.3(2.7)</td>
<td>3</td>
</tr>
<tr>
<td>India</td>
<td>11.3(3.4)</td>
<td>0.9(0.3)</td>
<td>11.7(2.6)</td>
<td>3</td>
</tr>
<tr>
<td>Jordan</td>
<td>11.2(3.2)</td>
<td>0.8(0.2)</td>
<td>9.9(4.2)</td>
<td>2</td>
</tr>
<tr>
<td>Kenya</td>
<td>13.7(0.4)</td>
<td>1.1(0.07)</td>
<td>10.5(0.1)</td>
<td>2</td>
</tr>
<tr>
<td>Kiribati</td>
<td>12.6(1.8)</td>
<td>0.8(0.2)</td>
<td>7.6(0.3)</td>
<td>1</td>
</tr>
<tr>
<td>Lao P.D.R.</td>
<td>16.7(5.1)</td>
<td>0.9(0.2)</td>
<td>12.8(2.6)</td>
<td>5</td>
</tr>
<tr>
<td>Lebanon</td>
<td>11.3(1.3)</td>
<td>0.9(0.1)</td>
<td>11.0(0.3)</td>
<td>1</td>
</tr>
<tr>
<td>Lithuania</td>
<td>14.5(0.8)</td>
<td>0.8(0.3)</td>
<td>10.3(2.8)</td>
<td>2</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>14.0(0.8)</td>
<td>0.7(0.3)</td>
<td>12.4(0.4)</td>
<td>2</td>
</tr>
<tr>
<td>Malaysia</td>
<td>16.5(0.8)</td>
<td>0.9(0.2)</td>
<td>11.2(1.3)</td>
<td>2</td>
</tr>
<tr>
<td>Mexico</td>
<td>15.1(0.7)</td>
<td>0.8(0.1)</td>
<td>13.2(0.3)</td>
<td>3</td>
</tr>
<tr>
<td>Mongolia</td>
<td>12.5(2.1)</td>
<td>0.7(0.1)</td>
<td>11.8(0.3)</td>
<td>1</td>
</tr>
<tr>
<td>Myanmar</td>
<td>13.9(1.6)</td>
<td>0.9(0.1)</td>
<td>11.3(2.8)</td>
<td>2</td>
</tr>
<tr>
<td>Nepal</td>
<td>18.6(3.5)</td>
<td>1.0(0.3)</td>
<td>13.3(1.8)</td>
<td>4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>11.9(1.1)</td>
<td>0.7(0.3)</td>
<td>9.6(0.3)</td>
<td>2</td>
</tr>
<tr>
<td>Pakistan</td>
<td>17.0(4.9)</td>
<td>1.3(0.5)</td>
<td>12.9(2.8)</td>
<td>2</td>
</tr>
<tr>
<td>Philippines</td>
<td>14.3(6.4)</td>
<td>0.7(0.9)</td>
<td>17.0(0.6)</td>
<td>2</td>
</tr>
<tr>
<td>Poland</td>
<td>13.0(1.4)</td>
<td>0.9(0.08)</td>
<td>11.3(0.7)</td>
<td>2</td>
</tr>
<tr>
<td>Romania</td>
<td>16.4(5.3)</td>
<td>0.9(0.05)</td>
<td>10.3(2.4)</td>
<td>2</td>
</tr>
<tr>
<td>Russia</td>
<td>11.6(3.9)</td>
<td>0.9(0.2)</td>
<td>11.7(3.5)</td>
<td>2</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>12.6(1.4)</td>
<td>1.0(0.1)</td>
<td>9.9(0.8)</td>
<td>2</td>
</tr>
<tr>
<td>Tonga</td>
<td>12.3(3.3)</td>
<td>0.8(0.5)</td>
<td>7.8(0.1)</td>
<td>2</td>
</tr>
<tr>
<td>Vietnam</td>
<td>13.7(2.6)</td>
<td>0.9(0.2)</td>
<td>12.3(2.5)</td>
<td>4</td>
</tr>
<tr>
<td>Western Samoa</td>
<td>14.5(1.1)</td>
<td>1.1(0.2)</td>
<td>12.3(0.2)</td>
<td>1</td>
</tr>
<tr>
<td>Yemen</td>
<td>13.1(2.3)</td>
<td>0.9(0.04)</td>
<td>11.9(0.3)</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean 13.7 (2.05) 0.9 (0.14) 11.6 (1.88)

Note. The average tar, nicotine, and CO yields (mg) for twenty-nine cigarette brands sold in developing countries. Source: Calafat et al., 2004.
A study that examined machine-smoked TSNA levels in cigarettes found differing levels between exported U.S. cigarettes and cigarettes made locally in other countries (Ashley et al., 2003). The study was conducted in two phases. Phase one examined the TSNA content of Marlboro brand, full flavor cigarettes made in or exported to 21 countries and compared this to the popular cigarette brands made locally in these countries. In 71% of the countries, Marlboro cigarettes had higher levels of TSNAs than the local, non-Marlboro brands. Phase two was similar and it included fourteen countries. The TSNA levels of Marlboro full flavor cigarettes made in or exported to these countries were compared to the TSNA levels found in the popular, locally made, full flavor cigarettes. In 85% of the countries, TSNA levels were higher in the Marlboro brand cigarettes than in the locally made cigarettes. In developing countries, the highest TSNA levels were found in Marlboro brands that were purchased in Bangladesh (1.9 µg/g ± 0.1 vs. 0.2 µg/g ± 0.02 local brand), Indonesia (1.9 µg/g ± 0.2 vs. 0.4 µg/g ± 0.03 local brand), and Kenya (1.8 µg/g ± 0.2 vs. 0.2 µg/g ± 0.02 local brand). The lowest TSNA levels were found in cigarettes that were made in Kenya (0.2 µg/g ± 0.02; Ashley et al., 2003). Again, determining the actual TSNA exposure of smokers in these countries requires clinical exposure studies. Clinical studies that examine carcinogen exposure in smokers in developing countries may help to predict disease rates, and will provide a baseline with which to compare efforts to reduce carcinogen levels in smokers (i.e., harm reduction efforts).

CO levels that cigarettes in developing countries yield. Several studies have used machine smoking methods to examine CO yield from cigarettes marketed in developing
countries. For example, Mitacek et al. (1990) examined six brands of locally made Thai cigarettes to determine their FTC CO yields and these yields were compared with the yields of two U.S. brands. Results indicated that, with the exception of one local brand (18.9 mg/cig), the mean CO yield of locally made filtered brands (16.8 mg/cig ± 1.6) is comparable to the mean yield of a U.S. filtered, full flavor brand (15.0 mg/cig; Mitacek et al., 1990). A similar study examined the ISO CO yields of the five most popular brands and two brands of recent popularity that are sold in Bahrain (Hamadeh et al., 1994). The mean CO yield was 12.7 mg/cig ± 1.4, also similar to the CO yield of light brands sold in the U.S. (Table 1). In cigarettes from 29 developing countries, the mean CO yield was 11.6 mg/cig ± 1.9, also similar to U.S. light cigarette brand yield (see Tables 1 and 2; Calafat et al., 2004). The CO yield of cigarettes from only one country (Philippines mean = 17.0 mg) was substantially higher than U.S. brands. Though the CO yields of cigarette brands in developing countries are comparable to those in developed countries, CO yield may not predict smokers’ CO exposure. As no clinical studies on CO exposure have been completed in these countries, smokers’ exposure to CO is unknown.

**Nicotine levels that cigarettes in developing countries yield.** Several studies have used machine smoking methods to examine nicotine yields in cigarettes sold in developing countries, though nicotine exposure is uncertain. For example, a study in India examined nicotine yields (FTC method) in Indian cigarettes as compared to U.S. cigarettes (Pakhale & Maru, 1988). Results indicated that Indian cigarettes had a higher yield of nicotine (2.58 mg) than the U.S. cigarettes (1.72 mg). These higher yields of
nicotine may lead to higher levels of nicotine dependence in smokers in this country (Pakhale & Maru, 1988) which could lead to higher rates of tobacco-related disease.

Seftel (1979) found similar results when nicotine yields of cigarettes sold in developing (South Africa, Malaysia) and developed countries (U.S., U.K.) were analyzed using FTC methods. The range of nicotine yields in cigarettes sold in South Africa was 1.04-1.93 mg while the range in American cigarettes was lower, 0.6-1.64 mg. Interestingly, the nicotine yield of one brand of cigarettes differed across countries: South Africa (1.72 mg), England (1.4 mg), and Malaysia (2.45 mg; Seftel, 1979). These nicotine levels are higher than those typically found in developed countries such as the U.S. (Table 1). However, different results were observed in a similar study (Calafat et al., 2004). FTC machine-smoked nicotine yields were determined from cigarettes that were made and sold locally in 35 countries and compared to the nicotine yields of Marlboro brand cigarettes that were either made in the U.S. and exported to or manufactured in these countries. The mean nicotine yields for local brands (0.9 mg/cig ± 0.2) were similar to mean yields for Marlboro cigarettes (0.9 mg/cig ± 0.1; Calafat et al., 2004).

These results highlight the need for more research on nicotine yields in order to resolve the above conflicting results. Nicotine exposure studies are also needed as previous studies have shown that yield does not represent actual exposure. Determining nicotine yields and exposure in developing countries is a very important step in creating cessation programs that are tailored to those smokers.
Cigarettes in developing countries: summary of carcinogen, CO, and nicotine yield and exposure. In contrast to developed countries, constituent yields of cigarettes in developing countries are only recently being studied. Some studies suggest that, in developing countries, the yield of some carcinogens (i.e., TSNAs; Ashley et al., 2003), is higher than in developed countries, potentially increasing the risk of cancer in smokers residing in these countries. However, several recent studies suggest that tar, CO, and nicotine yields in developed and developing countries may be comparable (e.g., Calafat et al., 2004; but see Mitacek et al., 1990 and Firat, 1996). TSNAs, tar, and CO exposure can lead to smoking-related morbidity and mortality (e.g., cancer and cardiovascular disease). Unfortunately, no data are available to determine definitively if smokers in developing countries are exposed to higher, lower, or similar levels of carcinogens, tar, CO, and/or nicotine, relative to smokers in developed countries. Regarding disease rates, some studies indicate that smoking-related mortality is actually lower in developing countries (Ezzati & Lopez, 2003), although several factors must be considered when interpreting this result. First, smoking prevalence has been increasing in developing countries (especially among women) and decreasing in developed countries, a fact that may not be reflected in mortality rates for several decades. Second, in developing countries, non-tobacco related sources of carcinogens and CO may be more common than in developed countries, thus rates of smoking attributable cancer and cardiovascular disease may appear lower due to non-smoking attributable morbidity and mortality (Ezzati & Lopez, 2003). Third, analyses of morbidity by region rather than country (i.e., as in Ezzati & Lopez, 2003) may obscure effects from countries where carcinogen and/or
CO yield are high (e.g., Nepal; Philippines; Calafat et al., 2004). Thus, differences in smoking related morbidity and mortality in developing countries, relative to developed countries, may become more apparent in the future, especially as research and reporting methods become more refined.

Clearly, exposure studies using smokers in developing countries are necessary for understanding the levels of carcinogens, CO, and nicotine that they receive, and may help to predict risk of cancer, cardiovascular disease, and addiction. In particular, understanding nicotine dependence levels may be relevant to planning effective cessation interventions in developing countries (Maziak et al., 2004). Thus, studying the smoke constituent exposure of smokers who smoke cigarettes marketed in developing countries is likely critical for understanding and reducing the impact of the global tobacco epidemic.

Despite the need for this type of research, no studies regarding the toxicant exposure of smokers in developing countries have been identified. Moreover, the puff topography and ventilation blocking of smokers in these countries is unknown. Thus, an important first step might be to examine the nicotine and CO exposure of smokers using cigarettes marketed in developing countries under conditions that do not allow changes in puff topography or blocking of filter ventilation holes. While not necessarily reflective of actual exposure, data collected under these conditions, when used in conjunction with machine smoke yield analysis, may provide a benchmark of CO and nicotine yield and exposure with which to compare data from more naturalistic smoke toxicant exposure studies.
Statement of Hypothesis

The results of interest will be smokers’ toxicant exposure measured by plasma nicotine levels and breath carbon monoxide (CO), as well as cardiovascular and subjective response (i.e. withdrawal effects) observed during the smoking sessions. The predicted results obtained under conditions where puff topography is held constant and ventilation hole blocking is not permitted are based on the following two hypotheses:

1. Relative to American full flavor and ultra light cigarettes with lower FTC nicotine and CO yields, cigarettes from a developing country (Syria) that have higher FTC nicotine and CO yields will expose smokers to a higher level of nicotine and CO.

2. Relative to American ultra light cigarettes that have lower nicotine and CO yields, American full flavor cigarettes that have higher nicotine and CO yields will expose smokers to higher levels of nicotine and CO.
Chapter 2

Method

This project involved two concurrent studies using methods that differed in only one respect: the brand of developing country cigarettes used (i.e., Syrian Alhamraa cigarettes were used in Study 1 and Syrian Al Sham cigarettes were used in Study 2). Because all other methods were identical across the two studies, one description is provided below.

Selection of Subjects

A combined total of 21 and 19 male and female tobacco cigarette smokers completed Studies 1 and 2, which involved a single session in which participants smoked one Syrian, one U.S. full flavor, and one U.S. ultra light cigarette. More specifically, 17 males (3 non-white) and 4 females (1 non-white) completed Study 1 and 16 males (5 non-white) and 3 females (0 non-white) completed Study 2. For each three-condition within-subject study, an n of 20 was sufficient in order to have an 80% chance of detecting a medium effect size (i.e., $f$ ~ .35) assuming a large within-subject correlation across repeated measures ($r > .50$; Barcikowski & Robey, 1985). ES is defined as the standard deviation of standardized means and is expressed as $f = \sqrt{\eta^2/(1-\eta^2)}$ where $\eta^2$ is equal to multiple $R^2$, which is an index of the proportion of the variability explained by the independent variable (Cohen, 1988). The within-subject correlation was expected to be large based on previous acute studies of changes in nicotine and CO levels across smoking episodes (i.e., Breland, Buchhalter, Evans, & Eissenberg, 2002a, b; Breland, Acosta, & Eissenberg, 2003).
Participants were recruited by word of mouth, IRB approved advertisements and fliers. All study-related activities took place on Virginia Commonwealth University’s Medical Campus in the Clinical Behavioral Pharmacology Laboratory.

Participants were healthy, regular smokers between the ages of 18 and 50 (Study 1 mean = 29.1, SD = 11.0, Study 2 mean = 29.5, SD = 10.3). Specific inclusion criteria were: 1) self-reported daily cigarette intake of at least ten cigarettes per day for the last year (Study 1 mean = 20.2, SD = 3.8, Study 2 mean = 22.4, SD = 10.4); 2) expired air sample containing ≥ 15 ppm CO (expired air was tested using non-invasive equipment and took about 30 seconds) to confirm smoking status (Study 1 mean = 26.2, SD = 9.0, Study 2 mean = 27.9, SD = 11.2. See Tables 3 and 4.); 3) usual cigarette brand that was king sized, full flavor, and non-mentholated, so that comparisons could be made with the two Syrian cigarette brands that were king-size, full flavor, and non-mentholated.

Exclusion criteria were 1) current pregnancy or breast feeding; 2) history of self-reported cardiovascular problems; 3) inability to respond to screening materials reliably; 4) inability to demonstrate controlled smoking parameters reliably (described below).

A total of 78 participants enrolled in Studies 1 and 2 and of those 78, 38 were excluded due to ineligibility: six had low screening CO (< 15 ppm), one was over the age limit of 50 years, thirteen smoked non-full flavor and/or non-king sized cigarettes, one smoked for < 1 year, one quit smoking once enrolled, one failed to demonstrate control over smoking parameters, and nine failed to return for the smoking session. The data of six participants (four from Study 1 and 2 from Study 2) were excluded at the end of the studies due to plasma nicotine levels that were inconsistent with 12 hours of abstinence.
Table 3
Demographics of participants (n=21) in Study 1

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhamraa</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.1 (11.0)</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>81.0%</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>81.0%</td>
</tr>
<tr>
<td>Employment (% unemployed)</td>
<td>43.0%</td>
</tr>
<tr>
<td>Education (years)*</td>
<td>12.7 (1.9)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>27.5 (7.2)</td>
</tr>
<tr>
<td>CPD</td>
<td>20.2 (3.8)</td>
</tr>
<tr>
<td>Smoking (years)</td>
<td>10.4 (9.7)</td>
</tr>
<tr>
<td>Quit attempts</td>
<td>1.8 (1.5)</td>
</tr>
<tr>
<td>FTND</td>
<td>5.4 (1.7)</td>
</tr>
<tr>
<td>Screening CO (ppm)</td>
<td>26.2 (9.0)</td>
</tr>
</tbody>
</table>

*N=20

Table 4
Demographics of participants (n=19) in Study 2

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Sham</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.5 (10.3)</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>84.2%</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>73.7%</td>
</tr>
<tr>
<td>Employment (% unemployed)</td>
<td>21.1%</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.4 (2.6)</td>
</tr>
<tr>
<td>Body mass index (BMI)*</td>
<td>28.7 (6.5)</td>
</tr>
<tr>
<td>CPD</td>
<td>22.4 (10.4)</td>
</tr>
<tr>
<td>Smoking (years)</td>
<td>9.0 (9.0)</td>
</tr>
<tr>
<td>Quit attempts</td>
<td>6.9 (22.6)</td>
</tr>
<tr>
<td>FTND</td>
<td>5.5 (1.9)</td>
</tr>
<tr>
<td>Screening CO (ppm)</td>
<td>27.9 (11.2)</td>
</tr>
</tbody>
</table>

*N=18
despite having provided a CO breath sample that was below the 10 ppm cut off value.

Participants had a mean Fagerström score of 5.4 (SD=1.7) for Study 1 and 5.5 (SD=1.9, P > .05; n.s.) for Study 2 indicating a moderate nicotine dependence level in both groups. The mean FTC yields for the tar, nicotine, and CO of participants' own brand of cigarettes are shown in Tables 5 and 6. Twenty participants reported full flavor and one participant reported medium cigarettes as own brand in Study 1. All participants in Study 2 reported full flavor as own brand. As medium cigarettes have similar FTC reported levels of tar, nicotine, and CO to full flavor cigarettes and higher FTC levels than light and ultra light cigarettes, the participant in Study 1 was not excluded.

Table 5

*Mean FTC yields of the cigarettes examined in Study 1 and participants' own brand*

<table>
<thead>
<tr>
<th>Cigarette</th>
<th>Tar (mg/cig) (SD)</th>
<th>Nicotine (mg/cig) (SD)</th>
<th>CO (mg/cig) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Own brand †</td>
<td>14.8 (1.1)</td>
<td>1.1 (0.1)</td>
<td>13.9 (0.5)</td>
</tr>
<tr>
<td>Marlboro Full Flavor</td>
<td>15.0</td>
<td>1.1</td>
<td>14.0</td>
</tr>
<tr>
<td>Marlboro Ultra Light</td>
<td>6.0</td>
<td>0.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Alhamraa*</td>
<td>23.1</td>
<td>1.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>

*FTC values obtained from independent analysis.
†N=19 for tar and for nicotine; N= 18 for CO.
Table 6
Mean FTC yields of the cigarettes examined in Study 2 and participants' own brand

<table>
<thead>
<tr>
<th>Cigarette</th>
<th>Mean mg/cig (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tar</td>
</tr>
<tr>
<td>Own brand †</td>
<td>15.1 (1.1)</td>
</tr>
<tr>
<td>Marlboro Full Flavor</td>
<td>15.0</td>
</tr>
<tr>
<td>Marlboro Ultra Light</td>
<td>6.0</td>
</tr>
<tr>
<td>Al Sham*</td>
<td>20.2</td>
</tr>
</tbody>
</table>

*FTC values obtained from independent analysis.
†N=18 for CO.

Procedure

After a telephone screening interview, potentially eligible individuals provided documented informed consent and completed an in-person screening. Eligible individuals then completed a single practice session and, at least 24 hours later were given an alternating assignment to one of the two studies. In each study, participants completed a single evaluation session in which they completed three smoking bouts, each separated by 90 min. In each bout they took 10,40 ml puffs (with a 30 second IPI). Bouts differed by the cigarette smoked (Syrian, U.S. full flavor, or U.S. Ultra light) and order of cigarette presentation was determined by Latin square. Blood and CO were sampled before and after each bout, as was self-reported withdrawal and direct effects of cigarettes; heart rate (HR) was measured continuously (although not primary outcome measures, subjective and HR effects were measured to compare the effects of Syrian and
U.S. cigarettes). In addition, puff topography was monitored and measured during each bout.

*Telephone screening.* Potential participants were screened over the telephone using questionnaires to assess self-reports of current health and smoking status (Appendix A). The questions were related to participants’ demographics, physical and mental health, smoking history, drug history (over-the-counter, prescription, and illicit drug use), and menstrual cycle information (women only). Participants’ nicotine dependence (CAGE questionnaire for smoking, Lairson et al., 1992; Fagerström Test for Nicotine Dependence, Heatherton, Kozlowski, Frecker, & Fagerström, 1991), alcohol use (CAGE questionnaire for alcoholism, Ewing, 1984), and marijuana use (questions are similar to the CAGE questionnaire for smoking/nicotine dependence) were also assessed (Appendix A). Individuals deemed potentially eligible based on their telephone screen results were invited to come to the laboratory to learn more about the study, provide informed consent, and to complete an in-person screening and training session.

*Informed consent and in-person screening.* The informed consent and in-person screening began with the research assistant reading the IRB approved consent form aloud to the participant (Appendix B). This method was used to be certain that the material in the consent form was presented to the potential participant, and also to address any questions or concerns regarding study procedures, risks, and benefits, as well as research participant rights. Participants had to provide voluntary, written, informed consent in order to proceed with the study.
Following the completion of the consent process, participants were asked to provide information about their demographics and smoking behavior using a variety of questionnaires (Appendix C). Many of the in-person screening questionnaires were identical or similar to those used in the telephone screen. This redundancy allowed an assessment of individuals' ability to report information reliably (as noted, unreliable individuals were excluded from participation). Data collected during the in-person screen were used to determine eligibility.

After completing in-person screening and verification of reliability, eligible individuals provided an expired air CO sample to verify current smoking status. Breath CO measurement is a non-invasive, reliable index of blood CO levels (Rawbone et al., 1976; Wald, Idle, Boreham, & Bailey, 1981; Guyatt et al., 1988). If breath CO levels did not reach or exceed 15 ppm (indication of recent smoking), the practice session was rescheduled. Once the CO criterion was met, participants were trained to smoke using the protocol-specific, controlled smoking parameters, as described below.

**Practice session.** Participants who qualified for the study based on the telephone and in-person screening process had to complete a practice session. The purpose of the practice session was twofold, as it allowed participants to: 1) familiarize themselves with all questionnaires used in the evaluation session, and 2) demonstrate their ability to control their smoking behavior.

Eligible participants began the practice session by reviewing and responding to the computerized questionnaires that were used to assess withdrawal and the direct effects of cigarettes during the evaluation session. This procedure was used to address
any issues regarding the questionnaires and to ensure participant familiarity with the scales and computer equipment. Once the questionnaires were completed and all issues addressed, the equipment and procedures used to control smoking (i.e., puff topography system) were introduced.

First, the research assistant activated the computerized “directed smoking” module of the laboratory software (CReSS; Plowshare Technologies, Baltimore, MD) and then inserted an unlit cigarette into the mouthpiece that was connected to the topography hardware (see below for description of this software and equipment). Participants were instructed to hold either the mouthpiece or the black tubing attached to the mouthpiece without touching the cigarette. The participants then observed the directed smoking screen on the computer, which provided the visual and auditory feedback that helped participants control their own smoking behavior (puff volume and inter-puff-interval, or IPI). Participants were instructed on how to make use of the feedback (e.g., how large their puffs should be, what the auditory cues mean, how long to wait between puffs, etc.). Specifically, participants were instructed to inhale from the cigarette until a warning beep sounded (at 35 ml), to stop inhaling when they reached the target puff volume as displayed on the screen (40 ml; values within the range of 37 to 43 ml were acceptable), and to wait for the 30 sec timer to count down to zero (and for the associated auditory cue) before taking their next puff. When the participants were comfortable with the procedure, they were instructed to attempt ten consecutive puffs of the target puff volume. The research assistant kept track of the number of puffs, restarting the count from one if the puff volume was not within the acceptable range. Ten
consecutive puffs within the acceptable range were required before the practice session was terminated and an evaluation session was scheduled. Once the ten puff criterion was reached, participants were paid $30 for their time and scheduled for the evaluation session.

*Evaluation session.* Prior to the onset of the evaluation session, each participant who had completed the practice session was assigned to a particular study (i.e., examining the Syrian cigarette brand “Al Sham” or “Alhamraa”) and then a particular Latin-square order of cigarette presentation within a session (e.g., Syrian, U.S. full flavor, U.S. ultra light). The Latin square ordering was used to minimize order effects. Thus, each study used a within-subject design to compare a Syrian brand with a U.S. brand and U.S. brands with each other.

The approximately 4-hour evaluation session had to be preceded by at least eight hours of cigarette abstinence (verified with expired air CO < 10 ppm; e.g., Buchhalter, Schrinel, & Eissenberg, 2001) and had to be separated from the practice session by at least 24 hours. Abstinence was required primarily so that plasma nicotine and expired air CO levels at baseline would be minimal, so that smoking-induced changes in these variables could be measured.

Once participants met the CO criterion, a research nurse inserted a heparinized catheter into a forearm vein to accommodate repeated blood sampling. A catheter was used because repeated venipuncture can be aversive and could have altered some outcome measures (e.g., HR). Once the catheter was inserted, continuous HR monitoring commenced and continued throughout the session. During the first 20 min of the session,
participants practiced the smoking procedure (using an unlit cigarette) so that they could re-establish control over their smoking behavior. HR data collected during the last five min of this practice period was used as a measure of baseline HR (see data analysis, below). At the end of the 20 min period, a 10 ml blood sample was drawn, breath CO was measured, and participants responded to computerized subjective questionnaires assessing tobacco/nicotine withdrawal (the Questionnaire of Smoking Urges, Tiffany & Drobes, 1991; and the Hughes-Hatsukami visual analog scales, Hughes & Hatsukami, 1986) and the direct effects of smoking (adapted from Pickworth, Bunker, & Henningfield, 1994). When the questionnaires were completed, a lit cigarette, corresponding to the appropriate group/condition, was inserted into the mouthpiece by the research assistant. The participant was instructed to begin the smoking portion of the bout by taking the first 40 ml puff and attending to the visual and auditory cues that indicated when the 30 sec IPI had been reached. When participants completed their fifth puff of the bout, a new cigarette of the same brand was lit and inserted into the mouthpiece; two cigarettes of each brand were used (five puffs from each) to control for the different burn times of the cigarette brands so that no cigarette burned to the end before a participant finished their tenth puff. Once participants had completed their tenth puff, another 10 ml of blood were drawn, participants responded again to the questionnaires, and, exactly five min after the tenth puff, expired air CO was measured (a five min delay ensured that the reading accurately reflected blood CO levels and not residual smoke from the mouth). This entire procedure (blood, CO, questionnaires, ten, 40-ml puffs with a 30 sec IPI, blood, questionnaires, five min post-puff CO) was repeated
every 90 min until each participant had taken ten puffs from all three brands used in that session. The inter-bout-interval of 90 min was chosen to reduce the influence that a first or second smoking bout would have on the second or third bout. However, because nicotine’s half-life is 60-120 min (Ahijevych, 1998; Benowitz, 1996; Zevin, Gourlay, & Benowitz, 1998), and because CO’s half-life is 240-300 min (Stewart, 1975) residual nicotine and CO were detectable after the first smoking bout. After the last CO measure of the last bout, the catheter was removed, HR recording discontinued, and participants were paid $150 for the time spent in the laboratory. Thus, with the practice session, each participant earned $180 for completing this study successfully.

Materials

The two brands of Syrian produced cigarettes used were Alhamraa and Al Sham. These brands were chosen because they are the most popular brands of Syrian produced cigarettes used by smokers in Syria (Dr. Wasim Maziak, personal communication). According to analyses performed by an independent laboratory, the mean (SD) FTC yields for Alhamraa cigarettes for tar are 23.1 (0.8) mg, for nicotine are 1.4 (0.04) mg, and for CO are 15.3 (0.6) mg (see Table 5). For Al Sham cigarettes, the mean (SD) FTC yields for tar are 20.2 (0.7) mg, for nicotine are 1.2 (0.06) mg, and for CO are 13.6 (0.4) mg (see Table 6).

Marlboro full flavor and ultra light cigarettes served as the U.S. cigarettes to which the Syrian brands were compared. Marlboro full flavor cigarettes are one of the most popular brands among full flavor smokers in the U.S. (CDC, 2004). The mean (SD) FTC yields for Marlboro full flavor cigarettes for tar are 15 (1.5) mg, for nicotine are 1.1
(0.15) mg, and for CO are 14 (1.5) mg. For Marlboro ultra light cigarettes, the mean
(SD) FTC yields for tar are 6 (1.5) mg, for nicotine are 0.5 (0.12) mg, and for CO are 7
(1.5) mg (FTC, 2000).

The FTC classifies domestic cigarettes into three categories depending on their
content of ‘tar’ and nicotine: typical regular (full flavor), typical “light”, and typical
“ultra light” (see Table 1). Full flavor cigarettes contain 15.63 mg tar and 1.15 mg
nicotine. “Ultra light” cigarettes contain 5.14 mg tar and 0.47 mg nicotine (FTC, 2000).

Opaque tape was used to conceal any identifying labels on all cigarettes; the tape
was positioned so that it did not block any filter ventilation holes.

**Primary Outcome Measures**

Primary outcome measures included plasma nicotine and expired air CO level.

*Plasma nicotine level.* Blood samples were centrifuged immediately and plasma
was stored at -70°C for later analysis of nicotine concentration using high performance
liquid chromatography and mass spectrometry (J. R. James, VCU Department of
Pharmaceutics, personal communication, March 5, 2004). This assay has a limit of
quantitation (LOQ; minimum detectable concentration) of 2.0 ng/ml.

*Expired air CO.* Expired air CO was measured at screening and before and 5 min
after participants took ten puffs from each cigarette, using a BreathCO monitor
(Vitalograph, Lenexa, KS).

**Secondary Outcome Measures**

Secondary outcome measures included cardiovascular response (i.e., heart rate),
puff topography, direct effects of smoking, and subjective measures of withdrawal.
**Hear rate.** During each session, HR was measured every 20 sec by non-invasive computerized equipment (Noninvasive Patient Monitor model 507E, Criticare Systems, Waukesha, WI).

**Puff topography measures.** Participants’ puff volume, number and IPI were monitored and measured using a desktop computerized puff topography measurement system that also administered all questionnaires and stored all physiological data (CReSS, Plowshare Technologies, Baltimore MD). The topography system provided feedback to help participants monitor and control puff volume and IPI. This system consisted of a mouthpiece, tubing, transducer/amplifier, and computer; cigarettes were smoked through the mouthpiece, and pressure changes created by an inhalation were transferred to the computer via the transducer/amplifier while smoking occurred. Puff topography has been found to be a valid and reliable index of smoking behavior (Lee, Malson, Waters, Moolchan, & Pickworth, 2003).

This computerized puff topography system was used to train and maintain participants’ puffing behavior. During training and evaluation sessions the screen displayed a target puff volume as well as counters for the current puff volume and IPI. At the beginning of the evaluation session, participants were handed a mouthpiece with a lit cigarette inside, and the screen flashed “Puff when ready.” As subjects inhaled, the current puff volume counter increased. A warning tone sounded when the current volume approached the target volume (at 35 ml), and the counter displayed the actual puff volume; thus both visual and auditory feedback were given. Once the computer determined that the puff was terminated (as measured by a lack of pressure in the
mouthpiece), the computer displayed the message “Puff again when you hear the tone”; the IPI counter counted down. When the IPI counter reached zero, a final tone sounded, the screen flashed “Please puff now” and the process was repeated. Actual puff topography data (volume, IPI) were recorded for later analysis and reporting. This procedure is a modified version of one used previously to control smoking behavior (e.g., Azorlosa, Heishman, Stitzer, & Mahaffey, 1992). In addition to the computerized measures, a research assistant recorded the puff numbers manually for reliability.

*Subjective measures of the direct effects of smoking and withdrawal.* In addition to physiological responses, participants responded to computerized questionnaires during the smoking session, prior to and after smoking from each brand of cigarette. Participants responded to visual analog scales (VAS) that assessed the direct effects of smoking. In addition, there were two questionnaires that measured subjective tobacco withdrawal: a visual analog scale derived from tobacco/nicotine withdrawal symptoms described by Hughes & Hatsukami (1986), and the Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991). Each measure is described in detail below.

The Direct Effects of Smoking scale is comprised of thirteen VAS items (Appendix F). A VAS item is presented as a word or a phrase centered above a horizontal line and anchored on the left with “not at all” and on the right with “extremely”. Using a computer mouse, subjects responded to each item by moving a cursor to place a vertical mark at any point on the horizontal line. Subjects could adjust the placement of the mark. Scores for each question were assessed as the distance of the vertical mark from the left anchor and calculated as a percentage of the length of the
horizontal line. The thirteen items in this scale were: “Was the cigarette satisfying?,” “Was the cigarette pleasant?,” “Did the cigarette taste good?,” “Did the cigarette taste bad?,” “Did the cigarette make you dizzy?,” “Did the cigarette calm you down?,” “Did the cigarette make you feel confused?,” “Did the cigarette help you concentrate?,” “Did the cigarette make you feel more awake?,” “Did the cigarette reduce your hunger for food?,” “Did the cigarette make you sick?,” “Did the cigarette make you sleepy?,” “Would you like to smoke another cigarette right now?” Participants responded to each of the items by using the mouse to place a mark on a horizontal line that was anchored between “Not at all” and “Extremely.” This scale was adapted from VASs that have been used previously to assess various characteristics of cigarettes (e.g., Pickworth et al., 1994).

The Hughes & Hatsukami (1986) questionnaire consists of thirteen VAS items (Appendix D). Past studies completed in this lab have used only the following eleven items: “Urges to smoke”, “Irritability/frustration/anger”, “Anxious”, “Difficulty concentrating”, “Restlessness”, “Hunger”, “Impatient”, “Craving a cigarette/nicotine”, “Drowsiness”, “Depression/feeling blue”, and “Desire for sweets”. The items of “Insomnia/increased sleep” and “Increased eating” are not presented to participants because they do not sleep or eat in the laboratory setting. This questionnaire is sensitive to deprivation-induced withdrawal and cigarette-induced withdrawal suppression (Buchhalter et al., 2001; Breland et al., 2002a, b).

The QSU (Tiffany & Drobes, 1991) is an empirically validated scale made up of 32 items related to smoking (e.g., “Smoking would make me feel very good right now”,


"I have an urge for a cigarette") (Appendix E). Subjects rated each item on a 7-point scale ranging from 1 (Strongly disagree) to 7 (Strongly agree). Using the computer mouse, subjects placed a mark in the appropriate box for a score ranging from 0 through 6. Items from the QSU were collapsed into two factors that have been previously defined by factor analysis: Factor 1 is related to intention to smoke and Factor 2 is related to anticipation of relief from withdrawal. This questionnaire is sensitive to deprivation-induced withdrawal and cigarette-induced withdrawal suppression (Buchhalter et al., 2001; Breland et al., 2002a, b).

Participant Safety and Rights

In this study, the risks smokers incurred were minimal relative to the risks they encountered daily as smokers. Participants may have suffered mild discomfort after eight or more hours of cigarettes abstinence. However, this mild discomfort was not medically dangerous. There were also minimal risks associated with blood sampling, which were reduced by having a trained nursing professional who used aseptic procedures. Finally, there was a very small risk of an unintended breach of confidentiality.

Trained staff ensured that the rights of the participants were protected at all times during study participation. Medical risks were minimized by careful monitoring throughout each experimental session, a nurse who was present during each session, and aseptic blood sampling procedures using only sterile, disposable equipment. Non-invasive computerized monitoring equipment allowed minute-by-minute, real-time monitoring of participants' HR. Research personnel were trained to call for medical assistance if HR exceeded 120 bpm. Emergency medical coverage was available via the
emergency room that was 1/2 block away from the laboratory. Confidentiality was ensured by referring to participants only by a code number and initials. All subject files are kept in a locked cabinet that resides in a locked laboratory. Potential participants were advised of these risks and the steps taken to minimize them, and were also advised of their right to refuse to participate or terminate their participation at any time during the study.

Data Preparation and Analysis

All data where pre- and post-smoking values were collected (i.e., every measure except topography and direct effects) were processed to form post-smoking difference scores. For each cigarette smoked, pre-smoking plasma nicotine levels in ng/ml (as determined through GC/MS) were subtracted from post-smoking nicotine levels, to form a “nicotine boost” difference score. Pre- and post-CO levels were processed identically, to form a “CO boost” difference score. Subjective assessments of withdrawal (Hughes-Hatsukami VAS and Tiffany-Drobes QSU) were averaged to determine mean pre- and post-smoking scores for each item. The Tiffany-Drobes QSU data were then placed into a set formula to determine Factor 1 and Factor 2 scores. Subjective assessments of direct effects of cigarettes were post-cigarette only and so were averaged into mean post-smoking scores.

HR for each participant was measured continuously throughout the entire evaluation session. Data from the session were taken from the 5 min periods before and after smoking each of the three cigarettes for each participant for analysis. These data were used to form a “HR boost” difference score.
Smoking topography data were collected during the smoking of each of the three cigarettes during the evaluation session. As in previous work (i.e., Breland et al., 2001; Baldinger, Hasenfratz, & Bättig, 1995), topography data was processed such that puffs that were separated by less than 250 ms were combined and, after that combination, any puffs smaller than 5 ml were deleted. These data were then analyzed using one-sample t-tests with set values for each measure (10 for puff number, 30 for IPI, and 40 for puff volume) to determine the consistency with which the directed smoking rules were followed (i.e., puff volume = 40 ml; IPI = 30 sec).

Data for all measures (except topography) were then entered in a single factor within-subjects analysis of variance (ANOVA), with three levels (cigarette: Syrian, U.S. full flavor, and U.S. ultra light). Huynh-Feldt corrections were used to adjust for any violations of the sphericity assumption. The sphericity assumption states that the variance of the difference scores in the levels of a within-subjects design is equal across the levels (Grimm and Yarnold, 2000). The sphericity assumption is made when statistical significance is assigned to an F-value derived from an ANOVA. Violating this assumption and leaving it uncorrected increases the likelihood of making a Type I error (falsely rejecting the null hypothesis) because the ANOVA underestimates the amount of variance associated with each variable. Therefore, in order to control for violations of this assumption, the Huynh-Feldt correction adjusts the degrees of freedom associated with the critical F-value such that this value will be more conservative (higher). As a consequence of increasing the critical F-value, the likelihood of making a Type I error is no longer inflated by the violation of the sphericity assumption.
After any significant ANOVA result, the post-hoc analysis, Tukey's Honestly Significant Difference [HSD], was used to explore possible differences among the means. Tukey’s HSD is a conservative post-hoc test designed to compare all possible pairs of means while maintaining the Type 1 error rate (Hurlburt, 1998). The experimentwise error rate can increase with each pairwise comparison that is made and Tukey’s HSD prevents this error rate increase. The mean square error terms for the overall interaction were used to conduct Tukey HSD post hoc tests. Finally, an alpha level of $P < .05$ was used to determine significance in all of the above analyses and Tukey's HSD was used to explore differences after a significant ANOVA.
Chapter 3

Results

The two studies reported here were designed to examine how two brands of Syrian cigarettes (Study 1 = Alhamraa; Study 2 = Al Sham) influenced smokers’ toxicant exposure (plasma nicotine; expired air CO) and cardiovascular and subjective response (i.e. withdrawal effects) under conditions where puff topography was held constant and ventilation hole blocking was not permitted. Results from the two studies are described below.

Primary Outcome Measures: Study 1 (Alhamraa)

Results of the statistical analysis of primary outcome measures are presented in Table 7 and are discussed below.

Nicotine boost. As Table 7 shows, for nicotine boost (post smoking plasma nicotine level minus pre smoking plasma nicotine level), a significant main effect of cigarette was observed. The data are displayed in Figure 1. As can be seen in the figure, on average, U.S. ultra light cigarettes produced less nicotine exposure (mean = 3.9 ng/ml, SD = 2.9) relative to U.S. full flavor cigarettes (mean = 10.4 ng/ml, SD = 9.8; P < .05, Tukey’s HSD), though no significant difference was observed between U.S. full flavor and Alhamraa cigarettes (mean = 7.3 ng/ml; SD = 8.3; difference between means n.s.; Tukey’s HSD).

CO boost. Also shown in Table 7, a significant main effect of cigarette was observed for CO boost (post smoking expired air CO minus pre smoking expired air CO). The data are displayed in Figure 1. As can be seen in the figure, on average, U.S. ultra
light cigarettes produced less CO exposure (mean = 2.7 ppm, SD = 1.8) relative to U.S.
full flavor cigarettes (mean = 5.3 ppm, SD = 2.9; P < .05, Tukey’s HSD) and Alhamraa
cigarettes (mean = 4.5 ppm; SD = 3.2; P < .05; Tukey’s HSD), though no significant
difference was observed between U.S. full flavor and Alhamraa cigarettes (difference
between means n.s.; Tukey’s HSD).

Secondary Outcome Measures

Results of the statistical analysis of secondary outcome measures are presented in
Tables 7 and are discussed below.

Heart rate. HR was averaged for the 5 minutes before and after smoking, and the
resulting post-smoking means were subtracted from pre-smoking means and reported as
HR boost. As Table 7 shows, there was a significant main effect of cigarette on this
outcome measure, with U.S. ultra light cigarettes producing, on average, less tachycardia
(mean = 9.0 bpm, SD = 4.0) relative to U.S. full flavor cigarettes (mean = 12.1 bpm, SD
= 5.5; P < .05, Tukey’s HSD). U.S. full flavor cigarettes produced, on average, more
tachycardia relative to Alhamraa cigarettes (mean = 9.7 bpm; SD = 3.7; P < .05, Tukey’s
HSD. See Figure 1).
Mean plasma nicotine, expired air CO, and heart rate boost (post-cigarette minus pre-cigarettes values) + 1 SEM for 21 participants who smoked one American ultra light (Marlboro), one American full flavor (Marlboro), and one Syrian (Alhamraa) cigarette at 90 min intervals in a 4 hour session. Asterisks (*) indicate a significant difference relative to American full flavor on that outcome measure for that cigarette and a cross (†) indicates a significant difference from American ultra light on that outcome measure for that cigarette (P < .05; Tukey’s HSD).
**Puff topography.** Topography data were analyzed to determine how well participants followed the directed smoking procedures across the three cigarette conditions. While there was some variability on all topography measures, a significant main effect was observed for puff volume only (see Table 7). On this measure, mean puff volume for the U.S. full flavor cigarettes (mean = 37.8 ml, SD = 5.1) was somewhat smaller than for either the U.S. ultra light (mean = 40.4 ml, SD = 4.0) or Alhamraa cigarettes (mean = 40.5 ml, SD = 4.5; all differences between means n.s.; Tukey's HSD). Importantly, all means were within the +/- 3 ml limits allowable in the procedure.

**Subjective measures of the direct effects of smoking and withdrawal.** For the direct effects VAS measures significant main effects were observed for VAS items assessing “Was the cigarette pleasant?,” “Did the cigarette taste good?,” “Did the cigarette taste bad?”; an additional item (“Was the cigarette satisfying?”) nearly attained conventional levels of significance (i.e., P < .08; see Table 7). Results indicated that, on these measures, participants indicated that smoking U.S. full flavor cigarettes were more pleasurable and less aversive than smoking either U.S. ultra light or Alhamraa cigarettes. For example, for “Was the cigarette pleasant?,” mean values for the U.S. full flavor were 71.6 (SD = 23.1) compared to 52.8 for Alhamraa cigarettes (SD = 27.5; P < .05; Tukey’s HSD) though no significant difference was found between U.S. full flavor and U.S. ultra light cigarettes (mean = 54.8, SD = 25.6; P <.05; difference between means n.s.; Tukey’s HSD). Also, for “Did the cigarette taste good?,” mean values for U.S. full flavor cigarettes were 72.0 (SD = 21.5) compared to 48.9 for U.S. ultra light (SD = 26.6; P < .05, Tukey’s HSD) and 47.4 for Alhamraa cigarettes (SD = 28.6; P < .05, Tukey’s HSD).
On the other hand, for “Did the cigarette taste bad?,” mean values for U.S. full flavor cigarettes were 20.3 (SD = 16.1) compared to 36.9 for U.S. ultra light (SD = 28.5) and 37.6 for Alhamraa cigarettes (SD = 29.0; P < .05; all differences between means n.s.; Tukey’s HSD).

For the Hughes-Hatsukami withdrawal VAS, administered before and after each cigarette, significant time by cigarette interactions were observed for three items: “Urges to smoke,” “Irritability/Frustration/Anger,” and “Restlessness” (See Table 8). Table 8 provides summary statistics for these measures and, for “Urges to smoke” shows that pre-smoking levels were similar across the three cigarettes, but that U.S. full flavor cigarettes suppressed urges more effectively than the other two brands (i.e., mean post-smoking scores for U.S. full flavor cigarettes were significantly lower than for U.S. ultra light or Alhamraa cigarettes; P < .05; Tukey’s HSD). A different pattern of results was observed for “Irritability/Frustration/Anger,” where pre- and post-smoking scores were significantly different only for U.S. ultra light cigarettes (P < .05; Tukey’s HSD). Similar results were seen for “Restlessness” where a significant difference between pre- and post-smoking scores in the U.S. ultra light cigarette condition seems to be the source of this interaction (P < .05, Tukey’s HSD; see Table 8).

A significant main effect of time was observed for almost every Hughes-Hatsukami item (see Table 8). Inspection of the data showed that scores, collapsed across cigarette, were high before smoking and significantly lower after smoking. For example, for “Craving a cigarette/Nicotine” (the item with the highest F value, see Table 8), the mean pre-smoking score was 80.5 (SD = 18.0) and post smoking score was 44.4
A similar pattern was observed on every measure with a significant time by cigarette interaction.

A significant main effect of cigarette was observed for “Craving a cigarette/Nicotine”. Collapsed across time, mean scores were 56.2 for U.S. full flavor (SD = 31.1), 68.9 for U.S. ultra light (SD = 20.8), and 62.3 for Alhamraa cigarettes (SD = 31.4; P < .05; all differences between means n.s.; Tukey’s HSD).

For both factors of the QSU, a significant main effect of time was observed. Inspection of the data showed that scores, collapsed across cigarette, were high before smoking and significantly lower after smoking. For example, for Factor 2, (the factor with the higher F value, see Table 8), the mean pre-smoking score was 31.0 (SD = 14.1) and post smoking score was 23.6 (SD = 14.3; P < .05, Tukey’s HSD).
Table 7
*Mean physiological boost scores, topography values, and direct effect scores of Study 1*

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>F</th>
<th>P</th>
<th>Ultra Light</th>
<th>Full Flavor</th>
<th>Alhamraa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine boost</td>
<td></td>
<td>8.0</td>
<td>&lt;.05</td>
<td>3.9 (2.9)*</td>
<td>10.4 (9.8)</td>
<td>7.3 (8.3)</td>
</tr>
<tr>
<td>CO boost</td>
<td></td>
<td>10.1</td>
<td>&lt;.001</td>
<td>2.7 (1.8)*</td>
<td>5.3 (2.9)</td>
<td>4.5 (3.2)</td>
</tr>
<tr>
<td>Heart Rate boost†</td>
<td></td>
<td>5.4</td>
<td>&lt;.01</td>
<td>9.0 (4.0)*</td>
<td>12.1 (5.5)</td>
<td>9.7 (3.7)*</td>
</tr>
</tbody>
</table>

**Topography**

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>F</th>
<th>P</th>
<th>Ultra Light</th>
<th>Full Flavor</th>
<th>Alhamraa</th>
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</thead>
<tbody>
<tr>
<td>Puff Number</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>10.3 (0.5)</td>
<td>10.4 (0.8)</td>
<td>10.5 (1.5)</td>
</tr>
<tr>
<td>Inter-puff-interval</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>31.9 (2.6)</td>
<td>30.9 (2.4)</td>
<td>31.6 (2.8)</td>
</tr>
<tr>
<td>Puff Volume</td>
<td></td>
<td>3.9</td>
<td>&lt;.05</td>
<td>40.4 (4.0)</td>
<td>37.8 (5.1)</td>
<td>40.5 (4.5)</td>
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</tbody>
</table>

**Direct Effects**

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>F</th>
<th>P</th>
<th>Ultra Light</th>
<th>Full Flavor</th>
<th>Alhamraa</th>
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<tbody>
<tr>
<td>Satisfy</td>
<td></td>
<td>2.8</td>
<td>&lt;.08</td>
<td>56.2 (30.2)</td>
<td>71.1 (22.2)</td>
<td>57.5 (25.8)</td>
</tr>
<tr>
<td>Pleasant</td>
<td></td>
<td>4.4</td>
<td>&lt;.05</td>
<td>54.8 (25.6)</td>
<td>71.6 (23.1)</td>
<td>52.8 (27.5)*</td>
</tr>
<tr>
<td>Good taste</td>
<td></td>
<td>6.7</td>
<td>&lt;.05</td>
<td>48.9 (26.6)*</td>
<td>72.0 (21.5)</td>
<td>47.4 (28.6)*</td>
</tr>
<tr>
<td>Bad taste</td>
<td></td>
<td>3.6</td>
<td>&lt;.05</td>
<td>36.9 (28.5)</td>
<td>20.3 (16.1)</td>
<td>37.6 (29.0)</td>
</tr>
<tr>
<td>Dizzy</td>
<td></td>
<td>2.1</td>
<td>ns</td>
<td>28.3 (31.0)</td>
<td>46.5 (29.2)</td>
<td>35.2 (35.6)</td>
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<tr>
<td>Calm</td>
<td></td>
<td>2.0</td>
<td>ns</td>
<td>49.5 (30.2)</td>
<td>62.5 (26.7)</td>
<td>55.0 (27.5)</td>
</tr>
<tr>
<td>Confused</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>11.5 (18.2)</td>
<td>16.0 (16.8)</td>
<td>12.0 (18.2)</td>
</tr>
<tr>
<td>Concentrate</td>
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<td>&lt;1.0</td>
<td>ns</td>
<td>30.9 (29.1)</td>
<td>37.2 (24.7)</td>
<td>34.4 (27.6)</td>
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<tr>
<td>Awake</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>47.2 (32.7)</td>
<td>49.2 (29.7)</td>
<td>43.3 (30.1)</td>
</tr>
<tr>
<td>Less hunger</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>39.1 (34.4)</td>
<td>39.5 (30.9)</td>
<td>37.8 (30.9)</td>
</tr>
<tr>
<td>Sick</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>4.6 (12.0)</td>
<td>7.6 (16.7)</td>
<td>6.5 (12.5)</td>
</tr>
<tr>
<td>Sleepy</td>
<td></td>
<td>&lt;1.0</td>
<td>ns</td>
<td>14.6 (26.5)</td>
<td>11.1 (16.5)</td>
<td>12.8 (21.7)</td>
</tr>
<tr>
<td>Another cig</td>
<td></td>
<td>1.2</td>
<td>ns</td>
<td>70.6 (26.6)</td>
<td>62.6 (30.6)</td>
<td>68.6 (34.1)</td>
</tr>
</tbody>
</table>

†N=20.

*Indicates significant difference from U.S. full flavor.
Table 8  
*Mean scores of withdrawal and craving for Study 1*

<table>
<thead>
<tr>
<th>Withdrawal</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean scores for Study 1</td>
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<tr>
<td></td>
<td>Ultra Light</td>
</tr>
<tr>
<td></td>
<td>Time</td>
</tr>
<tr>
<td></td>
<td>Time</td>
</tr>
<tr>
<td>Hughes Hatsukami</td>
<td></td>
</tr>
<tr>
<td>items</td>
<td></td>
</tr>
<tr>
<td>Urges to smoke</td>
<td>62.9</td>
</tr>
<tr>
<td>Irr/Frus/Ang</td>
<td>8.9</td>
</tr>
<tr>
<td>Anxious</td>
<td>12.8</td>
</tr>
<tr>
<td>Difficulty conc</td>
<td>8.5</td>
</tr>
<tr>
<td>Restlessness</td>
<td>24.7</td>
</tr>
<tr>
<td>Hunger</td>
<td>4.0</td>
</tr>
<tr>
<td>Impatient</td>
<td>28.6</td>
</tr>
<tr>
<td>Craving a cig/Nic</td>
<td>75.0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>12.6</td>
</tr>
<tr>
<td>Dep/Feel blue</td>
<td>1.1</td>
</tr>
<tr>
<td>Desire for sweets</td>
<td>2.7</td>
</tr>
<tr>
<td>Tiffany Drobes QSU</td>
<td></td>
</tr>
<tr>
<td>Factor 1</td>
<td>33.3</td>
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<tr>
<td>Factor 2</td>
<td>48.5</td>
</tr>
</tbody>
</table>

N=21  
*Indicates significant difference from U.S. full flavor.
Primary Outcome Measures: Study 2 (Al Sham)

Results of the statistical analysis of primary outcome measures are presented in Table 9 and are discussed below.

Nicotine boost. As Table 9 shows, for nicotine boost, a significant main effect of cigarette was observed. The data are displayed in Figure 2. As can be seen in the figure, on average, U.S. ultra light (mean = 4.0 ng/ml, SD=3.7) and Al Sham cigarettes (mean = 2.4 ng/ml; SD = 4.2) produced less nicotine exposure relative to U.S. full flavor cigarettes (mean = 11.3 ng/ml, SD=7.1, P < .05, Tukey's HSD). No significant difference was observed between U.S. ultra light and Al Sham cigarettes (difference between means n.s.; Tukey’s HSD).

CO boost. Also shown in Table 9, a significant main effect of cigarette was observed for CO boost. The data are displayed in Figure 2. As can be seen in the figure, on average, U.S. ultra light (mean = 2.4 ppm, SD = 1.3) and Al Sham cigarettes (mean = 2.8 ppm; SD = 1.3) produced less CO exposure relative to U.S. full flavor cigarettes (mean = 5.3 ppm, SD = 2.3; P < .05; Tukey’s HSD). No significant difference was observed between U.S. ultra light and Al Sham cigarettes (difference between means n.s.; Tukey’s HSD).

Secondary Outcome Measures

Results of the statistical analysis of secondary outcome measures are presented in Tables 9 and 10 and are discussed below.

Heart rate. As Table 9 shows, there was a significant main effect of cigarette on this outcome measure, with U.S. ultra light (mean = 7.8 bpm, SD = 5.3) and Al Sham
cigarettes (mean = 6.6 bpm; SD = 4.4) producing, on average, less tachycardia relative to U.S. full flavor cigarettes (mean = 14.5 bpm, SD = 7.2; P < .05, Tukey’s HSD). No significant difference was observed between U.S. ultra light and Al Sham cigarettes (difference between means n.s.; Tukey’s HSD).
Mean plasma nicotine, expired air CO, and heart rate boost (post-cigarette minus pre-cigarettes values) + 1 SEM for 19 participants who smoked one American ultra light (Marlboro), one American full flavor (Marlboro), and one Syrian (Al Sham) cigarette at 90 min intervals in a 4 hour session. Asterisks (*) indicate a significant difference relative to American full flavor on that outcome measure for that cigarette (P < .05; Tukey’s HSD).
**Puff topography.** While there was some variability on all topography measures, a significant main effect was observed for puff volume only (see Table 9). On this measure, mean puff volume for U.S. full flavor cigarettes (38.6 ml; SD = 5.3) was somewhat smaller for the U.S. ultra light (mean = 41.3 ml, SD = 3.8; difference between means n.s.; Tukey’s HSD) and Al Sham cigarettes (mean = 42.2 ml, SD = 2.9; P < .05; Tukey’s HSD). Importantly, though participants’ average puff volume was significantly smaller when smoking U.S. full flavor cigarettes relative to Al Sham cigarettes, all means were within the +/- 3 ml limits allowable in the procedure.

**Subjective measures of the direct effects of smoking and withdrawal.** For the direct effects VAS measures, significant main effects were observed for VAS items assessing “Did the cigarette make you dizzy?,” “Did the cigarette make you sick?”; two additional items (“Did the cigarette calm you down?,” “Did the cigarette make you feel confused?”) nearly attained conventional levels of significance (i.e., P < .10; see Table 9). Results indicated that, on these measures, participants indicated that smoking U.S. full flavor cigarettes made them feel more dizzy and sick than smoking either U.S. ultra light or Al Sham cigarettes. For example, for “Did the cigarette make you dizzy?,” mean values for U.S. full flavor cigarettes were 42.4 (SD = 31.9) compared to 5.8 for U.S. ultra light (SD = 11.4; P < .05, Tukey’s HSD) and 6.4 for Al Sham cigarettes (SD = 15.5; P < .05, Tukey’s HSD). Similarly, for “Did the cigarette make you sick?,” mean values for U.S. full flavor cigarettes were 15.6 (SD = 24.9) compared to 4.1 for U.S. ultra light (SD = 7.6; P < .05, Tukey’s HSD) and 3.7 for Al Sham cigarettes (SD = 6.9; P < .05, Tukey’s HSD).
For the Hughes-Hatsukami withdrawal VAS, administered before and after each cigarette, significant time by cigarette interactions were observed for one item: “Urges to smoke,” and one additional item (“Hunger”) nearly attained conventional levels of significance (i.e., P < .10; see Table 10). Table 10 provides summary statistics for these measures and, for “Urges to smoke” shows that pre-smoking levels were similar across the three cigarettes, but that both U.S. full flavor and ultra light cigarettes suppressed urges more effectively than Al Sham cigarettes (i.e., mean post-smoking scores for U.S. full flavor and ultra light cigarettes were significantly lower than Al Sham cigarettes; P < .05; Tukey’s HSD). A different pattern of results was observed for “Craving a cigarette/Nicotine,” where post-smoking scores were lower for all cigarettes with no difference between the brands (See Table 10). Finally, for “Desire for sweets,” there was a main effect of cigarette with the U.S. ultra light cigarettes showing the lowest score (all differences between means n.s.; Tukey’s HSD).

A significant main effect of time was observed for only two Hughes-Hatsukami items (see Table 10). Inspection of the data showed that scores, collapsed across cigarette, were high before smoking and significantly lower after smoking. For example, for “Craving a cigarette/Nicotine” (the item with the highest F value, see Table 10), the mean pre-smoking score was 64.9 (SD = 28.2) and post smoking score was 40.0 (SD = 30.2; P < .05, Tukey’s HSD). For “Urges to smoke,” the mean pre-smoking score was 67.5 (SD = 28.7) and post smoking score was 39.9 (SD = 31.6; P < .05; Tukey’s HSD). A similar pattern was observed on “Urges to smoke” which had a significant time by
cigarette interaction for the U.S. cigarettes (P < .05; Tukey’s HSD) but not for Al Sham cigarettes (difference between means n.s.; Tukey’s HSD).

A significant main effect of cigarette was observed for “Desire for sweets.” Collapsed across time, mean scores were 16.6 for U.S. full flavor (SD = 29.4), 21.5 for U.S. ultra light (SD = 30.0), and 27.8 for Al Sham cigarettes (SD = 33.0; all differences between means n.s.; Tukey’s HSD).

For both factors of the QSU, a significant main effect of time was observed. Inspection of the data showed that scores, collapsed across cigarette, were high before smoking and significantly lower after smoking. For example, for Factor 1, (the factor with the higher F value, see Table 10), the mean pre-smoking score was 70.0 (SD = 18.7) and post smoking score was 57.2 (SD = 23.9; P < .05, Tukey’s HSD).
Table 9
Mean physiological boost scores, topography values, and direct effect scores of Study 2

<table>
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<th>Mean (SD)</th>
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<tr>
<td>Nicotine boost</td>
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<tr>
<td>CO boost</td>
<td>24.4</td>
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<tr>
<td>Heart Rate boost</td>
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</table>

Topography

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<td>Puff Number</td>
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<td>Inter-puff-interval</td>
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<td>Puff Volume</td>
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Direct Effects

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<td>Less hunger</td>
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*Indicates significant difference from U.S. full flavor.
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<td>5.6</td>
<td>&lt;.05</td>
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<td>ns</td>
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<td>&lt;1.0 ns</td>
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<td>2.4 ns</td>
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N=19
Chapter 4

Discussion

As was discussed in previous chapters, there is little information about tobacco smokers in developing countries and no studies have been published regarding the cigarette toxicant levels to which these smokers are exposed. Exposure studies are necessary in order to understand the levels of carcinogens, CO, and nicotine these smokers receive from cigarettes; this information may help predict disease rates. Knowledge of nicotine exposure may be particularly important for planning effective cessation programs for these smokers. This chapter discusses the findings of the two studies reported here in terms of the:

1. Differences between U.S. and Syrian cigarettes.
2. Differences between U.S. full flavor and ultra light cigarettes.
3. Methods used to compare cigarette toxicant yields to human toxicant exposure.
4. Limitations of the study.

The differences between U.S. and Syrian cigarettes: Study 1 (Alhamraa)

In Study 1, the difference observed in the primary outcome measure of expired CO boost was between U.S. ultra light and the Syrian Alhamraa cigarette: Alhamraa cigarettes delivered 1.8 ppm more CO to smokers than the U.S. ultra light cigarettes. There was no significant difference observed between U.S. ultra light and Alhamraa cigarettes on plasma nicotine boost. There were also no significant differences observed
between U.S. full flavor and Syrian Alhamraa cigarettes on any primary or secondary outcome measure except HR.

One explanation for Alhamraa cigarettes exposing smokers to more CO than U.S. ultra light cigarettes is that they contain no obvious filter vent holes, while U.S. ultra light cigarettes have filter ventilation holes that dilute the smoke. Although smokers tend to cover ventilation holes under normal smoking conditions (Kozlowski et al., 1982), these holes were not occluded in this study. Thus, when participants smoked U.S. ultra light cigarettes they inhaled partially diluted smoke, but the smoke from Syrian Alhamraa cigarettes (and U.S. full flavor cigarettes) may not have been diluted. This potential for differential dilution likely underlies the lower levels of CO exposure observed when participants smoked U.S. ultra light cigarettes.

In terms of the secondary outcome measures of HR boost, puff topography, and subjective measures of direct effects and withdrawal, significant differences between the U.S. brands and Alhamraa were observed on some measures and not others. For example, significant differences were observed on HR boost between U.S. full flavor and Alhamraa cigarettes. Participants’ HR boost increased 2.4 bpm more, on average, after smoking U.S. full flavor cigarettes than after smoking Alhamraa cigarettes. Though the Alhamraa cigarettes exposed smokers to more nicotine (which can increase HR) than U.S. ultra light cigarettes, the HR boost did not differ between these two cigarette brands. Explanations for the failure to observe differences in HR between the U.S. ultra light and Alhamraa in the presence of differential nicotine exposure may involve ceiling effects for nicotine-induced tachycardia, and/or acute tolerance to nicotine’s cardiovascular effects.
The notion that there is a ceiling effect to nicotine-induced tachycardia is supported by the observation that the HR increases observed after 21 mg and 42 mg nicotine patch application sometimes do not differ (e.g., Evans, Weaver, Collins, & Eissenberg, 2005) while acute tolerance to nicotine’s cardiovascular effects is commonly observed in tobacco users (e.g., Perkins, Grobe, Mitchell, Goettler, Caggiula, Stiller, et al., 1995; Gire & Eissenberg, 2000).

For puff topography measures, IPI and number of puffs were quite similar across the three types of cigarettes, but the mean puff volume observed when participants were smoking U.S. full flavor cigarettes was less than that observed when participants were smoking U.S. ultra light or Alhamraa cigarettes. This difference, however, was within the +/- 3 ml limits that were allowed in this procedure and was not significant when the means were compared using the Tukey’s HSD. Overall, the fact that IPI, puff number, and puff volume were within the proscribed limits suggests that participants demonstrated that the study methods (auditory and visual feedback) were sufficient for them to learn to control their smoking behavior.

On measures of the direct effects of smoking, significant differences were observed when participants rated the taste and pleasantness of the cigarettes after smoking U.S. full flavor and Alhamraa cigarettes. Participants rated the U.S. full flavor cigarettes as better tasting and more pleasant than the Alhamraa cigarettes.

Finally on most withdrawal measures, no differences were observed when participants rated withdrawal symptom severity after smoking U.S. full flavor, U.S. ultra light, or Alhamraa cigarettes. One exception was the “Urges to smoke” item from the
Hughes-Hatsukami questionnaire. Participants rated their urges to smoke lower after smoking the U.S. full flavor cigarettes than after smoking Alhamraa cigarettes.

These observed differences in subjective ratings may be explained by the higher FTC determined yields of tar per cigarette in the Alhamraa brand relative to the U.S. full flavor brand. Participants’ possible exposure to these higher tar levels under the conditions of this study may have caused them to rate Alhamraa cigarettes as tasting bad and being less pleasant than the U.S. full flavor cigarettes. Another possible explanation is that the participants in this study were selected based upon their self-reported preference for U.S. full flavor cigarettes. Thus, the observed ratings on direct effects measures and withdrawal suppression may reflect this selection criterion.

Overall, results reported here suggest that the U.S. ultra light and Alhamraa cigarettes differ in toxicant exposure: when smoked under controlled topography conditions, Alhamraa cigarettes expose smokers to higher levels of CO than U.S. ultra light cigarettes. In contrast, under the conditions of the study, U.S. full flavor and Alhamraa cigarettes were similar in toxicant exposure: no differences were observed in nicotine or CO exposure. While Alhamraa cigarettes are not labeled or advertised in Syria as a specific type of cigarette (e.g. full flavor vs. ultra light, etc.), this brand may be best categorized as a “full flavor” product based on both its FTC determined constituent yields and its exposure to smokers of those constituents when smoking topography is controlled.
The differences between U.S. and Syrian cigarettes: Study 2 (Al Sham)

In Study 2, significant differences were observed on primary measures of plasma nicotine and CO boost when participants smoked U.S. full flavor brand cigarettes versus Syrian Al Sham cigarettes. Specifically, significant differences in plasma nicotine boost and expired air CO boost were observed after participants smoked U.S. full flavor and Al Sham cigarettes, with U.S. full flavor cigarettes delivering, on average, 8.9 ng/ml more nicotine and 2.5 ppm more CO to smokers than the Al Sham cigarettes.

In contrast, participants were exposed to similar levels of nicotine and CO when smoking U.S. ultra light and Al Sham cigarettes. These results suggest that Al Sham cigarettes are more like U.S. ultra light cigarettes than full flavor cigarettes, at least under the conditions reported here. Interestingly, the Syrian cigarette market does not differentiate between cigarettes using the full flavor/ultra light terminology, though the Al Sham cigarettes are considered to be less preferred than Alhamraa cigarettes (Dr. W. Maziak, personal communication).

In terms of the secondary outcome measures of HR boost scores, puff topography, and subjective measures of direct effects and withdrawal, significant differences were observed between the U.S. full flavor and Al Sham cigarettes. For example, participants’ HR increased, on average, 7.9 bpm more when smoking U.S. full flavor cigarettes than when smoking Al Sham cigarettes. In contrast, observed tachycardia was similar when participants were smoking U.S. ultra light and Al Sham cigarettes.

For puff topography measures, IPI and number of puffs were quite similar across the three types of cigarettes, but the puff volume observed when participants were
smoking U.S. full flavor cigarettes was 3.5 ml lower than that observed when participants were smoking Al Sham cigarettes. The observed difference in mean puff volumes between the U.S. full flavor and Al Sham cigarettes was significant when the differences were compared using Tukey’s HSD. The puff volume for the U.S. full flavor cigarette, however, is within the +/- 3 ml limits that were allowed in this procedure. Overall, the fact that IPI, puff number, and puff volume were within the proscribed limits suggests that the study methods (auditory and visual feedback) were sufficient for participants to learn to control their smoking behavior.

On the direct effects of cigarettes measure, there was an observed difference of participant ratings between U.S. full flavor and Al Sham cigarettes. Specifically, participants’ ratings were higher on the questions of feeling dizzy and feeling sick after smoking the U.S. full flavor cigarettes than after smoking Al Sham cigarettes. Though Al Sham cigarettes contain similar toxicant yields to U.S. full flavor cigarettes (as measured by the FTC method, see Table 6), participants may be exposed to lower levels of toxicants when smoking Al Sham cigarettes than when smoking U.S. full flavor cigarettes when topography conditions are controlled as in this study. Participants’ exposure to toxicants when smoking Al Sham cigarettes, as discussed in previous sections, was more similar to their toxicant exposure when smoking U.S. ultra light cigarettes. As inhalation into the lungs was not controlled for, it is possible that participants did not inhale the smoke from Al Sham cigarettes into their lungs. Low exposure levels of CO observed after smoking this brand support this inference.
Participants' exposure to lower levels of nicotine and CO may reduce their ratings of dizzy and sick after smoking Al Sham.

In terms of subjective withdrawal, the difference in scores between U.S. full flavor and Al Sham on the question of “Urges to smoke” was nearly significant. Participants reported lower urges to smoke after smoking U.S. full flavor cigarettes than after smoking Al Sham cigarettes. As participants were exposed to higher levels of nicotine and other toxicants when smoking U.S. full flavor cigarettes, their urges to smoke were suppressed more effectively than when smoking cigarettes which contain lower levels of nicotine and other toxicants, such as Al Sham cigarettes. However, studies have shown that stimuli other than smoke toxicants, such as olfactory and sensorimotor stimuli, can effectively suppress withdrawal for short periods of time (Baldinger et al., 1995; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999).

Overall, results reported here suggest that the U.S. full flavor and Al Sham cigarettes differ in toxicant exposure: when smoked under controlled topography conditions, U.S. full flavor cigarettes expose participants to higher levels of nicotine and CO than Al Sham. In contrast, under the conditions of the study, the U.S. ultra light and Al Sham cigarettes were similar in toxicant exposure: no differences were observed in nicotine and CO exposure. While Al Sham cigarettes are not labeled or advertised in Syria as a specific type of cigarette (e.g. full flavor vs. ultra light, etc.), this brand could categorized in the U.S. market as a “full flavor” product based on its FTC determined yield of tar, nicotine and CO. Al Sham cigarettes’ exposure to smokers of nicotine and CO when smoking topography is controlled, however, more closely resembles that of an
ultra light. This discrepancy between yield and exposure highlights the need for understanding the relationship between FTC method constituent yields and smokers’ actual constituent exposure under a variety of conditions.

*The differences between U.S. full flavor and ultra light cigarettes: Studies 1 and 2*

In Studies 1 and 2, significant differences were observed on measures of plasma nicotine and expired air CO when participants smoked U.S. full flavor and ultra light cigarettes. Specifically, participants’ nicotine (6.5 ng/ml Study 1 and 7.3 ng/ml Study 2) and CO boost (2.6 ppm Study 1 and 2.9 ppm Study 2) were greater when smoking the U.S. full flavor than when smoking the ultra light cigarettes (3.9 ng/ml Study 1 and 4.0 ng/ml Study 2 nicotine boost and 2.7 ppm Study 1 and 2.4 ppm Study 2 CO boost). These observed differences in nicotine and CO exposure may be explained by the uncovered filter vent holes in the ultra light cigarettes used in this study – covering vent holes, as often occurs during natural smoking (Kozlowski et al., 1982), may increase ultra light cigarette smokers’ nicotine and CO exposure, relative to the values reported here. However, the more controlled conditions reported here, where topography variables were fixed and filter vent holed were not covered demonstrates that, in some cases, ultra light cigarettes can lead to less toxicant exposure than full flavor cigarettes.

In terms of the secondary outcome measures of HR boost, puff topography, and subjective measures of direct effects and withdrawal, significant differences were observed between the U.S. full flavor and ultra light cigarettes on some measures. For example, when smoking U.S. full flavor cigarettes, participants’ HR increased an average
of 3.1 bpm (Study 1) or 6.7 bpm (Study 2) relative to when they smoked ultra light cigarettes. The increase in participants’ HR likely reflects greater nicotine exposure.

For puff topography measures, all variables were quite similar across these two types of cigarettes. Importantly, under more natural smoking conditions (i.e., when puff topography variables are free to vary), full flavor smokers who switch to ultra light cigarettes often take more or larger puffs with the ultra light brand, relative to their usual full flavor brand (Zacny & Stitzer, 1988; West & Gossop, 1994).

On measures of the direct effects of cigarettes in Study 1, participants’ ratings of good taste were an average of 23.1 points higher after smoking U.S. full flavor cigarettes than after smoking ultra light cigarettes (See table 7). However, no significant differences were observed between these cigarettes on this item in Study 2 (See table 9). In Study 2, participant’s ratings of dizzy and sick were 36.6 and 11.4 points higher after smoking U.S. full flavor than after smoking ultra light cigarettes, and no significant differences were observed between these cigarettes on these items in Study 1 (See tables 9 and 7).

On subjective measures of withdrawal, participants’ ratings of urges to smoke were 14.4 points lower after smoking U.S. full flavor cigarettes than after smoking ultra light cigarettes in Study 1 (See table 8). However, no significant differences were observed between these cigarettes on this item in Study 2 (See table 10). Participants’ post-smoking ratings of irritability/frustration/anger and restlessness were 14 and 22 points lower after smoking U.S. ultra light cigarettes while there was no observed significant drop in pre- to post-smoking scores on these items after smoking full flavor
cigarettes in Study 1. No significant differences between pre- to post-smoking scores for either cigarettes were observed on these items in Study 2. Also, there were no observed significant differences between the cigarettes on these items in Study 2 (See tables 8 and 10).

Overall, results reported here suggest that the U.S. full flavor and ultra light cigarettes differ in toxicant exposure: when smoked under controlled topography conditions, U.S. full flavor cigarettes expose smokers to higher levels of nicotine and CO than ultra light cigarettes (See tables 7 and 9). In contrast, under the conditions of the study, the U.S. full flavor and ultra light cigarettes were similar in withdrawal suppression on some items and not others: significant differences in ratings of taste observed in Study 1 were not found in Study 2 and significant differences in ratings of sick and dizzy observed in Study 2 were not found in Study 1. The observation that U.S. full flavor and ultra light cigarettes differed significantly on only a few subjective measures with effects that were not observed across both studies (i.e., direct effects, withdrawal suppression) but differed significantly on all measures of toxicant exposure (i.e., nicotine, CO) across both studies suggests that the oft-noted brand-induced changes in puff topography may not be related to inadequate withdrawal suppression, and may require further study.

The methods used to compare cigarette toxicant levels to human toxicant exposure

The FTC’s machine smoking method is an effective way to determine the toxicant yield of cigarettes under a specific set of rather arbitrary and non-natural smoking conditions. As these qualifiers imply, the FTC method does not reveal the level of
toxicants to which cigarette smokers will be exposed, because smokers’ topography and other factors (i.e., coverage of filter vent holes) can vary. Because smokers can alter their topography and machines cannot, clinical research (i.e., research with smokers) is necessary if the toxicant exposure of cigarettes is to be understood completely. One type of clinical research involves *ad lib* smoking behavior (i.e., allowing puff topography to vary, and using it as an outcome measure; Woodward & Tunstall-Pedoe, 1992; Sweeney et al., 1999; Breland et al., 2003) while the current study involved keeping puff topography fixed in order to understand cigarette effects under specific smoking conditions. Unlike machine smoking, which does not address smokers’ toxicant exposure under any conditions, this study demonstrated that smokers of some Syrian cigarettes are likely exposed to similar levels of CO and nicotine as are U.S. smokers. Also unlike machine smoking, which cannot address the subjective effects produced by smoking a cigarette, this study demonstrated that U.S. full flavor and ultra light cigarettes produce similar levels of withdrawal suppression under the controlled laboratory conditions reported here. Other studies have also controlled topography variables in order to determine the extent to which filter ventilation hole blocking influences toxicant exposure (e.g., Zacny et al., 1986). Thus, even when smoking behavior is controlled, clinical research provides valuable information that cannot be attained with FTC-like methods. Moreover, the methods reported here can be modified to mimic the FTC method, or any other smoking parameters of interest, in order to understand the relationship between machine testing and smokers’ toxicant exposure. This methodology
may be useful in understanding how machine smoking tests will predict human exposure within a broad range of topography parameters.

Limitations of Studies 1 and 2

These two studies had several limitations, including: 1) a too-brief inter-cigarette interval, 2) possibility of type I errors, 3) possibility of type II errors, 4) topography variable choice, and 5) length of studies.

Inter-cigarette-interval. In order to maximize convenience for participants, this study was designed to be completed in a single session. As three cigarettes were to be smoked in one session, a 90-min rest period was scheduled between cigarettes (i.e., a 90 min inter-cigarette interval) to allow toxicant levels (i.e., plasma nicotine, CO) to return to baseline (i.e., near-zero levels). This inter-cigarette interval was chosen, in part, because nicotine has a relatively brief half-life (60-120 min, Ahijevych, 1998; Benowitz, 1996). However, 90 minutes does not allow for complete clearance of nicotine, and CO has a half-life of 4-5 hours in a sedentary adult (Stewart, 1975), so the 90-min inter-cigarette interval was too short: plasma nicotine and expired air CO levels did not return to baseline levels in all participants, and thus “nicotine boost” and “CO boost” were determined instead of using pre- and post-smoking plasma nicotine and expired CO levels. Obviously, the ideal situation would be for toxicant levels produced after smoking one cigarette to decline to near-zero before participants smoked the next cigarette: in this manner, the absolute increase associated with each cigarette could be measured. Future studies may benefit from a longer inter-cigarette-interval, including the use of multiple sessions that occur across several days.
Type I error. The probability of a Type I error, alpha (α), may be an important study limitation. A Type I error occurs when the null hypothesis is rejected falsely. This error may have been made when the null hypothesis that states that the U.S. full flavor and ultra light cigarettes would expose smokers to the same levels of toxicants, was rejected as false. Generating multiple F tests (P < .05), as was done for the analysis of these data, can increase the experimentwise error rate. Tukey’s HSD was used to control this error rate increase. Tukey’s HSD is a conservative post-hoc test designed to compare all possible pairs of means while maintaining the Type I error rate (Hurlburt, 1998). Following significant F tests, Tukey’s HSD results indicated that U.S. ultra light cigarettes exposed participants to lower toxicant levels than the U.S. full flavor cigarettes under the conditions of these studies. The fact that these results were observed in Study 1 and Study 2, each of which had a different group of participants, suggests that they reflect the true state of the world, and are likely not a Type I error.

Type II error. The probability of a Type II error also may have been a study limitation. A Type II error occurs when the null hypothesis has not been rejected when it should have been, and real differences cannot be detected. A Type II error may have been made on any outcomes that were found to be non-significant. One example of a potential error is that no differences in toxicant exposure between the U.S. full flavor and Alhamraa cigarettes were detected in Study 1. Another example is that no differences in toxicant exposure or HR scores between U.S. ultra light and Al Sham were detected in Study 2. A larger sample size would have provided more power, thus decreasing the chances of making a Type II error.
Topography variable choice. The topography parameters used in these studies were set to the following values: 1, 40 ml puff (+/- 3 ml) every 30 sec for a total of 10 puffs per cigarette. These parameters were chosen as they were similar to the average of the most commonly used parameters in smoking studies (Lee et al., 2003). However, there is great variability in mean topography across studies. For example, though the puff volume of these smoking studies examined averaged 40 ml, there was a range from 21 ml to 66 ml. Also, the average puff number per cigarette was 10 puffs but the range was from 8-16 puffs (Lee et al., 2003). Future studies may want to manipulate topography variables systematically in order to characterize better the nicotine and CO exposure that cigarettes produce.

Length of studies. These two studies were short-term in order to evaluate smokers’ exposure to CO and nicotine associated with one cigarette over several hours. The ability of smokers to extract CO and nicotine may change over time and some toxicants, such as carcinogens, require longer evaluation periods to detect changes. Thus, a complete evaluation of a cigarette’s toxicant exposure to humans may require longer-term studies with repeated cigarette administration.

Summary

Twenty-one and 19 daily, full flavor cigarette smokers completed one 4.5 hour session in which they smoked three cigarettes, each separated by 90 min. The Latin square ordered cigarettes were U.S. full flavor, U.S. ultra light and either Syrian Alhamraa (Study 1) or Al Sham (Study 2). These two studies examined the short-term toxicant exposure to participants from these cigarettes of varying toxicant yields. As
smokers tend to change their smoking behavior when given cigarettes of varying yields, topography measures of puff number, volume and IPI were held constant to allow for a controlled comparison of the toxicant exposure participants received from these different cigarettes. Toxicant yield and exposure were similar for some cigarettes and not others under these controlled conditions (i.e., controlled topography measures and no filter vent blocking). For example, Alhamraa cigarettes were more similar to U.S. full flavor cigarettes in terms of nicotine and CO exposure. On the other hand, Al Sham cigarettes were more similar to U.S. ultra light cigarettes in terms of nicotine and CO exposure and changes in HR.

Even when toxicant yield and exposure were significantly different (i.e., U.S. full flavor vs. U.S. ultra light), few significant differences were observed on subjective reports of direct effects and withdrawal for these cigarettes and none of these differences were observed across both studies. Overall, these results emphasize the value of clinical research for understanding the smoke toxicants to which smokers of different cigarettes are exposed.


carcinogens delivered to cigarette smokers. *Journal of the National Cancer Institute*, 92(2), 106-111.


Appendices

Appendix A - Telephone Screening

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Eligibility: Coordinator circle and initial/date

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Interviewer: “I would like to ask you some questions about yourself and your health status as well as your use of nicotine, alcohol, and other drugs. The purpose of these questions is to determine whether or not you are eligible to participate in either the study/studies I just described or in any of the other studies being conducted in the lab. All of your responses are confidential. You are not required to answer any question and you may stop this interview at any time. May I begin the questions?”

Document caller’s response by circling either: Yes or No

If Yes: begin form. If No: thank caller for calling.

How did you hear about us/our studies?

Personal Information:

1. “What is your first name?”

2. “What is a phone number at which you can be contacted?”

3. “What time/day is best to call you?”

4. “If we call and you are not available, may we leave a message?”
   Circle Yes or No

5. “What is your date of birth?”

6. “What is your height?” _______ (feet and inches)

7. “What is your weight?” _______ (pounds)

8. “Did you graduate high school or obtain a GED?”
   Circle Yes or No

[Note to interviewer: If yes, please note which one]
9. “How many years of education have you completed?” _________ (years)
   (e.g., 12 yrs = high school diploma; 16 yrs = college degree)

General health status:
10. “Are you under a doctor’s care for a medical condition?” Circle Yes or No
    If Yes: “Please describe the condition”:

11. “Are you taking any prescription or over-the-counter medications?”
    Circle Yes or No
    If Yes: “Please identify the medication”:

12. “Do you have any chronic health concerns or problems?” Circle Yes or No
    If Yes: “Please describe the concern or problem”:

13. Do you have any heart conditions? Circle Yes or No
    If Yes: “Please describe the condition”:

14. Do you have any psychiatric conditions like depression or anxiety? Circle Yes or No
    If Yes: “Please describe the condition”:

15. “Have you ever been diagnosed with high or low blood pressure?” Circle Yes or No
    If Yes: “Please indicate whether it is high or low”:

16. “Do you have fainting spells?” Circle Yes or No
17. “Do you have seizures?” Circle Yes or No
18. “Do you have any kidney problems?” Circle Yes or No

Cigarette use:
19. “Do you smoke tobacco cigarettes?” Circle Yes or No
    If No: Skip the remainder of this section.
20. “What brand of cigarettes do you smoke?”
    Circle:
    Regular/Light/Ultra light
    Non-menthol/Menthol
21. “Hard pack or soft pack?”

22. “Regular or 100s?”

23. “Have you ever felt a need to cut down or control your smoking, but had difficulty doing so?”  
   Circle Yes or No

24. “Do you ever get annoyed or angry with people who criticize your smoking or tell you that you ought to quit smoking?”  
   Circle Yes or No

25. “Have you ever felt guilty about your smoking or about something you did while smoking?”  
   Circle Yes or No

26. “Do you ever smoke within half an hour of waking up (eye-opener)?”  
   Circle Yes or No

27. “How many cigarettes/day do you smoke?”  
   _______ (num of cigs)

   [Note to interviewer: Please note the exact number of cigarettes/day smoked, and ALSO circle the appropriate group]

28. “For how long have you smoked this number?”  
   _______ (mnths or yrs)

29. “How soon after you wake up do you smoke your first cigarette?”  
   Circle:
   Within 30 min.
   After 30 min.

30. “Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., at the library, at the movies)?”  
   Circle Yes or No

31. “Which cigarette would you hate to give up the most?”  
   Circle: 1st in the morning
   Any other

32. “Do you smoke more frequently during the first hours after awakening than during the rest of the day?”  
   Circle Yes or No

33. “Do you smoke if you are so ill that you are in bed most of the day?”  
   Circle Yes or No
Smokeless Tobacco Use:
34. “Do you use smokeless tobacco (i.e., snuff, dip, or chew)?” Circle Yes or No

If No: Skip the remainder of this section.

35. “What brand of smokeless tobacco do you use?”

36. “How many times/day do you use smokeless tobacco?”

37. “For how long have you used smokeless tobacco?” (mts or yrs)

-----------------------------------------------------------------------------------------------------

Interviewer: “I’d like to ask you some additional questions about your use of alcohol and other drugs.”

Alcohol use:
38. “Have you ever been treated for alcohol abuse/dependence?” Circle Yes or No

39. “Do you use (drink) alcoholic beverages?” Circle Yes or No

If Question #39 is No: Skip the remainder of this section.

40. “Have you ever felt you ought to cut down on your drinking?” Circle Yes or No

41. “Have people annoyed you by criticizing your drinking?” Circle Yes or No

42. “Have you ever felt bad or guilty about your drinking?” Circle Yes or No

43. “Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)?” Circle Yes or No

44. “How many alcoholic drinks (by alcohol I mean beer, wine, or liquor) do you have on a typical day?” (num of drinks)

45. “How many days out of the last 30 have you used alcohol?” (num of days)

-----------------------------------------------------------------------------------------------------

Marijuana use:
46. Have you ever, in your lifetime, smoked marijuana or hashish? Circle Yes or No

If No: Skip the remainder of this section.

47. “Have you smoked marijuana within the past month?” Circle Yes or No

If No: Skip to question 54.
48. “Have you ever felt a need to cut down or control your smoking of marijuana, but had difficulty doing so?”  
   Circle Yes or No

49. “Do you ever get annoyed or angry with people who criticize your marijuana smoking or tell you that you ought to quit smoking?”  
   Circle Yes or No

50. “Have you ever felt guilty about your marijuana smoking or about something you did while smoking?”  
   Circle Yes or No

51. “Do you ever smoke marijuana within half an hour of waking up (eye-opener)?”  
   Circle Yes or No

52. “How many days out of the last 30 have you smoked marijuana?” ______ (num of days)

53. “Can you estimate how much money you spend each month on marijuana?” ______ (dollars)

54. “Have you ever received medical treatment related to your marijuana use?”  
   Circle Yes or No

55. “Have you used any other illicit drugs within the past month?”  
   Circle Yes or No

If Yes: “Please identify which drug or drugs.”

56. “Are you currently pregnant?”  
   Circle Yes or No

57. “Are you currently breast-feeding a child?”  
   Circle Yes or No

58. “Which contraceptive method(s) are you currently using (including abstinence)?”

59. “What was the first day of the onset of your last period?”

Interviewer: “Thank you for responding to these questions. I need to pass on your responses to the principal investigator who will then determine whether or not you are eligible to participate in a study; someone will contact you within approximately two working days if you are eligible. If you are not eligible for any of our current studies, then you will not be contacted.”
[if respondent does not have a phone, they can call us back in a few days]
Additional studies
60. “Even if you are not eligible for one of our current studies, may we call you sometime in the future if there are additional studies for which you are qualified?”

Document caller’s response by circling either: Yes or No
Title. International cigarette comparison study

VCU IRB Protocol Number. 2898

Investigator. Dr. Thomas Eissenberg

Purpose of the study. The purpose of this research study is to determine the effects of different types of cigarettes, some from the U.S. and some not from the U.S.

Description of the study. This study involves determining the mood and physiological effects of cigarettes marketed in the U.S. and abroad. You will be asked to learn to take puffs of a specific size and then take 10 puffs each from three different cigarettes during an approximately 4-hour session.

Procedures. If you agree to join the study, we will ask you to practice some of the study procedures and then complete a single, approximately 4-hour session.

The study procedures that you will practice involve completing some computerized questionnaires and learning how to take puffs of a certain size from an unlit cigarette. A computer will help you learn to take the correct sized puffs. We will need to teach you to take the correct size puffs before you can participate in the 4-hour session. We can practice the study procedures today, or we can schedule another day for the practice. The practice period should take less than one hour, and we will pay you $50 for completing it.

Once you have learned the study procedures, we will schedule a time when you can come back to the laboratory and complete an approximately 4-hour session. Before the session we will ask you to abstain from smoking for at least 8 hours. For example, you may begin the session in the morning if you have not smoked since dinnertime the day before. Before the session we will test your breath to find out when you last smoked; the result of this test will determine if the session can begin. If the breath test indicates that a session may not begin, you may wait or reschedule the session for another day.

At the beginning of the session a research nurse will insert a thin needle into your arm (catheter) that will stay there for the duration of the session. This needle will be used to draw blood (about a tablespoonful) periodically. We use this method because participants tell us that it is more comfortable than repeated “sticks” with a needle whenever we need a blood sample. Although we will take as many as six blood samples in each session, the total that we take is less than ¼ of what is taken when you donate blood. Once the catheter is inserted, we will begin monitoring your heart rate with a small cuff placed over your finger, and ask you to practice the study puffing procedures one more time (from an unlit cigarette).
Each session will involve you taking puffs from lit cigarettes at three different times, with about 90 minutes of rest between each smoking time. The cigarettes will be either normally marketed U.S. cigarettes, or cigarettes that are marketed to smokers in another country. They may or may not be your own brand of cigarettes. Each time that you smoke you will take exactly 10 puffs from the cigarette; a research assistant and the computer will help you keep track of the number of puffs that you take. Also, the computer will tell you when to take each puff and will help you make sure that the puffs that you take are the same size.

Before and after each of the three smoking periods we will take a blood sample from the catheter and ask you to respond to some computerized questionnaires about your mood and the taste and other effects of the cigarette. We will also measure the amount of smoke in your breath. We will be monitoring your heart rate throughout the session.

After the third smoking period and all measurements are completed, the nurse will remove the catheter from your arm and you will be paid $130 for your time. This payment will end your study participation.

**Risks and Discomforts.** There are minimal risks associated with this study. Eight or more hours of cigarette abstinence may cause mild discomfort that is not medically dangerous. The blood drawing procedure involves minimal risks of infection that are reduced by the research nurse who will use sterile, disposable equipment. If you find any effects or data collection procedures unacceptable, you may stop your participation at any time.

As the study procedures might injure an unborn child, pregnant women may not participate.

You will be made aware of any significant new findings that may change your decision to remain in this study.

**Benefits.** This is not a treatment study, and you are not expected to receive any direct medical benefits from your participation in the study. The information from this research study may lead to better understanding of the effects of different brands of cigarettes.

**Costs.** There are no financial costs to you for participating in this research study. Participating will take about 4-5 hours of your time. You will be paid for your time and inconvenience.

**Payment for participation.** You will be paid $180 if you complete the entire study (practice and session). If you withdraw from the study before completion, you will be paid $5/hour for the time that you spent in the laboratory.
Alternative Treatment. This is not a treatment study. Your alternative is not to participate in this study.

Confidentiality. Confidentiality of personal information about you – including your medical records and personal research data gathered in connection with this study – will be maintained in a manner consistent with federal and state laws and regulations.

You should know that research data or (medical information if applicable) about you may be reviewed or copied by Virginia Commonwealth University or the U.S. Department of Health and Human Services. Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.

Compensation for Injury. Virginia Commonwealth University and the VCU Health System (formerly known as Medical College of Virginia Hospitals) have no plan for providing long-term care or compensation in the event that you suffer injury as a result of your participation in this research study.

If you are injured or if you become ill as a result of your participation in this study, contact your study doctor immediately. Your study doctor will arrange for short-term emergency care or referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

Voluntary Participation and Withdrawal. Your participation in this study is voluntary. If you do participate, you may freely withdraw from the study at any time. Your decision will not change your future medical care at this site or institution.

Your participation in this study may be stopped at any time by the study doctor without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions;
- administrative reasons require your withdrawal.

If you decide to withdraw from this study or if you are withdrawn by the study doctor, we will pay you for the time you spent in the study.

Questions. In the future, you may have questions about your study participation. You may also have questions about a possible side effect, or a possible research-related injury. If you have any questions, contact:
Subjects' Rights Information. If you have questions about your rights as a research subject, you may contact:

Office for Research Subjects Protection
Virginia Commonwealth University
800 East Leigh Street, Suite 111
P.O. Box 980568
Richmond, VA 23298
Telephone: 804-828-0868

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Consent. I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study.

__________________________________________________________________________
Participant’s Printed Name

__________________________________________________________________________
Signature of Participant
Date

__________________________________________________________________________
Signature of Person Performing Consent
Date

__________________________________________________________________________
Signature of Witness to Consent
Date

__________________________________________________________________________
Signature of Investigator
Date
Appendix C – Personal Information and Health Status Form

<table>
<thead>
<tr>
<th>Physical Information</th>
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</thead>
<tbody>
<tr>
<td>International Cigarette Comparison</td>
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<table>
<thead>
<tr>
<th>Participant’s ID</th>
<th>Today’s Date</th>
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</table>

Screening CO ________________ ppm

Screening Weight ________________ lbs (no shoes)

Screening Height ________________ feet and ________________ inches (no shoes)
## Appendix D – Demographic Information

### International Cigarette Comparison Study

<table>
<thead>
<tr>
<th>Participant’s Name</th>
<th>Today’s Date</th>
</tr>
</thead>
</table>

### Age
- Years: __________
- Exact date of birth: ____________________________

### Ethnicity
- o Hispanic or Latino
- o Not Hispanic or Latino

### Race
- o American Indian/Alaskan Native
- o Asian/Native Hawaiian or other Pacific Islander
- o Black or African American
- o White
- o Other/Unknown (_______)

### Gender
- o Male
- o Female

### Marital status
- o Single
- o Married
- o Separated
- o Divorced
- o Widowed

### Education
- Years: ________ (For example, High school = 12, College degree = 16, etc.)

### Primary employment
- o unemployed
- o PT (0-30 hrs/wk)
- o FT (>30 hrs/wk)
- o Student

### History of quit attempts
- o Never tried to quit
- o Tried to quit ________ times
- o Trying to quit now

### Previous experience with nicotine medications
- o No experience
- o At least one experience
- o Nicotine gum
- o Nicotine patch
- o Nicotine spray
- o Nicotine inhaler

By signing this form below, you indicate that you have answered the above questions truthfully.

<table>
<thead>
<tr>
<th>Participant’s Signature</th>
<th>Today’s Date</th>
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<table>
<thead>
<tr>
<th>Investigator’s Signature</th>
<th>Today’s Date</th>
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</table>
Appendix E – Fagerström Test for Nicotine Dependence

Smoking Behavior
International Cigarette Comparison

<table>
<thead>
<tr>
<th>Participant's ID</th>
<th>Today's Date</th>
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</table>

Please answer the following questions (mark an X in one box only):

1. How soon after you wake up do you smoke your first cigarette?
   - Within 5 minutes
   - Within 6-30 minutes
   - Within 31-60 minutes
   - After 60 minutes
   
   ![Selection](#)

2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, at the movies)?
   - Yes
   - No
   
   ![Selection](#)

3. Which cigarette would you hate to give up the most?
   - The first one in the morning
   - All others
   
   ![Selection](#)

4. How may cigarettes a day do you smoke?
   - 10 or less
   - 11-20
   - 21-30
   - 31 or more
   
   ![Selection](#)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
   - Yes
   - No
   
   ![Selection](#)

6. Do you smoke if your are so ill that you are in bed most of the day?
   - Yes
   - No
   
   ![Selection](#)
Appendix F - Nicotine/tobacco withdrawal VAS (Hughes & Hatsukami, 1986)

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you have felt over the last 24 hours by drawing a vertical mark anywhere along the horizontal line.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely</th>
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</thead>
<tbody>
<tr>
<td>1. URGES to smoke</td>
<td></td>
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<tr>
<td>2. Irritability/frustration/anger</td>
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<tr>
<td>3. Anxious</td>
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<td>4. Difficulty concentrating</td>
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<tr>
<td>5. Restlessness</td>
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<td>6. Hunger</td>
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<td>7. Impatient</td>
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<tr>
<td>8. CRAVING a cigarette/nicotine</td>
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<td>9. Insomnia/disturbed sleep</td>
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<td>10. Increased eating</td>
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<td>11. Drowsiness</td>
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Appendix G - Questionnaire of Smoking Urges (Tiffany & Drobes, 1991)

For each item please indicate how you feel RIGHT NOW by placing an X in the appropriate level.

1. Smoking would make me feel very good right now.

2. I would be less irritable now if I could smoke.

3. Nothing would be better than smoking a cigarette right now.

4. I am not missing smoking right now.

5. I will smoke as soon as I get the chance.

6. I don’t want to smoke right now.

7. Smoking would make me less depressed.

8. Smoking would not help me calm

Strongly disagree Strongly agree

Strongly disagree Strongly agree

Strongly disagree Strongly agree

Strongly disagree Strongly agree

Strongly disagree Strongly agree
down right now.

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<tr>
<td>9. If I were offered a cigarette, I would smoke it immediately.</td>
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<td>10. Starting now, I could go without smoking for a long time.</td>
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<td>11. Smoking a cigarette would not be pleasant.</td>
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<td>12. If I were smoking this minute, I would feel less bored.</td>
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<tr>
<td>13. All I want right now is a cigarette.</td>
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<td>14. Smoking right now would make me feel less tired.</td>
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<td>15. Smoking right now would make me feel happier now.</td>
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<td>16. Even if it were possible, I probably wouldn’t smoke right now.</td>
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<tr>
<td>17. I have no desire for a cigarette right</td>
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</table>
18. My desire to smoke seems overwhelming.

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<th>Strongly disagree</th>
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<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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19. Smoking right now would make things seem just perfect.

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<tr>
<th>Strongly disagree</th>
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<tbody>
<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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</table>

20. I crave a cigarette right now.

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<th>Strongly disagree</th>
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<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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</table>

21. I would not enjoy a cigarette right now.

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<th>Strongly disagree</th>
<th>Strongly agree</th>
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<tbody>
<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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</table>

22. A cigarette would not taste good right now.

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<th>Strongly disagree</th>
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<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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</table>

23. I have an urge for a cigarette.

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<th>Strongly disagree</th>
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<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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24. I could control things better right now if I could smoke.

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<tr>
<th>Strongly disagree</th>
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<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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25. I am going to smoke as soon as possible.

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<th>Strongly disagree</th>
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<td><img src="image" alt="Strongly disagree" /></td>
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26. I would not feel better physically if I

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<tr>
<td><img src="image" alt="Strongly disagree" /></td>
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</table>
were smoking.

27. A cigarette would not be very satisfying right now.  

28. If I had a lit cigarette in my hand I probably would not smoke it.  

29. If I were smoking right now I could think more clearly.  

30. I would do almost anything for a cigarette now.  

31. I need to smoke now.  

32. Right now, I am not making plans to smoke.
Appendix H – Direct Effects of Cigarettes Scale

1. Was the cigarette satisfying?

2. Was the cigarette pleasant?

3. Did the cigarette taste good?

4. Did the cigarette taste bad?

5. Did the cigarette make you dizzy?

6. Did the cigarette calm you down?

7. Did the cigarette make you feel confused?

8. Did the cigarette help you concentrate?

9. Did the cigarette make you feel more awake?

10. Did the cigarette reduce your hunger for food?

11. Did the cigarette make you sick?

12. Did the cigarette make you sleepy?

13. Would you like to smoke another cigarette RIGHT NOW?
Vita

Lynn Michelle Anderson was born in Silver Springs, Maryland on October 29, 1979. She is a graduate of Bowie High School in Bowie, Md, and has a B.A. in Psychology from Salisbury University in Salisbury, Maryland, which she received in 2001. She began the Biopsychology program at Virginia Commonwealth University in August 2002 and will receive her Masters of Science degree in December, 2005.