THE SCIENCE OF A NICOTINE STANDARD FOR COMBUSTED TOBACCO PRODUCTS

Updated June 2023

Contents

I. Executive Summary

Use of combusted tobacco products (i.e., cigarettes, cigarette tobacco, roll-your-own (RYO) tobacco, kreteks, bidis, cigars [including little cigars, large cigars, and cigarillos], pipe tobacco, and waterpipe tobacco) causes a tremendous burden of death and disease, with at least 480,000 people dying prematurely from a smoking attributable disease each year. These adverse health effects are ultimately the result of addiction to the nicotine in combusted tobacco products, which results in repeated use that continuously exposes users and non-users to toxicants in the smoke. Through this document, FDA indicates that it is considering the issuance of a product standard to set a maximum nicotine level in combusted tobacco products so that they are minimally addictive, using the best available science to determine a level that is appropriate for the protection of the public health.

After systematically reviewing the peer-reviewed literature regarding the likely effects of reducing nicotine in combusted tobacco, FDA concludes that extended exposure to combusted cigarettes containing very low nicotine content [VLNC][1] tobacco filler is associated with reduced addiction potential, dependence levels, number of cigarettes smoked per day, and increased quit attempts among current smokers, without evidence of increased toxicant exposure, craving, withdrawal, or compensatory smoking. There is no evidence of differential effects of VLNC cigarettes in vulnerable populations, such as adults with symptoms of mental health disorders or adolescents; however, the literature on the effects of VLNC cigarettes in youth is limited. While the reviewed literature shows some evidence of compensatory smoking during the intermediate stages of a gradual approach to reducing nicotine, immediate reduction approaches are associated with very little or no compensatory smoking and could therefore maximize the benefits of a nicotine tobacco product standard. The reviewed literature also indicates that, although most adult American consumers understand that nicotine is the addictive chemical in cigarettes, a substantial portion of adults also believe that nicotine is carcinogenic and is a main cause of smoking-related disease. Increased efforts to communicate the science behind a nicotine product standard will help educate the public prior to the implementation of a nicotine product standard.

[1] In the present document, "very low nicotine content (VLNC) cigarettes" refers specifically to cigarettes with ≤ 0.7 mg nicotine per cigarette (i.e., ≤ 1.0 mg nicotine per g of total tobacco), "low nicotine content (LNC) cigarettes" refers to cigarettes with > 0.7 mg and < 8 mg nicotine per cigarette, and "normal nicotine content (NNC) cigarettes" refers to cigarettes with ≥ 8 mg nicotine per cigarette.

If FDA were to establish a nicotine tobacco product standard that covered only cigarettes, a portion of addicted smokers could migrate to other, similar combusted tobacco products to maintain their nicotine dose (or engage in dual use without substantially reducing their combusted tobacco product use), thereby, reducing the positive public health impact of such a rule. FDA reviewed the literature on combusted tobacco products, including combusted cigarettes (which FDA has previously interpreted to include kreteks and bidis), cigarette tobacco, RYO tobacco, cigars (including little cigars, large cigars, and cigarillos), pipe tobacco, and waterpipe tobacco. Based on this review, FDA concludes that use of any of these combusted products is sufficient to create or sustain nicotine dependence and could therefore continue to expose users to toxicants. Therefore, if FDA were to establish a product standard to reduce the nicotine content of combusted cigarettes, the standard should also reduce the nicotine content of other combusted tobacco products.

Currently, more than half of adult cigarette smokers make a serious quit attempt each year (quit for at least a day), but many of them do not succeed due to the addictive nature of these products. In addition to increasing the likelihood of successful quit attempts, the establishment of a maximum nicotine level in combusted tobacco products could help prevent experimenters (mainly youth and young adults) from progressing to regular use. A simulation model found that reducing the nicotine level in cigarettes has the potential to substantially reduce the enormous burden of smoking-related death and disease. The model estimated that a nicotine product standard for cigarettes in the United States could save millions of lives and tens of millions of life-years over the next several decades. Rendering combusted tobacco products minimally addictive by reducing the nicotine content to 0.7 mg of nicotine per g of total tobacco is technically achievable and could help current users quit and prevent future users from becoming addicted and escalating to regular use.

II. Background

A. Purpose

On July 28, 2017, FDA announced a comprehensive approach to tobacco and nicotine regulation to protect youth and reduce tobacco-related disease and death. Nicotine, while addictive, can be delivered through a variety of products along a continuum of risk, with combusted cigarettes and other combusted tobacco products at the most harmful end of this continuum. Thus, the FDA's comprehensive approach began with a public dialogue about lowering nicotine levels in combusted cigarettes to minimally addictive levels through achievable product standards. On March 16, 2018, FDA issued an ANPRM to seek input on the potential public health benefits and any possible adverse effects of lowering nicotine in

cigarettes. Tobacco use is a major cause of death and disease every year; these adverse health effects are ultimately the result of addiction to the nicotine contained in combusted tobacco products (e.g., cigarettes), leading to repeated exposure to toxicants from those products (U.S. Department of Health and Human Services, 1988, 2010). This nicotine addiction causes users to engage in compulsive use, makes quitting less likely and, therefore, repeatedly exposes them (and others) to thousands of toxicants in combusted tobacco products (U.S. Department of Health and Human Services, 1988, 2010). Researchers have found that the mortality rate from any cause of death at any given age is 2 to 3 times higher among current cigarette smokers compared to never smokers (Carter et al., 2015). Through this document, FDA reviews the best available science in support of a product standard to set a maximum nicotine level in combusted tobacco products so that these products are minimally addictive and, therefore, appropriate for the protection of the public health.[2] Greatly reducing the addictiveness of combusted tobacco products would have significant benefits for youth, young adults, and adults.[3] More than half of adult cigarette smokers make a serious quit attempt each year (i.e., quit for at least a day), but many of them are not able to succeed due to the addictive nature of these products (Creamer et al., 2019; National Center for Health Statistics). The establishment of a maximum nicotine level in combusted tobacco products could increase the likelihood of successful quit attempts and help prevent experimenters (mainly youth) from progressing to regular use. Therefore, FDA hypothesizes that making combusted tobacco products minimally addictive, using the best available science to determine a level that is appropriate for the protection of the public health, would significantly reduce the morbidity and mortality caused by smoking.

Preventing nonsmokers, particularly youth and young adults, from becoming regular smokers due to nicotine addiction would allow them to avoid the severe adverse health consequences of smoking and would result in substantial public health benefits. It has been estimated that, without changes like those proposed here, 3.66 million youth under the age of 18 who were alive in 2018—and 2.54 million youth who are alive in 2024, accounting for the projected continued decline in smoking prevalence—will die prematurely later in life from a smoking-related disease (Warner, 2020). In 2009, Congress estimated that a 50 percent

[2] The Tobacco Control Act specifically prohibits the Agency from "requiring the reduction of nicotine yields of a tobacco product to zero" but generally authorizes FDA to issue a tobacco product standard setting a maximum nicotine level (Section 907(C)(3)(B) of the Federal Food, Drug, & Cosmetic Act [FD&C Act]).

[3] The definitions of "youth," "young adults," and "adults" can vary in scientific studies. The term "youth" generally refers to middle school and/or high school students. "Young adults" generally refers to individuals aged 18 to 24. In some studies, "adults" may encompass individuals aged 18 to 24 but generally refers to individuals aged 24 to 65.

reduction in youth smoking would also result in approximately $75 billion in savings[4] attributable to reduced health care costs (section 2(14) of the 2009; 21 USC 387 note). Although the 2019 National Youth Tobacco Survey (NYTS) saw the lowest numbers of youth tobacco use since its inception in 1999, approximately half of high school students and one-fourth of middle school students experimented with tobacco products, indicating that youth tobacco use is still a major public health concern (Wang et al., 2019). If combusted tobacco products were minimally addictive, it is expected that substantially fewer youth and young adults would be subjected to the impacts of nicotine (which has a significantly stronger effect on the developing brains of youth) (e.g., Poorthuis, Goriounova, Couey, & Mansvelder, 2009; U.S. Department of Health and Human Services, 2012), and therefore fewer would suffer from the associated health and mortality effects of combusted tobacco product use.

Nicotine is powerfully addictive. The Surgeon General has reported that 87 percent of adult smokers start smoking before the age of 18 and half of adult smokers become addicted before the age of 18, which is before the age at which they can legally buy a pack of cigarettes (U.S. Department of Health and Human Services, 2014). Nearly all smokers begin before the age of 25, which is the approximate age at which the brain has completed development (U.S. Department of Health and Human Services, 2012). Although recent legislation has increased the minimum purchase age from 18 to 21 nationwide, concerns regarding surreptitious access to tobacco among youth and young adults persist. Generally, those who begin smoking before the age of 18 are not aware of the degree of addictiveness and the full extent of the consequences of smoking when they begin experimenting with tobacco use (e.g., Slovic, 2001). Although youth generally believe they will be able to quit at will, in practice they have low success rates when making a quit attempt. For example, more than 60 percent of high school aged daily smokers have tried to quit, but less than 13 percent were successful at quitting for 30 days or more (Centers for Disease Control and Prevention, 2009b). In addition, one study found that only 3 percent of 12th grade daily smokers estimated that they would “definitely” still be smoking in 5 years, while in reality 63 percent of this population is still smoking 7 to 9 years later (Johnston, O’Malley, Bachman, & Schulenberg, 2005). Another survey revealed that “nearly 60 percent of adolescents believe that they could smoke for a few years and then quit” (Institute of Medicine of the National Academies, 2007). However, three out of four youth smokers continue to smoke into adulthood, even if they intended to quit (U.S. Department of Health and Human Services, 2012).

[4] Congress’ estimate of approximately $75 billion in savings, if adjusted for inflation, would amount to $83.63 billion in 2017.

Tobacco addiction is often accompanied by symptoms of nicotine dependence, including physical dependence such as tolerance to the effects of nicotine and withdrawal upon cessation of use. Among adolescent tobacco users in 2012, over half (52.2 percent) reported experiencing at least one symptom of tobacco dependence (Apelberg et al., 2014). Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood (Apelberg et al., 2014). In addition, one study found that symptoms of dependence, including urges to smoke, anxiety, and irritability can appear in youth just days or weeks after occasional smoking begins (DiFranza et al., 2000). Because it is such a powerful addiction, nicotine addiction is often lifelong (Levin et al., 2007). FDA expects that making cigarettes minimally addictive by reducing the nicotine content may have significant benefits for youth by reducing the risk that youth experimenters progress to regular use of combusted tobacco products as a result of nicotine dependence.

Data from animal studies show that the adolescent brain is more vulnerable to the reinforcing effects of nicotine, which makes adolescents more vulnerable to developing nicotine addiction compared to adults (Levin et al., 2007). Data from animal studies also indicate that brain changes induced by nicotine may have long-term consequences (i.e., long-term physical changes caused by adolescent nicotine exposure prevent the brain from reaching its full potential, which could result in permanent deficiencies) (Poorthuis et al., 2009; U.S. Department of Health and Human Services, 2012). Evidence from animal studies also indicates that exposure to substances such as nicotine can disrupt brain development and have long-term consequences for executive cognitive function (such as task-switching and planning) and for the risk of developing a substance abuse disorder and various mental health problems (particularly, affective disorders such as anxiety and depression) as an adult (Counotte, Smit, Pattij, & Spijker, 2011). Nicotine exposure can also have long-term effects, including decreased attention performance and increased impulsivity, which could promote the maintenance of tobacco use behavior (Counotte et al., 2011). Furthermore, the 2010 Surgeon General's Report noted that symptoms of dependence could result from even limited nicotine exposure during adolescence (U.S. Department of Health and Human Services, 2010).

Age restrictions on the sale of tobacco products by themselves are not entirely effective in preventing youth from obtaining cigarettes or other combusted tobacco products. Youth smokers get their cigarettes from a variety of sources, including directly purchasing them from retailers, giving others money to buy them, obtaining them from other youth or adults (with or without their knowledge), or using illegal means (i.e., shoplifting, stealing) (Lenk, Toomey, Shi, Erickson, & Forster, 2014). The 2015 National Youth Risk Behavior Surveillance Survey (YRBS) of

high school students in grades 9 through 12 found that 12.6 percent of current cigarette smokers under the age of 18 had purchased their cigarettes directly from stores or gas stations despite the Federal minimum age requirements for cigarettes (Kann et al., 2016). While continued vigorous enforcement of youth access restrictions is critical to protecting public health, FDA is considering taking this additional step to ensure that even if youth do obtain access to cigarettes, they will be less likely to: (1) become addicted to these products; (2) progress to regular use; and (3) increase their risk of the many diseases caused by combusted tobacco product use (Grucza et al., 2013).

For these reasons, FDA is considering mitigating the addictiveness of combusted tobacco products by setting a product standard that establishes a maximum nicotine level to help prevent experimenters (who are mainly youth) from becoming addicted to tobacco and, thus, prevent them from progressing to regular use and from increasing their risk of tobacco-related death and disease.

Similarly, limiting the nicotine in cigarettes could have significant benefits for adult tobacco product users, a large majority of whom want to quit but are unsuccessful because of the highly addictive nature of these products (e.g., Centers for Disease Control and Prevention, 2011). Data from the 2015 National Health Interview Survey show that 68 percent of current adult cigarette smokers in the United States wanted to quit and 55.4 percent of adult cigarette smokers made a past-year quit attempt of at least 1 day (Babb, Malarcher, Schauer, Asman, & Jamal, 2017). In high-income countries, about 7 of 10 adult smokers say they regret initiating smoking and would like to stop (Nayak, Pechacek, Slovic, & Eriksen, 2017; Prabhat & Chaloupka, 1999). Decreasing the nicotine in cigarettes so that they are minimally addictive (using the best available science to determine a level that is appropriate for the protection of the public health) could help users restore some autonomy and quit if they want to--as the large majority of users say they do (Centers for Disease Control and Prevention, 2011). Decreasing the nicotine content of combusted tobacco products could also cause smokers to switch to potentially less harmful tobacco products (Hatsukami et al., 2017; National Academies of Sciences, 2018).

Although many factors contribute to an individual's initial experimentation with tobacco products, the addictive nature of tobacco is the major reason people progress to regular use, and it is the presence of nicotine that causes youth, young adults, and adult users to become addicted to, and to sustain, tobacco use (e.g., Institute of Medicine of the National Academies, 2001; U.S. Department of Health and Human Services, 1988). Since the 1988 Surgeon General's Report (SGR), additional SGRs have confirmed that nicotine in tobacco causes addiction (U.S. Department of Health and Human Services, 1994; U.S. Department of Health and Human Services, 2004; U.S. Department of Health and Human Services, 2010b; U.S. Department of

Health and Human Services, 2012). Tobacco use disorder is a psychiatric disorder, defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) as being characterized by tolerance to the effects of tobacco products, withdrawal symptoms that are mitigated by the self-administration of nicotine-containing products, and unsuccessful attempts at reducing or quitting the use of nicotine-containing products (Baker, Breslau, Covey, & Shiffman, 2012). While nicotine is the primary addictive chemical in tobacco, sensorimotor stimuli that are repeatedly paired with nicotine through the process of smoking also develop into conditioned reinforcers that contribute to the persistent nature of nicotine dependence (Palmatier et al., 2007). In cigarette users, the sensory aspects of smoking, such as taste and smoking sensations (e.g., throat hit), become conditioned reinforcers due to repeated pairings with nicotine, a primary reinforcer. Thus, through conditioning, these non-nicotine stimuli become reinforcing in experienced users (Rose, Salley, Behm, Bates, & Westman, 2010). However, basic principles of behavior show that the reinforcing effects of conditioned reinforcers fade over time when these stimuli are no longer paired with primary reinforcers (Bouton, 2004).

Once tobacco users become addicted to nicotine, they require nicotine to avoid withdrawal symptoms. In the process of obtaining nicotine, combusted tobacco product users are exposed to an array of toxicants in tobacco and tobacco smoke that lead to a substantially increased risk of morbidity and mortality (e.g., Slovic, 2001). Although most current U.S. smokers report that they want to quit smoking, have attempted to quit, and regret starting (e.g., Fiore et al., 2008; Fong et al., 2004), many smokers find it difficult to break their addiction and quit. Because of nicotine addiction, many smokers lack the ability to choose whether to continue smoking these toxic combusted products despite their stated desire to quit (U.S. Department of Health and Human Services, 2010).

Accordingly, in deciding to issue a tobacco product standard reducing the nicotine content in combusted tobacco products to minimally addictive levels, FDA aims to: (1) reduce the risk of progression to regular use and nicotine dependence for persons who experiment with the tobacco products covered by the standard, and (2) give addicted users of combusted tobacco products the choice and increase the likelihood that they may quit or switch to potentially less harmful tobacco products by reducing the nicotine to a minimally addictive level. FDA hypothesizes that making combusted tobacco products minimally addictive, using the best available science to determine a level that is appropriate for the protection of the public health, could significantly reduce the morbidity and mortality caused by smoking.

B. Negative Health Effects of Combusted Tobacco Product Use

Cigarettes are responsible for hundreds of thousands of premature deaths every year from many diseases, put a substantial burden on the U.S. health care system, and cause massive economic losses to society (U.S. Department of Health and Human Services, 2014 at p. 659-666). Cigarette smoking causes more deaths each year than AIDS, alcohol, illegal drug use, homicide, suicide, and motor vehicle crashes combined (Stewart et al., 2008). Every year, cigarette smoking is the primary causal factor for 163,700 deaths from cancer, 160,600 deaths from cardiovascular and metabolic diseases, and 131,100 deaths from pulmonary diseases (U.S. Department of Health and Human Services, 2014 at p.659). In the United States, about 87 percent of all lung cancer deaths, 32 percent of coronary heart disease deaths, and 79 percent of all cases of chronic obstructive pulmonary disease (COPD) are attributable to cigarette smoking (U.S. Department of Health and Human Services, 2014).

Data from the CDC's Smoking-Attributable Mortality, Morbidity, and Economic Costs system for 2005-2009 (the most recent years for which analyses are available) indicate that cigarette smoking and exposure to cigarette smoke are responsible for at least 480,000 premature deaths each year (U.S. Department of Health and Human Services, 2014 at p.659). However, this estimate does not include deaths caused by other combusted forms of tobacco, such as cigars and pipes (U.S. Department of Health and Human Services, 2014 at p.665).[5] The three leading causes of smoking-attributable death for current and former smokers were lung cancer, heart disease, and COPD (U.S. Department of Health and Human Services, 2014 at p. 660). For every person who dies from a smoking-related disease, approximately 30 more people will suffer from at least one smoking-related disease (Alberg, Shopland, & Cummings, 2014).

Non-cigarette combusted tobacco products include kreteks and bidis, cigarette tobacco, RYO tobacco, cigars (including little cigars, large cigars, and cigarillos), pipe tobacco, and waterpipe tobacco. These combusted tobacco products, particularly those that could be cigarette alternatives if users were unable to continue smoking cigarettes, cause similar negative health effects. A long-standing body of research, including reports from the Surgeon

[5] As discussed in Nonnemaker et al. (Nonnemaker, Rostron, Hall, MacMonegle, & Apelberg, 2014), regular cigar smoking was responsible for approximately 9,000 premature deaths and more than 140,000 years of potential life lost among adults aged 35 years or older in 2010. The 2014 Surgeon General's Report states that the methodology for estimating the current population burden for use of combusted tobacco products other than cigarettes remains under discussion, but the number of added deaths is expected to be in the thousands per year (Shapiro, Jacobs, & Thun, 2000; U.S. Department of Health and Human Services, 2014 at p.665).

General and National Cancer Institute (NCI), demonstrates that cigar use can cause serious adverse health effects (Henley, Thun, Chao, & Calle, 2004; National Cancer Institute, 1998a at p.119-155; Rodriguez et al., 2010; U.S. Department of Health and Human Services, 1989). For example, little cigars and cigarillos expose users to toxicants known to impair vascular endothelial function (Ghosh et al., 2017; Liu et al., 2016) and cause oral, esophageal, and lung cancer (Chang, Corey, Rostron, & Apelberg, 2015). Researchers also have found that the risk of dying from tobacco-related cancers is higher for current exclusive pipe smokers and current exclusive cigar smokers than for those who reported never using combusted tobacco products (Christensen et al., 2018).

Cigarettes and other combusted tobacco products also have deadly effects on nonsmokers because they produce second-hand smoke. From 2005 to 2009, an estimated 7,330 lung cancer and 33,950 heart disease deaths were attributable to exposure to secondhand smoke (U.S. Department of Health and Human Services, 2014 at p. 660). It is well-established that secondhand tobacco smoke causes premature death and disease in children and adults who do not smoke (e.g., U.S. Department of Health and Human Services, 2006 at p.11). According to the 2014 Surgeon General's Report, smoking remains the leading preventable cause of disease and death in the United States, and cigarettes have been shown to cause an ever-expanding number of diseases and health conditions (U.S. Department of Health and Human Services, 2014). As also stated in this Report, "Cigarette smoking has been causally linked to diseases of nearly all organs of the body, to diminished health status, and to harm to the fetus … [and] the burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products" (U.S. Department of Health and Human Services, 2014 at p.7).

C. Nicotine in Combusted Tobacco Products and Its Influence on Addiction

Nicotine is a powerfully addictive chemical. The effects of nicotine on the central nervous system occur rapidly after absorption (U.S. Department of Health and Human Services, 1988 at p.12). Users of combusted tobacco products absorb nicotine readily from tobacco smoke through the lungs (U.S. Department of Health and Human Services, 1988, p. iii), and, from the lungs, nicotine is rapidly transmitted to the brain (U.S. Department of Health and Human Services, 1988 at p.12). With regular use, nicotine levels accumulate in the body during the day from the tobacco product use and then decrease overnight as the body clears the nicotine (U.S. Department of Health and Human Services, 1988 at p.iii). While mild nicotine intoxication can occur in first-time smokers (U.S. Department of Health and Human Services, 1988 at p. 15-16), tolerance to the effects of nicotine develops rapidly.

The addiction potential of a nicotine delivery system varies as a function of its total nicotine dosing capability, the speed at which it can deliver nicotine, the palatability and sensory characteristics of the system, how easy it is for the user to extract nicotine, and the cost of the delivery system (Henningfield et al., 1998). The amount of nicotine delivered and the means through which it is delivered can either reduce or enhance a product's potential for abuse and physiological effects (U.S. Department of Health and Human Services, 2010 at p.113). Quicker delivery, higher rate of absorption, and higher resulting concentration of nicotine increase the potential for addiction (U.S. Department of Health and Human Services, 2010 at p.113). A cigarette is an inexpensive and extremely effective nicotine delivery device that maximizes the cigarette's addicting and toxic effects (Henningfield et al., 1998).

Some evidence suggests nicotine is more addictive than many other common drugs of abuse. For example, one study showed the probability of transitioning from first use to dependence was 68% for nicotine, but less than 23% for alcohol, cocaine, and cannabis (Lopez-Quintero et al., 2011). While cigarettes are the most widely used tobacco products among adults, other combusted tobacco products that are possible targets of product migration (i.e., switch candidates for smokers to maintain their nicotine addiction) or dual use, have similar adverse health effects and also cause nicotine dependence (Huh & Timberlake, 2009; National Cancer Institute, 1998a). Cigar and pipe users are still subject to the addictive effects of nicotine through nicotine absorption (and to the health impacts of long-term use that may follow from regular use due to addiction) even if they report that they do not inhale (McDonald et al., 2002; Rodriguez et al., 2010; Weglicki, 2008).

a. Youth Cigarette Smoking Initiation and Dependence

The Surgeon General has reported that "most people begin to smoke in adolescence and develop characteristic patterns of nicotine dependence before adulthood" (U.S. Department of Health and Human Services, 1994 at p. 29). Adolescents develop physical dependence and experience withdrawal symptoms when they try to quit smoking (U.S. Department of Health and Human Services, 1994). Using the best available science to determine a nicotine level that is appropriate for the protection of the public health by making cigarettes minimally addictive would limit the number of youth and young adults who progress from experimentation to regular use and who, therefore, increase their risk for smoking-related diseases (see Section IV.C.c.i: *Adolescents*).

Researchers have determined that almost one-third of adolescents aged 11 to 18 (31 percent) are "early experimenters," meaning that they have tried smoking at least one puff of a cigarette, but smoked no more than 25 cigarettes in their lifetime (Mowery, Farrelly, Haviland,

Gable, & Wells, 2004). A study conducted in 2020 found that 9.4 percent of high school students and 3.4 percent of middle school students had tried at least one combusted tobacco product (Wang et al., 2020). The Centers for Disease Control and Prevention (CDC) and other researchers have estimated that 30 percent or more of people who have experimented with smoking (i.e., smoked fewer than 100 cigs in lifetime) become established smokers (Centers for Disease Control and Prevention, 1998; Choi, Pierce, Gilpin, Farkas, & Berry, 1997; Mowery et al., 2004). Given these past trends, if one applies the 30 percent estimate to the adolescents who were early experimenters in 2000, then 2.9 million of these early experimenters have now or will become established smokers (Mowery et al., 2004). Based on the number of persons aged 0 to 17 in 2012, the Surgeon General estimated that 17,371,000 of that group will become future smokers and 5,557,000 will die from a smoking-related disease (U.S. Department of Health and Human Services, 2014 at T. 12.2.1). These high numbers speak to the extreme vulnerability of today's children and adolescents to the health harms of tobacco use resulting from addiction.

Nicotine addiction is a critical factor in the transition of smokers from experimentation to sustained smoking and in the continuation of smoking for those who want to quit (U.S. Department of Health and Human Services, 2010 at p.113; 2014). Intermittent smokers, even very infrequent smokers, can become addicted to tobacco products (Shiffman, Ferguson, Dunbar, & Scholl, 2012). Longitudinal research has shown that smoking typically begins with experimental cigarette use and the transition to regular smoking can occur relatively quickly by smoking as few as 100 cigarettes (U.S. Department of Health and Human Services, 2012). Other research found that among the 3.9 million middle and high school students who reported current use of tobacco products (including cigarettes and cigars) in 2012, 2 million of those students reported at least one symptom of dependence (Apelberg et al., 2014).

Although the majority of adolescent daily smokers meet the criteria for nicotine dependence, one study found that the most susceptible youth lose autonomy (i.e., independence in their actions) regarding tobacco within 1 or 2 days of first inhaling from a cigarette (DiFranza et al., 2007; Kandel et al., 2005). Another study found that 19.4 percent of adolescents who smoked weekly also were nicotine dependent (O'Loughlin et al., 2003). In a study regarding nicotine dependence among recent onset adolescent smokers, individuals who smoked cigarettes at the lowest levels (i.e., smoking on only 1 to 3 days of the past 30 days) experienced nicotine dependence symptoms such as loss of control over smoking (42 percent) and irritability after not smoking for a while (23 percent) (Rose, Dierker, & Donny, 2010). Researchers in a 4-year study of sixth grade students also found that "[e]ach of the nicotine withdrawal symptoms appeared in some subjects *prior* to daily smoking" (DiFranza et al., 2007)

(emphasis added). Ten percent of the subjects showed signs of dependence to tobacco use within 1 or 2 days of first inhaling from a cigarette, and half had done so by the time they were smoking seven cigarettes per month (DiFranza et al., 2007).

b. Adults and Youth Cigarette Smoking Cessation and Relapse

It is clear that many youth and adult cigarette smokers want to quit. An analysis of data from the 2015 YRBS found that, of those students in grades 9 through 12 currently smoking cigarettes, 45.4 percent had tried to quit smoking cigarettes during the previous year (Kann et al., 2016). Likewise, an analysis of 2012 National Youth Tobacco Survey (NYTS) data revealed that 51.5 percent of middle and high school student smokers had sought to quit all tobacco use in the previous year (Tworek et al., 2014). Data from the 2015 National Health Interview Survey show that 68 percent of current adult smokers in the United States wanted to quit and 55.4 percent of adult smokers made a past-year quit attempt of at least 1 day (Babb et al., 2017). According to an analysis of this survey, only 7.4 percent of former adult cigarette smokers had recently quit (Babb et al., 2017).

For adult smokers who report quit attempts, many of these attempts are unsuccessful. For example, among the 19 million adults who reported attempting to quit in 2005, epidemiologic data suggest that only 4 to 7 percent were successful (Fiore et al., 2008 at p. 15). Similarly, the Institute of Medicine (IOM), considering data from 2004, found that although 40.5 percent of adult smokers reported attempting to quit in that year, only between 3 and 5 percent were successful (Institute of Medicine of the National Academies, 2007 at p. 82). Adult smokers may make as many as thirty or more quit attempts before succeeding (Chaiton et al., 2016). FDA also notes that adults with education levels at or below the equivalent of a high school diploma have the highest smoking prevalence levels but the lowest quit ratios (i.e., the ratio of persons who have smoked at least 100 cigarettes during their lifetime but do not currently smoke to persons who report smoking at least 100 cigarettes during their lifetime) (Centers for Disease Control and Prevention, 2009a). Nicotine addiction and associated withdrawal symptoms make it difficult for smokers to quit without using cessation counseling and/or cessation medications.

Relapse is the principal limiting factor in the transition of smoking to nonsmoking status (U.S. Department of Health and Human Services, 2010). Relapse refers to the point after an attempt to stop smoking when tobacco use begins again and becomes ongoing and persistent (U.S. Department of Health and Human Services, 2010 citing Brandon et al., 1986). Most smokers who ultimately relapse do so soon after their quit attempt (U.S. Department of Health and Human Services, 2010). One study found that 80 to 90 percent of those individuals who

were smoking at 6 months following a quit attempt had resumed smoking within 2 weeks following their quit attempt (Kenford et al., 1994). Data also suggest that most relapse occurs within the first 8 days of quitting (Hughes, Keely, & Naud, 2004). Long-term studies of individuals trying to quit smoking reveal that 30 to 40 percent of those who quit smoking for 1 year eventually relapsed (Kenford et al., 1994). In fact, one study following 840 participants for more than 8 years found that approximately one-half of smokers who stopped smoking for 1 year relapsed to regular smoking within the subsequent 7 years (Yudkin et al., 2003). Researchers have found that a higher frequency of smoking predicts more severe withdrawal symptoms and earlier relapse after an attempt to quit smoking and is associated with early lapses after cessation (U.S. Department of Health and Human Services, 2010 at p.119).

c. Impact of a Nicotine Product Standard on Combusted Product Users

Because nicotine is the primary addictive component of tobacco products, FDA hypothesizes that limiting the nicotine level in cigarettes would make them minimally addictive. Smokers would be unable to obtain enough nicotine from cigarettes to sustain addiction no matter how they smoked them (Benowitz et al., 2007; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010), making it potentially easier for smokers to make more successful quit attempts (Apelberg et al., 2018; Donny et al., 2015; Hatsukami et al., 2018).[6] Former smokers who choose to switch completely to a potentially less harmful nicotine delivery product to maintain their nicotine dose also would, to the extent that those products result in less harm, significantly reduce their risk of tobacco-related death and disease (National Academies of Sciences, 2018). Accordingly, rendering cigarettes minimally addictive (by reducing the nicotine content) could address the principal reason that smokers are unable to quit smoking.

D. Legal Authority

The Tobacco Control Act was enacted on June 22, 2009, amending the Federal Food, Drug, & Cosmetic Act (FD&C Act) and providing FDA with the authority to regulate tobacco products (Pub. L. 111-31). Section 901 of the FD&C Act (21 U.S.C. 387a), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), granted FDA the authority to regulate the manufacture, marketing, and distribution of cigarettes, cigarette tobacco, RYO tobacco, and smokeless tobacco to protect the public health and to reduce tobacco use by minors. The Tobacco Control Act also gave FDA the authority to issue a

[6] As stated throughout the document, in the event that a nicotine standard addresses only the nicotine content of cigarettes, FDA expects that, to maintain their nicotine dose, some number of addicted cigarette smokers could migrate to other similar combusted products (or engage in dual use with such products) after the standard goes into effect, reducing the benefits of the product standard.

regulation deeming other products that meet the statutory definition of a tobacco product to be subject to FDA's tobacco product authority under chapter IX of the FD&C Act. On May 10, 2016, FDA issued the deeming rule (81 FR 28973), extending FDA's tobacco product authority to all tobacco products, other than the accessories of deemed tobacco products, that meet the statutory definition of a tobacco product.

Among the authorities included in chapter IX of the FD&C Act is the authority to establish tobacco product standards. This includes the authority to adopt a tobacco product standard under Section 907 of the FD&C Act if the Secretary of Health and Human Services (HHS) finds that a tobacco product standard is appropriate for the protection of the public health. In making such a finding, the Secretary of HHS must consider scientific evidence concerning: (1) the risks and benefits of the proposed standard to the population as a whole, including users and nonusers of tobacco products; (2) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (3) the increased or decreased likelihood that those who do not use tobacco products will start using such products (Section 907(a)(3)(B)(i) of the FD&C Act).

Section 907(a)(4) of the FD&C Act states that tobacco product standards must include provisions that are appropriate for the protection of the public health. Section 907(a)(4)(B)(i) provides that a product standard must include, where appropriate for the protection of the public health, provisions respecting the construction, components, ingredients, additives, constituents, including smoke constituents, and properties of the tobacco product. In addition, Section 907(a)(4)(A)(i) states that provisions in tobacco product standards must include, where appropriate, provisions for nicotine yields. Section 907(a)(4)(B)(ii) also provides that a product standard must, where appropriate for the protection of public health, include "provisions for the testing (on a sample basis or, if necessary, on an individual basis) of the tobacco product." Furthermore, Section 907(a)(4)(B)(iv) provides that, where appropriate for the protection of public health, a product standard must include provisions requiring that the results of the tests of the tobacco product required under Section 907(a)(4)(B)(ii) show that the product is in conformity with the portions of the standard for which the test(s) were required. Finally, Section 907(d)(3)(B) of the FD&C Act prohibits the Agency from issuing a regulation that would require the reduction of nicotine yields of a tobacco product to zero.

The FD&C Act also provides FDA with the authority to issue regulations establishing restrictions on the sale and distribution of a tobacco product (Section 906(d)(1) of the FD&C Act (21 U.S.C. 387f(d)(1))). These restrictions may include restrictions on access to, and advertising and promotion of, the tobacco product, if the Secretary of HHS determines such regulation would be appropriate for the protection of the public health.

III. Scope

A tobacco product standard limiting the nicotine level in combusted tobacco products could address one of our nation's greatest public health challenges: the death and disease caused by cigarette and other combusted tobacco product use. Cigarettes are the tobacco product category that causes the greatest burden of harm to public health due to the prevalence of cigarette use and the toxicity and addictiveness of these products. Current research indicates that reduction of nicotine in cigarettes would reduce addiction potential, dependence levels, number of cigarettes smoked per day, and increase quit attempts among current smokers (see Section IV.B.b.i: *Smoking Cessation*). In light of these data, nicotine reduction could help prevent experimenters from becoming addicted to tobacco and progressing to regular tobacco use. Thus, FDA hypothesizes that a tobacco product standard limiting the nicotine level in combusted tobacco products could significantly increase the number of successful quit attempts by smokers seeking to quit smoking every year and potentially prevent experimenters from developing addiction to combusted cigarettes and becoming regular smokers. FDA intends that any nicotine tobacco product standard would cover all brands in a product category and, therefore, those products currently on the market, as well as any new tobacco products, would be expected to adhere to the standard.

A. Technical Achievability

The industry and consumer product companies have developed versions of denicotinized cigarettes and a range of brands with differing nicotine levels. By blending tobaccos based on nicotine levels, tobacco companies have manufactured their products to specifications that ensure the final product will have precise levels of nicotine and have ensured that nicotine levels vary only minimally within cigarette packs and from pack to pack (Office of the Federal Register, 1995 at 41505, 41509). In fact, the tobacco industry has had programs in place since the 1960s to obtain "any level of nicotine desired" (Griffiths, 1963; Wayne & Carpenter, 2009). The industry also has recognized that the techniques it has used to increase nicotine levels can be used to reduce nicotine levels as well (Office of the Federal Register, 1995 at 41722).

VLNC cigarettes have been produced since the 1970s. During this time, the National Cancer Institute (NCI) contracted for production of a line of cigarettes with widely varying nicotine concentrations (U.S. Department of Health and Human Services, 1981). In the late 1980s, a major cigarette manufacturer had plans to develop VLNC cigarettes with a reduction in mainstream nicotine yields of greater than 95 percent (RJ Reynolds, 1989). In 2003, Vector Tobacco began marketing the Quest brand of cigarettes, which was produced from genetically

modified tobacco and contained cigarettes with varying nicotine content (Dunsby & Bero, 2004). More recently, 22nd Century Group, Inc., acting as a vendor for RTI International's contract with the National Institute for Drug Abuse (NIDA), developed and manufactured SPECTRUM® research cigarettes, that are similar in many sensory characteristics to conventional cigarettes but with very low nicotine content (Ding et al., 2017; Richter et al., 2016). In 2019, 22nd Century Group, Inc. received FDA marketing authorization, and in 2021 received exposure modification orders for these VLNC cigarettes under the names VLN® King and VLN® Menthol King. Significant reductions of nicotine in combusted tobacco products can be achieved principally through tobacco blending and cross-breeding plants, genetic engineering, and chemical extraction. Agricultural practices (e.g., controlled growing conditions, fertilization, harvest) as well as more recent novel techniques can result in reduced nicotine levels. One or a combination of these processes could be used to achieve the nicotine levels that FDA is considering for a nicotine tobacco product standard.

a. Tobacco Blending/Cross Breeding

Most cigarettes sold in the United States are blended cigarettes (National Cancer Institute, 1996). A tobacco industry executive previously testified that the main component of a cigarette that contributes to nicotine delivery is the tobacco blend and that year-to-year crop variation does not determine the nicotine content in a cigarette (Wayne & Carpenter, 2009). The term "leaf blending" describes the selection of tobaccos to be used in a product by tobacco type (e.g., flue-cured, burley, oriental), geographical origin, year, and grade of the tobacco (Wayne, 2012). Blend differences can produce significant variations in nicotine concentration in the tobacco rod, leading to differences in smoke composition and yield (Wayne & Carpenter, 2009). Grading, which is used to evaluate and identify differences within tobacco types and is a function of both plant position (i.e., higher or lower leaf position on the stalk) and of quality (e.g., ripeness). Segregation of grades by nicotine content has become common practice (Wayne, 2012 at 2-3).

Many tobacco lines are available, including approximately 1,000 different tobacco varieties (National Cancer Institute, 1996). The tobacco industry has used breeding and cultivation practices to develop high nicotine tobacco plants to give manufacturers greater flexibility in blending and in controlling the amount of nicotine to be delivered (Office of the Federal Register, 1995 at 41694). These practices could be used to develop low nicotine plants as well. In fact, tobacco industry documents (Harwood, 1966; Lorillard, 1967) show that in the 1960s, tobacco companies recognized the increasing demand for low nicotine tobacco and began instituting projects that found low nicotine cigarettes can be made by selecting grades of tobacco with low nicotine content (Wayne, 2012).

Because the nicotine content of tobacco plants varies, manufacturers could replace more commonly used nicotine-rich varieties like *Nicotiana rustica* with lower nicotine varieties (Tengs, Ahmad, Savage, Moore, & Gage, 2005). For example, oriental Turkish-type cigarettes also deliver substantially less nicotine than cigarettes that contain air-cured Burley tobacco (Shelar, Bernasek, & Furin, 1992; Wayne & Carpenter, 2009). In addition, manufacturers could select specific tobacco seedlings that are low in nicotine and plant only those low nicotine seedlings (Dunsby & Bero, 2004). Even without this selective breeding, manufacturers could use careful tobacco leaf purchasing plans to control the nicotine content in their products (Office of the Federal Register, 1995 at 41694). By maintaining awareness of the differences and monitoring the levels in purchased tobacco, companies could produce cigarettes with nicotine deliveries consistent to one-tenth of one percent (despite annual variations of up to 25 percent in the nicotine content of the raw material grown in the same area) (Office of the Federal Register, 1995 at 41694).

The position of leaves on the plant stalk also affects nicotine levels; tobacco leaves located near the top of the plant can contain higher concentrations of nicotine, and lower stalk leaves generally contain lower nicotine levels (Tengs et al., 2005; Wayne & Carpenter, 2009). For example, flue-cured tobacco leaves harvested from the lowest stalk position may contain from 0.08 to 0.65 percent nicotine, whereas leaves from the highest positions may contain between 0.13 and 4.18 percent nicotine (National Cancer Institute, 1996; Tso, 1972). Therefore, substituting leaves found lower on the plants could reduce the nicotine content of tobacco products (Tengs et al., 2005).

A number of internal tobacco industry documents describe the use of leaf blending and tobacco selection to control the nicotine content of cigarettes (Wayne, 2012 at p.3). For example, one company project determined that low nicotine cigarettes can be made by selecting grades of tobacco with low nicotine content (Harwood, 1966; Wayne, 2012). Another observed that the demand for low nicotine tobacco has increased worldwide and necessitated a shift in purchasing standards (Borriston Lab, Hartman, Mulligan, Piccirillo, & Sexsmith, 1984; Wayne, 2012).

b. Chemical Extraction

Nicotine also can be removed from tobacco via chemical extraction technology. By the 1970s, tobacco manufacturers regularly practiced nicotine extraction as a method to control nicotine delivery (Ashburn, 1961; Crouse, 1987; Philip Morris, Year Unknown; Wayne, 2012). Extraction methods include water extraction (coupled with steam or oven drying), solvent extraction, and extractions of nicotine without usable leaf (Wayne, 2012). Supercritical fluid

extraction also yielded success in the 1990s, allowing for optimum extraction times and the elimination of more time-consuming steps (Fischer & Jefferies, 1996; Ruiz-Rodriguez, Bronze, & Ponte, 2008). FDA notes that existing patents for chemical extraction of nicotine in tobacco reveal that more than 96 percent of nicotine can be successfully extracted while achieving a product that "was subjectively rated as average in nicotine characteristics" (Grubbs, Prasad, & Howell, 1991; Roselius, Vitzthum, & Hubert, 1979).

In addition, a major tobacco manufacturer has used a high-pressure carbon dioxide process to remove nicotine; this is similar to the process used to decaffeinate coffee. In this process, tobacco leaf is treated with ammonium salt, then treated with carbon dioxide/water vapor, thereby achieving a 95 to 98 percent reduction in nicotine (Dunsby & Bero, 2004, citing Philip Morris, 1999). Although some manufacturers believe that previous water extraction practices may have rendered the tobacco "unsuitable for use," other water extraction projects yielded suitable smoking material with sizeable nicotine reductions (80 to 85 percent reduction in leaf nicotine) (Crouse & Eid, 1976; Groome, 1972; Reid, 1977; Wayne, 2012).

c. Genetic Engineering

Tobacco industry scientists have long recognized the potential for genetic engineering to control nicotine content (Hempfling, 1987). The first practical application of biotechnology by a major tobacco manufacturer was the development of low nicotine tobacco in the 1980s, which led to the receipt of a patent for biotechnology for altering nicotine in tobacco plants (Dunsby & Bero, 2004; Venable, 1997). Other tobacco researchers and major manufacturers also recognized the value of biotechnology for developing low nicotine tobacco for cigarettes, including for use as part of a smoking cessation program (RJ Reynolds, 1992).

Several American and international tobacco companies genetically engineered low nicotine varietals in the 1960s and 1970s, including a strain with nicotine levels as low as 0.15 percent (Boswall, 1971; British American Tobacco, 1972; Cohen, 1971; Evans, 1971; Meyer, 1971; Smith, 1972; Wayne, 2012). During that time period, the Kentucky Tobacco Research Board worked on genetic strains of low nicotine tobacco (with a nicotine content of 0.2 percent) to be used for experimental studies on the role of nicotine in smoking behavior (Hudson, 1973; Johnson, 1977; Ness Motley Law Firm, 1977; Neumann, 1977; Wayne, 2012). In addition, Canadian researchers examined low nicotine strains of tobacco, particularly in association with efforts to develop a strain of flue-cured or air-cured tobacco that would be suitable as the base material for reconstituted tobacco (Boswall, 1971; Cohen, 1971; Wayne, 2012). In 2003, Vector Tobacco began marketing the Quest cigarette, which was produced from genetically modified tobacco and contained only trace amounts of nicotine (Dunsby & Bero,

2004) (this product is no longer on the market). Genetic engineering has resulted in nicotine level reductions of 80 to 98 percent (Dunsby & Bero, 2004). In 2014, the U.S. Patent and Trademark Office granted two patents for two genes that may be suppressed to achieve a substantial decrease in nicotine in tobacco plants (Hashimoto & Kato, 2014). Additionally, US Patent #10,669,552 (Page & Todd, June 2, 2020) is a claim for modifying transcription factors that regulate the nicotinic alkaloid biosynthetic pathway in the Nicotiana tabacum plant. This method appears to work for any variety of Nicotiana tabacum; therefore, this method may be applicable to other combusted tobacco products that use Nicotiana tabacum (e.g., cigars). There are likely additional molecules that encode for other factors that are involved in the nicotine biosynthesis pathway that may be used to reduce the nicotine content in cigarettes and other combusted tobacco products.

d. Other Practices

Industry studies have shown that changes to growing and harvesting practices affect the development of tobacco chemistry, including nicotine content (Wayne, 2012). Some manufacturers have revised their agricultural practices specifically to meet new product development goals, such as the production of low nicotine tobacco (Wayne, 2012). For example, one manufacturer evaluated various experimental agricultural practices that could affect the tobacco's chemistry, including bulk-curing, once-over harvesting, and high plant density (RJ Reynolds, 1976; Wayne, 2012). In other cases, chemical agents were observed to reduce nicotine content (Imperial Tobacco Company, 1969; Passey, 1964; Unknown, 1980; Wayne, 2012, citing Imperial Tobacco Company, 1969; Passey, 1964; Philip Morris, 1980).

After tobacco is harvested, it is cured and aged before use in tobacco products. The aging process naturally changes the chemistry of the tobacco, including some reduction in nicotine content (Wayne, 2012). At least one manufacturer has explored efforts to speed up the process of aging tobacco, in part to alter or limit the changes in chemistry that naturally occur (American Tobacco, 1991; Wayne, 2012). Other approaches to curing and fermenting tobacco were explored as a method for altering nicotine content (Wayne, 2012). For example, in one manufacturer's report, researchers observed that the properties of tobacco, including nicotine content, could be altered without the need for nontobacco additives by modifying curing practices (Mitchell, 1973; Wayne, 2012). In addition, manufacturers have explored approaches to identify microbial bacteria that actively degrade nicotine while leaving other components of the leaf intact (Geiss, 1972, 1975; Wayne, 2012). Consumer product testing showed that the "product acceptability" of that tobacco was equal to that of untreated tobacco (Gravely, Newton, & Geiss, 1973; Wayne, 2012).

Researchers have developed novel approaches to reducing the nicotine in tobacco products in recent years. An example of reducing nicotine is through enzymatic digestion utilizing glucose oxidase harvested from the salivary excretion produced by a specific species of caterpillar. The extracted enzyme is applied to the harvested tobacco leaves, reducing the nicotine in the tobacco leaf by up to 75 percent, providing an "effective and economical system for producing tobacco products which contain about 0.01 mg nicotine per cigarette or less…while maintaining the other desirable ingredients for good taste and flavor" (Berger, 2009).

Conclusions

Tobacco product manufacturers have already designed and marketed reduced- or low-nicotine content cigarettes using a variety of approaches. A significant reduction of nicotine in combusted tobacco products is technically achievable through methods such as tobacco blending, chemical extraction, and genetic modification. Genetic modification is an example of one manufacturing process that may be used to reduce the nicotine content of other combusted tobacco products.

B. Maximum Nicotine Level

As discussed throughout this document, nicotine is addictive and is the primary reason why many smokers who want to quit are unable to do so. Accordingly, FDA is considering developing a product standard to make combusted tobacco products minimally addictive by setting a maximum nicotine level, using the best available science to determine a level that is appropriate for the protection of the public health. FDA has considered many peer-reviewed studies regarding the likely effects of reducing nicotine in combusted tobacco. A 2013 survey paper noted that researchers initially estimated that reducing the total nicotine content of cigarettes to 0.5 mg per cigarette would minimize addictiveness and that a "more recent analysis suggests that the maximum allowable nicotine content per cigarette that minimizes the risk of central nervous system effects contributing to addiction may be lower" (Benowitz & Henningfield, 2013). The study authors concluded that "[p]reventing children from becom[ing] addicted smokers and giving people greater freedom to stop smoking when they decide to quit by reducing the addictiveness of cigarettes is a policy that increasingly appears to be feasible and warranted" (Benowitz & Henningfield, 2013).

Some combusted cigarettes that were once referred to as "light" cigarettes achieved a reduction in machine-measured nicotine yield (e.g., International Organization for Standardization [ISO] smoking regimen) through a variety of means, including the use of ventilation holes; although the actual nicotine content of the tobacco filler was not low. This

increase in ventilation led to lower yields of tar and nicotine in smoke as measured by smoking machines, and these products were labeled and marketed as low nicotine yield or "light," "low," or "mild" cigarettes. However, cigarette users could engage in compensatory smoking by modifying their use behaviors to compensate for this increase in ventilation and extract more nicotine from the products. For example, the ventilation holes could be easily blocked by users' fingers or mouths, and larger or more frequent puffs could be taken by consumers (Scherer, 1999). As a result, these products were designed to make them appear light to the user but could deliver as much nicotine as machine-measured higher nicotine yield cigarettes. Through compensatory smoking behaviors, cigarette users were able to overcome the changes in ventilation in these products, resulting in no benefit to public health (National Cancer Institute, 2001).

Reduced nicotine content cigarettes, in contrast, have relied on reducing nicotine content in the tobacco filler rather than engineering changes to the cigarette. Patents reveal that more than 96 percent of nicotine can be successfully extracted while achieving a product that "was subjectively rated as average in smoking characteristics"(Grubbs et al., 1991) and that up to a 75 percent reduction in the nicotine contained in a tobacco leaf can be achieved with an "effective and economical system for producing tobacco products…while maintaining other desirable ingredients for good taste and flavor" (Berger, 2009).

In conventional cigarettes manufactured in the United States, nicotine accounts for approximately 1.5 percent of the cigarette weight, or 10-14 mg of nicotine per cigarette (Benowitz et al., 1983; Carmines & Gillman, 2019; Hukkanen, Jacob, & Benowitz, 2005; Jacob, Yu, Shulgin, & Benowitz, 1999; Kozlowski et al., 1998), and conventional cigarettes generally have nicotine smoke yields averaging 0.9 mg nicotine per cigarette. Certain reduced nicotine content cigarettes, known as VLNC cigarettes, have much lower nicotine contents (e.g., 0.2 – 0.7 mg nicotine per cigarette) and nicotine yields (e.g., 0.03 – 0.1 mg nicotine per cigarette) (see Table 1). Unlike modifications such as ventilation holes that affect nicotine yield in smoke but can be overcome through user behavior, reducing the nicotine content in the finished tobacco product places an absolute maximum limit on the amount of nicotine that can be extracted by the user from one cigarette.

Results of the studies reviewed in this document support setting a maximum nicotine level of 0.7 mg nicotine per g of total tobacco in all combusted tobacco products. This proposed limit is based on the analysis of studies regarding the likely effects of reducing nicotine (see Section IV: *VLNC Literature Review)*, which showed that extended exposure to VLNC cigarettes is associated with reduced addiction potential, dependence levels, number of cigarettes

smoked per day, and increased quit attempts among current smokers, without evidence of increased toxicant exposure, craving, withdrawal, or compensatory smoking.

Conclusions

Some combusted cigarettes that were once referred to as "light" cigarettes achieved a reduction in machine-measured nicotine yield; however, the actual nicotine content of the tobacco filler was not reduced. Therefore, cigarette smokers engaged in compensatory smoking to extract more nicotine from the products. In contrast, reduced nicotine content cigarettes have lower nicotine content in the tobacco filler, so smokers cannot circumvent the reduction in nicotine by engaging in compensatory smoking behavior. Thus, FDA is considering developing a product standard to make combusted tobacco products minimally addictive by setting a maximum nicotine level of 0.7 mg nicotine per g of total tobacco. This document reviews the best available science that was used to determine a nicotine level that is appropriate for the protection of the public health.

C. Inclusion of Combusted Products

The final decision on which combusted tobacco products will be included in a nicotine tobacco product standard will affect the magnitude of the standard's public health impact. A nicotine product standard that includes only cigarettes may prompt a subset of addicted cigarette smokers to switch to alternative combusted nicotine-containing products (e.g., RYO cigarettes, little cigars, cigarillos) or to engage in dual use with alternative combusted tobacco products; however, those who used non-cigarette combusted products prior to a nicotine tobacco product standard would continue using those products with no change. If the nicotine tobacco product standard encompasses all combusted tobacco products, it can be expected that a proportion of cigarette smokers as well as alternative combusted tobacco products users will switch to another nicotine containing tobacco product instead of quitting altogether, and will, therefore, switch to a non-combusted tobacco product.

Clinical studies show high levels of noncompliance with VLNC cigarettes due to reduced appeal (as discussed in Section V.C.a, *Noncompliance*), which results in participants supplementing VLNC cigarettes with usual brand cigarettes that contain a higher nicotine content or other sources of nicotine. If FDA implements a nicotine product standard that covers only cigarettes, it could be expected that smokers would respond similarly and seek out alternative sources of nicotine that have similar pharmacological and sensory characteristics as their usual brand cigarettes. Combusted tobacco product use is highly prevalent among both adolescents and adults (as discussed in Section II.C.c, *Impact of a Nicotine Product Standard on Combusted Product Users*), associated with significant negative health effects (as discussed in

Section II.B, *Negative Health Effects of Combusted Tobacco Product Use*), and each category of combusted tobacco products is sufficient to create or sustain nicotine dependence (as discussed in Section II.C, *Nicotine in Combusted Tobacco Products and Its Influence on Addiction*). Including all combusted tobacco products in a nicotine product standard would prevent current cigarette smokers from simply switching to another combusted product, prevent experimenters of other combusted products from becoming addicted to tobacco, and maximize the potential public health benefit for both youth and adults.

Conclusions

Results of the data reviewed in this document support the inclusion of all combusted tobacco products in a nicotine tobacco product standard. If the standard were only to cover cigarettes, a significant number of addicted cigarette smokers would switch to similar tobacco products to maintain their nicotine dose, undermining the benefits of the proposed product standard. Including all combusted tobacco products in a nicotine tobacco product standard would maximize public health benefits.

Further discussion about the justification for inclusion of all combusted tobacco products in a nicotine tobacco product standard can be found in Section V, *Justification for the Inclusion of Other Combusted Products in a Nicotine Tobacco Product Standard.*

D. Implementation (Immediate Reduction vs. Gradual Approach)

Two approaches have been suggested for enacting a nicotine product standard for combusted tobacco products. One is a gradual approach, which decreases the nicotine content in combusted tobacco products over time until it reaches a minimally addictive level. The other is an immediate reduction approach, which would immediately reduce the nicotine content to a minimally addictive level. Research on how these two approaches may affect compensatory smoking or other potential unintended consequences associated with nicotine reduction can help inform the best policy for reducing the nicotine content of combusted tobacco products. The results of several studies reviewed in this document suggest that neither gradual nor immediate reduction of nicotine in cigarettes leads to compensatory smoking after individuals switch to VLNC cigarettes; however, both approaches may increase the likelihood of smokers using alternative tobacco products. Limited evidence also suggests that gradual reduction may lead to compensatory smoking during the intermediate steps of a gradual reduction approach when participants are smoking products with low to moderate nicotine content, but this compensation does not persist after participants switch to VLNC cigarettes.

Several studies investigated the effects of gradual nicotine reduction on compensatory smoking (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Hammond & O'Connor, 2014;

Mercincavage et al., 2016). In these studies, participants were not interested in quitting and did not receive nicotine replacement therapy (NRT) or alternative tobacco products. Benowitz and colleagues conducted a pilot study and a clinical trial investigating whether a gradual reduction in cigarette nicotine content would increase exposure to tobacco smoke toxins due to compensatory smoking (e.g., Benowitz et al., 2012; Benowitz et al., 2007). Participants smoked their usual brand cigarettes during baseline and were then switched to normal nicotine content (NNC)[7], low nicotine content (LNC), and VLNC cigarettes containing 10.3 (NNC), 6.5 (LNC), 3.9 (LNC), 1.7 (LNC) and 0.5 (VLNC) mg nicotine per cigarette. In the 10-week pilot study, participants were switched weekly, and in the 6-month trial, participants were switched monthly. Little change in smoking behavior was observed; however, plasma cotinine concentration (a biomarker of nicotine exposure) decreased as a function of cigarette nicotine content, such that cotinine was lowest while participants were smoking VLNC cigarettes. The pilot study showed little evidence of compensation, as calculated based on cigarette consumption, carbon monoxide, and polycyclic aromatic hydrocarbon (PAH) metabolites (Benowitz et al., 2007). However, the 6-month trial calculated compensation based on plasma cotinine levels and found that cotinine levels were higher while smoking LNC cigarettes compared to VLNC cigarettes (Benowitz et al., 2012). Another study showed that compensatory smoking may increase when participants smoke reduced nicotine content cigarettes with intermediate levels of nicotine (e.g., LNC cigarettes) compared to usual brand cigarettes (Mercincavage et al., 2016). Taken together, tobacco users may attempt to compensate for the loss of nicotine during the early stages of a gradual approach by smoking more intensely because such compensatory smoking may allow the user to extract more nicotine from the intermediate-stage cigarettes (LNC cigarettes) than the VLNC cigarettes (e.g., Becker, Rose, & Albino, 2008; Benowitz et al., 2012; Hammond & O'Connor, 2014; Mercincavage et al., 2016). Studies have also shown that gradually reducing the nicotine content of cigarettes is associated with high levels of noncompliance when participants reach the VLNC cigarette phase of the intervention (e.g., Benowitz, Nardone, Hatsukami, & Donny, 2015; Hammond & O'Connor, 2014).

Several studies investigated whether an immediate reduction in cigarette nicotine content would increase compensatory smoking (e.g., Donny et al., 2015; Walker et al., 2015). Like the gradual reduction studies discussed above, participants in these immediate reduction

[7] In the present document, "very low nicotine content (VLNC) cigarettes" refers specifically to cigarettes with ≤ 0.7 mg nicotine per cigarette (i.e., ≤ 1.0 mg nicotine per g of total tobacco), "low nicotine content (LNC) cigarettes" refers to cigarettes with > 0.7 mg and < 8 mg nicotine per cigarette, and "normal nicotine content (NNC) cigarettes" refers to cigarettes with ≥ 8 mg nicotine per cigarette.

studies were not interested in quitting and did not receive NRT or alternative tobacco products. In the most comprehensive study, Donny and colleagues (2015) randomized 839 smokers to one 6-week condition, during which they smoked their usual brand cigarettes or immediately switched to research cigarettes containing either 15.8 (NNC), 5.2 (LNC), 2.4 (LNC), 1.3 (LNC), or 0.4 (VLNC) mg nicotine per g of total tobacco. Participants assigned to the LNC or VLNC cigarette groups who received cigarettes with nicotine content less than or equal to 2.4 mg nicotine per g of total tobacco smoked significantly fewer cigarettes per day (CPD) than participants assigned to the usual brand and NNC cigarette groups. Those who received LNC or VLNC cigarettes containing 5.2 mg nicotine per g of total tobacco or less had significantly lower urinary total nicotine equivalents (TNE) than those who received NNC cigarettes. No evidence of compensatory smoking was observed in participants who smoked reduced nicotine content cigarettes, as no differences in breath carbon monoxide (CO) measures were observed between groups. The total puff volume at Week 6 was significantly lower among participants who smoked VLNC cigarettes compared to those who smoked NNC cigarettes. However, much like the gradual reduction studies, a secondary analysis showed that noncompliance was high in participants randomized to the VLNC cigarette group (Nardone et al., 2016; Nardone et al., 2018). In another study, Walker et al. (2015) randomized 33 participants to receive VLNC cigarettes or to continue smoking their usual brand cigarettes for 12 weeks. Overall, participants in both groups smoked a similar total number of CPD, even though only the participants in the VLNC cigarette group received free cigarettes. These data demonstrate that an immediate decrease in cigarette nicotine content is unlikely to lead to significant compensation or increased toxicant exposure.

Hatsukami and colleagues (2015) conducted a secondary analysis pooling data from five clinical studies to examine the relationship between compensatory smoking and gradual versus immediate nicotine reduction. Two of the trials utilized a gradual reduction approach, and three of the trials utilized an immediate reduction approach. CPD, breath CO, and cotinine levels were compared between the immediate reduction group, the gradual reduction group, and a control group who received usual brand cigarettes. Relative to baseline, significant decreases in CPD were observed in participants in the gradual groups (5% decrease in CPD) and immediate groups (11% decrease in CPD), whereas significant increases in CPD were observed in participants in the usual brand groups (12% increase in CPD). Although significant changes in breath CO were not observed relative to baseline in any group, significant decreases in cotinine were observed among both gradual and immediate groups, but not in the usual brand cigarette group.

In the largest study on this topic, Hatsukami and colleagues (2018) conducted a 10-site, randomized, double-blind clinical study to compare the effects of gradual versus immediate nicotine reduction on toxicant exposure in 1,250 adult smokers. Participants were randomly assigned to an immediate reduction group that received VLNC cigarettes for 20 weeks, a gradual reduction group that received cigarettes containing progressively decreased nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, 0.4 mg nicotine per g of total tobacco) for 20 weeks, or a control group that received NNC cigarettes for 20 weeks. Any changes in biomarker levels observed between these two groups would indicate differences in smoking behavior (e.g., CPD, smoking topography, compensatory smoking). Completion rates were significantly lower for the immediate reduction group (68%) compared to the gradual reduction group (81%) and control group (86%). The immediate reduction group had significantly lower levels of the three primary biomarker outcomes (i.e., CO, 3-hydroxypropyl mercapturic acid [3-HPMA], and phenanthrene tetraol [PheT]) compared to the gradual reduction group, which did not differ from the control group. In addition, significantly lower levels of TNE, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 2-cyanoethylmercapturic acid (CEMA), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), and S-phenylmercapturic acid (S-PMA), but not 2-HPMA, were observed in the immediate reduction group compared to the gradual reduction group. The immediate reduction group smoked cumulatively less CPD over the course of the 20-week study and had lower nicotine dependence scores compared to the gradual reduction group, with no differences in CPD or dependence among the gradual reduction versus control groups. While there was no difference between immediate and gradual reduction groups in the proportion of participants with any cigarette-free days during the study, the immediate reduction group had a significantly higher number of cigarette-free days compared to the gradual reduction group. The immediate reduction group had significantly higher withdrawal scores at Week 1 compared to the gradual reduction group; however, these differences dissipated after the first week. The immediate reduction group had higher rates of noncompliance with non-study cigarette use and a higher drop-out rate, which may have impacted the various outcome measures (e.g., biomarkers of exposure). Additionally, the immediate reduction group had an increased number of adverse events (predominantly related to withdrawal) compared to the gradual reduction group. Nevertheless, this study provides further evidence that immediate nicotine reduction is associated with reduced toxicant exposure and nicotine dependence and increased smoking abstinence compared to gradual nicotine reduction. While the immediate reduction group had increased levels of nicotine withdrawal, this effect was time-limited, dissipating after 1 week (Hatsukami et al., 2018).

Conclusions

In sum, evidence from studies involving LNC and VLNC cigarettes suggests that a gradual nicotine reduction approach could lead to increased compensatory smoking during the intermediate steps of the reduction, thereby increasing smokers' exposure to harmful and potentially harmful constituents (HPHCs). However, there could be very little or no compensatory smoking with an immediate reduction approach, which would maximize the public health impact of a nicotine reduction policy. If individuals were to engage in compensatory smoking with an immediate reduction approach (i.e., at the maximum nicotine levels that FDA is considering here), research indicates that any compensatory smoking would be minimal and transient (Macqueen et al., 2012) (see Section IV.C.a: *Compensatory Smoking*). In addition, results from the above studies show higher levels of noncompliance with VLNC cigarettes in an immediate reduction approach relative to a gradual reduction approach (Hatsukami et al., 2018), which supports findings from other studies that show VLNC cigarette smokers are more likely to use alternative nicotine-containing products when such products are concurrently available (Hatsukami et al., 2017)(see Section V.C.a: *Noncompliance*).

E. Analytical Testing Method

FDA is considering whether a nicotine product standard should specify a method for manufacturers to use to detect the level of nicotine in their tobacco products. The results of any test method to measure the nicotine in combusted tobacco products should be comparable across different accredited testing facilities and products. It is critical that the results from the test method demonstrate a high level of specificity, accuracy, and precision in measuring a range of nicotine levels across a wide variety of tobacco blends and products.

A variety of methods in development allow nicotine in tobacco or tobacco product filler to be quantified for various products. For example, two Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) methods have undergone round-robin method validation studies in accordance with ISO standards for accuracy (5725-1 and 5725-2): (1) continuous flow analysis (CFA) and (2) gas chromatography-flame ionization detector (GC-FID) (CORESTA, 2005, 2017). The CFA method measured a nicotine range of 0.69-3.30 percent (6.9-33 mg nicotine per g of total tobacco) in burley and flue-cured tobaccos and exhibited a repeatability range of 0.03-0.17 and a reproducibility range of 0.12-0.67, dependent on the mean (Arrecis & McLeod). A GC-FID method for determining nicotine in fermented extractions from tobacco leaves was validated in accordance with FDA and International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use specifications, including specificity, linearity, precision, accuracy, and robustness (Millet, Stintzing, & Merfort, 2009). Gas chromatography-mass spectrometry (GC-MS) was used as the

confirmation technique in this study, in which a recovery of 117.8 percent was achieved; recovery was within FDA guidelines (<120 percent) (Millet et al., 2009). Nicotine content of 0.43 percent (4.3 mg nicotine per g of total tobacco) in the extract was reliably measured and stability testing on this same extract was conducted for 360 days (Millet et al., 2009). In addition, the WHO's Tobacco Laboratory Network (TobLabNet) has developed a standard operating procedure for measuring nicotine in cigarette tobacco filler using gas chromatography (GC) (World Health Organization, 2014). The WHO's TobLabNet determined that this method is suitable for the quantitative determination of nicotine in cigarette tobacco filler by GC.

CORESTA Method No. 62 is a standard method used to analyze nicotine in tobacco filler and smokeless tobacco products (CORESTA, 2005). Method No. 62 describes two methods of extracting nicotine from solid tobacco, using either a hexane or methyl tert-butyl ether (MTBE) extraction solution.

FDA is also aware of other methods that have been used to analyze nicotine levels. Such methods include GC combined with various detectors, GC-MS with solid-phase microextraction as a preconcentration step for low detection, other formats of GC-FID, capillary electrophoresis combined with either ultraviolet (UV) or electrochemical detection, and alternative chromatography techniques including supercritical fluid chromatography-ion mobility detection (Wu, Siems, Hill, & Hannan, 1998), reversed phase ion-pair liquid chromatographic extraction (Ciolino et al., 1999), and high-pressure liquid chromatography with UV detection (Švob Troje, Fröbe, & Perović, 1997).

Conclusions

Either international standard test methods or equivalent test methods may be used to analyze nicotine levels. However, it is crucial that the accredited test laboratory performing the analysis demonstrates the method is validated, including specificity, accuracy, and precision of measuring nicotine levels extended to include very low nicotine content in tobacco products.

IV. Very Low Nicotine Content (VLNC) Cigarette Literature Review

A. VLNC Cigarettes

The first VLNC cigarettes studied by researchers were produced by Philip Morris and marketed under the brand name "Next," which was reported to contain 0.4 mg nicotine per g of total tobacco (Djordjevic, Sigountos, Brunnemann, & Hoffmann, 1990). Later, NIDA

contracted with the Ultratech/Lifetech Corporation[8] to produce VLNC cigarettes for research purposes (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999). The two types of cigarettes produced were: (1) 8.0 – 10.3 mg nicotine per gram of total tobacco and (2) 0.6 – 0.7 mg nicotine per gram of total tobacco[9] (Pickworth, Fant, et al., 1999).

Researchers also have used Quest cigarettes, produced by Vector Tobacco, to study the impact of reduced nicotine (Becker et al., 2008). Commercially available Quest cigarettes utilized genetically modified tobacco to create cigarettes with three distinct nicotine contents (i.e., Quest 1, Quest 2, and Quest 3) (Table 1). These cigarettes were used in much of the VLNC research prior to development of SPECTRUM® research cigarettes. In addition, 22nd Century Group, Inc. is using genetic engineering and plant breeding to produce very low nicotine tobacco for cigarettes. In 2014, the company was granted patents for its process to dramatically reduce the nicotine in tobacco plants (National Cancer Institute, 1998b). Furthermore, low-nicotine cigarettes are produced and distributed for research purposes by RTI International, under a contract with NIDA's Drug Supply Program (National Institute on Drug Abuse, 2014). 22nd Century Group is acting as a vendor for RTI for this contract, manufacturing SPECTRUM® cigarettes that were reported to contain 0.4 mg nicotine per g of total tobacco (National Institute on Drug Abuse, 2014). 22nd Century Group Inc., who make SPECTRUM® research cigarettes and whose genetically engineered tobacco was used to make Quest cigarettes, submitted a modified risk tobacco product application to the FDA, which reported that after 9 years of sampling by the company, the average nicotine content of their genetically engineered VLNC tobacco is 0.6 mg nicotine per gram of total tobacco, with a range of 0.4 to 0.7 mg nicotine per g of total tobacco. It is likely that the Quest and SPECTRUM® cigarettes, used throughout the scientific literature, also contained between 0.4 to 0.7 mg nicotine per g of total tobacco (FDA). Finally, Philip Morris manufactured cigarettes with varying nicotine levels for research only (Unknown, 1994).

Researchers who use VLNC cigarettes often use the terms "yield" and "content" to describe the amount of nicotine in cigarettes. Importantly, these two terms are not interchangeable. As indicated above, nicotine "yield" refers to the amount of nicotine in tobacco smoke as measured through machine-generated smoking methods (e.g., ISO machine

[8] Both Ultratech and Lifetech have been reported as being the company through which NIDA manufactured research cigarettes.

[9] These cigarettes were reported as containing 0.0 mg nicotine per cigarette; however, FDA estimated these levels to be between 0.6 and 0.7 mg nicotine per gram of total tobacco (see Table 1).

smoking method). Nicotine yield can be altered by a variety of cigarette design features (e.g., ventilation holes) and by user behavior (e.g., puffing topography). However, nicotine "content" refers to the amount of nicotine present in tobacco filler, regardless of smoking behavior or cigarette design features. Reduced nicotine content cigarettes are manufactured with chemical, genetic, agricultural or other methods that reduce the nicotine content of the tobacco filler (e.g., the tobacco is washed with an alkaline solution or the tobacco filler is derived from genetically modified tobacco plants with low levels of nicotine). As a result, reduced nicotine content cigarettes also have lower nicotine yields than conventional cigarettes. The nicotine levels of reduced nicotine content cigarettes discussed in this document refer to nicotine content. If a nicotine level cited in this document refers to nicotine yield, then the level will be explicitly described as "yield."

Although many of the studies summarized in this document investigated the effects of VLNC cigarettes, some studies also investigated the effects of cigarettes with higher levels of nicotine, often as comparators. In the present document, "very low nicotine content (VLNC) cigarettes" refers specifically to cigarettes with less than or equal to 0.7 mg nicotine per cigarette (i.e., ≤ 1.0 mg nicotine per g of total tobacco), "low nicotine content (LNC) cigarettes" refers to cigarettes with > 0.7 mg and < 8 mg nicotine per cigarette, and "normal nicotine content (NNC) cigarettes" refers to cigarettes with ≥ 8 mg nicotine per cigarette. Importantly, these categories are descriptive only. In other words, these categories were not determined based on any differential effects on study outcomes observed across cigarette nicotine content categories. Table 1 displays the reduced nicotine content cigarettes that were administered in studies summarized in this document and their reported nicotine levels.

Table 1. Filler Nicotine Content for Normal, Low, and Very Low Nicotine Content Cigarettes Made Available Either Commercially or for Research

Brand	Manufacturer	Nicotine Content Category	Nicotine Content (mg/g)
Magic[1]	22nd Century Group, Inc.	VLNC	1.0*
Next[2]	Philip Morris International	VLNC	0.4*
Philip Morris 1 mg[3]	Philip Morris Tobacco Company	VLNC	0.7 - 0.9*
Philip Morris 2 mg[3]	Philip Morris Tobacco Company	LNC	2.1 -2.4*
Philip Morris 4 mg[3]	Philip Morris Tobacco Company	LNC	5.0 - 5.6*
Philip Morris 8 mg[3]	Philip Morris Tobacco Company	LNC	9.3 - 10.6*
Philip Morris 12 mg[3]	Philip Morris Tobacco Company	NNC	14.4 - 14.7*
Quest 1	Vector Group Ltd.	NNC	12.7*
Quest 2	Vector Group Ltd.	LNC	7.3*
Quest 3	Vector Group Ltd.	VLNC	0.9*
SPECTRUM® 0.4 mg (NRC102 - NRC105)[4]	22nd Century Group, Inc.	VLNC	0.4 - 0.7
SPECTRUM® 1.3 mg (NRC200, NRC201)[5]	22nd Century Group, Inc.	LNC	0.9 - 1.3
SPECTRUM® 2.4 mg (NRC300, NRC301)[5]	22nd Century Group, Inc.	LNC	1.9 - 2.4
SPECTRUM® 5.2 mg (NRC400, NRC401)[5]	22nd Century Group, Inc.	LNC	4.6 - 5.2
SPECTRUM® 15.8 mg (NRC600, NRC601)[5]	22nd Century Group, Inc.	NNC	15.5 - 17.3
Ultratech/Lifetech denicotinized[6]	Ultratech Inc./Lifetech Corp.	VLNC	0.6 - 0.7*
Ultratech/Lifetech nicotine[6]	Ultratech Inc./Lifetech Corp.	LNC	8.0 - 10.3*
Xodus[7]	22nd Century Limited, LLC	LNC	1.2 - 1.7*

Abbreviations: VLNC = very low nicotine content cigarette (≤0.7 mg nicotine per cigarette); LNC = low nicotine content cigarette (> 0.7 mg and < 8 mg nicotine per cigarette); NNC = normal nicotine content cigarette (> 8 mg nicotine per cigarette).

[1] Nicotine content from Walker et al., 2015.

[2] Nicotine content from Djordjevic et al., 1990.

[3] Nicotine content from Benowitz et al., 2012; Benowitz, Jacob, & Herrera, 2006.

[4] Nicotine content from FDA, 2021.

[5] Nicotine content from Donny et al., 2015 (supplement).

[6] Nicotine content estimated by FDA based on nicotine yield data from Pickworth et al., 1999.

7 Nicotine content from Hatsukami et al., 2013.

* For these cigarettes, FDA calculated mg of nicotine per gram of total tobacco based on reports of mg of nicotine per cigarette. Calculations were based on an estimate of 0.7 g tobacco per cigarette.

B. Estimate of Addiction Threshold Levels

In 1994, Benowitz and Henningfield proposed the idea of federal regulation of nicotine content in combusted tobacco products to a level below an addiction threshold that could result in lower intake of nicotine and a lower level of nicotine dependence (Benowitz & Henningfield, 1994). However, FDA acknowledges that there is individual variability in dose sensitivity to all addictive substances, making it difficult to determine a single addiction threshold that would apply across the population. A proposal to lower the nicotine in conventional cigarettes, or any tobacco product, could merit consideration only if there were a threshold nicotine exposure level below which the nicotine did not produce significant reinforcing effects or sustain addiction in a majority of the population. To inform a product standard for reducing nicotine content in combusted tobacco products, FDA continues to assess VLNC cigarette studies analyzing addiction threshold levels, as discussed in this section.

a. History of the Estimation of an Addiction Threshold

In their 1994 paper, Benowitz and Henningfield considered the smoking habits of a small population of smokers who demonstrate reduced nicotine dependence (a group sometimes referred to as tobacco "chippers") to inform indirect estimates of an addiction threshold (Benowitz & Henningfield, 1994). Chippers are typically characterized by smoking five or fewer cigarettes per day, with limited or no withdrawal symptoms, and able to skip smoking for days at a time (Benowitz & Henningfield, 1994). After analyzing the average daily intake of nicotine from chippers, the authors proposed a threshold level of nicotine per cigarette that should be low enough to prevent or limit the development of nicotine addiction in most young people. Based on existing studies at the time, they proposed that "0.17 mg of nicotine [exposure] per cigarette is the threshold level for a less-addictive cigarette [and, assuming] a maximal bioavailability of 40 percent with intensive smoking, an absolute limit of 0.4 to 0.5 mg of nicotine per cigarette should be adequate to prevent or limit the development of addiction in most young people" (Benowitz & Henningfield, 1994).

In a study designed to determine the dose discrimination threshold among adult smokers, participants were presented with cigarettes of decreasing nicotine content, starting with the highest concentration of 17 mg nicotine per g of total tobacco (NNC cigarette), to the lowest concentration of 0.4 mg nicotine per g of total tobacco (VLNC cigarette) (Perkins, 2019). The study found that, although the threshold to detect differences in nicotine concentration varied widely among participants, the majority were able to detect VLNC cigarettes when compared with NNC cigarettes; however, only 7% of participants were able to discriminate between VLNC cigarettes and LNC cigarettes of the next highest nicotine concentration, 1.3 mg

nicotine per g of total tobacco. This study indicates that VLNC cigarettes are below the nicotine discrimination threshold for a majority of smokers (Perkins, 2019), despite evidence suggesting they still produce some pharmacological effects (e.g., see Section IV.B.d: *Lower nAChR Occupancy and Cerebral Response from the Use of VLNC Cigarettes*).

In another study seeking to estimate a reinforcement threshold, scientists reviewed several studies, including one in which abstinent smokers received intravenous nicotine injections by pulling a lever in a fixed ratio task (Sofuoglu, Yoo, Hill, & Mooney, 2008). A study on intravenous nicotine administration suggests that a nicotine reinforcement threshold (i.e., the minimum amount of intravenous nicotine intake required to initiate or maintain self-administration) is between 0.1 to 0.4 mg/70 kg in humans (Sofuoglu & LeSage, 2012). Although the study's authors noted potential limitations (i.e., intravenous delivery does not mimic inhalation; administration of nicotine alone omits other psychoactive constituents in tobacco smoke; other factors such as age, sex, and genetic variations may influence nicotine's reinforcing properties) (Sofuoglu & LeSage, 2012), the estimated reinforcement threshold in these studies was comparable to the addiction threshold estimated by Benowitz and Henningfield (1994). Despite limitations associated with both estimates, they provide evidence for a potential range of nicotine doses that may be below an addiction threshold.

b. Biological and Behavioral Outcomes Related to Cessation, Use Behaviors, Biomarkers of Exposure, and Physiological Effects of VLNC Cigarettes

Many studies have investigated the effects of VLNC cigarettes on behavioral outcomes, including smoking cessation, use behaviors, biomarkers of exposure, and physiological effects. Findings from these studies are discussed below, and they suggest that individuals who smoke VLNC cigarettes with nicotine levels similar to what FDA is considering for the product standard may be more likely to make a quit attempt, demonstrate reduced exposure to HPHCs, and demonstrate similar or reduced physiological responses to cigarettes relative to individuals who smoke usual brand or NNC cigarettes. Thus, results from these and other studies reviewed in this document suggest that switching to VLNC cigarettes does not lead to compensatory smoking (see Section IV.C.a: *Compensatory Smoking*).

i. Smoking Cessation

A number of studies investigated the effects of VLNC or LNC cigarettes alone or in combination with NRT on smoking cessation in smokers interested in quitting (e.g., Becker et al., 2008; Dermody, Donny, Hertsgaard, & Hatsukami, 2015; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; McRobbie, Przulj, Smith, & Cornwall, 2016; Rezaishiraz, Hyland, Mahoney, O'Connor, & Cummings, 2007; Rose, Behm, Westman, & Kukovich, 2006; Walker et

al., 2012) and those uninterested in quitting (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Klemperer, Hughes, & Callas, 2019; Smith, Koopmeiners, et al., 2019; Walker et al., 2015).

In one of the only randomized controlled trials (RCTs) to date that has examined the effects of VLNC cigarettes alone on smoking cessation in smokers who were interested in quitting, 165 smokers were randomized to use LNC cigarettes, VLNC cigarettes, or 4 mg nicotine lozenges for 6 weeks (Hatsukami et al., 2010). While there were no significant differences between groups in point prevalence abstinence rates at 1-4-week follow-up visits, biochemically-verified abstinence rates at the Week-6 follow-up visit were significantly higher in the VLNC cigarette group (47%) and nicotine lozenge group (37%) relative to the LNC cigarette group (23%). In another RCT of 346 smokers interested in quitting, 32.8% were biochemically confirmed as smoking abstinent after using a combination of VLNC cigarettes (nicotine was gradually reduced from NNC to LNC to VLNC cigarettes every two weeks) and nicotine patch for 6 weeks, 21.9% were abstinent after using NNC cigarettes and a placebo patch, and 16.4% were abstinent after using VLNC cigarettes and a placebo patch (Becker et al., 2008), suggesting that the combination of VLNC cigarettes and NRT is more effective at promoting continuous abstinence than VLNC cigarettes alone. However, abstinence at 3- and 6-month follow-ups could not be adequately assessed due to attrition (Becker et al., 2008).

Many other studies conducted in individuals interested in quitting investigated the effects of LNC or VLNC cigarettes combined with NRT (Hatsukami, Hertsgaard, et al., 2013; Klemperer, Hughes, & Callas, 2019; McRobbie et al., 2016; Rezaishiraz et al., 2007; Rose et al., 2006; Walker et al., 2012). In a study conducted in New Zealand, 1,410 callers to a Quitline were randomized to receive VLNC cigarettes with usual Quitline care (8 weeks of NRT and behavioral support) or usual care alone (Walker et al., 2012). Six months after the quit date, 7-day self-reported point-prevalence abstinence rates were significantly greater in participants using VLNC cigarettes with usual care (33%) compared to the usual care group (28%). Furthermore, self-reported continuous abstinence rates at Month 6 were significantly higher for participants who received VLNC cigarettes with usual care (23%) compared to those who received usual care alone (15%). In another study, 98 heavy smokers received either VLNC cigarettes and a 21 mg nicotine patch or NNC cigarettes for 2 weeks prior to quitting (Rezaishiraz et al., 2007). After the quit date, all participants wore nicotine patches for up to 8 weeks. Participants who smoked VLNC cigarettes and received patches reported less frequent and less intense cravings, but the self-reported quit rate did not differ significantly between groups.

Several other studies investigated the effects of VLNC or LNC cigarettes on smoking cessation among individuals uninterested in quitting (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Klemperer, Hughes, & Callas, 2019; Smith, Koopmeiners, et al., 2019; Walker et al., 2015). Using a 2 x 2 RCT design, Smith and colleagues (2019) randomized participants to receive either NNC cigarettes or VLNC cigarettes (blinded), and to receive or not receive a transdermal nicotine patch (open label) for 7 weeks. At Week 7, participants were provided a daily descending monetary bonus for refraining from using any cigarettes. Participants randomized to receive NRT were encouraged to continue using their patches. During the abstinence period, no groups differed significantly from the NNC-only group in time to lapse or number of days abstinent; however, these results may have been influenced by low adherence to VLNC cigarette use in this study (Smith, Koopmeiners, et al., 2019). Benowitz and colleagues conducted a series of studies wherein participants received gradually reduced nicotine content cigarettes over a period of 6 months, beginning with NNC cigarettes and ending with VLNC cigarettes (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015). A significantly greater proportion of participants who received reduced nicotine content cigarettes considered quitting at the end of the study, compared to those in a control group who smoked their usual brand cigarettes throughout the study (Benowitz et al., 2012). In a follow-up study in which a subset of participants was followed for 2 years, cotinine levels in the gradual nicotine reduction group rose to baseline levels or levels similar to those of the control group after 12 months during which both groups could freely smoke usual brand cigarettes (Benowitz, Nardone, Dains, et al., 2015). Quit rates were low among both groups. Although 7.5% of participants in the gradual reduction group compared to 2% of participants in the usual brand control group were biochemically verified to have quit smoking at the 24-month follow-up, this difference was not statistically significant (Benowitz, Nardone, Dains, et al., 2015). In another study, 33 participants were randomized to receive VLNC cigarettes or to continue to smoke their usual brand cigarettes for 12 weeks. The availability of VLNC cigarettes increased quit attempts in smokers who had no intention of quitting (Walker et al., 2015).

In addition, several extended duration VLNC cigarette studies assessed self-reported quit attempts as a secondary study aim. While one study showed no significant differences in quit rates among nondaily smokers who used VLNC or NNC cigarettes for 10 weeks (Shiffman, Kurland, Scholl, & Mao, 2018), other studies showed that participants who smoked VLNC cigarettes were more likely to report a quit attempt after 6 weeks of VLNC cigarette use (Donny et al., 2015) and had a greater number of cigarette-free days after 18 weeks of VLNC cigarette use (Hatsukami et al., 2018) compared to those who smoked NNC cigarettes. In Hatsukami et al.

(2018), those who smoked menthol cigarettes had less biochemically verified abstinence than those individuals who smoked non-menthol cigarettes; however, both menthol and non-menthol smokers in the VLNC cigarette group were more likely to report a cigarette-free day than those assigned to NNC cigarettes (Denlinger-Apte, Kotlyar, et al., 2019).

Conclusions

Among the studies evaluating smoking cessation following VLNC cigarette use, few utilized a randomized controlled trial design, and results were sometimes inconsistent, particularly related to long-term follow-up. However, the weight of evidence from these studies suggests that among smokers interested in quitting, using VLNC cigarettes may facilitate initial smoking abstinence, particularly when used along with NRT and/or behavioral intervention. Among smokers uninterested in quitting, VLNC cigarette use did not increase quit rates; however, it did increase quit attempts. It is important to note that studies evaluating smoking cessation following VLNC cigarette use took place in an environment where NNC cigarettes and other combusted tobacco products remained readily available. For this reason, the available data may represent a conservative estimate of cessation rates following the implementation of a nicotine product standard because NNC cigarettes would no longer be available, making relapse to these cigarettes no longer possible.

ii. Cigarettes Per Day (CPD)

Researchers typically assess CPD via participant self-report or by counting cigarette filters or packs returned by participants. By measuring CPD during an extended exposure trial, researchers can determine whether switching to VLNC cigarettes produces changes in CPD compared to usual brand or NNC cigarette conditions.

Many studies reviewed in this document measured VLNC CPD under conditions of extended exposure (e.g., several consecutive weeks or longer). These studies varied in sample size, duration of exposure, average CPD requirements to enter the study, participants' intentions to quit smoking, and the method in which participants transitioned from usual brand cigarettes to VLNC cigarettes (i.e., gradual versus immediate reduction in nicotine content). Despite these differences in study methods and participant characteristics, nearly all of the studies came to similar conclusions: relative to usual brand or NNC cigarette conditions, CPD was similar (e.g., Bandiera et al., 2015; Becker et al., 2008; Benowitz, Nardone, Dains, et al., 2015; Ding, Ward, Hammond, & Watson, 2014; Donny & Jones, 2009; Hammond & O'Connor, 2014; Mercincavage et al., 2016; Rose, Behm, Ramsey, & Ritchie, 2001; Rose et al., 2006; Walker et al., 2015) or lower in VLNC cigarette conditions (e.g., Donny et al., 2015; Dermody et al., 2016; Donny, Houtsmuller, & Stitzer, 2007; Hatsukami et al., 2015; Hatsukami, Heishman, et

al., 2013; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; Hatsukami et al., 2018; Shiffman, Kurland, et al., 2018). Notably, studies that found lower CPD while participants smoked VLNC cigarettes tended to have larger sample sizes (e.g., Donny et al., 2015; Hatsukami et al., 2018), which may have had more statistical power to detect relatively small but consistent differences in CPD across conditions.

One such study (Donny et al., 2015) was a double-blind, parallel, randomized clinical trial conducted between June 2013 and July 2014 that evaluated 840 participants (780 completed the 6-week study) who were not interested in quitting smoking. During the sixth week of the study, the average number of CPD was lower for participants randomly assigned to cigarettes containing 2.4, 1.3, or 0.4 mg of nicotine per g of total tobacco (16.5, 16.3, and 14.9 CPD, respectively) than for those assigned to their usual cigarette brand (22.2 CPD) or cigarettes containing 5.2 or 15.8 mg of nicotine per g of total tobacco (20.8 and 21.3 CPD, respectively) (Donny et al., 2015). Those participants who used VLNC cigarettes (0.4 mg nicotine per g of total tobacco), demonstrated reduced use and dependence with minimal evidence of withdrawal-related discomfort or safety concerns. The authors concluded that this study provides data that "suggest that if nicotine content is adequately reduced, smokers may benefit by smoking fewer cigarettes and experiencing less nicotine dependence, with few negative consequences" (Donny et al., 2015).

Another study assessed the potential effects of VLNC cigarettes on compensatory smoking behaviors when participants were confined to a hotel (Smith, Koopmeiners, White, et al., 2020). Smokers completed two 4-night stays; during their first stay, participants were randomized to receive either NNC or VLNC cigarettes and were randomized to the other group during their second stay. Furthermore, participants were given an "account balance" where they could purchase study cigarettes from a "cigarette store" during the study. Investigators found that the number of cigarettes participants smoked did not differ significantly between the NNC and VLNC stays, indicating that smokers may not engage in compensatory smoking behavior when only VLNC cigarettes are available (Smith, Koopmeiners, White, et al., 2020).

One limitation of some studies that examined the effects of VLNC cigarette smoking on CPD is that comparisons between VLNC CPD and usual brand or NNC CPD were made without taking into account the number of non-study cigarettes smoked per day in experimental conditions. A measure of "total CPD" in VLNC cigarette conditions would include the number of study-assigned VLNC cigarettes plus the number of usual brand or non-study cigarettes smoked by participants who were not fully compliant with study procedures. Few studies have compared total CPD across VLNC and usual brand or NNC cigarette conditions. One study found that, relative to usual brand and NNC cigarette conditions, the combination of study- and non-

study-assigned CPD was lower in VLNC and LNC cigarette conditions when nicotine content was ≤ 2.4 mg of nicotine per g of total tobacco (Donny et al., 2015). Another study found that fewer combusted tobacco products were smoked during LNC cigarette conditions relative to a NNC cigarette condition (Hatsukami et al., 2017). Nevertheless, noncompliance with VLNC cigarettes is a concern discussed more thoroughly in Section V.C.a: *Noncompliance*. Briefly, the results of studies that examined VLNC cigarette noncompliance by measuring non-study CPD and biomarkers of exposure concluded that VLNC cigarette use does not increase overall exposure to combusted tobacco via compensatory smoking or use of alternative combusted tobacco products.

Another important methodological detail to note is that, in these studies, cigarettes were provided to participants for free. Also referred to as the "Free Cigarette Effect," studies show that providing free cigarettes to participants increases CPD irrespective of the nicotine content (e.g., Donny et al., 2015). For this reason, it is more appropriate to compare changes in CPD between VLNC and NNC cigarette groups, which both received free cigarettes throughout the study, as opposed to changes within the VLNC cigarette group compared to baseline. In the open marketplace, VLNC cigarettes would not be free to consumers as they are in research studies, and this may impact the rate of VLNC cigarette smoking (e.g., CPD may be lower than rates observed in clinical studies since cigarettes would not be free to consumers).

Importantly, one study ensured participants were compliant with study-assigned cigarettes by admitting them to a residential research facility. The results of this study showed that when smokers had access to only VLNC cigarettes for 11 days, they smoked significantly fewer CPD than smokers who had access to only NNC cigarettes (Donny et al., 2007).

Conclusions

Results of the studies reviewed in this document show that extended use of VLNC cigarettes does not produce increases in CPD. Rather, switching to LNC or VLNC cigarettes may produce modest decreases in CPD. These findings suggest that, if a nicotine standard were implemented, VLNC cigarette smokers would not increase CPD to compensate for reduced nicotine exposure, and CPD may decrease over time.

iii. Smoking Topography

Smoking topography measures provide data on various aspects of smoking behavior, including number of puffs per cigarette, total time spent smoking, puff volume (i.e., puff size), puff velocity (i.e., puff intensity), puff duration, and inter-puff interval (i.e., length of time between puffs). Although some of these outcomes (e.g., puffs per cigarette) can be measured via direct observation, smoking topography is typically assessed with an electronic puff

topography device attached directly to a cigarette. Smoking topography measures that indicate more intense smoking behavior may be attributed to compensatory smoking.

Some studies reviewed in this document found no differences in smoking topography between VLNC and NNC or usual brand cigarette conditions (e.g., Barrett, 2010; Branstetter, Nye, Sipko, & Muscat, 2019; Brody, Mandelkern, Olmstead, et al., 2009; Denlinger-Apte, Donny, et al., 2020; Faulkner et al., 2019; Hasenfratz, Baldinger, & Battig, 1993; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Stitzer, et al., 2017; Tidey et al., 2019). However, many other studies found that smoking topography differed between cigarette conditions. Some of the more reliable findings replicated across studies were the effects of VLNC cigarettes on total puff volume and number of puffs per cigarette. Under conditions of brief (e.g., several hours) and extended (e.g., several weeks) exposure, studies found that total puff volume was lower (e.g., Donny et al., 2015; Donny & Jones, 2009; Mercincavage et al., 2016; Rose & Behm, 2004a; Tidey, Cassidy, & Miller, 2016) and number of puffs per cigarette was lower (e.g., Donny et al., 2007; Hammond & O'Connor, 2014; Mercincavage et al., 2016; Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007; Tidey, Cassidy, et al., 2016) when participants smoked VLNC cigarettes relative to usual brand or NNC cigarettes. However, two brief exposure studies showed higher puff volumes (Macqueen et al., 2012; Strasser et al., 2007) and puff duration when participants smoked VLNC cigarettes under acute conditions (Macqueen et al., 2012). Another brief exposure study conducted in adolescents showed that VLNC cigarettes produced higher numbers of puffs relative to NNC cigarettes; however, additional measures were not collected to determine whether this was a transient or lasting effect (Kassel, Greenstein, et al., 2007). An extended exposure study showed initial decreases in puff volume when participants smoked VLNC cigarettes relative to NNC cigarettes, but these differences dissipated over the course of 7 days (Donny & Jones, 2009). Finally, limited evidence suggests that VLNC cigarettes are smoked faster (e.g., Benowitz, Jacob, & Herrera, 2006; Juliano, Fucito, & Harrell, 2011), increase peak velocity (Mercincavage et al., 2016), and may decrease inter-puff intervals when compared to NNC cigarettes (Tidey, Cassidy, et al., 2016).

Conclusions

Results of the studies reviewed in this document demonstrate somewhat mixed findings on the effects of VLNC cigarettes on smoking topography. However, the majority of studies show that individuals who smoke VLNC cigarettes demonstrate no differences in smoking topography relative to those who smoke usual brand or NNC cigarettes, or they demonstrate changes in smoking topography measures that are associated with reductions in tobacco smoke exposure (e.g., lower total puff volume) rather than increased compensatory smoking.

iv. Choice

Choice procedures have been used to evaluate the abuse liability of cigarettes varying in nicotine content. When individuals are given the choice to smoke VLNC or NNC cigarettes, they reliably show a preference for NNC cigarettes, indicating lower abuse liability for VLNC cigarettes (Cassidy et al., 2019; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Perkins & Karelitz, 2019, 2020; Perkins, Kunkle, Michael, et al., 2016). Rather than directly assessing choice between two tobacco products, some studies evaluate how much smokers are willing to work to earn puffs from cigarettes when the number of responses required to earn a puff from a cigarette progressively increases (i.e., a progressive ratio task). Donny and colleagues (2007) found smokers assigned to an NNC cigarette group were willing to work significantly harder to earn puffs from their study-assigned cigarette than smokers assigned to a VLNC cigarette group, indicating greater abuse liability of the NNC cigarette (Donny et al., 2007).

Hypothetical choice tasks (e.g., Cigarette Purchase Task, Multiple Choice Questionnaire) are also used to characterize reinforcing efficacy by determining how changes in the cost of a commodity affect its consumption. These tasks typically involve prior experience with the product or brief laboratory exposure, followed by a series of questions asking participants to either (1) report how many cigarettes they would consume at a variety of escalating prices, or (2) choose between cigarettes or money at a variety of prices. Studies that used hypothetical choice tasks to assess VLNC cigarette reinforcement showed that participants find VLNC cigarettes to be less reinforcing than NNC cigarettes (e.g., Cassidy et al., 2019; Hatsukami, Heishman, et al., 2013; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Kaplan et al., 2022; Smith et al., 2017; Tucker et al., 2017). In one study, Smith and colleagues (2017) examined the reinforcing efficacy of cigarettes varying in nicotine content following 6 weeks of access to the products. Compared to the NNC cigarette group, those in the VLNC cigarette group estimated that they would smoke fewer cigarettes if the cigarettes were free, spend less for the VLNC cigarettes, and quit smoking VLNC cigarettes at a lower price point (i.e., a price point at which participants would continue to pay for NNC cigarettes). Responses on the hypothetical choice task were highly correlated with the actual number of cigarettes smoked during Week 6 of that study.

Hypothetical choice tasks can also be used to investigate the substitutability of tobacco products. For example, Tucker and colleagues (2017) employed a cross-price elasticity task in which the price of VLNC cigarettes was held constant while the price for usual brand cigarettes was manipulated. When usual brand cigarette price increased, demand for VLNC cigarettes

increased and demand for usual brand cigarettes decreased, indicating VLNC cigarettes are partially substitutable for usual brand cigarettes (Tucker et al., 2017).

Additional studies assessed factors that may contribute to preference for cigarettes of varying nicotine content and found that various factors, such as perceptions and beliefs, genetic factors, endogenous opioid reward pathways, and threshold for nicotine discrimination may impact preference. For example, participants self-administer more cigarettes when they are told the cigarettes contain nicotine versus when they are told the cigarettes are denicotinized (Darredeau et al., 2013); females who have a common single nucleotide polymorphism in the mu-opioid receptor gene associated with nicotine reward, nicotine withdrawal severity, and smoking relapse (the OPRM1 G allele) may be less sensitive to the reinforcing effects of nicotine (Ray et al., 2006; Ray et al., 2011); and naltrexone, an opioid receptor antagonist, reduces the relative reinforcing effects of NNC cigarettes (Rukstalis et al., 2005). Finally, smokers who are able to discriminate VLNC cigarettes from cigarettes of varying nicotine content (from 1.3-17 mg nicotine per g of total tobacco) show greater preference for higher nicotine content cigarettes, compared with smokers unable to discriminate differences in nicotine (Perkins, 2019).

Conclusions

The results of studies reviewed in this document show that when participants make a real or hypothetical choice between VLNC cigarettes and NNC cigarettes, they reliably choose NNC cigarettes, demonstrating that VLNC cigarettes have lower abuse liability than NNC cigarettes. These findings may indicate that VLNC cigarette smokers would use NNC cigarettes if a nicotine standard were implemented and such products were still readily available (e.g., via illicit trade). However, research has also shown the choice between VLNC and NNC cigarettes can be influenced by factors such as cost. When the cost or effort required to obtain NNC cigarettes increases, smokers may switch their preference from NNC cigarettes to VLNC cigarettes (Branstetter et al., 2019; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017). For example, Branstetter et al. (2019) found that, although participants rated VLNC cigarettes as less satisfying than both LNC and NNC cigarettes, they purchased significantly more puffs of the VLNC cigarettes when LNC and NNC cigarettes were more expensive. Thus, if a nicotine standard is implemented and the cost, effort, or risk associated with obtaining NNC cigarettes increases (e.g., through illicit trade), preference may shift to VLNC cigarettes, and these cigarettes may become viable economic substitutes for NNC cigarettes.

If a nicotine product standard only applies to cigarettes and not all combusted tobacco products, these findings also indicate that cigarette users who do not quit tobacco products will likely be willing to switch to other normal nicotine content combusted products rather than

using VLNC cigarettes or switching to a non-combusted tobacco product. If this were the case, the public health benefit of a nicotine product standard would be limited as that portion of cigarette users, as well as the existing non-cigarette combusted tobacco product users, would continue to use combusted tobacco products.

v. Biomarkers of Exposure

Some of the most commonly measured biomarkers of tobacco smoke exposure are CO (measured as breath CO or carboxyhemoglobin [COHb]), plasma nicotine, cotinine (collected through plasma, saliva, or urine), total nicotine equivalents (TNE; a combination of nicotine, cotinine, and other nicotine metabolites collected through plasma, saliva, or urine), and other HPHCs or their metabolites (e.g., N-Nitrosonornicotine [NNN], NNAL, Benzo[a]pyrene [BAP], 3-HPMA, S-PMA). While nicotine and its metabolites would be expected to decrease in individuals who switch from NNC to VLNC cigarettes, other biomarkers of exposure would be expected to remain the same if smoking behavior remains unchanged. Thus, any changes in biomarker levels observed between NNC and VLNC cigarette conditions in clinical studies would indicate differences in smoking behavior (e.g., changes in CPD or smoking topography) between these two groups. Notably, due to the short half-lives of some biomarkers (e.g., breath CO), decreases in smoking can produce decreases in these biomarkers during brief exposure studies. However, decreases in smoking may not produce decreases in some biomarkers (e.g., NNAL) under such conditions due to the prolonged half-lives of these biomarkers.

Most studies have found no differences in CO exposure between participants who smoke VLNC cigarettes and those who smoke usual brand or NNC cigarettes (e.g., Baldinger, Hasenfratz, & Battig, 1995c; Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Breland, Buchhalter, Evans, & Eissenberg, 2002; Cobb, Weaver, & Eissenberg, 2010; Denlinger-Apte, Cassidy, Colby, Sokolovsky, & Tidey, 2019c; Denlinger-Apte, Donny, et al., 2020; Denlinger-Apte, Kotlyar, et al., 2019; Donny et al., 2015; Donny & Jones, 2009; Eid, Fant, Moolchan, & Pickworth, 2005; Greenstein et al., 2010; Gross, Lee, & Stitzer, 1997; Harrell & Juliano, 2012; Hasenfratz et al., 1993; Hatsukami et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano, Donny, Houtsmuller, & Stitzer, 2006; Juliano et al., 2011; Kamens et al., 2020; Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007; Rose & Behm, 2004a; Rose, Behm, Westman, & Johnson, 2000; Smith, Koopmeiners, et al., 2019; Smith, Koopmeiners, White, et al., 2020; Strasser et al., 2007). This finding may be somewhat unexpected as many studies have found that participants smoke fewer CPD when they smoke VLNC cigarettes relative to NNC or usual brand cigarettes (see Section IV.B.b.ii: *Cigarettes Per Day*). However, although CO is positively

associated with CPD, the correlation is of only moderate strength (Deveci, Deveci, Açik, & Ozan, 2004). Furthermore, CO may be impacted by noncompliance with study cigarettes (see Section V.C.a: *Noncompliance*). Nevertheless, differences were observed between VLNC and NNC cigarette conditions in a few studies. Two brief exposure studies in which participants were given limited access to reduced nicotine content cigarettes over the course of several hours under controlled laboratory conditions found increases in breath CO following VLNC cigarette use relative to NNC cigarette use (Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Westman, Behm, & Rose, 1996). In addition, an extended exposure study (35 days) showed that CO boost initially increased when participants switched from usual brand cigarettes during baseline to VLNC cigarettes; however, these effects dissipated over time as CO boost eventually returned to baseline levels (Mercincavage et al., 2016). As discussed in Section IV.C.a: *Compensatory Smoking*, these limited increases in CO exposure may be due to changes in smoking topography. Notably, however, at least one extended exposure study found decreases in CO boost after VLNC cigarette use compared to usual brand cigarettes (Hammond & O'Connor, 2014). In another study, one group of participants smoked NNC cigarettes throughout the study, a second group smoked study cigarettes with gradually reducing nicotine contents, and a third group immediately switched to VLNC cigarettes. This study found that subjects in the immediate VLNC cigarette group had significantly lower CO than did the NNC cigarette or gradual reduction groups. Breath CO for participants in the NNC cigarette and gradual reduction groups did not differ significantly from each other (Hatsukami et al., 2018.) Moreover, the only study to date that examined the effects of VLNC cigarettes on breath CO in smokers who inhabited a residential research facility found that when smokers only had access to study cigarettes for 11 days, those who were assigned VLNC cigarettes had significantly lower breath CO than those who were assigned NNC cigarettes. Further, these differences increased over the course of each day such that they were much larger in the afternoon than in the morning (Donny et al., 2007).

The results of studies that examined nicotine, cotinine, or TNE levels had overwhelming concurrence regarding the effects of either brief or extended exposure to VLNC cigarettes compared to usual brand or NNC cigarettes. VLNC cigarettes produced substantially lower nicotine, cotinine, and TNE than usual brand or NNC cigarettes (e.g., Baldinger, Hasenfratz, & Battig, 1995a; Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Branstetter et al., 2019; Breland et al., 2002; Cobb et al., 2010; Dallery et al., 2003; Denlinger-Apte, Kotlyar, et al., 2019; Denlinger et al., 2016; Ding et al., 2014; Donny et al., 2015; Donny & Jones, 2009; Gross et al., 1997; Hammond & O'Connor, 2014; Hasenfratz et al., 1993; Hatsukami et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2017; Hatsukami et al., 2018;

Kamens et al., 2020; Klemperer, Hughes, Callas, Benner, & Morley, 2019; Kuwabara et al., 2014; Mercincavage et al., 2016; Rose & Behm, 2004a; Rose et al., 2000; Rose, Behm, Westman, Mathew, et al., 2003; Smith, Koopmeiners, et al., 2019; Smith, Koopmeiners, White, et al., 2020; Westman et al., 1996). One within-subjects laboratory study compared the nicotine pharmacokinetic profile of SPECTRUM® VLNC, LNC, NNC, and usual brand cigarettes in 12 daily smokers (Kamens et al., 2020).While each of the four cigarettes produced significant increases in plasma nicotine boost (i.e., peak plasma nicotine level minus baseline level) after smoking the cigarettes, the VLNC and LNC cigarettes had significantly lower plasma nicotine boost and $AUC_{0\text{-}120}$ (i.e., plasma nicotine area under the curve calculated using the trapezoidal rule to 120 minutes) compared to the NNC and usual brand cigarettes. These data show that although VLNC cigarettes are associated with significantly lower nicotine uptake compared to NNC and usual brand cigarettes, the cigarettes still deliver a measurable amount of nicotine.

The effects of VLNC cigarette exposure on other HPHCs were less reliable across studies. Nevertheless, studies consistently found that VLNC cigarette exposure either reduced or did not change exposure to NNN, NNAL, urinary 1-hydroxypyrene (1-HOP), or BAP relative to NNC or usual brand cigarettes (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Donny et al., 2015; Ding et al., 2014; Hammond & O'Connor, 2014; Hatsukami et al., 2010; Hatsukami et al., 2017; Mercincavage et al., 2016). None of these studies found that VLNC cigarette use resulted in increases in any of these biomarkers. One study also examined 3-HPMA and S-PMA levels and found that these biomarkers decreased in VLNC cigarette conditions compared to LNC cigarette conditions (Hatsukami et al., 2010). Another study found that switching to VLNC cigarettes significantly reduced exposure to acrolein and phenanthrene tetraol, though there were no significant differences in exposure levels between subjects who immediately switched to VLNC cigarettes versus those whose nicotine exposure was gradually reduced through the study (Hatsukami et al., 2018). The reductions in HPHCs that were observed in some of these studies following VLNC cigarette exposure were typically correlated with decreases in CPD or other smoking behaviors. Thus, as expected, fewer CPD resulted in overall reductions in HPHC exposure.

Conclusions

Results from studies reviewed in this document demonstrate that, following VLNC cigarette use, some biomarkers of exposure (e.g., CO) are typically similar to those observed following NNC cigarette use, while other biomarkers (e.g., TNE) are typically lower following VLNC cigarette use. However, no biomarkers of exposure are reliably observed to be higher following VLNC cigarette use relative to NNC cigarette use.

vi. Physiological Effects

Physiological measures may be proxy measures for the stimulant effects of nicotine. Pharmacodynamic effects of nicotine include central and peripheral nervous system stimulation, arousal, and increased heart rate or blood pressure. Nicotine is a known stimulant, but physiological effects may occur in response to combusted tobacco products even in the absence of nicotine in experienced users due to conditioning or other psychoactive chemicals in tobacco smoke.

Some studies show that, regardless of nicotine content, acute cigarette smoking is associated with an increase in baseline heart rate (e.g., Benowitz et al., 2006; Cobb et al., 2010; Dallery et al., 2003; Eid et al., 2005); however, these increases were either less pronounced following VLNC cigarette use compared to NNC cigarette use (e.g., Benowitz et al., 2006; Cobb et al., 2010) or were less consistent (i.e., observed at some but not all time points following use) (Eid et al., 2005). Some research has shown that escalations in heart rate dissipate after repeated exposure to VLNC cigarettes but not usual brand cigarettes (Cobb et al., 2010). In contrast, other studies did not observe increases in heart rate when participants smoked VLNC cigarettes (e.g., Gross et al., 1997; Penetar, Lindsey, Peters, Juliano, & Lukas, 2012; Pickworth, Nelson, Rohrer, Fant, & Henningfield, 1999; Rose et al., 2000), and several studies showed significantly reduced escalations in heart rate compared to acute LNC, NNC, or usual brand cigarette administration (e.g., Baldinger et al., 1995c; Buchhalter et al., 2005; Donny et al., 2007; Hasenfratz et al., 1993; Hatsukami, Heishman, et al., 2013; Juliano et al., 2006; Rose, Westman, Behm, Johnson, & Goldberg, 1999; Schlagintweit & Barrett, 2016).

Some studies also investigated the effects of VLNC cigarettes on other physiological outcomes. Several studies found no differences in blood pressure after smoking a VLNC cigarette compared to an LNC cigarette (e.g., Buchhalter et al., 2005; Dallery et al., 2003), NNC cigarette (e.g., Benowitz et al., 2006), or usual brand cigarette (e.g., Benowitz et al., 2006). However, other studies showed significantly greater increases in blood pressure after smoking NNC or usual brand cigarettes relative to VLNC cigarettes (e.g., Hasenfratz et al., 1993; Hatsukami, Heishman, et al., 2013). While one study included in this document showed that skin temperature decreased to a greater extent with NNC cigarettes compared to VLNC cigarettes (Benowitz et al., 2006), other studies found no differences in skin temperature as a function of nicotine content in cigarettes (e.g., Penetar et al., 2012). Another study found no significant differences in skin conductance between VLNC and NNC cigarettes (Naqvi & Bechara, 2006).

Conclusions

While there is variability in the physiological effects data reviewed in this document, evidence suggests that, relative to VLNC cigarettes, NNC cigarettes are associated with greater increases in the physiological responses that are typically expected from nicotine administration.

c. Self-Reported Outcomes Related to Subjective Effects, Dependence, and Relief of Withdrawal Symptoms Associated with VLNC Cigarettes.

i. Drug Liking and Other Subjective Effects

Self-reported subjective effects (e.g., drug "liking" and "satisfaction") are widely used measures of reinforcing efficacy and abuse liability of drugs and tobacco products. Drug "liking" is associated with drug self-administration and has been shown to be the most sensitive and reliable subjective effects measure of abuse liability (Carter & Griffiths, 2009). Several studies compared the subjective effects of VLNC, LNC, NNC or participants' usual brand cigarettes using self-reported measures of drug effects (e.g., Cigarette Evaluation Scale, Smoking Effects Questionnaire, Visual Analogue Scale items).

Under conditions of brief exposure when participants were given limited access to reduced nicotine content cigarettes typically over the course of several hours under controlled laboratory conditions, several studies found that VLNC cigarettes were rated lower in cigarette "liking" compared to NNC cigarettes (e.g., Branstetter et al., 2019; Cassidy, Colby, et al., 2018b; Denlinger-Apte, Kotlyar, et al., 2019; Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Lindsey et al., 2013; Perkins, Ciccocioppo, et al., 2008; Perkins et al., 2006; Perkins et al., 2004; Perkins & Karelitz, 2019; Perkins, Karelitz, Conklin, Sayette, & Giedgowd, 2010; Perkins, Karelitz, & Kunkle, 2018, 2018; Schlagintweit & Barrett, 2016; Tidey et al., 2019) and usual brand cigarettes (e.g., Gross et al., 1997; Rose et al., 2004). However, other studies found no significant differences in "liking" as a function of nicotine content in cigarettes (e.g., Barrett, Tichauer, Leyton, & Pihl, 2006; Dallery et al., 2003; Juliano et al., 2006; Westman et al., 1996). Other subjective effects (e.g., "good" or "positive" effects; "bad" or "negative" effects) co-vary with drug "liking." On average, VLNC cigarettes were rated lower on other positive subjective effects items (e.g., "satisfaction," "pleasure," "taste," "strength," and "stimulation") compared to LNC cigarettes (e.g., Cook, Spring, & McChargue, 2007; Dallery et al., 2003; Greenstein et al., 2010; Hatsukami, Heishman, et al., 2013), NNC cigarettes (e.g., Darredeau et al., 2013; Hatsukami, Heishman, et al., 2013; Juliano et al., 2011; Macqueen et al., 2012; Perkins et al., 2010; Perkins et al., 2018, 2018) and usual brand cigarettes (e.g., Baldinger et al., 1995c; Brauer, Behm, Westman, Patel, & Rose,

1999; Cobb et al., 2010; Gross et al., 1997; Hasenfratz et al., 1993). VLNC cigarettes were also rated lower on items such as “aversiveness,” “sickness,” and “dizziness” (e.g., Brauer, Cramblett, Paxton, & Rose, 2001; Chukwueke et al., 2020; Harrell & Juliano, 2012; Hasenfratz et al., 1993; Juliano et al., 2011; Kelemen, 2008), and higher on items such as “dislike” and “unpleasant” compared to NNC or usual brand cigarettes (e.g., Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013). These seemingly contradictory findings (e.g., lower liking and lower aversiveness) contribute to the understanding that positive and negative subjective effect subscales capture different aspects of reinforcing efficacy and abuse liability, and these two subscales may independently predict preference for VLNC versus NNC cigarettes (Arger et al., 2017; Hatsukami, Heishman, et al., 2013).

Although often assumed, recent findings confirm that greater immediate positive subjective effect ratings (e.g., “liking”, “satisfaction”) predict greater acute reinforcing effects of cigarettes of varying nicotine content (Karelitz & Perkins, 2021). Several factors have been shown to influence subjective effects ratings of VLNC and NNC cigarettes. These factors include participants’ ability to discriminate the nicotine content of cigarettes. For example, NNC cigarettes have increased ratings of positive subjective effects when participants are able to discriminate them from VLNC cigarettes (Perkins & Karelitz, 2020; Perkins, Kunkle, Michael, et al., 2016). In addition, positive subjective effects ratings are higher when participants are told that they are receiving a nicotine-containing cigarette, regardless of the actual nicotine content of the cigarette (e.g., Denlinger-Apte, Joel, Strasser, & Donny, 2017; Perkins, Ciccocioppo, et al., 2008; Perkins et al., 2006; Perkins et al., 2004; Schlagintweit & Barrett, 2016).

Several studies assessed subjective effects of VLNC cigarettes following extended exposure when participants were given less restricted access to reduced nicotine content cigarettes in their natural environments, typically over the course of several weeks. Findings from these studies were relatively similar to findings from brief exposure studies. On average, VLNC cigarettes were rated as less appealing (e.g., lower ratings of “liking”, “satisfaction”, and “pleasure”) compared to LNC and NNC cigarettes (e.g., Buchhalter et al., 2005; Denlinger-Apte, Kotlyar, et al., 2019; Mercincavage et al., 2016; Smith, Donny, et al., 2019). However, at least one study found no differences in subjective effects as a function of nicotine content in cigarettes (Benowitz et al., 2012). Positive subjective effects ratings for VLNC cigarettes were shown to remain constant or decrease over time (e.g., Buchhalter et al., 2005; Walker et al., 2012).

Donny and colleagues (2007) conducted the only study to date that examined the effects of VLNC cigarettes on subjective effects in smokers who inhabited a residential research facility throughout the study. During 11 days of exposure to study cigarettes, participants

assigned to the VLNC cigarette group rated positive subjective effects of cigarettes (e.g., "enjoyable") lower and negative subjective effects (e.g., "unpleasant") higher than baseline subjective effects of usual brand cigarettes. Similarly, during the first few days of exposure to study cigarettes, participants who received NNC study cigarettes rated positive subjective effects of cigarettes lower and negative subjective effects higher than baseline subjective effects of usual brand cigarettes; however, these effects dissipated over time such that subjective ratings of NNC cigarettes were similar to usual brand cigarettes by the end of the study (Donny et al., 2007).

Finally, gender may influence differences in subjective effects. In one study, women rated all cigarettes as more flavorful than men, and an interaction was observed between gender and nicotine content such that women demonstrated less sensitivity than men to the differential subjective effects of NNC and VLNC cigarettes (Perkins et al., 2018). Another study found women reported increased satisfaction with VLNC or LNC cigarettes alone, while men reported greater satisfaction when these cigarettes were combined with NRT (Vogel et al., 2014). Finally, one study found that women reported higher psychological reward than men across all nicotine contents tested (Streck et al., 2019).

Conclusions

Studies typically find that VLNC cigarettes are liked less than NNC and usual brand cigarettes, indicating a lower abuse liability of VLNC cigarettes. None of the studies reviewed found that VLNC cigarettes were liked significantly more than NNC or usual brand cigarettes.

ii. Dependence

Over the course of regular use, combusted tobacco product smoking can lead to symptoms of nicotine dependence, which may include tolerance to the effects of nicotine, withdrawal upon cessation of use, craving, and unsuccessful efforts to quit smoking. Because dependence takes time to develop or change, it is often measured under conditions of extended exposure. Studies typically assess dependence with the Fagerström Test for Nicotine Dependence (FTND), Fagerström Test for Cigarette Dependence (FTCD), Nicotine Dependence Syndrome Scale (NDSS), and Wisconsin Inventory of Smoking Dependence Motives (WISDM).

In studies that gradually reduced the nicotine content of cigarettes over the course of weeks or months, the effects of VLNC cigarettes on dependence were somewhat mixed. In a study wherein nicotine content was gradually reduced (NNC, LNC, and VLNC cigarettes) over the course of 4 weeks, there were few differences in dependence scores between conditions, but there was a trend towards significance (p= 0.06) in overall reduction of dependence scores across conditions (Hammond & O'Connor, 2014). Another gradual reduction study found no

difference in dependence when comparing data from baseline to week 26 in 135 participants who smoked either gradually reduced nicotine content cigarettes over the course of 6 months or their own brand cigarettes for the same duration. However, when comparing only data from week 14 to week 26, while participants were primarily smoking VLNC cigarettes, there was a significant decrease in dependence in the group that received gradually reduced nicotine content cigarettes (Benowitz et al., 2012). A secondary analysis of data from 51 smokers who participated in this study demonstrated that participants with higher FTND scores at baseline were more likely to demonstrate signs of dependence during the study, regardless of the nicotine content of their study cigarettes (Bandiera et al., 2015). In a follow-up study, participants assigned to receive gradually reduced nicotine content cigarettes were given VLNC cigarettes for an additional 6 months (Benowitz, Nardone, Dains, et al., 2015), and no significant changes in dependence were observed.

Immediate nicotine reduction from usual brand cigarettes to LNC or VLNC cigarettes resulted in reduced dependence in smokers compared to those who smoked NNC or usual brand cigarettes for 6 weeks (Donny et al., 2015), 10 weeks (Shiffman, Scholl, & Mao, 2019), or 12 weeks (Walker et al., 2015) in participants not interested in quitting smoking. In smoking cessation studies in which participants endorsed wanting to quit, VLNC cigarettes were also associated with reductions in nicotine dependence over time (e.g., Hatsukami et al., 2010; Klemperer, Hughes, Callas, et al., 2019; Rose & Behm, 2004a; Rose et al., 2006). Conversely, a trial in which non-treatment seeking smokers with serious mental illness were randomized to use either VLNC or NNC cigarettes for 6-weeks, showed no significant differences in FTCD scores across VLNC and NNC cigarette groups (Tidey et al., 2019). However, these results may be explained by the high level of noncompliance reported in the VLNC cigarette condition (Tidey et al., 2019).

To date, one study compared the effects of gradual versus immediate nicotine reduction on FTND and WISDM dependence scores (Hatsukami et al., 2018). In a 20-week double-blind, parallel design study, adult smokers (N = 1,250) were randomized to an immediate reduction group that received VLNC cigarettes, a gradual reduction group that received cigarettes containing progressively decreased nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, 0.4 mg nicotine per g of total tobacco), or a control group that received NNC cigarettes. At the conclusion of 20 weeks, the immediate reduction group showed significantly lower FTND and WISDM dependence scores compared with the gradual reduction group and the NNC cigarette control group; no significant differences in dependence scores were observed between gradual reduction and control group. These results suggest that immediate nicotine reduction is

associated with reduced nicotine dependence compared to gradual reduction or continued use of NNC cigarettes (Hatsukami et al., 2018).

The delay to smoking the first cigarette of the day is a strong predictor of dependence. In the only study to date that examined the effects of VLNC cigarettes on latency to smoke in smokers inhabiting a residential research facility, time to first cigarette was significantly longer among smokers who only had access to VLNC cigarettes for 11 days compared to those who only had access to NNC cigarettes (Donny et al., 2007).

Conclusions

While some studies found no evidence of a change in dependence when smokers switched to VLNC cigarettes, more evidence indicated that switching to VLNC cigarettes decreases dependence. Moreover, the evidence suggests that immediate nicotine reduction is more likely to lead to decreases in dependence than gradual reduction. These findings fit with the hypothesis that lowering the nicotine content in combusted products will reduce nicotine exposure and, thereby, nicotine dependence in smokers who choose not to switch to another nicotine-containing tobacco product.

iii. Relief from Withdrawal Symptoms

Symptoms of nicotine and tobacco withdrawal may include irritability, depression, insomnia, headache, or increased craving. Although craving is often characterized as a symptom of nicotine and tobacco withdrawal, it is also a symptom of dependence, and it can occur in the absence of other withdrawal symptoms. Thus, craving is usually measured and reported separately from withdrawal. Studies typically assess craving and withdrawal with the Questionnaire of Smoking Urges (QSU), QSU-Brief, Minnesota Nicotine Withdrawal Scale (MNWS), Shiffman-Jarvik Withdrawal Scale, and Visual Analogue Scale items.

In brief exposure studies wherein participants were given limited access to reduced nicotine content cigarettes, typically over the course of several hours under controlled laboratory conditions, VLNC cigarettes suppressed craving and withdrawal relative to baseline measures that were typically assessed following overnight abstinence (e.g., Adams, Attwood, & Munafo, 2015; Addicott et al., 2014; Barrett, 2010; Barrett, Campbell, Roach, Stewart, & Darredeau, 2013; Barrett & Darredeau, 2012; Brauer et al., 1999; Guillot et al., 2015; Rose, Salley, et al., 2010; Tidey, Rohsenow, Kaplan, Swift, & Ahnallen, 2013). Furthermore, many studies showed that VLNC cigarettes can reduce craving and withdrawal as much as usual brand or NNC cigarettes (e.g., Baldinger et al., 1995a; Baldinger, Hasenfratz, & Battig, 1995b; Breland et al., 2002; Buckley, Holohan, Mozley, Walsh, & Kassel, 2007; Cobb et al., 2010; Dallery et al., 2003; Eid et al., 2005; Faulkner et al., 2019; Gross et al., 1997; Higgins, Heil, Sigmon, Tidey,

Gaalema, Hughes, et al., 2017; Juliano et al., 2006; Perkins et al., 2006; Perkins & Karelitz, 2015; Perkins et al., 2010; Ray et al., 2006; Rose et al., 2000; Rukstalis et al., 2005). However, some studies observed that suppression of craving and withdrawal was lower after smoking VLNC cigarettes than usual brand or NNC cigarettes (e.g., Brauer et al., 2001; Dedert et al., 2012; Hatsukami, Heishman, et al., 2013; Juliano et al., 2011; Kamens et al., 2020; Kelemen, 2008; Rose, Behm, Westman, Bates, & Salley, 2003; Rose et al., 1999; Smith, Koopmeiners, White, et al., 2020; Tidey et al., 2019). In addition, results from a few studies suggest VLNC cigarettes influence craving more than withdrawal. For example, one study found VLNC cigarettes suppressed craving similarly to NNC cigarettes, but also produced an increase in other withdrawal symptoms (Attwood, Penton-Voak, & Munafo, 2009). Other studies have found no effects of VLNC cigarettes on withdrawal symptoms (e.g., Harrell & Juliano, 2012; Rose et al., 2004; Schlagintweit & Barrett, 2016). Notably, some of these brief exposure studies reported differences between genders and generally found that female smokers experienced greater reductions in craving (e.g., Barrett et al., 2013; Barrett & Darredeau, 2012; Hatsukami, Heishman, et al., 2013) or withdrawal (e.g., Barrett, 2010; Perkins & Karelitz, 2015) compared to male smokers after smoking VLNC cigarettes. However, Perkins et al. (2006) found that, after smoking VLNC cigarettes, male smokers had greater reductions in craving compared to female smokers (Perkins et al., 2006).

During extended exposure studies, when participants smoked VLNC cigarettes from 4 days to 1 year, ratings of withdrawal (e.g., Benowitz et al., 2012; Buchhalter et al., 2005) and craving were generally similar compared to ratings observed in usual brand and NNC cigarette conditions (e.g., Buchhalter et al., 2005; Donny & Jones, 2009; Smith, Koopmeiners, et al., 2019). One study found that, after switching to VLNC cigarettes from usual brand cigarettes for 1 week, withdrawal symptoms increased with no reported change in craving (Hatsukami et al., 2010). However, these effects were relatively brief, and, within 6 weeks, withdrawal symptoms returned to baseline levels, and craving steadily decreased below baseline levels. Results from another study showed VLNC cigarettes can produce persistent reductions in craving characterized by participants as “moderate” or “a lot” after 3 and 6 weeks of exposure; however, some participants reported that no relief from craving occurred during the 6-week study (Walker et al., 2012). In addition, one study demonstrated that 6 weeks of exposure to LNC and VLNC cigarettes resulted in less craving and no difference in other withdrawal symptoms compared to NNC cigarettes (Dermody et al., 2018). Finally, during week-1 of a 20-week trial, smokers randomized to immediately reduce nicotine with VLNC cigarettes reported significantly more withdrawal symptoms compared to smokers who gradually reduced nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, 0.4 mg nicotine per g of total tobacco) and

compared to a control group using NNC cigarettes (Hatsukami et al., 2018). However, at the conclusion of 20 weeks, the immediate reduction group reported significantly lower smoking urges compared with the gradual reduction group and the NNC cigarette control group. No significant differences in smoking urges were observed between the gradual reduction group and the NNC cigarette control group. Similar to findings from brief exposure studies, female smokers experienced a reduction in craving after switching to LNC cigarettes for 1 week, whereas male smokers showed no change in craving upon switching. Overall, withdrawal symptoms increased in both male and female smokers after 1 week. However, these differences from baseline were short-lived. Ratings of both craving and withdrawal symptoms were no different than baseline over the remaining 6 weeks of the study (Vogel et al., 2014).

Craving and withdrawal were also assessed in several smoking cessation studies wherein participants were provided VLNC cigarettes along with pharmacotherapies (e.g., NRT, varenicline) before a designated quit date. In these studies, participants who received VLNC cigarettes plus a nicotine patch experienced less severe cravings, with no difference in withdrawal (Rose et al., 2007), a greater reduction in craving and withdrawal (Rose et al., 2006), and less frequent and less intense cravings before and after quit date (Rezaishiraz et al., 2007) compared to those who received NNC cigarettes before the quit date. Another study found that LNC cigarettes plus either varenicline or NRT resulted in decreases in craving compared to pharmacotherapy alone, with no differences in withdrawal across groups (McRobbie et al., 2016).

Conclusions

Due to their lower nicotine content, VLNC cigarettes might be expected to increase craving and withdrawal relative to usual brand or NNC cigarettes. However, results of studies reviewed in this document show that VLNC cigarettes typically do not produce greater reports of craving or withdrawal. Although findings from some brief exposure studies are mixed, the results of many studies suggest that brief and extended exposure to VLNC cigarettes can suppress craving and withdrawal just as effectively as NNC and usual brand cigarettes.

d. Lower nAChR Occupancy and Cerebral Response from the Use of VLNC Cigarettes

The main target of nicotine in the central nervous system is the nicotinic acetylcholine receptor (nAChR). These receptors are composed of five subunits, ranging from α1-7 and β1-4. Although nicotine can bind to each nAChR subtype, it does so with different strengths and different effects, making the actions of nicotine in the brain complex and diverse (Albuquerque, Pereira, Alkondon, & Rogers, 2009; Dani & Bertrand, 2007).

The most common nAChR subtype, α4β2, is of interest in the context of nicotine addiction for two major reasons: 1) it upregulates (i.e., increases in number) as a result of exposure to chronic nicotine, and 2) this subtype is potently desensitized by nicotine (Flores, Rogers, Pabreza, Wolfe, & Kellar, 1992; Whiting, Esch, Shimasaki, & Lindstrom, 1987; Zoli, Léna, Picciotto, & Changeux, 1998). In vivo PET imaging data, using a radiotracer specific for α4β2 nAChRs, showed a significantly stronger signal in the brains of smokers when compared to the signal from nonsmokers' brains, indicating that α4β2 receptors are upregulated as a result of chronic nicotine self-administration (Esterlis et al., 2014; Wüllner et al., 2008).

The interplay between upregulation and desensitization can be seen as an attempt for the central nervous system to maintain "normal" cholinergic transmission in the brain despite regular nicotine self-administration. Because chronic nicotine increases the overall number of nAChRs, the strength of cholinergic transmission increases, potentially causing some symptoms of withdrawal. In order to minimize these symptoms, the smoker self-administers nicotine (i.e., smokes a cigarette), which desensitizes these additional receptors and weakens cholinergic transmission, further driving the cycle of nicotine addiction (Dani & Heinemann, 1996; Hussmann et al., 2014; Watkins, Koob, & Markou, 2000). PET and MRI data obtained from human smokers using an α4β2-specific radiotracer indicates that after smoking a VLNC cigarette, α4β2 receptors located in numerous areas of the brain are occupied despite the lower nicotine content of VLNC cigarettes (Brody, Mandelkern, Costello, et al., 2009).

Nicotine also activates the dopaminergic brain reward system, which results in dopamine release and a pleasure response. Nicotinic acetylcholine receptors are plentiful in the midbrain dopamine centers, specifically the ventral tegmental area (VTA), where they influence dopamine release (Drenan et al., 2008; Watkins et al., 2000; Wooltorton, Pidoplichko, Broide, & Dani, 2003). Preclinical studies show that systemic administration of nicotine increases midbrain dopamine release (Nisell, Marcus, Nomikos, & Svensson, 1997), and studies on dopaminergic neurons in preclinical models and the human VTA have shown that a variety of nAChR subtypes, including, but not limited to α4β2 (Drenan et al., 2008; Wu et al., 1998; Zoli et al., 1998), increase and control the activity of these neurons to both stimulate the release of dopamine and strengthen the synapses in the reward circuit, making nicotine self-administration intrinsically pleasurable while fortifying the habit in smokers (Schilström, Rawal, Mameli-Engvall, Nomikos, & Svensson, 2003). The release of dopamine also initiates an adaptive process in which an individual forms learned associations between the subjective state (e.g., pleasure) and the object or context that led to that state (e.g., the act of smoking a cigarette) (Brody, Mandelkern, Olmstead, et al., 2009). Through this process, both nicotine

administration and smoking stimuli (e.g., a cigarette, a lighter) contribute to the cycle of nicotine dependence (Caggiula et al., 2009).

While the endogenous opioid receptor system is also thought to influence nicotine reinforcement, a study assessing μ-opioid receptor binding after participants smoked a VLNC or NNC cigarette found no difference in μ-opioid receptor binding as a function of nicotine content (Kuwabara et al., 2014). Studies have also examined the effects of cigarette nicotine content on electroencephalogram (EEG) measures. Within some frequency bands, studies have found differential effects of VLNC cigarettes on EEG power relative to usual brand (Baldinger et al., 1995c) and LNC cigarettes (Pickworth, Nelson, et al., 1999). Smoking NNC cigarettes to satiety results in near-complete occupancy of nAChRs in the brain (Brody et al., 2006; Esterlis et al., 2010). In contrast, although there is enough nicotine in VLNC cigarettes to bind to nAChRs in the brain and to release dopamine, there is not enough to consistently produce the magnitude of subjective craving or withdrawal responses observed following use of NNC cigarettes (e.g., Rose, Behm, Westman, Mathew, et al., 2003).

Conclusions

Taken together, these findings suggest that concentrations of nicotine in the brain provided by VLNC cigarettes are high enough to occupy sufficient α4β2 nAChRs to mitigate feelings of withdrawal and craving experienced by smokers in need of a cigarette. However, these concentrations of nicotine may not be enough to fully act upon the diverse nAChR subtypes in the midbrain dopaminergic centers, thereby not reinforcing the rewarding aspects of nicotine self-administration.

C. Unintended Consequences

Section VI: *Potential Public Health Benefits of Preventing Initiation to Regular Use and Increasing Cessation*, discusses some of the potential benefits that FDA expects could occur as a result of a nicotine tobacco product standard. There may also be unintended consequences that could diminish the expected population health benefits. As part of any subsequent rulemaking, FDA will assess both expected benefits and unintended consequences, including among vulnerable populations and other population subgroups.

a. Compensatory Smoking

One common concern with switching from usual brand or NNC cigarettes to VLNC cigarettes is the potential for compensatory smoking, which is a change in normal smoking behavior that would increase exposure to cigarette smoke to compensate for reduced nicotine intake. In other words, compensatory smoking or compensation occurs when smokers seek to

obtain the amount of nicotine needed to sustain their addiction by smoking more cigarettes per day, taking more and deeper puffs, or puffing with a faster draw rate. In both brief and extended exposure studies with VLNC cigarettes, compensation was measured using CPD, puff topography measures, and biomarkers of CO exposure, such as breath CO or carboxyhemoglobin (COHb).

When exposure to VLNC cigarettes is brief (e.g., limited to one or two exposures), transient compensatory smoking may occur. In brief exposure studies, changes in smoking topography (e.g., Kassel, Greenstein, et al., 2007; Macqueen et al., 2012; Strasser et al., 2007) and increases in CO (e.g., Eid et al., 2005; Strasser et al., 2007; Westman et al., 1996) have been observed. For example, one study demonstrated the transient nature of compensatory smoking by showing increases in smoking topography and CO exposure during the first and second exposures to VLNC cigarettes, followed by the subsequent dissipation of these effects by the third and fourth exposures (Macqueen et al., 2012). Similarly, White and colleagues (2022) found that during a five-day study where participants checked into a hotel and were restricted to only study cigarettes, mouth-level nicotine exposure indicated that participants initially puffed VLNC cigarettes with greater intensity than NNC cigarettes; however, this effect diminished across sessions. However, results from the majority of studies reviewed showed no compensatory smoking as a result of switching from usual brand or NNC cigarettes to VLNC cigarettes. Although not all studies examined every measure of compensatory smoking, most studies that examined these measures found no differences between control and VLNC cigarette conditions in CPD (e.g., Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Dermody et al., 2016; Hasenfratz et al., 1993; Hatsukami et al., 2015; Hatsukami, Heishman, et al., 2013; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; Hatsukami et al., 2017; Juliano et al., 2006; Juliano et al., 2011; Rose & Behm, 2004a; Smith, Koopmeiners, White, et al., 2020), CO exposure (e.g., Bandiera et al., 2015; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Denlinger-Apte, Donny, et al., 2020; Denlinger-Apte, Kotlyar, et al., 2019; Greenstein et al., 2010; Gross et al., 1997; Harrell & Juliano, 2012; Hasenfratz et al., 1993; Hatsukami, Heishman, et al., 2013; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; Hatsukami et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano et al., 2011; Kamens et al., 2020; Rose & Behm, 2004a; Smith, Koopmeiners, Hatsukami, et al., 2020; Tidey et al., 2013), smoking topography (e.g., Bandiera et al., 2015; Eid et al., 2005; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano et al., 2006), or all three measures (e.g., Branstetter et al., 2019; Ding et al., 2014; Donny & Jones, 2009; Faulkner et al., 2019; Hammond & O'Connor, 2014; Mercincavage et al., 2016). Finally, one study found that smokers using VLNC cigarettes

smoked significantly fewer CPD and had lower CO levels compared to controls (Hatsukami et al., 2018). In a 20-week trial, smokers randomized to an immediate reduction group that received VLNC cigarettes, a gradual reduction group that decreased cigarette nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, 0.4 mg nicotine per g of total tobacco), or a control group using NNC cigarettes. The immediate reduction group smoked cumulatively less CPD over the course of the 20-week study and had lower CO compared to the control group, with no differences in CPD or CO across the gradual reduction and control groups.

Notably, compensatory smoking has been observed with some reduced nicotine content cigarettes containing intermediate levels of nicotine (e.g., LNC cigarettes). For example, in a study of 165 smokers assigned to switch to LNC cigarettes or VLNC cigarettes, researchers found small but statistically significant differences in CPD between the LNC and VLNC cigarette conditions, such that LNC CPD increased over the course of the 6-week intervention, while VLNC CPD decreased (Hatsukami et al., 2010). However, one of the largest studies involving reduced nicotine content cigarettes found no compensatory smoking behavior for cigarettes containing intermediate levels of nicotine (Donny et al., 2015).

Conclusions

The results of studies reviewed in this document suggest that some transient compensatory smoking may occur following initial VLNC cigarette exposure. However, after continued use of VLNC cigarettes, smokers stop compensating, leading to reduced nicotine exposure.

b. Illicit Tobacco Products

While some consumers would be satisfied with quitting, using VLNC cigarettes, or with dual use or switching to non-VLNC legally marketed tobacco products, FDA expects that there would be a subset of consumers uninterested in these options. This subset of consumers may seek to obtain illicit tobacco products after a standard becomes effective (Griffiths, 2018; Hall, Byron, Brewer, Noar, & Ribisl, 2019). Accordingly, FDA is considering whether an increase in illicit trade might occur following implementation of a nicotine tobacco product standard and how that could impact the marketplace and public health. The analysis of possible illicit trade includes considerations regarding the sources of tobacco, how illicit tobacco products might be manufactured, possible workarounds (such as adding nicotine in liquid or other form to a product with minimally addictive nicotine levels), the ability to distribute illicit products, the development of consumer awareness, and how illicit trade sales might take place (Griffiths, 2018). The capacity to produce illicit tobacco products would depend upon a variety of factors, including the ease of acquiring the raw materials (particularly tobacco), the sophistication

required to construct the desired product, and the purpose (whether it is for an individual's personal use or for wider distribution and sale). Large commercial tobacco product manufacturers have the resources, sophistication, and ability to manufacture illicit tobacco products (Griffiths, 2018). Illicit tobacco products also may be smuggled and sold through the Internet (Ribisl, Hatsukami, Huang, Williams, & Donny, 2019). It is unclear, however, to what extent such companies would be willing to risk their businesses (and resulting profits) to manufacture illicit tobacco products (Griffiths, 2018). Tribal manufacturers are an additional source of tobacco products, having relatively high sophistication and machinery in some instances, but they are also subject to the same disincentives as large manufacturers and generally lack widespread distribution and sales capabilities (Griffiths, 2018).

The IOM has explored the issue of possible illicit trade if FDA were to issue a tobacco product standard limiting the levels of nicotine in combusted tobacco products. The IOM found that, although there is insufficient evidence to draw firm conclusions regarding how the U.S. illicit tobacco market would respond to regulations requiring a reduction in the nicotine content of these products, limited evidence suggests that the demand for illicit conventional cigarettes would be "modest" (Institute of Medicine of the National Academies, 2015). The IOM suggests that demand would be limited, because some smokers may quit and others will use modified products or seek legal alternatives (Institute of Medicine of the National Academies, 2015). Although some smokers may seek to purchase illicit products if available and accessible, the IOM finds that this "would require established distribution networks and new sources of product (which would either have to be smuggled from other countries or produced illegally) to create a supply of cigarettes with prohibited features" (Institute of Medicine of the National Academies, 2015). Given that individuals have utilized distribution networks to smuggle cigarettes and avoid higher taxes, FDA is considering whether there might be additional incentive to create or obtain the prohibited full nicotine combusted tobacco products that are not available elsewhere in the United States. In addition, the report explains that comprehensive interventions by several countries show that it is possible to reduce the size of the illicit tobacco market through enforcement mechanisms and collaborations across jurisdictions (Institute of Medicine of the National Academies, 2015).

In addition to the above-described disincentives to pursuing illicit full nicotine products, research has also shown that the choice between VLNC and NNC cigarettes can be influenced by factors such as cost. As stated above, data show that when the cost or effort required to obtain NNC cigarettes increases, smokers may switch their preference from NNC cigarettes to VLNC cigarettes (Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017). Thus, if a nicotine standard is implemented and the cost, effort, or risk associated with obtaining NNC cigarettes

increases through illicit trade, preference may shift to VLNC cigarettes, and these cigarettes may become viable economic substitutes for NNC cigarettes.

If a nicotine tobacco product standard prompts the development of an illicit market, FDA has the authority to take enforcement actions regarding the sale and distribution of illicit tobacco products. The FD&C Act provides FDA with several tools that it may use against noncompliant parties. For example, FDA could issue a Warning Letter, which is an advisory action in which FDA notifies a regulated entity that FDA has found evidence that the party violated the law. A Warning Letter is used to achieve prompt voluntary compliance. In a Warning Letter, FDA informs the regulated entity that failure to comply with the requirements of the FD&C Act and its implementing regulations may result in FDA enforcement action. These actions may include initiating administrative actions or referring cases to the Department of Justice for initiation of judicial action. FDA may seek to initiate an administrative legal action against a regulated entity that can result in the imposition of a fine or civil monetary penalty. Possible judicial actions may include seizures, injunctions, and criminal prosecution.

Conclusions

Limited evidence suggests that there would be a modest subset of consumers who may seek to obtain illicit tobacco products after a standard becomes effective. The demand for illicit tobacco products would be limited by the availability of illicit distribution networks. If a nicotine tobacco product standard prompts the development of an illicit market, FDA has the authority to take enforcement actions regarding the sale and distribution of illicit tobacco products.

c. Impact on Vulnerable Populations

i. Adolescents

Few studies have assessed the effects of VLNC cigarette use in adolescent and young adult smokers. To date, studies that have investigated the effects of VLNC cigarettes in adolescent smokers have done so under conditions of brief exposure (e.g., single exposure to a VLNC cigarette in a laboratory setting). One such study investigated the effects of nicotine content on breath CO in adolescent smokers across four study cigarettes ranging from NNC to VLNC cigarettes (Cassidy, Colby, et al., 2018a; Cassidy, Tidey, et al., 2018). No effect of nicotine content on breath CO was observed. Another study comparing VLNC and LNC cigarette smoking topography in adolescent smokers found that participants took significantly more puffs from the VLNC cigarette compared to the LNC cigarette, and a non-significant trend emerged such that increases in breath CO were higher after smoking the VLNC cigarette compared to the LNC cigarette (e.g., Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007). However, participants in this study received a single study cigarette. Thus, it is unclear whether compensatory

smoking would have continued under conditions of extended exposure to VLNC cigarettes. Notably, transient compensatory smoking has been observed in adult smokers of VLNC cigarettes under conditions of brief exposure, but these effects diminish under conditions of extended exposure (see Section IV.C.a: *Compensatory Smoking*).

Similar to studies in adult smokers, studies in adolescent smokers have shown that positive subjective effects ratings are lower for VLNC cigarettes compared to LNC and NNC cigarettes. For example, one study found an LNC cigarette was rated as significantly more pleasant than a VLNC cigarette (Kassel, Greenstein, et al., 2007). Another study found that NNC cigarettes were associated with greater reductions in craving and increased smoking satisfaction relative to VLNC cigarettes in adolescents (Cassidy, Colby, et al., 2018a). A similar laboratory study in young adults (ages 18 - 25) found no influence of nicotine content on total nicotine withdrawal score, affect, or smoking topography; however, NNC cigarettes were associated with increased subjective effects ratings compared to LNC and VLNC cigarettes (Faulkner et al., 2017). Notably, a secondary analysis of data from Donny et al. (2015) found that, at the end of the 6-week trial, there was no influence of age on subjective effects, TNE levels, or puff volume in participants who smoked LNC or VLNC cigarettes (Cassidy, Colby, et al., 2018a).

Another laboratory study on the effects of nicotine content and menthol preference among adolescent smokers (15-19 years of age) found VLNC cigarettes were rated significantly lower than NNC cigarettes, with no significant interaction of menthol status and nicotine content on subjective or behavioral measures (Denlinger-Apte, Cassidy, et al., 2019c). Similarly, Cassidy et al. (2019) observed lower demand for LNC and VLNC cigarettes than NNC cigarettes among adolescent smokers (15-19 years of age). One study also found that young adult smokers (18-24 years of age) exhibited lower demand for LNC and VLNC cigarettes than adults > 24 on three of the five Cigarette Purchase Task (CPT) indices, but there were no other differences between the two age groups in smoking topography, breath CO, cigarette puffs, craving, withdrawal, or smoking urge measures (Davis, Parker, et al., 2019). Finally, Faulkner and colleagues (2019) investigated how nicotine exposure contributes to relief of craving and negative affect among young adult smokers (18-25 years of age) and found that smoking reduced craving and negative affect regardless of nicotine content, and smoking topography did not vary as a function of nicotine content (Faulkner et al., 2019).

While it is unethical to conduct research that exposes nonsmokers to VLNC cigarettes, animal models provide an opportunity to address the question of how adolescents and nonsmokers might respond, should they experiment with VLNC cigarettes. A preclinical study compared self-administration of low nicotine doses in nicotine-naïve adult rats (i.e., a model of

nonsmokers) and rats previously exposed to nicotine (i.e., a model of current users of NNC cigarettes). Adult rats with a history of nicotine exposure responded at a higher rate for a low nicotine dose than nicotine-naïve rats, suggesting that nonsmokers who initiate smoking VLNC cigarettes are likely to be less sensitive to nicotine's reinforcing effects than current smokers (Smith, Schassburger, Buffalari, Sved, & Donny, 2014). Another study that compared nicotine-naïve male and female adolescent and adult rats found that adult rats acquired self-administration at lower nicotine doses than adolescents, suggesting that nicotine doses that are below the reinforcement threshold in adults are likely to be below the threshold for smoking initiation in adolescents (Schassburger et al., 2016).

Conclusions

In sum, existing data suggests adolescent smokers like VLNC cigarettes less than LNC and NNC cigarettes. Data on the effects of VLNC cigarettes on compensatory smoking in adolescents are limited and mixed, with the results of one brief exposure study showing that adolescents took more puffs from a VLNC cigarette than an LNC cigarette. As discussed in Section IV.C.a: *Compensatory Smoking*, compensation typically dissipates after repeated exposure. Thus, in the absence of extended exposure studies, it is difficult to draw conclusions regarding the effects of VLNC cigarette use on compensatory smoking in adolescents and young adults. While there are limitations with preclinical research related to generalizability to humans, animal studies provide the only ethical opportunity to assess the potential effects of VLNC cigarettes in nonsmokers. Animal studies suggest that VLNC cigarettes should be similarly or less reinforcing to adolescents and nonsmokers compared to current smokers, suggesting that they should not increase the likelihood of progression to regular smoking in nicotine-naïve individuals who may experiment with VLNC cigarettes.

The information detailed in Sections II.C.a and II.C.b: *Youth Initiation and Dependence* and *Adults and Youth Cessation and Relapse* makes it clear that the nicotine in combusted products can quickly cause youth experimenting with combusted tobacco products to develop dependence and become established users. With a nicotine tobacco product standard in place, youth experimentation with tobacco products would likely continue. However, available clinical and preclinical data support that significantly fewer individuals would become established combusted tobacco product users; thereby, dramatically reducing the long-term health impact of chronic combusted tobacco product use (Apelberg et al., 2018).

ii. Individuals with Symptoms of Mental Health and Substance Use Disorders

Cigarette smoking is overrepresented in individuals with symptoms of mental health disorders. Smokers with symptoms of mental health disorders have increased nicotine

withdrawal symptoms when trying to quit (e.g., Breslau, Kilbey, & Andreski, 1992; Weinberger, Desai, & McKee, 2010) and are more likely to smoke to ameliorate negative mood (e.g., Marshall et al., 2008). As a result, this population is less responsive to standard smoking cessation treatments (Hitsman et al., 2013)) and has increased risk of tobacco-related mortality (e.g., Callaghan et al., 2014). However, should smokers with mental health disorders quit smoking, not only would they reduce their risk of tobacco-related death and disease, but they may also experience improvements in their mental health (Taylor et al., 2021). Researchers have investigated the effects of VLNC cigarettes in smokers with symptoms of mental health disorders to determine whether VLNC cigarettes are associated with differential effects on craving, withdrawal, smoking topography, or use behavior among this group compared to the general population. In smokers with symptoms of mental health disorders, as in the general population, NNC cigarettes were associated with greater reductions in craving and withdrawal symptoms compared to VLNC cigarettes. Among this group, VLNC cigarettes were not associated with increased markers of compensatory smoking (e.g., smoking topography, CO) compared to the general population. Researchers also assessed psychiatric symptomatology as a function of VLNC cigarette use and found that VLNC cigarettes were associated with improvements in mood symptoms, likely due to the anxiety-increasing properties of nicotine.

Several studies investigated the effects of VLNC cigarettes on mood following mood induction (i.e., an experimental method for inducing a specific mood state) in smokers with symptoms of mental health disorders (e.g., Buckley et al., 2007; Cook et al., 2007; Spring et al., 2008). These studies found that, following positive mood induction, LNC cigarettes as compared to VLNC cigarettes were associated with an enhancement of positive mood among depression-prone or anhedonic smokers, but not control participants (e.g., Cook et al., 2007; Spring et al., 2008). In addition, LNC cigarettes, but not VLNC cigarettes, were associated with a worsening of negative mood in response to negative mood induction among smokers, regardless of baseline mental health status (Spring et al., 2008). Similarly, following an anxiety-eliciting mood induction, participants with post-traumatic stress disorder reported greater relief of anxiety after smoking LNC cigarettes compared to VLNC cigarettes; however, LNC cigarettes increased autonomic arousal (e.g., skin conductance, heart rate) relative to VLNC cigarettes (Buckley et al., 2007). Additionally, several secondary analyses investigated the effects of extended exposure to VLNC or LNC cigarettes on negative affect and found no significant association between negative affect and CPD (Robinson et al., 2017; Robinson et al., 2019).

A secondary analysis from an extended exposure study (Donny et al., 2015) assessed the effects of cigarettes varying in nicotine content on changes in psychiatric symptomatology among those with and without elevated depression symptoms (Tidey, Pacek, et al., 2017).

Among participants with elevated depression symptoms, those assigned to smoke LNC or VLNC cigarettes for 6 weeks had lower depressive symptoms at the end of the study compared to those assigned to smoke NNC cigarettes. Additional secondary analyses from Donny et a. 2015 showed that VLNC cigarette use over 6 weeks was not associated with compensatory alcohol use, binge drinking, or frequency of cannabis use among this sample (Dermody et al., 2016; Pacek et al., 2016). Another study that assigned participants with serious mental illness to receive either NNC or VLNC cigarettes saw no change in participants' psychiatric symptoms at the end of 6 weeks (Tidey et al., 2019).

Several studies assessed the effects of VLNC cigarettes on smoking rates, nicotine craving, dependence, withdrawal, and subjective effects among those with symptoms of mental health disorders (Buckley et al., 2007; Dedert et al., 2012; Denlinger-Apte, Donny, et al., 2020; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Stitzer, et al., 2017; Tidey et al., 2019; Tidey, Pacek, et al., 2017; Tidey et al., 2013). While some studies found no significant differences in craving or withdrawal as a function of nicotine content following brief smoking abstinence in these vulnerable populations (Buckley et al., 2007; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Stitzer, et al., 2017; Tidey et al., 2013), others showed that usual brand cigarettes were associated with larger decreases in craving and withdrawal compared to VLNC cigarettes (e.g., Dedert et al., 2012). At least one extended exposure study found that relative to NNC cigarettes, LNC and VLNC cigarettes reduced smoking rates, nicotine dependence, and cigarette craving, and these effects were not moderated by baseline depressive symptoms (Tidey, Pacek, et al., 2017). In addition, similar to the general population, smokers with poor mental health rate NNC cigarettes as more rewarding (e.g., taste and satisfaction) compared to VLNC cigarettes (Cook et al., 2007; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Stitzer, et al., 2017; Spring et al., 2008; Tidey et al., 2013).

Several studies investigated the effects of reduced nicotine content cigarettes on smoking behavior in other vulnerable populations. Higgins and colleagues (2017) found no significant differences in smoking topography or breath CO as a function of nicotine content in adult smokers from three vulnerable populations (opioid-dependent individuals, economically disadvantaged women, and individuals with affective disorders). Subsequent analyses of this study also found that cannabis use status, presence of chronic health conditions, and sex did not correlate with differences in smoking topography or the reinforcing effects of nicotine among smokers (Parker et al., 2018; Streck et al., 2018; Streck et al., 2019). Furthermore, menthol did not differentially influence smokers' response to reduced nicotine cigarettes for

outcomes of economic demand, withdrawal/craving, or smoking topography, suggesting that beneficial effects of reduced nicotine cigarettes may extend to menthol smokers belonging to vulnerable populations (Davis et al., 2019). In addition, Tidey and colleagues (2013) found that smokers with schizophrenia and control participants smoked fewer puffs and had lower total puff volumes, shorter inter-puff intervals, longer puff durations and marginally higher puff volumes when smoking VLNC cigarettes compared to usual brand cigarettes. However, these differences were not associated with subsequent increases in breath CO boost (Tidey, Cassidy, et al., 2016).

Several studies used laboratory paradigms to assess the effects of alcohol on specific components of smoking behavior for nicotine versus non-nicotine factors in heavy drinkers. One study found that alcohol increased smoking urge and subjective ratings of smoking for both NNC and VLNC cigarettes (King, McNamara, Conrad, & Cao, 2009), while another study found that NNC cigarettes were associated with increases in subjective effects and a greater reduction in cigarette craving than VLNC cigarettes, and these effects were enhanced by ethanol self-administration. In addition, NNC cigarettes reduced craving and increased cognitive performance compared to VLNC cigarettes (Rose et al., 2004).

Conclusions

In sum, results of studies reviewed in this document provide little to no evidence that VLNC cigarettes result in differential effects on craving, withdrawal, smoking topography, or use behavior among representative vulnerable groups compared to the general population. Importantly, there is little to no evidence that VLNC cigarettes increase risk of adverse effects (e.g., exacerbations of psychiatric symptomatology) in smokers with symptoms of mental health disorders.

The FDA takes into consideration the impact that any tobacco product standard has on vulnerable populations, and so, this document aims to reflect the current literature focused on these groups and will provide updates to this information reflecting future publications. These updates could include additional reports on drug or alcohol dependent populations (with and without concomitant mental health disorders) and adolescents, as well as research on pregnant women, individuals with low socioeconomic status, and other vulnerable populations.

V. Justification for the Inclusion of all Combusted Products in a Nicotine Tobacco Product Standard

A. Who Uses Combusted Tobacco Products?

a. Cigarettes

In 2020, 1.6% of middle school students and 4.6% of high school students reported current use of cigarettes (smoked at least once during the past 30 days) (Wang et al., 2020). While cigarette smoking among adolescents and young adults has generally declined, this decline has slowed in recent years and there was no significant decrease between 2016 and 2017 (Wang et al., 2018). Cigarette smoking prevalence rates among adults have also declined in recent years (from 20.9% in 2005 to 15.1% in 2015). However, in 2015 the smoking prevalence rates among males, young adults, American Indian/Alaska Natives, those with low socioeconomic status, those in the Midwest, the uninsured, sexual minorities, and those with physical or mental disabilities, was higher than that of the general population (Jamal et al., 2016). For example, in 2015 40.6% of adults with serious psychological distress smoked cigarettes compared to 14.0% of those without serious psychological distress (Jamal et al., 2016). In addition to declines in the overall prevalence of smoking among adults, the number of daily smokers decreased from 36.5 million to 27.6 million between 2005 and 2015; and among daily smokers, average CPD decreased from 16.7 to 14.2 (p for trend <0.05) (Jamal et al., 2016). However, the number of smokers who smoked on some days increased from 8.7 million to 8.9 million between 2005 and 2015 (p for trend <0.05) (Jamal et al., 2016).

b. Cigars

Among high school students, the most commonly used forms of tobacco other than cigarettes are e-cigarettes (19.6%), cigars (5.0%), smokeless tobacco (3.1%), hookah (2.7%), heated tobacco products (1.4%), and pipe tobacco (0.7%) (Wang et al., 2020). In 2020, the rate of current cigar use (i.e., smoking on one or more of the past 30 days) among middle and high school students was 1.5% and 5.0% respectively. Among middle and high school students, reported use among males was 1.4% and 5.4%, respectively and among females was 1.6% and 4.7%, respectively (Wang et al., 2018; Wang et al., 2020). Moreover, cigars were the most commonly used tobacco product among non-Hispanic black high school students (7.8%) (Wang et al., 2018). Although cigar use has not changed significantly, with 5.0% of high school students reporting use in 2020, cigars remain the second most used tobacco product among high school students (Wang et al., 2020). While these data indicate a high burden of current cigar smoking, the true prevalence of cigar use is likely higher. Several studies have shown that youth tend to underreport cigar smoking if brand name identifiers are not provided (Nasim, Blank, Berry, & Eissenberg, 2012; Terchek, Larkin, Male, & Frank, 2009; Trapl et al., 2011). In one study of Virginia high school students, the reported prevalence of cigar use nearly doubled after accounting for students who reported smoking Black & Mild (a brand name of cigarillos); previously, the students had not acknowledged using cigars, cigarillos, or little cigars (Nasim et

al., 2012). Among adults, approximately 3.6% reported smoking cigars, cigarillos, or filtered little cigars "every day" or "some days," in 2019 with reported use higher among males (6.3%) than females (1.1%). The prevalence of cigar smoking is also higher among adults with poor mental health (6.3%), as compared to those with better mental health (3.3%) (Phillips et al., 2017).

c. Waterpipes

In 2020, 1.3% of middle school students and 2.7% of high school students smoked a waterpipe at least once in the past 30 days (Wang et al., 2018; Wang et al., 2020). Waterpipe or hookah tobacco smoking also appears to be increasing worldwide, especially among young adults (Maziak et al., 2015). In 2019, 1.0% of U.S. adults reported using regular pipes, waterpipes, or hookahs "every day" or "some days", and use was highest among younger adults (Cornelius et al., 2020). Wave 1 (2013 -2014) data from the Population Assessment of Tobacco and Health (PATH) study showed that 10.7% of young adults aged 18-24 smoked a waterpipe in the past month (Salloum et al., 2017). Another study analyzing the Wave 1 PATH data found that of the 16.4% of adults who reported ever smoking tobacco from a hookah, 58.6% were ages of 18-24 (Robinson, Wang, Jackson, Donaldson, & Ryant, 2018). While these data indicate a high burden of waterpipe smoking, epidemiological studies may underestimate rates of waterpipe smoking as many smokers do not believe that waterpipe smoking is a form of tobacco use (Creamer et al., 2016; Jawad & Millett, 2015). Waterpipe smoking is also highly correlated with use of other tobacco; approximately 70% of young adult waterpipe smokers are polytobacco users (Salloum et al., 2017).

d. Loose Tobacco

Loose tobacco use, such as that used in RYO tobacco or in pipes, appears relatively uncommon among youth. In 2020, the rate of current pipe tobacco use among middle and high school students was 0.4% and 0.7% respectively, which decreased significantly among high school but not middle school students compared to rates in 2016 (Wang et al., 2018; Wang et al., 2020). To our knowledge, no studies have characterized loose tobacco use among youth. Among adults, 1.0% endorsed current pipe, waterpipe, or hookah use (e.g., smoking on one or more of the past 30 days) in 2019 (Cornelius, Wang, Jamal, Loretan, & Neff, 2020; Kasza et al., 2017). However, these numbers likely underestimate the number of smokers who use pipe tobacco to roll their own cigarettes. Exclusive RYO users tend to be of low socioeconomic status, older and male; however, young adult smokers have also engaged in RYO use as a result of financial stress (Young et al., 2012). In all, the lack of data on RYO cigarette use and the

limitations in how national surveys assess loose tobacco use inhibit our ability to draw conclusions regarding appeal of loose tobacco among youth and adults.

e. Polytobacco Use

In 2020, 5.9% and 2.8% of middle and high school students (combined) used two or more tobacco products on at least one day in the past month (Gentzke et al., 2020). Among youth in 2014 who used tobacco in the past month, 43% used multiple products, with 71.4% of polytobacco users using cigarettes, 53.7% using e-cigarettes, and 46% using cigarillos (Kasza et al., 2017). Kasza et al. found that the most common combinations of products used were cigarettes plus e-cigarettes (accounting for 15.1% of multiple-product users) and cigarettes plus cigarillos (accounting for 10.1%). Among youths who used tobacco, 57.0% used one product, 23.7% used two products, and 19.3% used three or more products (Kasza et al., 2017).

In 2015, 3.9% of U.S. adults used two or more tobacco products in the past month, with males, low-income adults, sexual minorities, and those with disabilities or poor mental health most likely to be polytobacco users (Phillips et al., 2017). PATH Wave 1 data indicate that among adult tobacco users, the prevalence of polytobacco use was 37.8% in 2014, with 76.2% of polytobacco users using cigarettes and at least one other product (Kasza et al., 2017). The most common combination was cigarettes plus e-cigarettes (22.5%) (Kasza et al., 2017). Among adults who used tobacco, 62.2% used one product, 22.5% used two products, and 15.3% used three or more products (Kasza et al., 2017).

B. Abuse Potential of Non-Cigarette Combusted Tobacco Products

a. Cigars

A 1998 NCI Monograph chapter on cigar pharmacology and abuse potential cited more than 40 studies and concluded that the nicotine delivery characteristics and daily patterns of smoking among cigar smokers suggest a distinct potential for cigars to produce dependence (Baker et al., 2000; National Cancer Institute, 1998b). Since the publication of the NCI Monograph, several acute laboratory studies have provided additional evidence to suggest that cigar smoking is sufficient to create or sustain nicotine dependence among users. Through cigar smoke, nicotine can be absorbed by inhalation (like cigarettes) or through the oral mucosa (like smokeless tobacco). Multiple studies found that cigar smokers inhale (as evidenced by CO levels, topography) and plasma nicotine levels are similar to those of cigarette smokers (Blank, Cobb, Eissenberg, & Nasim, 2016; Blank, Nasim, Hart, & Eissenberg, 2011; Koszowski et al., 2015; Pickworth, Rosenberry, & Koszowski, 2017; Rosenberry, Pickworth, & Koszowski, 2016). Furthermore, using the Questionnaire of Smoking Urges, an established measure of tobacco craving, several studies found that cigars reduce craving and urge to smoke to a similar

magnitude as cigarettes (Koszowski et al., 2015; Pickworth et al., 2017; Rosenberry et al., 2016). Cigars have also been shown to decrease acute nicotine withdrawal symptoms (e.g., craving, anxiousness) (Blank et al., 2016). However, dual cigarette and cigar users rate cigarettes as more subjectively appealing (i.e., Duke Sensory Questionnaire Cigarette Evaluation Scale; Cigarette Evaluation Scale) compared to cigars (Koszowski et al., 2015; Pickworth et al., 2017).

Several additional studies have used epidemiological data to compare nicotine dependence levels among polytobacco users, exclusive cigarette smokers, and exclusive cigar smokers (Rostron, Schroeder, & Ambrose, 2016; Strong et al., 2015; Strong et al., 2017). The data show that a significant proportion of exclusive cigar users display characteristics of tobacco dependence such as craving (Rostron et al., 2016); however, polytobacco and exclusive cigarette smokers showed the highest levels of dependence, followed by exclusive cigar smokers (Rostron et al., 2016; Strong et al., 2015; Strong et al., 2017). None of the analyses distinguished between types of cigars, limiting data specificity and interpretation of dependence due to product differences in smoking topography and nicotine yield.

b. Waterpipes

Several acute laboratory studies have provided evidence to suggest that waterpipe smoking is sufficient to create or sustain nicotine dependence among users. Waterpipe users inhale (as evidenced by CO levels, topography), and plasma nicotine levels are elevated after use and are similar to or greater than those of cigarette smokers (Blank, Cobb, et al., 2011; Cobb, Sahmarani, Eissenberg, & Shihadeh, 2012; Cobb, Shihadeh, Weaver, & Eissenberg, 2011; Eissenberg & Shihadeh, 2009; Jacob et al., 2011, 2013; Maziak et al., 2011; Shafagoj, Mohammed, & Hadidi, 2002). In addition, cardiovascular functioning (e.g., heart rate) is altered after waterpipe use, suggesting that physiologically active doses of nicotine have been delivered (Blank, Cobb, et al., 2011; Eissenberg & Shihadeh, 2009; Jacob et al., 2013). Furthermore, waterpipe use significantly ameliorates abstinence-induced nicotine craving and withdrawal (Blank, Cobb, et al., 2011; Cobb et al., 2011; Maziak et al., 2009; Rastam et al., 2011), and several studies show these abstinence suppressing effects to be similar to those of cigarettes (Cobb et al., 2011; Rastam et al., 2011).

Several cross-sectional studies have accessed nicotine dependence symptoms among waterpipe users. A waterpipe-specific measure of dependence, the Lebanese Waterpipe Dependence Scale (LWDS-11), has been developed and used in the Eastern Mediterranean Region (Salameh, Waked, & Aoun, 2008). Higher levels of dependence, as assessed using this measure, were associated with increased frequency and duration of waterpipe sessions (Kassim, Al-Bakri, Al'Absi, & Croucher, 2014) and a more intensive smoking topography profile

(e.g., more puffs, longer puff duration, decreased time between puffs) (Alzoubi et al., 2013). A study to assess waterpipe dependence among U.S. youth and young adult populations found that approximately 50% of past-year users endorsed at least one marker of dependence (Sidani, Shensa, Shiffman, Switzer, & Primack, 2016).

c. Loose Tobacco

Laboratory studies have provided evidence to conclude that loose tobacco smoking is sufficient to create or sustain nicotine dependence among users. Studies show that RYO tobacco smokers inhale (as evidenced by smoking topography) (Koszowski, Rosenberry, Viray, Potts, & Pickworth, 2014; Shahab, West, & McNeill, 2008) and plasma nicotine levels are similar to those of smokers of factory-made cigarettes (Koszowski et al., 2014). Furthermore, RYO tobacco reduces craving and urge to smoke at a similar magnitude and is rated similarly with regard to subjective appeal as factory-made cigarettes (Koszowski et al., 2014).

d. Other Combusted Products

Acute laboratory studies show increases in heart rate, blood pressure and plasma nicotine levels after smoking bidis and kreteks that are similar to or greater than those of cigarette smokers (Malson, Lee, Moolchan, & Pickworth, 2002; Malson, Lee, Murty, Moolchan, & Pickworth, 2003). An epidemiological study that examined dependence symptoms among smokers of kreteks and bidis showed that after adjusting for differences in smoking frequency, smokers of bidis and kreteks may have an increased likelihood of nicotine dependence than smokers of conventional cigarettes (Huh & Timberlake, 2009).

C. Potential for Non-Cigarette Combusted Tobacco Product Switching

The foundation of FDA's comprehensive approach to nicotine regulation is that nicotine can be delivered through products that represent a continuum of risk, with combusted tobacco products at the most harmful end of this continuum (Gottlieb & Zeller, 2017). This approach strikes a balance between protecting public health by reducing combusted tobacco product use (and therefore reducing exposure to harmful toxicants created through combustion) while continuing to make potentially less harmful, non-combusted tobacco products available for tobacco users who still need or want them. It is FDA's expectation that once a nicotine product standard for combusted tobacco products is in place, a significant portion of combusted tobacco product smokers would choose to switch completely to a potentially less harmful nicotine delivery product to maintain their nicotine dose (National Academies of Sciences, 2018). Those who switch completely may sustain their nicotine dependence but would significantly reduce their risk of tobacco-related death and disease to the extent that the products they switch to result in less harm. That is, while dependence on any tobacco product

remains a health concern, particularly among youth, nicotine alone is not directly responsible for tobacco-related cancer, lung disease, and heart disease (Gottlieb & Zeller, 2017). Switching completely to a non-combusted tobacco product would reduce exposure to the chemical constituents created through combustion, which are the primary contributors of tobacco-related harm.

If a nicotine product standard were to apply to cigarettes only, it could have substantially less impact on improving public health outcomes for combusted tobacco product users. Specifically, FDA expects that, to maintain their nicotine dose, some number of addicted cigarette smokers would choose to migrate to other similar combusted products (or begin to engage in dual use with such other products) after the standard went into effect. FDA would also expect that users of non-cigarette combusted tobacco products would continue their existing use patterns. Together, both outcomes would reduce the benefits of the nicotine product standard.

a. Noncompliance

In clinical studies that investigated the effects of VLNC cigarettes, researchers typically instructed participants assigned to VLNC cigarette groups to use only study-provided cigarettes (i.e., to refrain from using usual brand cigarettes or other tobacco products during experimental conditions). Noncompliance with these instructions during a clinical trial may indicate the likelihood VLNC cigarette smokers would use alternative combusted nicotine-containing products if a nicotine standard were implemented (e.g., NNC little cigars or cigarettes available through illicit trade).

Studies that gradually reduced the nicotine content of cigarettes showed that noncompliance is high once participants reach the VLNC cigarette phase of the intervention (e.g., Benowitz, Nardone, Hatsukami, et al., 2015; Hammond & O'Connor, 2014; Smith, Donny, et al., 2019). For example, a within-subject, unblinded study wherein participants received three gradually reduced nicotine content cigarettes (i.e., NNC, LNC, and VLNC cigarettes) over the course of 3 weeks found that significantly more participants self-reported smoking at least one usual brand cigarette during the VLNC cigarette phase (44%) relative to the LNC cigarette phase (31%) and the NNC cigarette phase (28%) (Hammond & O'Connor, 2014). A secondary analysis of two gradual reduction studies in smokers with mood or anxiety disorders found that 36 - 42% of participants were biochemically confirmed to be noncompliant at the end of the 18-week studies (Foulds et al., 2018). Notably, a secondary analysis of a study that compared gradual reduction and immediate reduction (Hatsukami et al., 2018) found that participants assigned to the immediate reduction group had higher rates of noncompliance than those

assigned to the gradual reduction group (Smith, Donny, et al., 2019). Noncompliance may occur when participants immediately switch to reduced nicotine content cigarettes, regardless of the amount of nicotine in the reduced nicotine content cigarettes (e.g., LNC or VLNC cigarettes). However, noncompliance appears to be higher when smokers switch to lower nicotine content cigarettes. For example, Hatsukami and colleagues (2013) randomized 36 participants to receive VLNC, LNC, or NNC cigarettes for one week. Participants kept a daily diary of all experimental and usual brand cigarettes smoked. Participants in the NNC cigarette group smoked significantly more experimental cigarettes during the study than participants in the VLNC cigarette group. Noncompliance with study-assigned cigarettes was observed in all groups, such that 38% (n = 5), 36% (n = 4) and 17% (n = 2) of participants in the VLNC, LNC, and NNC cigarette groups, respectively, smoked at least one usual brand cigarette during the experimental week. These results are consistent with the largest analysis of VLNC cigarette noncompliance in a study that immediately switched participants to reduced nicotine content cigarettes (Nardone et al., 2016). This study showed that 39% of participants self-reported noncompliance during the last week of a 6-week intervention (Nardone et al., 2016). However, biochemical methods that were used to assess noncompliance suggested 75 - 78% of participants may have been noncompliant with VLNC cigarettes. Notably, 57% of participants assigned to the NNC cigarette group reported noncompliance at some point during the study, suggesting difficulty with "brand-switching" regardless of nicotine content. Results from this study also showed higher rates of noncompliance among younger smokers, those less satisfied with VLNC cigarettes, and those with higher nicotine dependence scores (Nardone et al., 2016).

Two studies co-administered NRT while manipulating the amount of nicotine that participants were exposed to from their cigarettes. In one study, all participants were assigned transdermal nicotine patches, and participants were assigned to either a gradual nicotine reduction group (i.e., the nicotine content of their cigarettes decreased during the study) or a CPD reduction group (i.e., the number of their CPD decreased during the study). Participants in the CPD reduction group used more non-study cigarettes than did participants in the nicotine reduction group (Klemperer, Hughes, Callas, et al., 2019). In another study, participants were assigned to either an NNC cigarette group or a VLNC cigarette group, and all participants were also assigned to receive NRT (in the form of a transdermal patch) or not receive NRT. Participants assigned to receive VLNC cigarettes, with or without NRT, were more likely to use non-study cigarettes than participants assigned to receive NNC cigarettes (Smith et al., 2019).

Importantly, noncompliance with VLNC cigarettes does not appear to increase overall exposure to tobacco smoke when biomarkers of exposure are compared between control and VLNC cigarette conditions (see Sections IV.B.b.v and IV.C.a: *Biomarkers of Exposure* and

Compensatory Smoking). In addition, compliance may improve over time. For example, Hatsukami and colleagues (2013) found improvements in compliance after 6 weeks of VLNC cigarette use compared to compliance at week 1.

Notably, NRT may improve compliance by reducing rates of usual brand cigarette smoking (e.g., Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2017); however, findings from one study are mixed (Smith, Koopmeiners, et al., 2019). In the context of a smoking cessation study utilizing VLNC and LNC cigarettes, Hatsukami and colleagues (2013) found the highest rates of usual brand cigarette use among participants assigned to NRT alone (43%), followed by VLNC/LNC cigarettes alone (33%), and then among participants assigned to a combination of VLNC/LNC cigarettes plus NRT (14%). Similarly, when provided the opportunity to use alternative nicotine and tobacco products in addition to LNC cigarettes, no differences were observed between LNC and NNC cigarette groups in the number of usual brand cigarettes smoked (Hatsukami et al., 2017). Conversely, one study found that use of VLNC cigarettes along with nicotine patch did not significantly reduce rates of noncompliance (i.e., usual brand cigarette smoking) compared with use of VLNC cigarettes alone (Smith, Koopmeiners, et al., 2019).

Conclusions

Several studies reviewed in this document assessed biochemical or self-reported measures of VLNC cigarette noncompliance. These studies have shown high levels of noncompliance with VLNC cigarettes, suggesting that VLNC cigarettes have lower appeal and abuse potential compared to NNC cigarettes. In addition, these findings suggest that VLNC cigarette smokers are likely to use alternative combusted nicotine-containing products if such products are concurrently available. Notably, evidence suggests that providing NRT to VLNC cigarette smokers may reduce rates of alternative combusted tobacco use.

b. Tobacco Product Switching in Clinical Studies

To our knowledge, only one study has directly quantified alternative tobacco product use in the context of an extended exposure VLNC cigarette study. Hatsukami and colleagues (2017) conducted a study to compare the use of alternative tobacco products and smoking behavior in 136 smokers unwilling to quit. Participants were randomly assigned to one of three conditions and instructed to use only study-assigned tobacco products for 8 weeks. The “LNC1” group received LNC cigarettes combined with non-combusted tobacco products (i.e., smokeless tobacco, ENDS, NRT) and combusted non-cigarette tobacco products (i.e., cigars, cigarillos), the “LNC2” group received LNC cigarettes combined with only non-combusted tobacco products, and the NNC cigarette group received NNC cigarettes combined with non-combusted and

combusted non-cigarette products. Participants who received LNC cigarettes used more alternative combusted and non-combusted tobacco products. However, these participants also smoked fewer total combusted tobacco products and had more quit attempts. Furthermore, tobacco toxicant levels in participants who received LNC cigarettes and only non-combusted products were significantly lower than those of participants who received NNC cigarettes, while toxicant levels in those who received LNC cigarettes and had access to both combusted and non-combusted products did not differ from the NNC cigarette group (Hatsukami et al., 2017).

Another clinical trial of LNC cigarettes examined alternative tobacco product use in participants who were non-daily smokers. Among participants who were not e-cigarette users at baseline, new use of e-cigarettes was significantly higher during the study in the LNC cigarette group compared to the NNC cigarette group (Shiffman, Kurland, et al., 2018).

c. Cigarette Price Increases

Studies investigating the effects of cigarette taxation on product substitution may also be used as an indicator of potential product switching in response to a reduced nicotine standard for cigarettes, because reducing the nicotine content of cigarettes reduces their reinforcing efficacy (Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017) and is functionally similar to increasing their price (Smith, Sved, Hatsukami, & Donny, 2014). Taxation and price increases, some of the most effective tobacco control policies, are associated with significant declines in overall tobacco consumption as well as reductions in youth initiation rates (Chaloupka, Straif, & Leon, 2011). However, taxation and price increases are also associated with a range of tax avoidance behaviors such as substitution with a cheaper product, purchasing from low or untaxed sources, or purchasing in bulk (Betzner, Boyle, & St Claire, 2016), and this behavior is more likely to occur among smokers of lower socioeconomic status (Licht et al., 2011).

Delnevo and colleagues (2004) used epidemiological data from New Jersey's 2001 and 2002 Adult Tobacco Survey (NJATS) to determine whether cigarette smokers switched to cigars following an increase in the state cigarette excise tax (US $0.80 to US $1.50 per pack). In 2001, the cigarette smoking prevalence rate in New Jersey was 22.1%. Following a large cigarette excise tax increase, cigarette prevalence rates decreased to 18%. There were no significant differences in cigar smoking prevalence rates between 2001 and 2002; however, ever cigar use increased significantly for current smokers and increased slightly for recent quitters. In 2001, current cigarette smokers had the highest rate of current cigar use (13.9%), while recent quitters of cigarettes had the lowest rate (2.6%). In contrast, in 2002, while current cigarette smokers again reported the highest rate of current cigar use (13.2%), recent cigarette quitters

had the second highest rate of current cigar use (11.1%). The authors concluded that after a cigarette excise tax increase, a small but notable proportion of recently quit cigarette smokers tried cigars, substituted cigars for cigarettes, or remained combusted tobacco users in the form of cigars (Delnevo et al., 2004). Additional indirect evidence assessing trends in internet searches following the 2009 U.S. federal tobacco tax increase showed that after the tax was announced, search queries increased for both combusted and non-combusted non-cigarette tobacco products (Jo et al., 2015).

Similarly, several studies assessed changes in loose tobacco sales following a large tax increase in RYO tobacco and found decreases in RYO tobacco sales and increases in pipe tobacco sales as soon as the tax rate changed (Agaku & Alpert, 2016; Morris & Tynan, 2012; Tynan, Morris, & Weston, 2015; Wang, Kenemer, Tynan, Singh, & King, 2016). Wang and colleagues (2016) analyzed publicly available federal excise tax data from 2000–2015 and found that total RYO tobacco sales significantly decreased by 70.0%; however, total pipe tobacco sales increased by 556.4%. Agaku and colleagues (2016) found similar trends in pipe tobacco sales using federal excise tax data; however, self-reported pipe tobacco use, assessed via the National Survey on Drug Use and Health, remained consistent, and RYO consumption increased. The authors speculated that individuals may have purchased pipe tobacco that had been relabeled as "dual use or multi-use" to use as RYO tobacco (Agaku & Alpert, 2016). These data suggest that following the implementation of a tobacco control policy, manufacturers may modify their products and a significant proportion of consumers may modify their behavior to adapt to the changes, blunting the intended effect of the policy.

d. Behavioral Economics Data

Behavioral economics utilizes principles of psychology and economics to predict purchasing behavior as a function of different market constraints (Hursh, 1984). Several studies have used real or hypothetical data to investigate the impact of a change in price or availability of a given tobacco product on subsequent purchasing or use of another tobacco product. Purchasing behaviors observed in behavioral economics studies have been shown to be concordant with tobacco consumption and real purchase estimates (MacKillop et al., 2008; Smith et al., 2017; Wilson, Franck, Koffarnus, & Bickel, 2016).

Several studies used retail sales data to investigate tobacco substitution as a function of price (Gammon et al., 2016; Huang et al., 2018; Zheng, Zhen, Dench, & Nonnemaker, 2017). Gammon and colleagues (2016) investigated relationships between purchasing patterns and price of cigarettes and little cigars. In 2013, a pack of little cigars was approximately 32-37% cheaper than a pack of cigarettes. A 10% increase in the price of little cigars was associated with

a 31.7% decrease in per capita little cigar sales, while a 10% increase in the price of cigarettes was associated with a 27.3% increase in per capita little cigar sales. The authors concluded that smokers are price sensitive and avoided the higher cost of cigarettes by switching to little cigars (Gammon et al., 2016). Zheng and colleagues (2017) conducted an analysis to estimate demand for cigarettes, little cigars/cigarillos, large cigars, e-cigarettes, smokeless tobacco, and loose tobacco using Nielsen's Convenience Track retail scanner database. They found that e-cigarettes substituted for cigarettes, wherein a 10% increase in the price of cigarettes resulted in an 18.6% increase in e-cigarette demand. Large cigars, smokeless tobacco, and loose smoking tobacco were not associated with increased use in response to increasing cigarette prices (Zheng et al., 2017). Huang and colleagues (2018) also used Nielsen data to examine demand for various tobacco products and found that little cigars, RYO tobacco, and pipe tobacco each serve as substitutes for cigarettes.

Studies have also used hypothetical purchase tasks to investigate smokers' responses to tobacco policy changes or price increases (Heckman et al., 2017; Quisenberry, Koffarnus, Hatz, Epstein, & Bickel, 2016). Quisenberry and colleagues (2016) used a simulated tobacco marketplace to measure purchasing behaviors in cigarette smokers. Participants could purchase cigarettes, e-cigarettes, cigarillos, gum, dip, lozenges, and snus. When cigarette price increased, cigarillo and e-cigarette purchasing increased. However, the substitution was only statistically significant for e-cigarettes but not cigarillos. Heckman and colleagues (2017) conducted a study in the Netherlands utilizing a similar hypothetical tobacco marketplace to investigate hypothetical purchases for VLNC cigarettes as a function of varying scenarios. Most relevant was the scenario where participants made hypothetical purchases for VLNC cigarettes, e-cigarettes and NRT in a marketplace where NNC cigarettes were unavailable. VLNC cigarettes had the highest rate of purchase, followed by e-cigarettes, and then NRT. Approximately 20% of participants reported that they would not purchase any of the products if NNC cigarettes were unavailable.

Conclusions

In all, the available evidence suggests that cigarette smokers are willing to shift consumption toward non-cigarette tobacco products in times of economic or product constraint. However, the proportion of smokers who would shift consumption toward combusted versus non-combusted products remains largely unknown. Of additional concern is the potential for increased use of combusted non-cigarette tobacco product substitution among vulnerable populations, who are more likely to engage in tax avoidance behaviors compared to those of higher socioeconomic status (Licht et al., 2011).

VI. Potential Public Health Benefits of Preventing Initiation to Regular Use and Increasing Cessation

This section briefly describes the potential public health benefits that could result from the increased cessation and decreased initiation to regular use that FDA expects could occur if cigarettes and other combusted tobacco products were minimally addictive. It also references findings from a population-based simulation model that quantified the potential public health impact of enacting a regulation lowering nicotine levels in cigarettes and some other combusted tobacco products to minimally addictive levels, utilizing inputs derived from empirical evidence and expert opinion.

A. Smoking Cessation Would Lead to Substantial Public Health Benefits for People of All Ages

Significant declines in mortality caused by combusted tobacco product use can be achieved by reducing the prevalence of smoking cigarettes and other combusted tobacco products. Smoking cessation has major and immediate health benefits for men and women of all ages, regardless of health status (U.S. Department of Health and Human Services, 1990 at p. i). Smoking cessation decreases the risk of adverse health consequences, and former smokers live longer than continuing smokers. For example, persons who quit smoking before age 50 have one-half the risk of dying in the next 15 years compared with continuing smokers (U.S. Department of Health and Human Services, 1990, p. v).

Smoking cessation reduces the risk of cancers throughout the body (U.S. Department of Health and Human Services, 1990). For example, although the risk of dying from lung cancer is 22 times higher for male smokers than male nonsmokers (and 12 times higher for female smokers than female nonsmokers), the risk of lung cancer after 10 years of abstinence is 30 to 50 percent that of continuing smokers (Centers for Disease Control and Prevention, 2017a; U.S. Department of Health and Human Services, 1990; World Health Organization).

Smoking cessation also reduces the risk of other life-threatening illnesses that occur in smokers. In addition to reducing the risk of cancers and the mortality rates of smoking-related diseases, smoking cessation substantially reduces the risk of other dangerous diseases that can lead to death or disability and cause a financial strain on health care resources. For example, smoking cessation substantially reduces the risk of peripheral artery occlusive disease, which can cause complications that lead to loss of limbs (U.S. Department of Health and Human Services, 1990). Former smokers also have half the excess risk of experiencing an abdominal aortic aneurysm compared to current smokers (U.S. Department of Health and Human Services, 1990). Cigarette smoking also complicates many diseases (e.g., smokers with diabetes have

higher risk of complications, including heart and kidney disease, poor blood flow in the legs and feet, retinopathy and peripheral neuropathy), and smoking cessation can alleviate those complications as well (U.S. Department of Health and Human Services, 2010).

Youth and young adults would experience the greatest benefits from a nicotine tobacco product standard, because many of them may not progress beyond experimentation and, therefore, may not experience dangerous and deadly tobacco-related health effects. Fetuses and children would also benefit if their parents quit smoking, given the negative health consequences to the fetus of a smoking mother and the dangers of secondhand smoke. In addition, children of parents who smoke, when compared with children of nonsmoking parents, have an increased frequency of respiratory infections like pneumonia and bronchitis (U.S. Department of Health and Human Services, 1990). Smoking cessation reduces the rates of these respiratory symptoms and infections (U.S. Department of Health and Human Services, 2004 at p.467). Children exposed to tobacco smoke in the home also are more likely to develop acute otitis media (middle ear infections) and persistent middle ear effusions (thick or sticky fluid behind the eardrum) (U.S. Department of Health and Human Services, 1990). If parents were more able to quit because these products become minimally addictive, the incidence of these health problems among youth would be expected to decline.

Although the health benefits are greater for people who stop smoking at earlier ages (U.S. Department of Health and Human Services, 1990, 2004), researchers estimate that smokers can gain years of additional life expectancy no matter when they quit (Jha et al., 2013). In addition, scientists using data from the Cancer Prevention Study (CPS-II), but accounting for bias caused by smoking cessation after baseline, found that even smokers who quit at age 65 had an expected life expectancy increase of 2 years for men and 3.7 years for women (Taylor, Hasselblad, Henley, Thun, & Sloan, 2002).

The benefits continue for those who remain smoke free. At year one, an individual's added risk of coronary heart disease becomes half that of a smoker's (Centers for Disease Control and Prevention, 2017a). Between 2 and 5 years after cessation, an individual's stroke risk is reduced to that of a nonsmoker (Centers for Disease Control and Prevention, 2017a). In addition, a former smoker's risk of cancers of the mouth, throat, esophagus, and bladder is halved within 5 years (Centers for Disease Control and Prevention, 2017a). By 10-years post cessation, an individual's risk of cancers of the kidney and pancreas decreases (Centers for Disease Control and Prevention, 2017a). The risk of coronary heart disease becomes that of a nonsmoker after 15 years of abstinence (Centers for Disease Control and Prevention, 2017a).

B. A Nicotine Tobacco Product Standard Could Lead to Substantial Improvement in Public Health

As stated throughout this document, nicotine at levels currently found in tobacco products is highly addictive, and addiction to nicotine is the "fundamental reason that individuals persist in using tobacco products" (U.S. Department of Health and Human Services, 2010 at p. 105). Although nicotine itself is not the direct cause of most tobacco-attributable disease, addiction to the nicotine in tobacco products is the proximate cause of these conditions because it sustains tobacco use (Benowitz, 2010; Henningfield et al., 1998). Addiction caused by nicotine in tobacco is critical in the transition of smokers from experimentation to sustained smoking and in the maintenance of smoking for those who want to quit (U.S. Department of Health and Human Services, 2010; 2014 at p.113). As a result, FDA expects that making cigarettes minimally addictive would reduce tobacco-related harms by promoting smoking cessation or complete migration to alternative, potentially less harmful non-combusted products and by reducing initiation. In this section, we summarize the approach used to describe the possible impact of a potential nicotine tobacco product standard to the population as a whole and present the findings of this analysis.

To assess the impact of one potential option that might maximize the potential public health impact, FDA considered a simulation model by Apelberg and colleagues (Apelberg et al., 2018) of a policy scenario in which the scope of a potential product standard restricted the nicotine level in cigarettes, cigarette tobacco, RYO tobacco, cigars (including little cigars, large cigars, and cigarillos, but not so-called "premium" cigars), and pipe tobacco (other than waterpipe/hookah tobacco). As part of a formal expert elicitation process, eight subject matter experts were asked to provide their individual estimates of the anticipated impacts of a hypothetical policy (setting a "maximum limit on the amount of nicotine in cigarette tobacco filler" for the purpose of reducing nicotine in cigarettes "to minimally addictive levels") and to develop subjective probability distributions for parameters of interest.

A more detailed description of the methodology, data sources and inputs, and results from this analysis can be found in two peer-reviewed publications (Apelberg et al., 2018; Vugrin et al., 2015).

a. Approach to Estimating Impacts to the Population as a Whole

As described in this document, FDA expects that making cigarettes minimally addictive would impact currently addicted smokers by increasing their ability to quit smoking or switch to other non-combusted tobacco products and affect nonsmokers by reducing the likelihood that they would become established and addicted smokers. Apelberg et al. (2018) updated a

previously published discrete system dynamic population model to compare projected outcomes for a status-quo scenario, in which no regulation limiting the maximum nicotine level in cigarettes or other combusted tobacco products is implemented, with outcomes for a policy scenario, in which a hypothetical regulation lowering nicotine in cigarettes and selected other combusted tobacco products to a minimally addictive level is implemented[10] (Apelberg et al., 2018).

Based on estimates of subject matter experts, the model incorporated the following tobacco use transitions to estimate the impact of the policy: (1) cigarette smoking cessation; (2) cigarette smokers switching to non-combusted tobacco products (e.g., smokeless tobacco and/or e-cigarettes) rather than quitting tobacco use entirely; (3) continuing smokers becoming dual users of cigarettes and non-combusted tobacco products; (4) nonsmokers initiating regular cigarette smoking; and (5) nonsmokers who have been dissuaded from smoking cigarettes and certain other combusted tobacco products, who may instead initiate use of a non-combusted tobacco product. The model, based on input parameters derived from expert estimates, projected the impact of the policy on four main outcomes: (1) prevalence of cigarette smoking and non-combusted tobacco product use; (2) number of individuals dissuaded from cigarette smoking; (3) cumulative number of tobacco-attributable deaths avoided; and (4) cumulative life-years gained as a result of a regulation setting a maximum nicotine level.

The methodology implemented in this analysis has been detailed elsewhere (Apelberg et al., 2018; Vugrin et al., 2015). Briefly, the simulation begins with an initial population that reflects the sex, age, and tobacco use distribution (i.e., never, current, and former use of cigarettes and non-combusted products) of the U.S. population in 2015, based on U.S. Census Bureau estimates. The analysis projects population changes for 2016-2100 in 1-year increments, while accounting for births, net migration (which accounts for immigration and emigration) and deaths, the last of which is a function of age, sex, and tobacco use status. Baseline estimates for tobacco use status (combinations of current, former, and never use for cigarettes and non-combusted products) by sex, age, and time since cessation (for cigarettes only) were obtained from the 2015 National Health Interview Survey (NHIS) for adults (National Center for Health Statistics) and the 2015 NYTS for youth (Centers for Disease Control and Prevention, 2017b). Mortality rates and relative risks by tobacco use status were obtained from

[10] The policy scenario presented in Apelberg et al. 2018 (Apelberg et al., 2018) did not define a specific level of nicotine as minimally addictive. Rather, the policy scenario simulated implementation of a hypothetical standard in which cigarettes and certain other combusted tobacco products were made minimally addictive, informed by a formal expert elicitation process (Apelberg et al., 2018), used to estimate the impact of decreasing the addictiveness of cigarettes on certain tobacco use behaviors.

U.S. vital statistics data, NHIS data linked for mortality follow-up (for never smoker mortality rates and cigarette smoking relative risks), and the CPS-II (for smokeless tobacco product relative risks). In the absence of data on the long-term health risks of e-cigarettes, Apelberg et al. assumed that the e-cigarettes products carried the same risks associated with traditional smokeless tobacco (Apelberg et al., 2018).

Quantitative inputs for rates of post-policy smoking cessation, switching, and dual use in the hypothetical policy scenario were obtained through a formal expert elicitation process. The methodology used to identify experts, develop the protocol, conduct the elicitation, and summarize the findings has been described in detail elsewhere (Apelberg et al., 2018 at Appendix). Briefly, elicitation candidates with expertise in tobacco science and policy were identified, ranked, and recruited in accordance with a pre-specified protocol, based on publication history and accounting for potential conflicts of interest. Candidates were required to self-certify that they were free of any actual, apparent, or potential conflicts of interests. The elicitation process centered around three online conferencing sessions held during January and February 2015, following a written protocol designed to elicit opinions using a structured, standardized approach. Briefing books with key papers on the topics of interest as well as background data on tobacco use and policy were provided to a panel of eight experts prior to the conference sessions. Experts were asked to identify any other relevant information to share with the panel. Detailed written questionnaires were completed by each expert as independent take-home exercises. To maintain the independence of the experts and encourage open discussion, involvement of FDA staff was limited.

To explore the potential impact of a product standard that would maximally benefit population health, the experts were asked to assume that combusted tobacco products that could be viewed as highly likely to serve as substitutes for traditional cigarettes (i.e., RYO tobacco, pipe tobacco, nonpremium cigars) would be included in the policy, while other tobacco products (i.e., premium cigars, waterpipe/hookah, e-cigarettes, smokeless tobacco) would be excluded.[11] The eight experts were asked to predict and quantify the anticipated impact of the policy on the following model parameters: cigarette smoking cessation rates; switching from cigarette smoking to other tobacco products excluded from the hypothetical policy scenario; dual use rates; cigarette smoking initiation rates; and initiation rates for other tobacco products excluded from the hypothetical policy scenario. Each of the eight experts was

[11] While the policy scenario presented in Apelberg et al. (Apelberg et al., 2018) is based on reduction in nicotine level in cigarettes, cigarette tobacco, RYO tobacco, certain cigars and pipe tobacco, the estimated population impact is based on reductions in cigarette smoking. FDA notes that not accounting for reductions in the use of other combusted tobacco products may underestimate the overall impact of this policy scenario.

asked to provide his or her best estimate of the parameters' true value, estimates of the minimum and maximum plausible values, and estimates of the 5th, 25th, 75th and 95th percentile values. Experts were asked first about impacts in the first year immediately following the potential product standard's implementation and then about the impacts in the years following the first full year of implementation. Experts had the option of providing separate estimates of impacts for males and females for the initial and subsequent years. For each question, experts were asked to provide the factors they considered pertinent to answering the question, including the studies and research findings most influential to informing their views, and to rate their familiarity with the relevant literature. The elicitation process provided the experts with opportunities to interact and discuss divergent views, from which each expert generated his/her initial and final estimates.

The eight experts' judgments about the potential values of these parameters are published in Apelberg et al. (2018). While parameter estimates and their probability distributions varied somewhat among participants, most experts had the view that making cigarettes and certain other combusted tobacco products minimally addictive would lead to substantial initial and long-term increases in smoking cessation among cigarette smokers and decreased initiation among nonsmokers. Distributions provided by the eight experts' parameter estimates fell within a broad range. For example, for both male and female non-smokers, the median minimum and maximum estimates from the eight experts on the "percent of reduction in annual smoking initiation rates" after the first year in response to the policy ranged from 10.0% to 90.0%. For both male and female smokers, the median minimum and maximum estimates from the eight experts on the "percent of current smokers who quit smoking as a result of the policy" within the first year after policy implementation ranged from 4.0% to 50.0%.

To account for uncertainty associated with the expected impact of the policy scenario, Apelberg et al. (2018) used the distributions of the experts' estimates in a Monte Carlo simulation. A Latin Hypercube sampling with 1,000 sample values was performed for each of the expert's response distributions. For each simulation, the policy scenario was compared to the baseline scenario to estimate changes in the outcomes described above. A summary of distribution responses is provided in Apelberg et al. (2018).

b. Projected Impacts to Users, Nonusers, and the Population as a Whole

Using the experts' input estimates for the parameters described previously, and assuming that the hypothetical policy (i.e., product standard) is implemented in 2020, the simulation model projected that cigarette smoking prevalence declines substantially after the

first year of implementation of the hypothetical policy scenario to a median value of 10.8 percent compared with 12.8 percent in the baseline scenario (Apelberg et al., 2018 at Figure 1). In subsequent years, the model projects that the difference in cigarette smoking prevalence between the scenarios continues to grow due to the experts' estimates of sustained increases in cessation and decreases in initiation following policy implementation. The projected smoking prevalence drops to a median value of 1.4 percent (5^{th} and 95^{th} percentile projections range from 0.2 percent to 5.9 percent) under the policy scenario by 2060 compared to 7.9 percent under the baseline. Smoking prevalence estimates for the year 2100 are comparable to those for 2060.

Concurrent with a projected reduction in cigarette smoking is a projected increase in non-combusted product use. Adult non-combusted tobacco product use is higher in the hypothetical policy scenario compared to the baseline scenario within the first year of policy implementation, due to estimated increases in switching from cigarette smoking and transitions to dual cigarette and non-combusted product use. The prevalence of non-combusted tobacco product use remains higher in the policy scenario over time due to the experts' predictions that there would be both increased uptake among smokers (through either complete switching or dual use) and increased initiation due to some dissuaded cigarette initiators taking up non-combusted products instead.

Table 2 provides a projection of the number of individuals who would not become cigarette smokers over time as a result of the hypothetical policy scenario. Since it is assumed, based on expert input, that there would be a sustained decrease in cigarette smoking initiation rates, the model projects that the cumulative number of dissuaded smoking initiates continues to increase over time. By 2100, the median estimate from the model, based on the experts' estimates of potential initiation rates after policy implementation, is that more than 33 million youth and young adults who would have otherwise initiated regular smoking would not start (5^{th} and 95^{th} percentile projections range from 8.0 million to 64.1 million).

Using the eight experts' estimates for the percentage of current smokers who would quit smoking after policy implementation (estimates ranged from 4.0% to 50.0% of smokers), over 5 million additional smokers are estimated to quit smoking within one year after implementation (5^{th} and 95^{th} percentile projections range from 110,000 to 19.7 million), compared to the baseline scenario. The number of additional smokers quitting would increase by nearly 13 million within 5 years after policy implementation (5^{th} and 95^{th} percentile projections range from 430,000 to 30.5 million), compared to the baseline scenario.

Table 2. Projected Number of Individuals Who Would Not Initiate Regular Smoking as a Result of a Hypothetical Nicotine Tobacco Product Standard Implemented in 2020

	Cumulative New Smoking Initiates Avoided (in millions)		
Year	5th percentile	Median	95th percentile
2040	2.0	8.1	15.6
2060	3.9	16.0	31.0
2080	5.9	24.4	47.2
2100	8.0	33.1	64.1

Table 3 presents the estimated cumulative number of tobacco-attributable deaths potentially avoided and life-years gained due to the experts' determination that smoking rates would decrease as a result of policy implementation. By 2060, it is estimated that a median value of almost 3 million deaths due to tobacco would be avoided (5^{th} and 95^{th} percentile projections range from 0.7 million to 4.3 million), rising to 8.5 million by the end of the century (5^{th} and 95^{th} percentile projections range from 2.2 million to 11.2 million). The reduction in premature deaths attributable to the hypothetical policy scenario would result in approximately 33 million life-years gained by 2060 (5^{th} and 95^{th} percentile projections range from 7.8 million to 53.9 million) and over 134 million life-years gained by 2100 (5^{th} and 95^{th} percentile projections range from 31.6 million to 183.0 million).

Table 3.--Projected Number of Tobacco-Attributable Deaths Avoided and Life-Years Gained Due to Reduced Smoking as a Result of a Hypothetical Nicotine Tobacco Product Standard Implemented in 2020

	Cumulative Tobacco Attributable Deaths Avoided (Millions)			Cumulative Life-Years Gained (Millions)		
Year	5th Percentile	Median	95th Percentile	5th Percentile	Median	95th Percentile
2040	0.3	0.9	1.4	2.5	6.8	11.5
2060	0.7	2.8	4.3	7.8	33.1	53.9
2080	1.3	5.6	7.9	16.5	79.6	118.0
2100	2.2	8.5	11.2	31.6	134.4	183.0

Conclusions

In sum, given that research studies cannot easily replicate the condition of a nationally-enforced restriction on nicotine to minimally addictive levels in cigarettes, FDA sought expert opinion through an established elicitation process to provide the best estimates for the

potential values and associated ranges of the likely impact of a hypothetical reduction in cigarettes' nicotine content (to be achieved by a potential product standard) on tobacco use behaviors. Based on the experts' judgments that reducing nicotine levels in combusted tobacco products would increase smoking cessation and decrease smoking initiation, and calculations from the simulation model describing the potential impact of reducing nicotine to minimally addictive levels in cigarettes and selected other combusted tobacco products, FDA anticipates a significant public health benefit to the United States. This hypothesis is based on the assumption that the reduction in nicotine levels in combusted tobacco products would create substantial reductions in smoking prevalence due to increased smoking cessation and reduced initiation of regular smoking.

While the simulation model projections of the potential impact from reducing nicotine to minimally addictive levels in cigarettes suggest a significant public health benefit to the United States resulting from substantial reductions in smoking prevalence, the analysis does not address certain potential added benefits. First, the model does not account for increased quality of life from decreased tobacco-related morbidity, nor does it account for cost savings from medical care averted. Second, the analysis does not account for the public health impact of reduced secondhand smoke exposure. Third, the analysis does not account for reductions in harm caused by smoking-related fires. Fourth, it does not account for the potential impact on population health from use of the other combusted products (e.g., cigars, pipes) if the assumed rule were to cover such products. Finally, these projections do not assess whether there could be potential health benefits associated with smokers cutting down on the number of cigarettes smoked as a result of the standard.

VII. The Impact Perceptions Around Nicotine and Reduced Nicotine May Have on a Proposed Nicotine Standard

In order to inform regulatory efforts related to a nicotine standard for combusted tobacco products, FDA reviewed social science literature relevant to consumer knowledge, attitudes, perceptions, beliefs, and planned behavior regarding reduced nicotine tobacco products (a full description of the methods used can be found in Appendix B). This review revealed strong, consistent evidence that a substantial majority of US adults believe that nicotine is carcinogenic and is a main cause of smoking-related disease despite data to the contrary in the scientific literature. This review also revealed strong, consistent evidence that a substantial majority of US adults believe that nicotine is the substance in cigarettes that maintains addiction. This review also revealed that a majority of US adults believe that reduced nicotine cigarettes are less harmful to health compared to NNC cigarettes. This review also revealed strong evidence that a significant minority (25%-35%) of US adults believe reduced

nicotine content (RNC) cigarettes[12]are safer than NNC cigarettes and a substantial minority of US adults believe that RNC cigarettes are less addictive than NNC cigarettes. In addition to the findings about consumer perceptions of nicotine, RNC cigarettes, and a low nicotine product standard, this review found evidence that there are effective messaging strategies that can be used to improve consumer understanding of nicotine and a proposed low nicotine product standard. The results of this literature review may help to inform and improve public communication efforts around a reduced nicotine standard.

A. Consumer Knowledge, Attitudes, Beliefs, or Perceptions About Nicotine

Twenty-seven studies examined consumer knowledge, attitudes, perceptions, or beliefs regarding nicotine, but not within the specific context of RNC cigarettes. These studies provide strong evidence that the majority of US adults incorrectly believe nicotine causes cancer and is directly harmful to health. Additionally, there is strong evidence that the majority of US adults believe nicotine is addictive. Across nationally representative studies, there was strong evidence that incorrect perceptions about nicotine harm vary by gender (females have more incorrect beliefs about nicotine harm than males), ethnicity (black and Hispanic individuals have more misperceptions than white individuals), education (people with fewer years of education have more misperceptions than those who have more years of education), age (older adults have more misperceptions about nicotine than younger adults), and tobacco use status (people who do not use tobacco have more misperceptions about nicotine than those who use tobacco, especially ENDS).

a. Studies Examining Knowledge, Attitudes, Beliefs, or Perceptions About the Harms of Nicotine

In studies examining nicotine harm beliefs in the general population, the belief that nicotine causes cancer was endorsed by 40% to 78% of participants (Cummings 2004b; Denlinger-Apte et al. 2021; Jackson et al. 2022; Peterson et al., 2022; Snell et al. 2022). Some studies examined rates of endorsement for this misperception in different tobacco user populations; these studies found that around 46% of current ENDS users, around 52% to 61% of current cigarette users, and around 84% of non-users endorse the misperception that nicotine

[12] RNC cigarettes in this context refers to any cigarette with a lower amount of nicotine than NNC cigarettes. FDA notes that studies focusing on consumer perceptions of RNC cigarettes typically do not differentiate between RNC, LNC, and VLNC cigarettes. However, when describing studies that focus on consumer behavior and perceptions of VLNC cigarettes specifically, FDA uses the term VLNC cigarettes. FDA notes that studies in this domain typically use consumer perceptions of RNC cigarettes to form conclusions about consumer perceptions about VLNC cigarettes and the FDA's proposed reduction of nicotine more broadly.

causes cancer or that nicotine is the major contributing component in cigarettes that leads to cancer (Lin et al., 2021; Shi et al. 2021, Weiger et al., 2022).

Multiple nationally representative survey studies identified in this review found evidence of nicotine misperceptions in the general population. Kemp et al. (2018) reported that the majority of participants (83.2%) in a nationally representative survey characterized the amount of nicotine usually found in tobacco products as definitely harmful to children. Peterson et al. (2022) found a low prevalence of correct nicotine cancer harm perceptions across all years of HINTS data they analyzed. Correct responses to the question of whether nicotine was the chemical most responsible for causing cancers from smoking decreased over time from 27.1% in 2015, 25.9% in 2017, and 22.0% in 2019. Snell et al. (2022) analyzed PATH data and found that incorrect responses to a question about nicotine's harmfulness to health were reported by 68.9% of participants (SE: 0.56); 64.6% incorrectly reported that nicotine in cigarettes was very/extremely or not at all harmful to health (SE: 0.53), and 63.3% thought that nicotine was probably or definitely the main contributor to smoking-related cancers (SE: 0.63). Across these nationally representative studies, there was strong evidence that incorrect perceptions about nicotine harm vary by gender (females have more incorrect beliefs about nicotine harm than males), ethnicity (black and Hispanic individuals have more misperceptions than white individuals), education (less educated have more misperceptions than college educated), and age (older adults have more misperceptions about nicotine than younger adults).

Multiple nationally representative studies identified in this review examined nicotine harm perceptions by tobacco use status. Lin and Muscat (2021) conducted a secondary analysis of nationally representative health information national trends survey (HINTS) data (Cycle 3, 2019) and reported that among dual cigarette/ENDS users, exclusive cigarette users, and tobacco non-users, the dual user group had the highest percentage of respondents that correctly responded that nicotine did not cause cancer (40.40%), exclusive cigarette users had fewer respondents that correctly responded (21.81%), and the non-user group had the lowest percentage of correct answers (15.75%). Additionally, 22.47% of non-users reported that they did not know if nicotine caused cancer. Shi et al. (2021) reported that over half of the respondents in their study who smoke cigarettes incorrectly believed that nicotine caused a "relatively large part" (33.2%), "very large part" (18.1%), or "all" (5.4%) of the health risks caused by smoking. Weiger et al. (2022) used nationally representative PATH data to find that 61.2% of people who use cigarettes believe that nicotine is the chemical that causes most of the cancer from smoking.

Multiple studies identified in this review used convenience sampling to examine nicotine misperceptions across sub-populations. Patel et al. (2013) conducted a cross-sectional

survey among full-time faculty on two university campuses in the US and reported that 51% of all respondents ranked nicotine as high risk for general health. Pacek et al. (2017) used a cross-sectional survey to examine nicotine knowledge and beliefs in a convenience sample of HIV-positive people who smoke cigarettes and reported that the majority of participants incorrectly identified nicotine as the cause of most smoking-related cancers and as a primary cause of lung cancer, asthma, heart disease, stroke, heart attack, and impotence. Villanti et al. (2019) surveyed young adults about harm perceptions of nicotine containing products and reported that respondents believed that a relatively or very large part of the health risks (66%) or cancer (60%) caused by smoking come from the nicotine. Borelli and Novak's (2007) survey of nurses found that a majority of participants endorsed the belief that nicotine is a cause of cancer. Bansal-Travers et al. (2010) conducted a study with adults who smoke and want to quit, and the majority of participants believe that nicotine is primarily responsible for smoking-related cancers. Finally, Loud et al. 2021 conducted qualitative focus groups consisting of participants with different tobacco use histories; participants in all groups tended to incorrectly believe that nicotine causes some of the major health effects of smoking. Although these studies focused on incorrect beliefs about nicotine harms in specific sub-populations, demographic characteristics associated with rates of incorrect beliefs were similar to those in nationally-representative surveys. Specifically, incorrect beliefs that nicotine is a cause of cancer or is responsible for the health risks caused by smoking were more prevalent among people who do not use tobacco compared to those that do, for females compared to males, for blacks and Hispanics compared to whites), for those with less than some college education (vs. at least some college), and for older respondents compared to younger respondents (compared to older respondents).

b. Studies Examining Knowledge, Attitudes, Beliefs, or Perceptions of the Addictiveness of Nicotine

Seven of the studies identified in this review focused on details about consumer perceptions of the addictiveness of nicotine (Peterson 2022; Snell et al. 2022; Pacek et al. 2017; Loud et al 2021; Patel et al. 2019: Lin & Muscat 2021; Jackson et al. 2022). These studies indicated that US adults believe that nicotine is addictive. Lin & Muscat (2021) found that more than 83% of people who do not smoke cigarettes and people who exclusively smoke cigarettes as well as 97% of people who use cigarettes and e-cigarettes know that nicotine is addictive. Peterson (2022) found a high prevalence of correct perceptions of nicotine's addictive properties in 2015, 2017, and 2019 HINTS data, and the prevalence of correct responses increased between 2015 to 2019 (2015 = 83.5%, 2017 = 84.7%, 2019 = 85.8%). In each HINTS cycle, an estimated 12% of people living in the United States reported they do not know if nicotine was the main substance in tobacco that makes people want to smoke. Snell et al.

(2022) reported that 82.9% of participants agreed that nicotine was responsible for "driving continued cigarette use"; however, only 13.1% agreed that reducing nicotine would make cigarettes less addictive. Patel et al. (2019) examined current cigarette users' nicotine addiction knowledge in a nationally representative study and reported that most people who use cigarettes (63%) indicated that nicotine alone was the substance in cigarettes that caused addiction. Jackson et al. (2022) found that the majority of people who smoke cigarettes and people who use e-cigarettes in a nationally representative survey agreed that nicotine is addictive. Pacek et al. (2017) reported that the majority of participants in their study of HIV-positive people who smoke cigarettes correctly identified nicotine as the substance that makes cigarettes addictive. Loud et al. 2021 conducted qualitative focus groups with participants with different tobacco use histories; most participants understood that nicotine was addictive. However, this qualitative study reported that even if consumers believe that nicotine is addictive, they also believe that an addiction to cigarettes comes from more than just nicotine.

c. Studies Examining Messaging Interventions to Correct Nicotine Misperceptions

Eleven studies identified in this review examined the impact of different messaging formats and content to correct nicotine misperceptions. Overall, these studies reported that messaging increased the endorsement of correct beliefs about the harms of nicotine (i.e., that nicotine does not cause cancer and that nicotine is the not the major source of health harms in cigarettes). Many of these studies reported that messaging resulted in more correct beliefs that nicotine is not the main cause of cancer or other heath harms from cigarettes, and some studies found that messaging resulted in more accurate beliefs about the relative harm of RNC cigarettes. One experimental study (Villanti et al. 2019) examined the effect of a nicotine fact sheet on how people who smoke cigarettes rate the perceived risk and addictiveness of nicotine. Before exposure to the nicotine fact sheet, most people who smoke understood that nicotine is the main cause of tobacco addiction, but incorrectly believed that nicotine was the main cause of smoking-related health problems. However, viewing the nicotine fact sheet doubled the probability of disagreeing that nicotine is the main cause of smoking-related disease. Another experimental study (Yang, Owusu, & Popova, 2020) examined the effect of nicotine educational messages on harm and risk beliefs about nicotine and reduced nicotine content cigarettes. Participants who viewed a message about nicotine had more correct responses to the statement that nicotine is a cause of cancer than participants in other conditions. Exposure to nicotine messaging was also associated with lower rates of false beliefs about nicotine and RNC cigarettes. A third experimental study (Shi et al. 2021) randomized subjects to view a control, or one of three messages designed to correct nicotine misconceptions (correction about nicotine only, correction about nicotine in NRT, and

correction on nicotine in e-cigarettes). All three of these messages lowered subjects' perception of nicotine harm compared to the control. A fourth experimental study by Differding et al. (2022) randomized participants to view one of six messages designed to describe a low nicotine product standard and define VLNC cigarettes. Participants who viewed messages that included information about the addictiveness and harm of VLNC cigarettes were less likely to believe that nicotine caused cancer.

B. Consumer Knowledge, Attitudes, Beliefs, or Perceptions Regarding Reduced Nicotine Tobacco Products

Twenty-seven studies examined consumer knowledge, attitudes, beliefs, or perceptions regarding the harm or addictiveness of RNC cigarettes. These studies provided evidence in three categories: studies that examined consumer perceptions of RNC cigarette harms, studies that examined consumer perceptions of RNC cigarette addictiveness, and studies that examined how to increase correct perceptions about the harm and addictiveness of RNC cigarettes. These studies provide strong evidence that a significant minority of U.S. adults (25-35%) believe that RNC cigarettes are safer and less carcinogenic than NNC cigarettes; current cigarette users may have slightly higher rates of this misperception (12%-54%). These studies provide strong evidence that 60-77% of U.S. adults believe that RNC cigarettes are equally or more addictive than NNC cigarettes; rate of holding this misperception do not vary by tobacco use status. Finally, there is evidence that advertisements for RNC cigarettes have the potential to correct misperceptions about the harm and addictiveness of RNC cigarettes. Further research to inform effective public health communications include studies of effective framing and message content for priority populations, including people who use cigarettes and people who have never used cigarettes.

a. Perceived Relative Harm of Reduced Nicotine Cigarettes

All fifteen studies examined how consumers perceive the relative harm of RNC cigarettes. There is strong and consistent evidence that a quarter or more of consumers believe that these products are safer than NNC cigarettes, including a quarter or more of current tobacco users. These studies included experimental designs where participants used an RNC or VLNC cigarette or cross-sectional and qualitative designs where individuals provided their perceptions of these products in a hypothetical setting.

Four experimental studies that assessed participants' perceptions of the safety of RNC or VLNC cigarettes after using them reported that participants perceive RNC or VLNC cigarettes to be significantly less harmful to health and less likely to cause cancer than NNC cigarettes (Pacek et al., 2018; Denlinger-Apte et al., 2017; Hatsukami et al., 2013; Denlinger-Apte et al.

2019a). However, there was variation in whether these evaluations were related to the type of cigarettes participants were assigned to smoke. For example, Pacek et al. (2018) conducted an experiment where adults who smoke cigarettes were randomly assigned to smoke cigarettes of varying nicotine levels. They found that perceived nicotine content was significantly and positively associated with perceived health risks, regardless of the actual nicotine content of the cigarettes assigned to participants. Denlinger-Apte et al. (2019a) conducted a similar experiment with adolescents who smoke cigarettes but found that respondents who smoke VLNC cigarettes perceive them to be less likely to cause lung disease and cancer than those who smoke NNC cigarettes.

A wider variety of studies examined consumer perceptions of the relative harm or safety of RNC cigarettes without asking respondents to use a product. These studies reported that a significant minority of consumers incorrectly believe that RNC cigarettes are safer and less carcinogenic than NNC cigarettes. Studies employing nationally representative surveys have found that anywhere between approximately 25% and 35% of the general population believe that RNC cigarettes are less harmful than NNC cigarettes (O'Brien et al., 2017; Nguyen et al., 2018; Popova et al., 2019). For example, O'Brien et al. (2017) used nationally representative data to find that 30% of respondents rate RNC cigarettes as less harmful than NNC cigarettes while 64% rate them as equally harmful. O'Connor et al. (2005) asked a nationally representative sample an open-ended question to identify a product that potentially reduced cigarette risk. Quest low nicotine cigarettes were the most cited product with 27% of respondents identifying them as a reduced risk product. There is some variation across subgroups in beliefs about harm. Nguyen et al. (2018) found that approximately 28% of US-born respondents in a nationally representative survey believe that RNC cigarettes are slightly or much less harmful than NNC cigarettes, and approximately 22% of US-born respondents believe they are much or slightly less likely to cause lung cancer. These percentages were significantly higher among the foreign-born population than the US-born population; approximately 32% of foreign-born respondents believe that RNC cigarettes are slightly or much less harmful than NNC cigarettes and approximately 28% believe that using RNC cigarettes would lead to a lower risk of lung cancer. Finally, Smith et al. (2012) found that a majority of their sample of college students do not believe that reducing levels of nicotine in cigarettes makes them less dangerous to smokers.

The proportion of people who smoke cigarettes that believe RNC cigarettes are safer than NNC cigarettes varies considerably across studies. In two related studies using nationally representative data, Cummings et al. reported that approximately 54% of respondents that currently smoke cigarettes believe that reducing nicotine in cigarettes makes them less dangerous, and this misperception was slightly higher among respondents that smoke light

cigarettes compared to those that smoke full-flavored cigarettes (Cummings et al., 2004a; Cummings et al., 2004b). Similarly, Byron et al. (2018) found that 47.1% of people who smoke cigarettes believe that smoking RNC cigarettes over 30 years would reduce your cancer risk relative to smoking NNC cigarettes. Denlinger-Apte et al. (2021a) used a subsample of people who exclusively smoke cigarettes from the PATH study and found that between 12.38% and 25.53% of respondents across racial categories believe that RNC cigarettes are less harmful than NNC cigarettes, or do not know how harmful they are relative to NNC cigarettes. This rate was significantly higher for Asian respondents compared to white respondents. Jackson et al. (2022) found that about 23% of people who smoke cigarettes and people who use e-cigarettes believe that RNC cigarettes were less harmful than NNC cigarettes. In general, the misperception that RNC cigarettes are safer than NNC cigarettes tends to be more common among non-white people who smoke cigarettes relative to white people who smoke and among older people who smoke (Mercincavage et al., 2019; Denlinger-Apte et al., 2021a; Byron et al., 2018).

a. **Perceived Addictiveness of Reduced Nicotine Cigarettes**

Eight studies describe consumers' beliefs and perceptions of the addictiveness of RNC cigarettes relative to NNC cigarettes. Survey studies reported that respondents believe that RNC cigarettes are equally or more addictive than NNC cigarettes; however, the one experimental study on this topic found that consumers that use VLNC cigarettes believe that they are less addictive.

Six studies used nationally representative surveys to assess consumer perceptions of the addictiveness of RNC cigarettes relative to NNC cigarettes without using these products. All six studies reported that consumers believe that RNC cigarettes are equally or more addictive than NNC cigarettes. The percentage of respondents that hold this belief ranges from 60% to 77%. O'Brien et al (2017) and Nguyen et al. (2018) found that 65% and about 64% of respondents respectively believe that RNC cigarettes are equally addictive to NNC cigarettes. Villanti et al. (2019a) found that 60% of US young adults (aged 25-34) do not believe the claim that low nicotine cigarettes are less addictive. Tobacco use status does not appear to significantly change misconceptions about the addictiveness of LNC cigarettes (Lin and Muskat, 2021). Jackson et al. and Denlinger-Apte et al. reported that between 77% (Jackson et al., 2022) and 80% (Denlinger-Apte et al., 2021a) of people who smoke cigarettes believe that LNC cigarettes are equally or more addictive than NNC cigarettes. In addition to these six nationally representative survey studies, Mercincavage et al. (2019) analyzed baseline survey responses collected before two separate experiments and reported that 63.4% of participants did not believe that RNC cigarettes were less addictive and would be easier to quit than NNC cigarettes.

Only one study found that consumers understand that RNC cigarettes are less addictive than NNC cigarettes. Hatsukami at al. (2013) conducted an experiment where participants were randomly assigned to smoke cigarettes with varying levels of nicotine. They found that participants rated high nicotine cigarettes as having a significantly higher risk of addiction compared to low and intermediate nicotine cigarettes. This result suggests that using RNC cigarettes may affect perceptions of the addictiveness of these products relative to NNC cigarettes.

b. Studies Examining Advertising and Messaging Interventions to Correct Misperceptions of Reduced Nicotine Content Cigarettes

Eleven experimental, quasi-experimental, and qualitative studies focus on understanding the impact of advertising and messaging on misperceptions about the harm and addictiveness of RNC cigarettes. Studies focused on advertising suggest that it can lead to misperceptions of RNC cigarettes but that removing misleading text and adding corrective statements can help consumers better understand the relative harm and addictiveness of these products. Studies of general messaging strategies find that there is a challenge in identifying messages that correct both misperceptions about the addictiveness and health risks of RNC cigarettes simultaneously, and that efficacy messages are the most appealing to smokers. One potential concern with these advertising and messaging studies is that they measured short term impacts, so it is unclear whether any changes in advertising or new message campaigns will have a long-term impact on reducing misperceptions of RNC cigarettes.

Experimental and quasi-experimental studies identified in this study reported that advertisements can contribute to misperceptions of RNC cigarettes but can also be used to correct pre-existing misperceptions. Two studies conducted with Quest cigarette stimuli reported that viewing advertisements for a low nicotine product is associated with believing this product is lower in nicotine and incorrectly believing that the product is healthier than regular cigarettes (Mercincavage et al., 2017; Shadel et al., 2006). Subsequent studies reported that altering an advertisement by removing misleading text or adding corrective messages may help reduce these misperceptions (Lochbuehler et al., 2016; Strasser et al., 2008; Mercincavage et al., 2021). For example, Mercincavage et al. (2021) found that relative to an ad with no disclaimer at all, an industry-proposed disclaimer on RNC cigarettes that emphasizes that the products “contain nicotine” and that “less nicotine does not mean a safer cigarette” is associated with greater perceived health and addiction risk beliefs and fewer false beliefs about RNC products.

Although there is evidence that messages can help correct misperceptions about nicotine content and addictiveness, correcting one type of error can lead to the introduction or strengthening of misperceptions about cancer and health risks of RNC cigarettes (Byron et al., 2019; Differding et al., 2022). Byron et al. (2019) used an experimental design in which respondents were randomly assigned to view different messages describing a low nicotine product standard. They found that some messages lead to more accurate perceptions about the nicotine content and addictiveness of RNC cigarettes but also lead to less accurate perceptions about their cancer risks. Messages can be designed to explicitly overcome this problem (Popova et al., 2019; Differding et al., 2022). For example, Differding et al. (2022) conducted an experiment in which participants were randomized to view one of the messages that Byron et al. (2019) identified, or a variant of that message that added additional details about harm, addictiveness, or youth use. They found that people who view messages that include information about the addictiveness and harm of VLNC cigarettes are less likely to believe that nicotine and VLNC cigarettes cause cancer and that VLNC cigarettes are safer than NNC cigarettes. These three studies indicate that messages need to be carefully crafted to avoid simultaneously correcting one misconception about RNC cigarettes while strengthening or introducing another.

There is also evidence that people who smoke prefer messages that focus on quitting efficacy (Reynolds et al., 2022; Duong et al., 2022, Ranney et al., 2022). Duong et al. (2022) conducted a series of focus groups with people that use tobacco and those that do not use tobacco to examine how messages about reduced nicotine in cigarettes. They found that for people who exclusively smoke cigarettes, efficacy messages about breaking addiction and messages about smoking risks are the most effective at encouraging attention, liking, and processing of message content. However, they also found that people who do not use tobacco felt that efficacy messages downplayed the risks of smoking. Reynolds et al. (2022), conducted an experiment to estimate the impact of seven different messages on attitudes about a low nicotine product standard. They found that participants perceive messages that describe RNC cigarettes as increasing quitting efficacy, as being less addictive, and as containing 95% less nicotine to be the most positive.

C. Consumer Knowledge, Attitudes, Beliefs, Perceptions, or Planned Behavior Regarding FDA Regulation of Nicotine in Tobacco Products

Thirteen studies examined consumer knowledge, attitudes, beliefs, perceptions, or planned behavior with respect to FDA regulation of nicotine in cigarettes and other tobacco products. There is moderate evidence that between 45% and 77% of US adults support a low nicotine product standard. There is also some evidence for variation in support across racial and

tobacco user subgroups. African American respondents tend to be more likely than white respondents to support a product standard. People who use cigarettes are less likely to support a nicotine product standard than non-users, although studies that focus exclusively on tobacco users suggest that as many as two-thirds to three-quarters of people who use cigarettes support a low nicotine product standard. This review provided evidence that further research into consumer perceptions of the nicotine product standard would improve the accuracy of these estimates of support for the standard. Qualitative evidence indicates that consumers may not fully understand the purpose, feasibility, and goals of a low nicotine product standard. Additionally, these estimates are based on surveys conducted before 2019 and included survey effects that influenced how people responded.

Evidence from nationally representative surveys suggest that between 45% and 77% of US adults support a low nicotine product standard (Connolly et al., 2012; Pearson et al., 2013; Ali et al., 2019). The highest estimate comes from Connolly et al. (2012) who found that approximately two-thirds of respondents support the FDA reducing nicotine in cigarettes either immediately or gradually. They found that support was highest, approximately 77%, if the product standard was framed as reducing cigarette addictiveness for children. The lowest estimate came from Pearson et al. (2013) who found that approximately 45% of participants agree with the idea that government should regulate nicotine. Ali et al. (2019) reported that the majority of respondents favored a proposed nicotine reduction (52.4% “Strongly Favor”, 28.6% “Somewhat Favor”).

Additional evidence shows that support for a low nicotine product standard varies across racial and tobacco use subgroups. African American respondents tend to be more supportive of a low nicotine product standard than white, non-Hispanic respondents (Pearson et al., 2013; Ali et al., 2019; Kulak, et al., 2020). Support for a product standard also varies with tobacco use. People who smoke tend to be less likely to support a product standard than others unless they plan to quit (Pearson et al., 2013; Ali et al., 2019; Kulak et al., 2020). However, nationally representative surveys of people who smoke suggested that as many as two-thirds to three-quarters would support a low nicotine product standard (Fix et al., 2011; Patel et al., 2019). Pepper et al. (2020) found that people who currently dual use cigarettes and ENDS who also strongly agree with a proposed nicotine standard believe that that the standard will help smokers quit; however, those people also believe that reducing the amount of nicotine in cigarettes would reduce perceived harms of smoking. Those that disagreed with a proposed nicotine standard believe the nicotine standard would hamper individual freedom or represent government overreach. Additionally, Denlinger-Apte et al. (2019) conducted an experiment and found that using VLNC cigarettes for an extended time does not impact support for a proposed nicotine reduction.

While the evidence above suggests that support for a low nicotine product standard is strong, it is unclear to what extent these estimates reflect the current level of support for a nicotine product standard because public opinion changes rapidly. Furthermore, there is reason to believe that survey effects (including the content in survey item stems and the ordering of response options) artificially inflate agreement with proposed product standards (Kulak et al., 2020). Qualitative research also shows that consumers may struggle to fully understand the purpose of a product standard, how it would work, and the impact it would have. Some consumers believe a low nicotine product standard would be designed to benefit tobacco companies or promote e-cigarette use (Henderson et al., 2022). Many consumers are confused about why nicotine is being removed rather than other harmful chemicals and do not believe that reducing nicotine would limit the addictiveness of smoking and instead might even lead to compensatory smoking (Ranney et al., 2021; Henderson et al., 2022, Loud et al., 2021). Some preliminary experimental research has begun to explore how different messaging strategies can correct these misperceptions but thus far the results are still mixed. Differding et al. (2022) tested six different potential messages to describe a proposed nicotine reduction and found that none of these messages impact participants' support for a low nicotine product standard. Reynolds et al. (2022) found that messages focusing on the reduced addictiveness of RNC cigarettes, lower nicotine content, and increased quitting efficacy led respondents to feel more positive about a low nicotine product standard, while messages focusing on chemicals in RNC cigarettes, and their harm led individuals to perceive a product standard more negatively.

Conclusions

Taken together, there is strong and consistent evidence that the majority of US adults incorrectly believe that nicotine is a carcinogen and a primary cause of smoking-related disease. These findings were consistent across multiple study designs and study populations, although there is evidence that population characteristics such as ethnicity, gender, education, and smoking status are correlated with rates of incorrect beliefs about nicotine and VLNC cigarettes. In a likely related finding, there is strong and consistent evidence that a substantial minority (25-35%) of US adults endorse the incorrect beliefs that RNC cigarettes are less harmful to health and that their use is less likely to result in negative health outcomes compared to NNC cigarettes. Explicit messaging and information about nicotine in cigarettes affect beliefs about addictive properties of RNC and VLNC cigarettes (compared to NNC cigarettes); additionally, experiences using NNC and VLNC cigarettes affect beliefs about the addictiveness of VLNC cigarettes without explicit messaging about nicotine content.

There are multiple opportunities for public health messaging to promote a more accurate understanding of VLNC cigarettes and the proposed nicotine product standard while

also communicating the risks of using VLNC cigarettes. To ensure the product standard has a positive net impact on population health, it will be important to ensure that consumers understand that nicotine is addictive but is not a carcinogen nor the primary cause of smoking-related disease. It may also be valuable to explicitly differentiate VLNC cigarettes from low yield/high ventilation light/low/mild cigarettes, as previous public health messaging campaigns have informed consumers that these products, which were sometimes marketed as being lower in nicotine, are not safer. Public health messaging designed to educate consumers on actual risks of nicotine and VLNC cigarettes may be more effective if they communicate how a nicotine product standard improves population health while still emphasizing the harms associated with using combusted cigarettes. There may also be opportunities to improve understanding of nicotine and VLNC cigarette risks by tailoring information to specific population subgroups, although there is insufficient evidence to identify messaging needs for specific population subgroups such as members of racial/ethnic minorities, foreign-born populations, women, and sexual/gender minorities, among others.

Finally, there is evidence that as many as that 45%-77% of US adults support a nicotine product standard, and studies focused exclusively on people who use tobacco reported that two-thirds to three-quarters of people who smoke cigarettes support a nicotine product standard. However, this support may be due to the misperception that nicotine is a major cause of smoking-related disease. Additionally, there is evidence that consumers may not understand the purpose, feasibility, and impact of a low nicotine product standard. These misperceptions may explain why consumers have such a wide range of reported behavioral intentions in response to lower nicotine products: consumers' reported behavioral intentions if a nicotine standard is put in place include quitting smoking combusted cigarettes, continuing to smoke VLNC cigarettes or other combusted tobacco products, or switching to non-combusted tobacco products. Studies included in this review indicate that the content and framing of messaging about reduced nicotine products can impact consumers' behavioral intentions about tobacco product use if a reduced nicotine policy is put in place.

VIII. Overall Conclusions

Combusted tobacco use causes a tremendous burden of death and disease, which is ultimately the result of addiction to the nicotine in these products. Currently, more than half of adult cigarette smokers make a serious quit attempt each year, but many of them do not succeed due to the addictive nature of these products. Establishing a maximum nicotine level in combusted tobacco products could increase the likelihood of successful quit attempts and help prevent experimenters (mainly youth and young adults) from progressing to regular use.

Indeed, systematic review of the peer-reviewed literature shows that VLNC cigarettes have lower abuse liability than NNC cigarettes; and extended use of VLNC cigarettes is associated with reduced dependence, fewer cigarettes smoked per day, and increased quit attempts relative to use of NNC cigarettes. At least one simulation model has shown that a product standard that renders combusted tobacco products minimally addictive by reducing the nicotine content of the tobacco filler could save millions of lives over the next several decades in the United States.

The best available evidence suggests that a product standard limiting the nicotine content of combusted tobacco products to 0.7 mg of nicotine per g of total tobacco would make these products minimally addictive. If FDA were to establish a nicotine tobacco product standard that covered only cigarettes, a portion of addicted smokers could migrate to other, similar combusted tobacco products to maintain their nicotine dose, thereby, reducing the positive public health impact of such a rule. FDA reviewed the literature on combusted tobacco products, including combusted cigarettes, cigarette tobacco, RYO tobacco, cigars (including little cigars, large cigars, and cigarillos), pipe tobacco, and waterpipe tobacco. Based on this review, FDA concludes that use of any of these combusted products is sufficient to create or sustain nicotine dependence and could therefore continue to expose users to toxicants. Therefore, a product standard to reduce the nicotine content of combusted cigarettes should also reduce the nicotine content of other combusted tobacco products.

FDA has considered potential unintended consequences associated with reducing the nicotine content of combusted tobacco products, including the impact of such a standard on vulnerable populations and the potential for reduced nicotine products to lead to compensatory smoking and increased toxicant exposure among smokers. After systematically reviewing the peer-reviewed literature regarding the likely effects of reducing nicotine in combusted tobacco, FDA found little to no evidence that VLNC cigarettes have differential or undesirable effects in vulnerable populations (e.g., VLNC cigarettes do not appear to exacerbate psychiatric symptomatology in smokers with symptoms of mental health disorders). Further, FDA concludes that extended exposure to VLNC cigarettes is associated with no evidence of increased toxicant exposure. Following VLNC cigarette use, some biomarkers of exposure (e.g., CO) are typically similar to those observed following NNC cigarette use, while other biomarkers (e.g., TNE) are typically lower following VLNC cigarette use. However, no biomarkers of exposure are reliably observed to be higher following VLNC cigarette use relative to NNC cigarette use. While the reviewed literature shows some evidence of compensatory smoking during the intermediate stages of a gradual approach to reducing nicotine, immediate reduction approaches are associated with very little or no compensatory smoking and could

therefore maximize the benefits of a nicotine tobacco product standard. Immediate nicotine reduction approaches may also have other benefits, including leading to quicker decreases in dependence relative to gradual nicotine reduction.

The peer-reviewed literature shows that the majority of American adults incorrectly believe that nicotine is a carcinogen and a primary cause of smoking-related disease. There is also consistent evidence that the majority of American adults endorse the incorrect beliefs that reduced nicotine content cigarettes are less harmful to health and that their use is less likely to result in negative health outcomes compared to NNC cigarettes. Public health messaging can be used to promote a more accurate understanding of VLNC cigarettes and the proposed nicotine product standard, while also communicating the risks of using VLNC cigarettes.

Taken together, FDA concludes that rendering combusted tobacco products minimally addictive by reducing the nicotine content to 0.7 mg of nicotine per g of total tobacco is technically achievable and could help current users quit and prevent future users from becoming addicted.

IX. Abbreviations

Term	Definition
1-HOP	urinary 1-hydroxypyrene
2-HPMA	2-hydroxypropyl mercapturic acid
3-HPMA	3-hydroxypropyl mercapturic acid
BAP	Benzo[a]pyrene
CEMA	2-cyanoethylmercapturic acid
CO	carbon monoxide
COHb	carboxyhemoglobin
CPD	cigarettes per day
CPT	cigarette purchase task
FD&C Act	Federal Food, Drug, & Cosmetic Act
e-cigarette	electronic cigarette
ENDS	electronic nicotine delivery system (e.g., e-cigarettes)
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHC	harmful and potentially harmful constituents
ISO	International Organization for Standardization
LNC	low nicotine content
MMD	major depressive disorder
NCI	National Cancer Institute
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNC	normal nicotine content
NNN	N-Nitrosonornicotine
NRT	nicotine replacement therapy
NYTS	National Youth Tobacco Survey
PAH	polycyclic aromatic hydrocarbon
PATH	Population Assessment of Tobacco and Health
PheT	r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4 tetrahydrophenanthrene
RYO	roll-your-own
SGR	Surgeon General's Report
S-PMA	S-phenylmercapturic acid
TNE	total nicotine equivalents
VLNC	very low nicotine content
YRBS	2015 National Youth Risk Behavior Surveillance Survey

Appendix A: Reproducible Transparent Document Review of Clinical Research Related to the Abuse Liability of VLNC Cigarettes

A. Executive Summary

The Behavioral and Clinical Pharmacology (BCP) Branch conducted a Reproducible Transparent Document (RTD) review to identify research on the abuse liability of very low nicotine content (VLNC) cigarettes. This RTD may be used to inform regulatory decisions related to a proposed product standard that would reduce the nicotine content of combusted cigarettes. Results from 155 studies are summarized in this RTD. Findings suggest that VLNC cigarettes have lower abuse liability than normal nicotine content (NNC) cigarettes, and switching to VLNC cigarettes from NNC cigarettes may reduce exposure to nicotine and other HPHCs.

B. Methods

On November 23, 2016, three electronic databases were searched for peer-reviewed scientific articles. No additional restrictions were placed on electronic searches (e.g., article publication date). Although the same search terms were entered into each database, the search strings varied depending on the formatting requirements of each database. Table A.1 displays the search terms that were entered into each database and the number of results retrieved from each source. After eliminating duplicates, 955 records were identified.

Table A.1: Database Search Results for Original Search

Database	Search String	Results
PubMed	("reduced nicotine" OR "nicotine reduction" OR "low nicotine" OR denicotinized OR denicotinised OR “nicotine free” OR VLNC OR “placebo cigarettes” OR "spectrum cigarettes" or "quest cigarettes" OR "nicotine infusion" OR "intravenous nicotine") AND cigar*	569
Web of Science	TOPIC: (("reduced nicotine" OR "nicotine reduction" OR "low nicotine" OR denicotinized OR denicotinised OR “nicotine free” OR VLNC OR “placebo cigarettes” OR "spectrum cigarettes" or "quest cigarettes" OR "nicotine infusion" OR "intravenous nicotine") AND cigar*)	653
Embase	'reduced nicotine' OR 'nicotine reduction' OR 'low nicotine' OR denicotinized OR denicotinised OR 'nicotine free' OR vlnc OR 'placebo cigarettes' OR 'spectrum cigarettes' OR 'quest cigarettes' OR 'nicotine infusion' OR 'intravenous nicotine' AND cigar*	701

Note: The term "cigar*" was used to retrieve any word that began with "cigar," including "cigar," "cigars," "cigarette," and "cigarettes."

a. Eligibility Criteria

Article eligibility was assessed through title and abstract review conducted by two independent reviewers. Eligible articles were: reviews, commentaries, nonhuman animal studies, and human studies of the effects of variable doses of nicotine (delivered intravenously or via cigarette or cigar) on addiction-related outcomes that were published in English. Articles ineligible for review were: poster abstracts, studies not published in peer-reviewed journals (e.g., book chapters, theses, dissertations), *in vitro* studies, and studies that only characterized the physical or chemical properties of reduced nicotine content cigarettes or cigars.

An article was selected for full-text review if at least one of two independent reviewers indicated that the article met eligibility criteria. Using this method, 424 articles were determined eligible for full-text review. Two independent reviewers agreed 531 articles were ineligible and excluded these articles from full-text review. The article selection process is diagramed in Figure A.1.

b. Selection Criteria

i. Inclusion Criteria

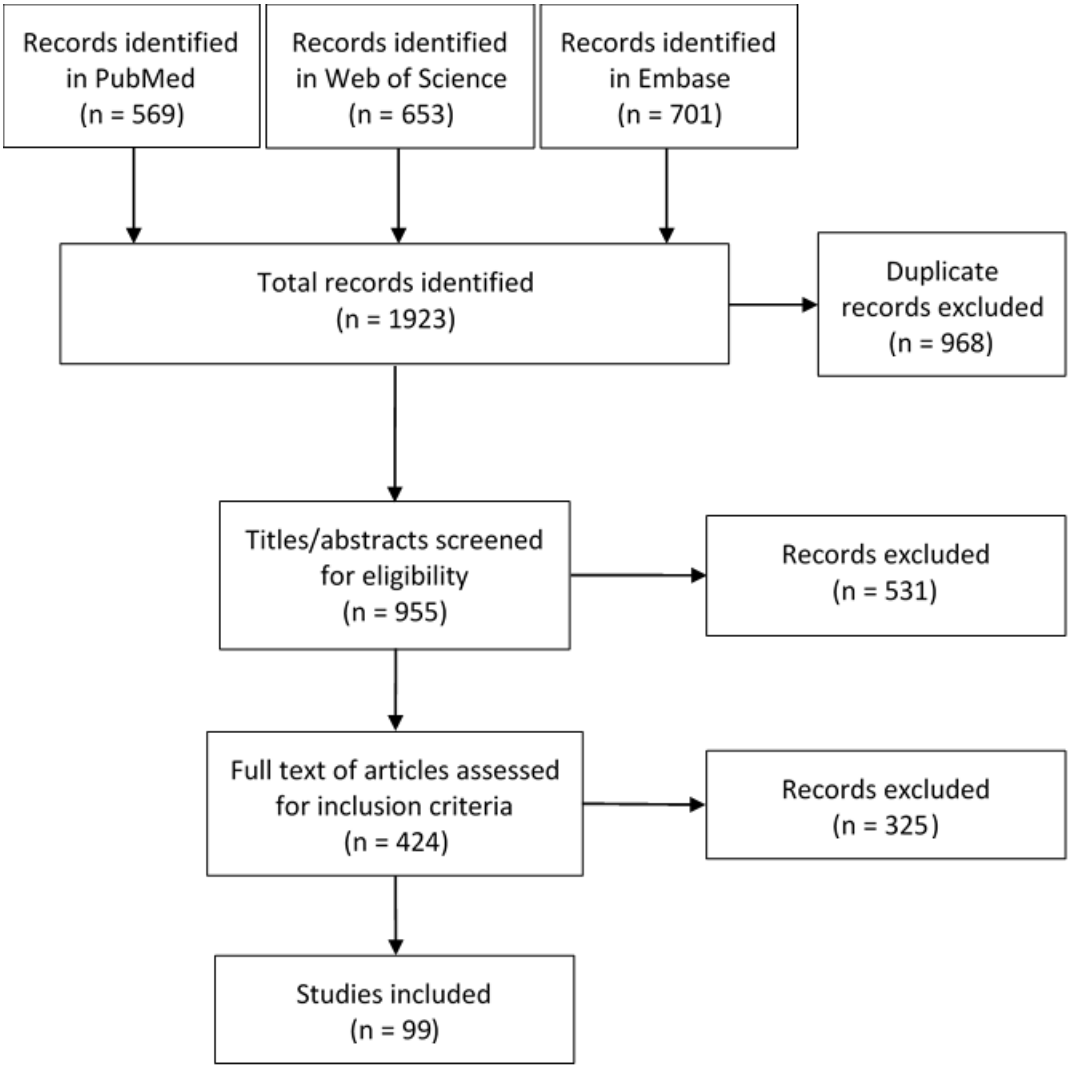
Articles selected for inclusion were peer-reviewed, published or in-press clinical studies of the effects of reduced nicotine content cigarettes or cigars on behavioral or self-reported measures of use, craving, withdrawal, reward, or dependence. These articles were also required to provide enough information about the research cigarettes (e.g., brand, manufacturer, nicotine content) to allow reviewers to identify them as reduced nicotine content cigarettes and not simply reduced nicotine yield cigarettes. Reduced nicotine content cigarettes are manufactured with chemical methods that reduce the nicotine content of the tobacco filler (e.g., the tobacco is washed with an alkaline solution) or with tobacco filler derived from genetically modified tobacco plants with low levels of nicotine. Cigarettes that are manufactured exclusively with other characteristics that lower nicotine yields (e.g., increased ventilation) did not meet our definition of reduced nicotine content cigarettes.

ii. Exclusion Criteria

Articles selected for exclusion were conference abstracts, commentaries, editorials, letters, case reports, reviews, studies not published in peer-reviewed journals, nonclinical studies, and studies that did not provide enough information for reviewers to identify the nicotine content of the study cigarettes.

Reviewers documented the reasons why each article met inclusion and exclusion criteria. These criteria were discussed among at least two independent reviewers during regular meetings to determine whether to include or exclude each article. Ninety-nine articles were selected for inclusion.

Figure A.1. Article Selection for Original Search

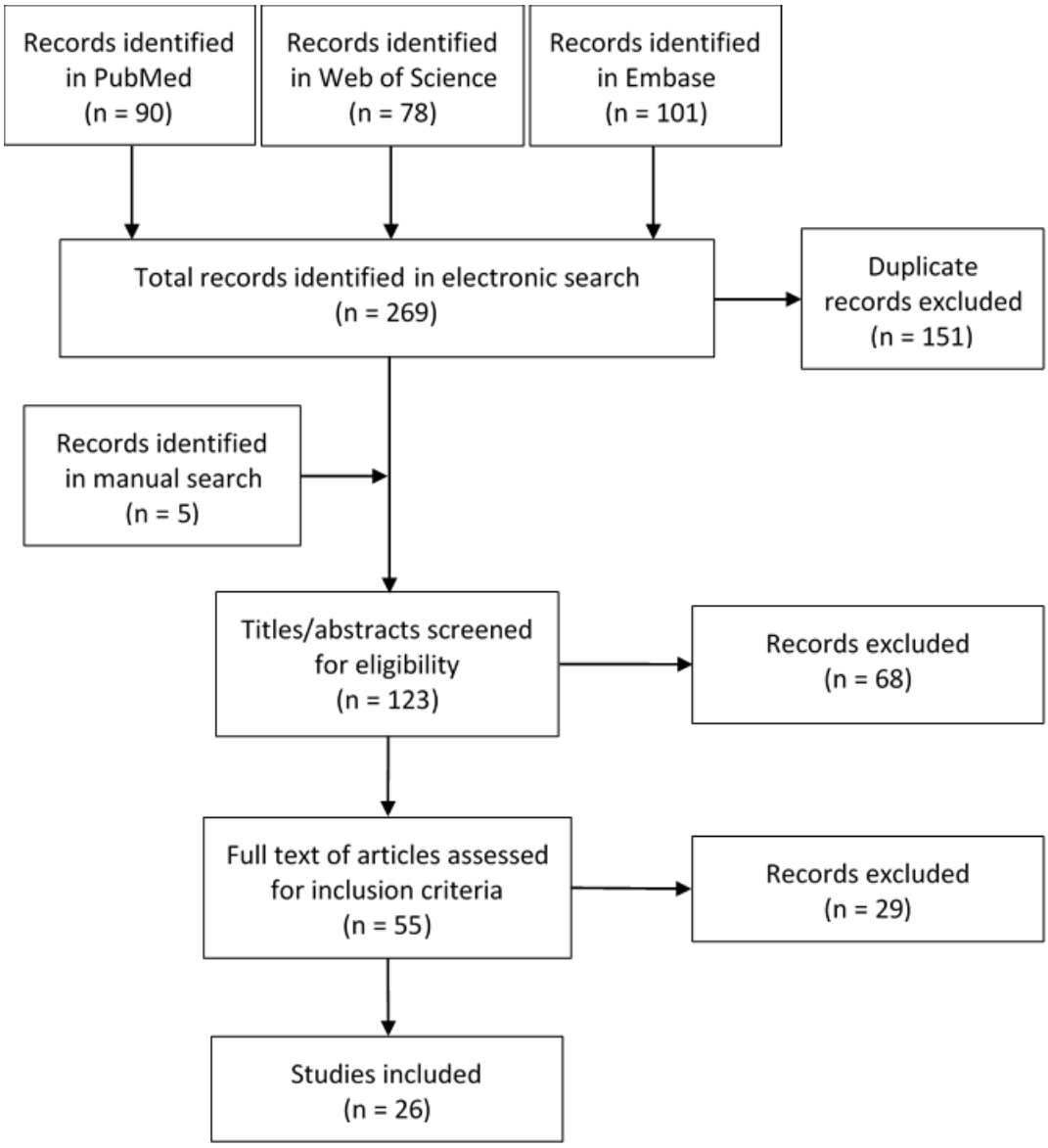


c. Search Update

On June 19, 2018, a second search was conducted to identify relevant peer-reviewed scientific articles published since the original search was conducted. The same methods were applied to this search that were applied to the previous search (e.g., identical search strings were used in the databases, and the same eligibility and selection criteria were applied to article review). After eliminating duplicates, 118 new records were identified, and an additional

5 records were identified through subsequent manual search (see Figure A.2). Twenty-six articles were selected for inclusion.

Figure A.2. Article Selection for Second Search

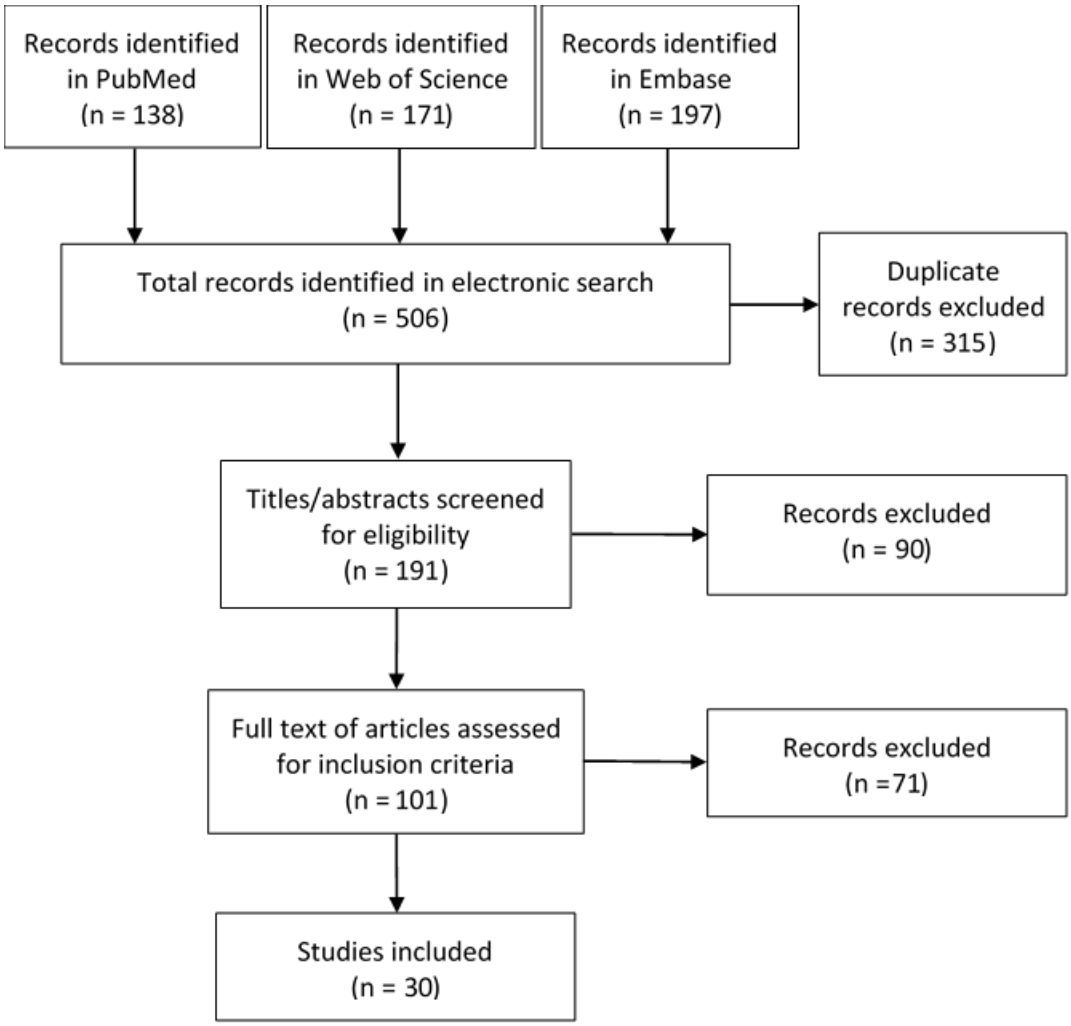


d. Search Update

On May 12, 2020, a third search was conducted to identify relevant peer-reviewed scientific articles published since the second search was conducted on June 19, 2018. The same methods were applied to this search that were applied to the previous searches. After

eliminating duplicates, 191 new records were identified. 101 of these articles were determined eligible for full-text review (see Figure A.3). Thirty articles were selected for inclusion.

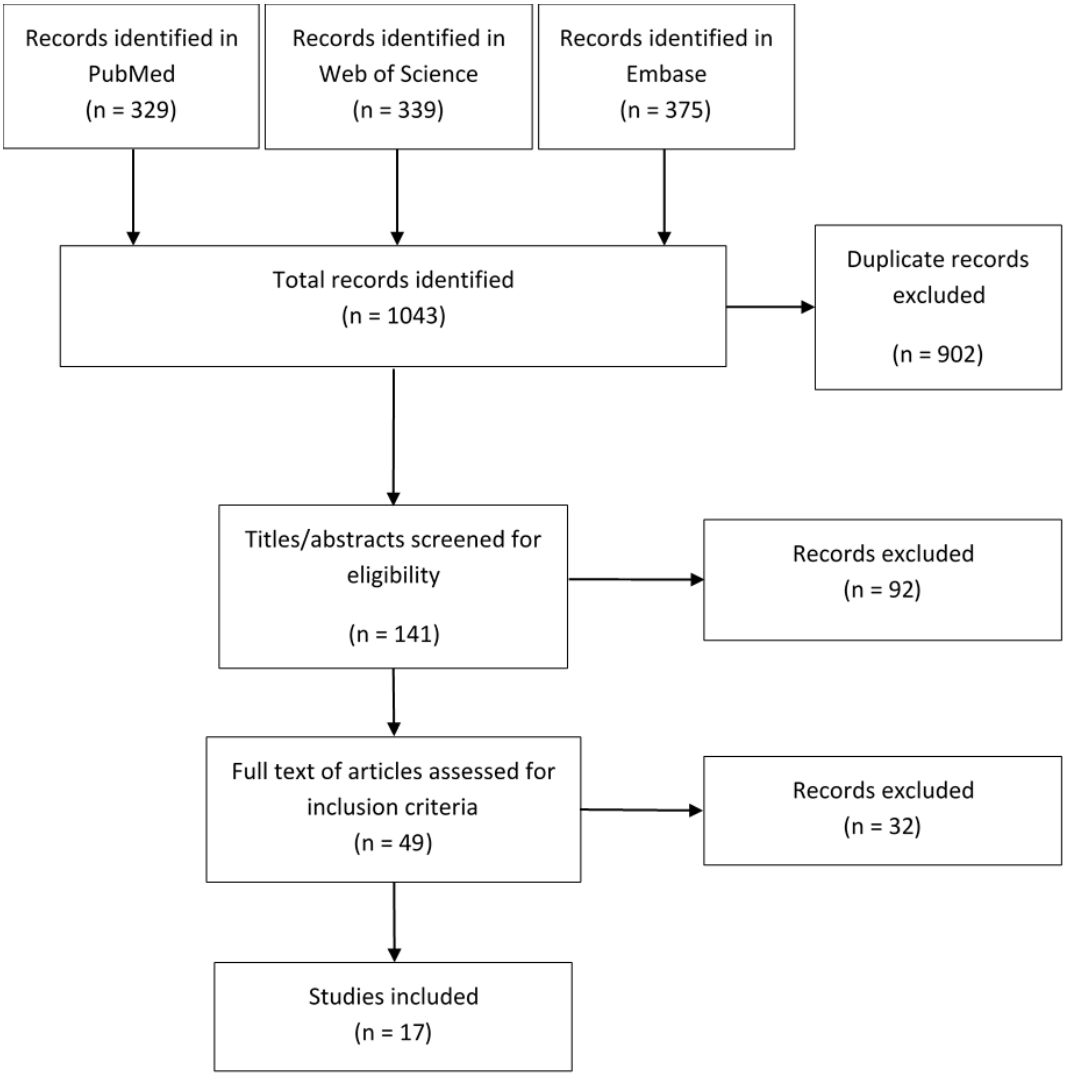
Figure A.3. Article Selection for Third Search



e. Search Update

On November 23rd, 2021, a fourth search was conducted to identify relevant peer-reviewed scientific articles published since the second search was conducted on May 12th, 2020. The same methods were applied to this search that were applied to the previous searches. After eliminating duplicates, 141 new records were identified. 49 of these articles were determined eligible for full-text review (see Figure A.4.). Seventeen articles were selected for inclusion.

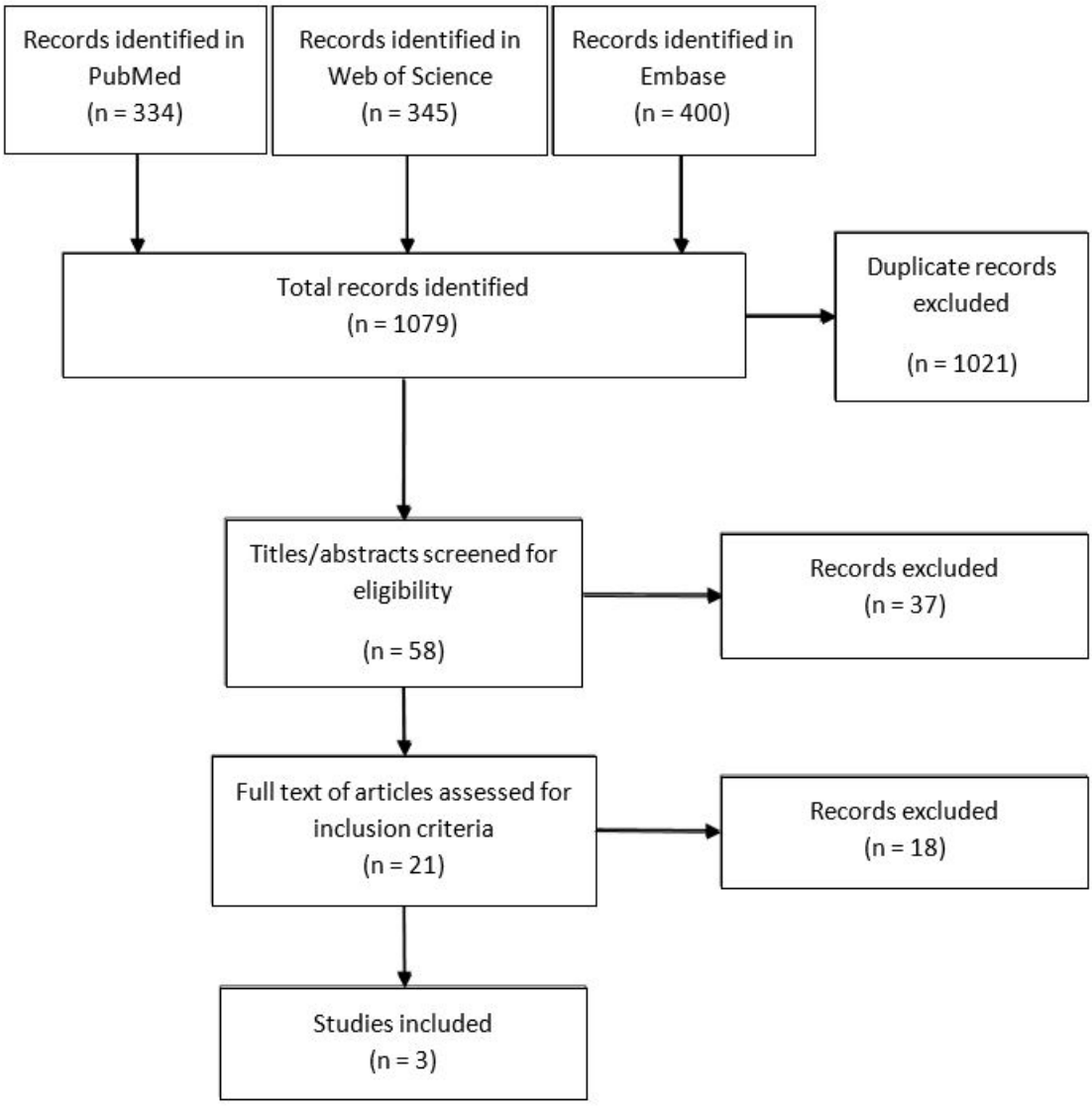
Figure A.4. Article Selection for Fourth Search



f. Search Update

On May 17th, 2022, a fifth search was conducted to identify relevant peer-reviewed scientific articles published since the fourth search was conducted. The same methods were applied to this search that were applied to the previous searches. After eliminating duplicates, 58 new records were identified. 21 of these articles were determined eligible for full-text review (see Figure A.5.). Three articles were selected for inclusion.

Figure A.5. Article Selection for Fifth Search



C. Results

One hundred seventy-five articles were selected for inclusion in this RTD (99 articles from the first search, 26 articles from the second search, 30 articles from the third search, 17 articles from the fourth search, and 3 articles from the fifth search). Each of these articles is individually summarized below and organized alphabetically based on the last name of the first author, with one exception: summaries of studies that are secondary analyses or follow-up

studies to previous publications are listed and indented directly below the summary of the original publication.

All summaries are divided into two major categories. Studies that involved brief exposure to reduced nicotine content cigarettes are summarized below in Section a.: *Individual Studies of Reduced Nicotine Content Cigarettes: Brief Exposure Studies*. In these studies, participants were given limited access to reduced nicotine content cigarettes over the course of several hours or several days, typically under controlled laboratory conditions. Studies that involved extended exposure to reduced nicotine content cigarettes are summarized below in Section b.: *Individual Studies of Reduced Nicotine Content Cigarettes: Extended Exposure Studies*. In these studies, participants were given less restricted access to reduced nicotine content cigarettes in their natural environments, typically over the course of several weeks.

Individual study summaries are followed by a "Summaries and Conclusions" section at the end of the RTD. In this section, overall summaries and conclusions based on similarities and differences in findings across studies are discussed.

a. Individual Studies of Reduced Nicotine Content Cigarettes: Brief Exposure Studies

Adams et al. (2015) conducted two experiments to examine the effects of nicotine on cognitive and subjective effects. In Experiment 1, after 12 hours of abstinence, 46 smokers were randomized to continue to abstain from smoking or to smoke a usual brand cigarette. Craving increased in the abstinent group. In Experiment 2, craving was assessed after 96 social smokers (< 3 cigarettes per day [CPD]) were randomly assigned to smoke Quest 3 VLNC cigarettes or Quest 1 NNC cigarettes. Participants were also randomly assigned to one of the following groups: (1) they were told that the cigarette contained nicotine, or (2) they were told that the cigarette did not contain nicotine. Craving and mood decreased after smoking in all participants (Adams et al., 2015).

Addicott et al. (2014) investigated the effects of VLNC cigarettes on craving and withdrawal in 29 smokers. For 24 hours prior to each session, participants wore a nicotine patch (21 mg) or placebo patch and smoked Quest 3 VLNC cigarettes or abstained from smoking in four within-subject conditions: (1) nicotine patch plus VLNC cigarette, (2) nicotine patch plus abstinence, (3) placebo patch plus VLNC cigarette, and (4) placebo patch plus abstinence. No main effect of condition on gray matter cerebral blood flow was observed. However, there was a main effect of patch condition on the left temporal lobe regional cerebral blood flow. Smokers reported more withdrawal symptoms with the placebo patch than the

nicotine patch. Smokers also self-reported more withdrawal symptoms in the abstinence conditions compared to the VLNC cigarette conditions (Addicott et al., 2014).

Attwood et al. (2009) investigated the effects of nicotine on subjective effects and hedonic behaviors, such as facial attractiveness. Following 24-hour abstinence, 48 non-dependent smokers (< 3 Fagerström Test for Nicotine Dependence [FTND] score) were randomized to smoke either a Quest 1 NNC cigarette or a Quest 3 VLNC cigarette. Each participant then rated the attractiveness of photographs of 20 male and 20 female faces. Ratings of attractiveness were higher among participants who smoked an NNC cigarette. Craving decreased from pre-cigarette to post-cigarette in both cigarette conditions. Irritability also decreased from pre-cigarette to post-cigarette in both conditions, and this decrease was greater in the NNC cigarette condition. At the end of the session, participants were also asked if they thought they smoked a nicotine-containing or denicotinized cigarette, and 57% of the participants answered correctly (Attwood et al., 2009).

Attwood et al. (2012) investigated the independent and combined effects of nicotine and alcohol on subjective measures in 96 participants who were social drinkers (5-35 units of alcohol per week) and light smokers (≤ 14 cigarettes per week and no smoking within the first hour of waking). Participants were randomized into one of four groups and received either a non-alcoholic or alcoholic beverage (0.4 g/kg of alcohol) and a Quest 1 NNC cigarette or a Quest 3 VLNC cigarette. Participants completed questionnaires before and after smoking, and they rated the attractiveness of photographs after the session. The lowest ratings of attractiveness were observed in participants who smoked a VLNC cigarette and consumed a non-alcoholic beverage, and the highest ratings were observed in participants who smoked an NNC cigarette and consumed an alcoholic beverage. Ratings of intoxication increased over time in all groups, and they were highest in participants who smoked an NNC cigarette and consumed an alcoholic beverage. Higher nicotine craving scores were observed in the alcohol conditions. After the full session was completed, participants were asked if they received alcohol, nicotine, or placebo. Seventy-seven percent of participants correctly identified alcohol in their beverage, and 68% correctly identified nicotine in their cigarettes (Attwood, Penton-Voak, Goodwin, & Munafo, 2012).

Baldinger and colleagues (1995a) investigated the effects of nicotine on cognitive and subjective measures in 15 adult female smokers who smoked usual brand cigarettes and Next VLNC cigarettes during separate sessions. Participants completed questionnaires and two cognitive tasks: the self-paced rapid information processing task and the fixed rate rapid information processing task. Nicotine decreased reaction time in the fixed rate rapid information processing task but increased reaction time in the self-paced rapid information

processing task. Cigarette consumption was comparable across cigarette conditions, but salivary cotinine levels and ratings of taste and strength were higher for the usual brand cigarettes than the VLNC cigarettes. Usual brand cigarettes also reduced craving significantly more than VLNC cigarettes (Baldinger et al., 1995a).

Baldinger and colleagues (1995b) investigated the effects of nicotine in 12 adult female smokers while participants smoked their usual brand cigarettes, Next VLNC cigarettes, or abstained from smoking during two 3-day monitoring periods. Salivary cotinine was higher on days participants smoked their usual brand cigarettes compared to days they smoked VLNC cigarettes or abstained from smoking. CPD did not differ between cigarette conditions. Craving, desire to smoke, and time spent smoking and thinking about smoking were similar across cigarette conditions. Strength and taste were rated higher for usual brand cigarettes than VLNC cigarettes. Ratings of impatience and irritability were similar on days participants smoked usual brand cigarettes and VLNC cigarettes, and these ratings were higher on days participants abstained from smoking (Baldinger et al., 1995b).

Baldinger and colleagues (1995) examined the effects of nicotine and tar on smoking-related outcomes in 12 female smokers during three laboratory sessions. During each session, participants smoked one of three types of cigarettes in a within-subject design: 1) usual brand cigarettes that produced conventional nicotine and tar yields, 2) “ultralight” cigarettes of the same or similar brand as participants’ usual brand, which produced low nicotine and tar yields, and 3) Next brand VLNC cigarettes that produced low nicotine and conventional tar yields. Breath CO boost was higher in the usual brand cigarette condition relative to the “ultralight” cigarette condition, but not relative to the VLNC cigarette condition. Heart rate increased more following usual brand and “ultralight” cigarette smoking relative to VLNC cigarette smoking. Usual brand and “ultralight” cigarettes increased EEG power in the beta band, but VLNC cigarettes did not. Taste and strength were rated higher for usual brand cigarettes than for “ultralight” or VLNC cigarettes. Enjoyment was rated lower for VLNC cigarettes than for usual brand or “ultralight” cigarettes (Baldinger et al., 1995c).

Barrett et al. (2006) investigated the effects of nicotine on alcohol self-administration and subjective measures in 15 non-dependent (FTND score = 0) Canadian male smokers. Participants attended two laboratory sessions 14 days apart wherein they smoked either four NNC cigarettes (Players Light Tobacco, 1.2 mg nicotine yield per cigarette) or four Quest 3 VLNC cigarettes at 30-minute intervals. Throughout the session, participants could earn water or alcohol by pressing a computer key on a progressive ratio schedule of reinforcement. Relative to VLNC cigarettes, NNC cigarettes increased alcohol self-administration but not water self-

administration. In addition, NNC cigarettes significantly increased subjective ratings of intoxication (Barrett et al., 2006).

Barrett and colleagues (2010) conducted a laboratory study to evaluate the acute subjective and reinforcing effects of nicotine in 22 smokers with either high or low levels of nicotine dependence. The study employed a within-subject design wherein participants completed four separate sessions that differed by tobacco product: Quest 1 NNC cigarette, Quest 3 VLNC cigarette, nicotine inhaler, and placebo inhaler. In each cigarette condition, two cigarettes were smoked *ad libitum*, separated by a 10-minute break. In each inhaler condition, participants were instructed to take one deep inhalation every 10 seconds throughout the 20-minute session. Following each session, participants rated craving, withdrawal, and subjective effects and completed a self-administration task during which they could earn puffs of their usual brand cigarette. Relative to inhalers, both NNC and VLNC cigarettes decreased ratings of craving. Women experienced greater withdrawal-related craving relief than men following self-administration of VLNC cigarettes. Onset of usual brand cigarette self-administration was delayed in both the NNC and VLNC cigarette conditions compared to both inhaler conditions; however, only the NNC cigarette condition was associated with reduced self-administration of usual brand cigarettes. Generally, both the NNC and VLNC cigarette conditions were associated with increased ratings of positive subjective effects compared to the inhaler conditions. In sum, while VLNC cigarettes resulted in significant satisfaction and reduced craving, only NNC cigarettes were associated with suppression of smoking (Barrett, 2010).

Barrett and colleagues (2012) conducted a laboratory study to examine the effects of acute nicotine administration on the subjective and behavioral responses to VLNC cigarettes in 27 smokers. The study employed a two-session, within-subject design wherein participants were administered a nicotine or placebo lozenge and then smoked a Quest 3 VLNC cigarette. Following each session, participants rated craving, withdrawal, and subjective effects and completed a self-administration task during which they could earn additional puffs of a VLNC cigarette. Relative to the placebo lozenge, the nicotine lozenge was associated with reduced levels of VLNC cigarette smoking. VLNC cigarette smoking was associated with reduced craving and increased ratings of positive subjective effects under both lozenge conditions. In sum, VLNC cigarettes were associated with relief from craving and increased positive subjective effects; however, only nicotine lozenge decreased VLNC cigarette smoking (Barrett & Darredeau, 2012).

Barret et al. (2013) investigated the effects of alcohol consumption on cigarette smoking in 17 nicotine dependent (FTND score ≥ 3) and 23 non-dependent (FTND score = 0) Canadian smokers who were regular consumers of alcohol (≥ 4 drinks ≥ 1 occasion per week during the previous month). Participants drank a beverage and smoked a cigarette in four double-blind 2-

hour sessions. The beverage contained either alcohol or placebo, and the cigarette was either a Quest 1 NNC cigarette or a Quest 3 VLNC cigarette. Participants completed subjective effects questionnaires before and after consuming a beverage and smoking a cigarette. Participants could then earn additional puffs of the same type of cigarette by pressing a computer key on a progressive ratio schedule of reinforcement. Dependent smokers earned more puffs during the progressive ratio task than non-dependent smokers across all conditions. Alcohol consumption increased NNC and VLNC cigarette smoking in non-dependent smokers and increased NNC cigarette smoking in dependent smokers. Craving decreased in dependent smokers after smoking an NNC cigarette and consuming a placebo beverage, and craving remained relatively high after smoking an NNC cigarette and consuming an alcoholic beverage (Barrett et al., 2013).

Benowitz and colleagues (2006) used a within-subject crossover design to investigate the effects of usual brand cigarettes and five Philip Morris research cigarettes varying in nicotine content (one NNC cigarette, one VLNC cigarette, and three intermediate LNC cigarettes) in 12 adult smokers. Although there were no differences in puffs per cigarette, participants took longer to smoke usual brand cigarettes than the three lowest nicotine content cigarettes. Plasma nicotine increased as a function of cigarette nicotine content; however, there were no differences in carboxyhemoglobin (COHb) levels among cigarettes. Nicotine level was associated with subjective ratings, such that LNC and VLNC cigarettes were rated as significantly milder, less flavorful, smoother, of poorer quality, and less satisfying than usual brand cigarettes. The VLNC cigarette was rated as only slightly satisfying and of overall poor quality, whereas LNC and NNC cigarettes were rated as fairly satisfying and of fair quality. Smoking decreased skin temperature and increased heart rate. Skin temperature decreased more when higher nicotine content cigarettes were smoked, and heart rate increased more when participants smoked their usual brand cigarettes compared to the VLNC cigarette (Benowitz et al., 2006).

Blendy and colleagues (2005) conducted a within-subject laboratory study to evaluate nicotine reward and smoking behavior in obese (n = 17) and non-obese smokers (n=37). Participants first sampled Quest 1 NNC and Quest 3 VLNC cigarettes and then completed four separate choice sessions wherein they could choose four standardized puffs from any combination of the two cigarette types (16 total choices). Subjective effects were assessed after the fourth choice trial. Overall, VLNC cigarettes were associated with significantly lower subjective effects ratings of satisfaction, psychological relief, liking, and strength compared to NNC cigarettes. Fewer NNC cigarette puffs were chosen among obese (48%) than non-obese (70%) participants. Obese participants also reported less difference in satisfaction and liking between NNC and VLNC cigarettes. The study also included an animal experiment in which 12

mice (6 normal diet, 6 high fat diet) completed a conditioned place preference task to assess nicotine reward. Nicotine was less reinforcing to mice maintained on a normal diet compared to those on a high fat diet. Combined, these studies suggest nicotine may be less reinforcing to obese smokers, and, compared to non-obese smokers, smoking behavior may be more strongly maintained by non-nicotine factors (Blendy et al., 2005).

Branstetter and colleagues (2019) conducted a within-subject, 3 (nicotine content) x 3 (price) factorial design laboratory study in which they tested the hypothesis that LNC cigarettes at a lower price would be preferred over NNC cigarettes at a higher price. Participants were 20 adult smokers of non-menthol cigarettes and were overnight abstinent from all nicotine products prior to attending a 3-hour free-choice session, in which they were provided a fixed income and SPECTRUM® VLNC, LNC, and NNC cigarettes (unblinded) according to an escalating price structure per puff (VLNC cigarettes as least expensive to NNC cigarettes as most expensive). Participants were asked to purchase puffs as long as they had remaining income, as well as rate craving and desire to smoke for all cigarettes. All puffs were recorded by a smoking topography device. Urinary TNE was also measured. Participants rated VLNC cigarettes as less satisfying than both other cigarettes; however, they more often selected the VLNC cigarettes over more expensive NNC cigarettes and purchased significantly more VLNC cigarette puffs than both LNC and NNC cigarettes. No significant difference was observed in puff topography; however, TNE differed in a dose-dependent manner (Branstetter et al., 2019).

Brauer and colleagues (1999) investigated the effects of naltrexone on smoking behavior in 19 adult smokers using a double-blind, double-dummy, within-subject design during four conditions. At the beginning of each condition, participants received a 1-week supply of blinded tablets (placebo or 50 mg naltrexone tablets) and transdermal patch (placebo or 21 mg nicotine). On the 7th day of each condition, participants visited a laboratory and smoked a nicotine-containing (brand unspecified) or Next VLNC cigarette and completed subjective assessments. Ratings of enjoyment and arousal were significantly lower after smoking VLNC cigarettes. In addition, the nicotine-containing cigarette produced greater decreases in negative affect than the VLNC cigarette, an effect which was significantly diminished after pretreatment with transdermal nicotine (Brauer et al., 1999).

Brauer et al. (2001) used a 2 x 3 within-subject design to investigate the effects of haloperidol on smoking reward in 20 adult smokers. Participants attended six sessions, each separated by 1 week, wherein they received either placebo, 1 mg, or 2 mg of haloperidol and smoked either a usual brand cigarette or a Next VLNC cigarette under prescribed puffing conditions (10 puffs at 1-minute inter-puff intervals) followed by 3 hours of *ad libitum* smoking.

Generally, haloperidol reduced the number of cigarettes smoked in both usual brand and VLNC cigarette conditions. Usual brand cigarettes were rated higher than VLNC cigarettes on aversiveness, enjoyment of sensations, psychological reward, craving reduction, smoking satisfaction, and strength of respiratory tract sensations (Brauer et al., 2001).

Breland and colleagues (2002) used a within-subject design to investigate the acute physiological, behavioral, and subjective effects of usual brand cigarettes, Ultratech VLNC cigarettes, and Accord (Philip Morris Inc., Richmond, VA) and Eclipse (R. J. Reynolds, Inc., Winston-Salem, NC) tobacco products in 20 adult smokers. Participants attended four sessions, each following overnight abstinence and separated by at least 24 hours. A different tobacco product was used in each session, and each session included four bouts of product use. Except for the Accord, all products decreased smoking urges after the first bout. Except for VLNC cigarettes, all products increased plasma nicotine concentration (Breland et al., 2002).

Brody et al. (2009) investigated the role of nicotine in smoking-related dopamine release. In this study, 62 treatment-seeking adult smokers smoked either their usual brand cigarettes or Quest 3 VLNC cigarettes prior to an imaging session (positron emission tomography [PET] and magnetic resonance imaging [MRI]). An MRI scan was completed within 1 week of the PET scan, and the images were combined. During PET scanning, participants smoked a cigarette through a puff topography device. No differences in puff volume, number of puffs, reduction in craving, or reduction in anxiety were observed between usual brand and VLNC cigarettes. Usual brand cigarettes produced greater dopamine release than VLNC cigarettes, and this correlated with improvements in mood (Brody, Mandelkern, Olmstead, et al., 2009).

Buckley and colleagues (2007) investigated the effects of nicotine in 88 smokers diagnosed with post-traumatic stress disorder (PTSD). Participants were randomized into one of two groups: (1) exposure to anxiety-eliciting conditions or (2) exposure to neutral conditions. Within each group, half of participants smoked Ultratech LNC cigarettes and the other half smoked Ultratech VLNC cigarettes. Participants self-reported a higher anxiolytic effect after smoking LNC cigarettes compared to VLNC cigarettes (Buckley et al., 2007).

Cassidy and colleagues (2018a) conducted a within-subject laboratory study to evaluate the effects of VLNC cigarettes in 50 adolescent smokers. Participants were 15–19 years old, smoked at least one cigarette per day on 28 of the last 30 days, and were daily smokers for at least the last 6 months. Participants completed four separate sessions under double-blind conditions wherein they smoked a single SPECTRUM® NNC (15.8 mg nicotine per g of total tobacco) LNC (5.2 and 1.3 mg nicotine per g of total tobacco) and VLNC (0.4 mg nicotine per g of

total tobacco) cigarette through a smoking topography device and then completed self-report questionnaires. This procedure was repeated for each of the four study cigarettes. There was no effect of nicotine content on withdrawal, negative affect, or CO boost. However, higher nicotine content was associated with a greater reduction in craving. Adolescents with higher nicotine dependence levels had greater decreases in craving in response to higher nicotine content cigarettes. Cigarettes with higher nicotine content were associated with significantly greater smoking satisfaction, psychological reward, craving reduction, enjoyment of respiratory sensations, and aversion. The authors concluded that lower nicotine content cigarettes are associated with reduced abuse liability in adolescent smokers (Cassidy, Colby, et al., 2018a).

Denlinger-Apte and colleagues (2019) conducted a secondary analysis of data from Cassidy, Colby, et al. (2018a) on the effects of cigarette nicotine content and menthol preference on subjective ratings and breath CO boost among 50 adolescent smokers (15-19 years of age). Following overnight abstinence, participants sampled SPECTRUM® VLNC and NNC research cigarettes (menthol status consistent with participants' usual brand) in a counterbalanced order and completed subjective ratings measures after each session. Breath CO was obtained pre- and post-smoking. VLNC cigarettes were rated significantly lower than NNC cigarettes. Menthol cigarettes were rated higher with respect to psychological reward, but lower with respect to satisfaction, craving reduction, and enjoyment in the respiratory tract. Menthol smokers reported less craving reduction, but there was not a significant interaction of menthol status with nicotine content. Craving reduction was lowest for female menthol smokers with NNC cigarettes. There was no effect of nicotine content or menthol status on breath CO boost (Denlinger-Apte, Cassidy, et al., 2019c).

Chukwueke and colleagues (2020) conducted a double-blind, multi-site laboratory study to measure the reinforcing effects of NNC cigarettes (Quest 1 NNC cigarettes, Player's Rich brand NNC cigarettes, or SPECTRUM® NNC cigarettes) and VLNC cigarettes (Quest 3 VLNC or SPECTRUM® VLNC cigarettes) among 104 adult smokers. Three phases took place during a single session: smoking deprivation, cigarette exposure, and forced-choice trials. Self-reported ratings of reinforcing efficacy and the number of puffs taken were recorded. Overall, NNC cigarettes were more highly rated as reinforcing than VLNC cigarettes across multiple domains,

except aversion, and participants chose significantly more puffs from the NNC than VLNC cigarettes. Despite the multiple brands used in the study, no effect of brand was observed (Chukwueke et al., 2020).

Butler, Chenoweth and colleagues (2021) conducted a secondary analysis of Chukwueke et al. (2020) in which the authors investigated the impact of CYP2A6 (the primary enzyme responsible for nicotine metabolism) activity on nicotine reinforcement and cue-reactivity. CYP2A6 activity was indexed in smokers who completed a forced-choice and cue-induced craving task. Controlling for race and sex, those categorized as normal nicotine metabolizers selected a greater proportion of NNC puffs on the forced-choice task than reduced nicotine metabolizers. CYP2A6 activity, however, was not associated with tobacco cue-reactivity (Butler et al., 2021a).

Butler, Forget and colleagues (2021) conducted a secondary analysis of Chukwueke et al. (2020) in which the authors investigated the associations between nicotine reinforcement and cue reactivity in humans. Nicotine reinforcement was assessed in human smokers using a forced-choice task between NNC and VLNC cigarettes, and self-reported cue-induced craving was assessed following exposure to smoking and neutral cues. Overall, greater preference for the NNC cigarettes was associated with the presence of smoking over neutral cues (Butler et al., 2021b).

Cobb and colleagues (2010) conducted a laboratory study to evaluate the acute subjective and physiological effects of potential reduced exposure products (PREPs) in 28 adult smokers. The study employed a within-subject design wherein participants completed seven separate sessions that differed by tobacco product: usual brand cigarette, sham smoking (i.e., puffing on an unlit cigarette), Quest 3 VLNC cigarette, ARIVA dissolvable tobacco, Camel Snus, Marlboro Snus, and COMMIT lozenge. In each session, the tobacco product was administered twice separated by 60-minute breaks, while plasma nicotine, breath CO, and subjective effects were assessed repeatedly. Plasma nicotine levels increased significantly from baseline following administration of participants' usual brand cigarette, but not after VLNC cigarette or sham smoking conditions. Camel snus increased plasma nicotine levels from baseline at 15 minutes post-administration during only one of the two trials. Heart rate increased significantly from baseline after smoking both usual brand cigarettes, but only at the first time point following the first VLNC cigarette. Camel snus increased heart rate at one time point after the first administration. Breath CO increased significantly from baseline in both the usual brand and

VLNC cigarette conditions. There were significant reductions from baseline in craving and withdrawal following usual brand and VLNC cigarette conditions. PREPs suppressed craving and withdrawal at irregular time points, but to a lesser magnitude than usual brand smoking. Ratings of enjoyment and satisfaction were significantly higher for usual brand cigarettes relative to all other conditions. In sum, usual brand and VLNC cigarettes reduced nicotine craving and withdrawal to a similar extent, but VLNC cigarettes were rated as less appealing (Cobb et al., 2010).

Cook and colleagues (2007) examined the influence of nicotine and individual differences in hedonia on affective response to a positive mood induction in 50 smokers (25 hedonic, 25 anhedonic). The study employed a counter-balanced, within-subject design wherein participants underwent positive mood induction while smoking either a LifeTech LNC or VLNC cigarette. Irrespective of hedonia status, participants rated the VLNC cigarette as less satisfying and harsher than the LNC cigarette. In addition, the anhedonic group experienced a significant increase in positive affect following the LNC but not VLNC cigarette condition (Cook et al., 2007).

Dallery and colleagues (2003) examined the role of nicotine and sensory cues in mediating craving and smoking in 15 heavy smokers. The study employed a within-subject design involving four sessions: rapid or self-paced smoking of Ultratech LNC cigarettes, and rapid or self-paced smoking of Ultratech VLNC cigarettes. Assessments of craving and latency to smoke during subsequent smoking opportunities followed each session. In both the rapid and self-paced sessions, participants smoked fewer LNC cigarettes than VLNC cigarettes. While nicotine levels were significantly higher following the LNC cigarette conditions, breath CO was significantly higher following the VLNC cigarette conditions. There was no effect of nicotine condition on heart rate or blood pressure. Craving was suppressed after each of the four sessions. The VLNC cigarette was associated with poorer subjective effects. In the rapid smoking conditions, latency to smoke was about 50% longer after smoking an LNC cigarette, and participants smoked fewer cigarettes and took fewer puffs compared to the VLNC cigarette. In the self-paced conditions, there were no differences in smoking latency, number of cigarettes smoked, or number of puffs as a function of nicotine content (Dallery et al., 2003).

Darredeau and colleagues (2013) examined the effects of nicotine and expectancy on subjective and behavioral effects in 30 dependent and 30 non-dependent smokers. The study employed a balanced placebo design, wherein participants completed two laboratory sessions during which they were provided with either Quest 1 NNC or Quest 3 VLNC cigarettes for both sessions, but they were told that they received nicotine-containing cigarettes in one session and denicotinized cigarettes in the other session. During each session, participants completed

subjective assessments before and after taking three puffs from the assigned cigarette and earning cigarette puffs in a progressive ratio task. Dependent smokers earned more puffs than non-dependent smokers regardless of nicotine expectancy or nicotine content. Irrespective of dependence level, participants earned more puffs when they were told the cigarettes contained nicotine than when they were told the cigarettes were denicotinized. Only participants who received NNC cigarettes showed increases in positive subjective effects. In sum, while NNC cigarettes led to greater increases in positive subjective effects, expectancy may influence behavioral responses to the nicotine content of cigarettes (Darredeau et al., 2013).

Dedert and colleagues (2012) examined associations between PTSD, nicotine, and the conditioned reinforcing effects of smoking on nicotine withdrawal symptoms in 37 smokers with and without PTSD. The study employed a within-subject design wherein participants completed three experimental sessions that differed by smoking condition: usual brand cigarette, Quest 3 VLNC cigarette, and no cigarette. After the smoking manipulation, the PTSD group showed significantly less relief from craving compared with the non-PTSD group. Across groups, usual brand cigarettes were associated with the greatest decrease in craving, followed by VLNC cigarettes and no smoking. There were no statistically significant differences in negative affect between PTSD groups following the cigarette conditions; however, the PTSD group reported increased negative affect following the no smoking condition. There was a significantly greater reduction in habit withdrawal following the usual brand condition compared to VLNC cigarette or no smoking conditions (Dedert et al., 2012).

Denlinger-Apte and colleagues (2017) conducted a single-session within-subject laboratory study to assess subjective effects of VLNC cigarettes in 68 adult daily smokers. Participants smoked two identical Quest 3 VLNC cigarettes, separated by 45 minutes, but they were told that one contained “average” nicotine content and the other contained “very low” nicotine content. After smoking each cigarette, participants completed subjective effects measures. The “very low” nicotine cigarette was rated as having significantly less nicotine than the “average” nicotine cigarette. The “very low” nicotine cigarette was rated as less risky to health compared to the “average” nicotine cigarette for all disease risks, including addiction. Participants rated the “very low” nicotine cigarette as less satisfying, rewarding, and enjoyable from respiratory sensations compared to the “average” nicotine cigarette, but there were no differences on aversion or craving reduction subscales. Participants endorsed greater interest in quitting smoking if they could only purchase the “very low” nicotine cigarette compared to the “average” nicotine cigarette. The authors concluded that knowledge of reduced nicotine content influences smokers’ perceptions of the cigarettes (Denlinger-Apte et al., 2017).

Eid and colleagues (2005) employed a within-subject experimental design to examine physiological and subjective effects of mentholated Ultratech LNC and VLNC cigarettes in eight adult menthol smokers. At the beginning of each session, participants smoked a single cigarette of their usual brand. Participants then smoked the LNC or VLNC cigarettes every 30, 60, or 240 minutes, such that each participant smoked one, four, or eight experimental cigarettes per 4-hour experimental session. Thus, over the course of six sessions, all participants smoked both types of experimental cigarettes at all three smoking intervals. Heart rate and breath CO were assessed before and after participants smoked their usual brand cigarette as well as before and after they smoked the final experimental cigarette of each session. Self-reported craving and urge to smoke were assessed at 15-minute intervals throughout each session. Both LNC and VLNC cigarettes produced decreases in subjective measures of craving and urge to smoke, indicating that non-nicotine features of the reduced nicotine content cigarettes were sufficient to produce reductions in craving. The LNC cigarette produced increases in heart rate following all smoking intervals, whereas the VLNC cigarette produced increases in heart rate only after the 30- and 240-minute smoking intervals. The VLNC cigarette increased breath CO at all intervals, whereas the LNC cigarette increased breath CO only after the 60- and 240-minute smoking intervals. The authors concluded that acute tobacco cravings can be diminished during repeated administration of VLNC cigarettes (Eid et al., 2005).

Faulkner and colleagues (2017) conducted a five-session, double-blind, within-subject laboratory study to assess the effects of nicotine metabolism and nicotine content in 46 young adult smokers (18-25 years of age) who smoked at least 5 cigarettes per day for at least 1 year. In each session, participants smoked one usual brand or SPECTRUM® research cigarette that varied in nicotine content (0.4 mg nicotine per g of total tobacco VLNC cigarette, 2.4 mg nicotine per g of total tobacco LNC cigarette, 5.2 mg nicotine per g of total tobacco LNC cigarette, and 15.8 mg nicotine per g of total tobacco NNC cigarette). All SPECTRUM® cigarettes significantly reduced total nicotine withdrawal score, with no effect of nicotine content and no difference in withdrawal reduction between research cigarettes and usual brand cigarettes. Compared to slow nicotine metabolizers, normal metabolizers had greater decreases in withdrawal while smoking all cigarettes. The usual brand cigarette produced greater reductions in withdrawal than the research cigarettes in normal metabolizers compared to slow metabolizers. Research cigarettes increased positive affect and reduced negative affect, with no effect of nicotine content. The NNC cigarette was associated with higher subjective effects ratings of strength, perceived nicotine content, liking, and disliking compared to the LNC and VLNC cigarettes. There were no differences in smoking topography as a function of nicotine

content. Plasma nicotine increased as nicotine content increased, but it was not significantly different between slow and normal metabolizers (Faulkner et al., 2017).

> Faulkner and colleagues (2018) conducted a secondary analysis of data from Faulkner et al. (2017) to assess sex differences in the influence of cigarettes varying in nicotine content on craving, withdrawal, and affect in 46 young adult smokers. There were no sex differences in smoking topography or plasma nicotine levels. Smoking any of the research cigarettes significantly reduced total withdrawal score more in women than in men, with no effect of nicotine content. In addition, smoking increased positive affect and decreased negative affect more in women than in men, with no effect of nicotine content. As nicotine content increased, men, but not women, reported greater craving reduction and "liking." The authors concluded that men may be more sensitive to cigarette nicotine content than women (Faulkner et al., 2018).
>
> Faulkner and colleagues (2019) conducted a secondary analysis of data from Faulkner et al. (2017) to investigate how nicotine exposure contributes to relief of craving and negative affect among 21 young adult smokers (18-25 years of age). Testing occurred in the morning after overnight abstinence from smoking and again immediately after *ad libitum* smoking of one of four research cigarettes (SPECTRUM® VLNC, LNC [with two different nicotine contents], and NNC non-mentholated cigarettes) in randomized order across four sessions. Smoking topography was also measured. Smoking reduced craving and negative affect regardless of nicotine content, and smoking topography did not vary by nicotine content (Faulkner et al., 2019).

Greenstein and colleagues (2010) investigated the effects of nicotine and alcohol on subjective effects and memory in 127 adult smokers under controlled laboratory conditions. At the beginning of the experimental session, participants smoked one usual brand cigarette before half of the participants were randomly assigned to smoke two Ultratech VLNC cigarettes, and the other half were assigned to smoke two Ultratech LNC cigarettes under prescribed puffing conditions. In addition, half of participants in each group were randomly assigned to consume three alcoholic beverages, and the other half consumed three placebo beverages. Participants were blinded to the nicotine content of the cigarettes and the alcohol content of the beverages. Regardless of alcohol condition, participants rated LNC cigarettes as stronger and more pleasant than VLNC cigarettes. In addition, participants assigned to smoke the LNC

cigarettes performed worse on the recall task after smoking than participants who were assigned to smoke the VLNC cigarettes (Greenstein et al., 2010).

Gross and colleagues (1997) investigated physiological and subjective effects of cigarettes in 10 adult non-menthol smokers under prescribed smoking conditions. The study employed a within-subject design to compare the effects of participants' usual brand cigarettes to the effects of Next VLNC cigarettes and Winston Salem Lights cigarettes during three laboratory sessions. Plasma nicotine levels increased significantly after participants smoked their usual brand cigarettes but not after they smoked VLNC and "light" cigarettes. Heart rate increased significantly after smoking usual brand and light cigarettes but not after smoking VLNC cigarettes. Breath CO increased after smoking each brand of cigarette, but the increases were not significantly different between cigarette conditions. Ratings of enjoyment and satisfaction were significantly higher for usual brand cigarettes relative to light and VLNC cigarettes. There were also differences in some subjective measures of sensory characteristics between cigarette conditions (e.g., usual brand cigarettes were rated as significantly "stronger" than VLNC cigarettes). Following a 90-minute period of deprivation, there were no significant differences in ratings of craving or withdrawal between cigarette conditions (Gross et al., 1997).

Guillot and colleagues (2015) investigated physiological and subjective effects of nicotine and expectancy on tobacco withdrawal in a preliminary study of 32 adult smokers. Participants were randomized to one of eight conditions in a 2 x 2 x 2 factorial design with the following factors: nicotine (participants received a 21 mg transdermal nicotine patch or they received a placebo patch), expectancy (participants were told the patch they received contained nicotine or they were told it was a placebo), and sensorimotor effects of smoking (participants smoked Magic VLNC cigarettes or they did not smoke). Participants attended a single experimental session. The transdermal nicotine or placebo patch was applied for 3.5 hours. During this time, repeated subjective and physiological measures were assessed, and participants who received VLNC cigarettes were instructed to smoke four cigarettes under prescribed smoking conditions. They were informed that the cigarettes contained no nicotine. An hour after the patch and prescribed smoking period, participants completed a smoking lapse analogue task, during which they could smoke their usual brand cigarettes at any time, but they received $0.20 for each 5-minute period they delayed smoking for up to 50 minutes. After 50 minutes or upon lapse, a 1-hour self-administration period began, during which $0.20 was deducted from a $1.60 credit for each cigarette that was lit. The task was followed by a 2-hour no-smoking period. Due to the small sample size of this study, only the main effects of each factor (i.e., nicotine, expectancy, sensorimotor effects of smoking) were examined. During the 3.5-hour transdermal patch period, negative affect, urge to smoke, and withdrawal symptoms

were significantly lower in participants who smoked VLNC cigarettes relative to those who received no VLNC cigarettes. In addition, participants who received VLNC cigarettes delayed smoking significantly longer and smoked significantly fewer usual brand cigarettes during the smoking lapse analogue task than those who received no VLNC cigarettes (Guillot et al., 2015).

Harrell and Juliano (2012) investigated the effects of nicotine expectancy on cognitive and subjective effects in 80 adult smokers. Participants were assigned to one of four conditions: (1) they were given a Quest 1 NNC cigarette and told they were given a nicotine-containing cigarette that would enhance motor performance, (2) they were given a Quest 3 VLNC cigarette and told they were given a nicotine-containing cigarette that would enhance motor performance, (3) they were given a Quest 1 NNC cigarette and told they were given a nicotine-containing cigarette that would impair motor performance, and (4) they were given a Quest 3 VLNC cigarette and told they were given a nicotine-containing cigarette that would impair motor performance. Participants attended a single laboratory session during which they smoked the study-assigned cigarette and completed assessments, including a task to assess motor performance. Regardless of expectancy, nicotine improved motor performance, decreased craving, increased smoking satisfaction, and increased dizziness. Breath CO was not significantly different across conditions (Harrell & Juliano, 2012).

Hasenfratz et al (1993) investigated the effects of nicotine on smoking behavior and physiological outcomes in 12 female adult smokers. Participants attended three laboratory sessions, each separated by one week. In a within-subject design, participants smoked one of the following three cigarettes in each session: (1) usual brand cigarettes, (2) “ultra-light” cigarettes (of the same brand if possible), and (3) Next VLNC cigarettes. In addition, participants smoked the assigned cigarette throughout the day preceding the laboratory session. Behavioral, physiological, and subjective effects were compared between sessions. During laboratory smoking sessions, plasma nicotine was significantly different across cigarette conditions, such that usual brand cigarettes produced the greatest increase in plasma nicotine, ultra-light cigarettes produced an intermediate increase, and VLNC cigarettes produced only a negligible increase. Increases in heart rate and diastolic blood pressure after smoking followed a similar pattern and were also significantly different across conditions, with the greatest increases observed in the usual brand cigarette condition. Ratings of positive subjective effects also showed a similar pattern and were generally highest for usual brand cigarettes, lowest for VLNC cigarettes, and intermediate for ultra-light cigarettes. All cigarettes reduced craving, but the reduction was greatest for usual brand cigarettes. Smoking patterns during sessions (e.g., puffs per cigarette) and during the preceding day (e.g., inter-cigarette interval) did not differ significantly between conditions. After a day of smoking study-assigned cigarettes, plasma

cotinine was highest in the usual brand cigarette condition, lowest in the VLNC cigarette condition, and intermediate in the ultra-light cigarette condition (Hasenfratz et al., 1993).

Hatsukami and colleagues (2013) conducted two pilot studies (published together) that examined relations between nicotine content and various subjective and physiological effects of SPECTRUM® research cigarettes. In the first experiment, 51 adult smokers attended one laboratory session wherein they smoked one usual brand cigarette, followed by three SPECTRUM® research cigarettes: VLNC, LNC, and NNC cigarettes (reported as 0.4, 5.7–5.8, and 11.4–12.8 mg nicotine per gram of total tobacco, respectively) in random order. Participants were assigned menthol or nonmenthol cigarettes based on their preference. Participants took 4 puffs from each cigarette separated by a 30-second inter-puff interval, and cigarettes were separated by a 30-minute inter-cigarette interval. Positive subjective effects were significantly higher for the NNC cigarette relative to the VLNC cigarette. Reductions in craving were also higher for the NNC cigarette relative to the VLNC cigarette. In a monetary decision task, participants were asked the price at which they would switch to money over a pack of cigarettes. This price was significantly higher for the NNC and LNC cigarettes relative to the VLNC cigarettes, indicating that VLNC cigarettes were not as valuable or rewarding to participants as the higher nicotine content cigarettes. Participants were also asked to rank the cigarettes in order of preference. NNC and LNC cigarettes were significantly more likely to be ranked higher than VLNC cigarettes. Perceived health risk was significantly higher for the NNC cigarettes relative to the VLNC cigarettes. Heart rate and blood pressure were also significantly higher after participants smoked the NNC and LNC cigarettes compared to the VLNC cigarettes. In the second experiment, 36 participants were instructed to smoke their usual brand cigarettes during Week 1 before they were randomly assigned and instructed to exclusively smoke NNC, LNC, or VLNC cigarettes during Week 2. Throughout the study, participants kept a daily diary of all experimental and usual brand cigarettes smoked. Subjective effects, biomarkers, and physiological outcomes were assessed. Participants smoked significantly more NNC cigarettes than VLNC cigarettes during Week 2. In addition, participants in the NNC cigarette group smoked more study cigarettes during Week 2 relative to usual brand cigarettes during Week 1, whereas participants in the LNC and VLNC cigarette groups did not smoke significantly different numbers of cigarettes during Week 2 relative to usual brand cigarettes during Week 1. Noncompliance with study-assigned cigarettes was observed in all groups, as some participants reported smoking their usual brand cigarettes during Week 2. At the end of Week 2, total cotinine, total nicotine equivalents (TNE), and breath CO were lower in the VLNC cigarette group relative to the NNC cigarette group among participants with available biomarker data who smoked fewer than four usual brand cigarettes during Week 2. Participants rated NNC

cigarettes significantly more satisfying and enjoyable than VLNC cigarettes. The price at which participants reported they were willing to switch from cigarettes to money in the monetary choice task was higher in the NNC cigarette group relative to the VLNC cigarette group. Thus, results from these pilot studies demonstrated that participants found the NNC cigarettes more reinforcing than the VLNC cigarettes (Hatsukami, Heishman, et al., 2013).

Heil and colleagues (2020) conducted a within-subject laboratory study to assess the abuse potential of LNC and VLNC cigarettes among 10 adult, pregnant (< 25 weeks gestational age) cigarette smokers using an experimental design similar to Higgins et al. (2017). Briefly, in Phase 1, participants blindly sampled two SPECTRUM® research cigarettes, LNC and VLNC cigarettes, and their usual brand NNC cigarette in separate sessions, and then completed a behavioral economic simulation task and measures of subjective effects, craving/withdrawal, and smoking topography. During Phase 2, the abuse liability of the NNC, LNC, and VLNC cigarettes was assessed using concurrent choice testing. Finally, in Phase 3 the NNC and VLNC cigarette nicotine-content pairs were tested where NNC puffs could be earned on a progressive-ratio schedule. Overall, the NNC cigarettes were chosen more often than LNCs and VLNCs in the Phase 2 testing, and preference for NNC cigarettes was reduced in Phase 3 when access to NNCs was put on a progressive-ratio schedule. Hypothetical cigarette demand and positive subjective effects decreased as a function of increasing price and decreasing nicotine content. All cigarettes significantly reduced nicotine withdrawal symptoms and craving. There were no significant differences in smoking topography or breath CO levels as a function of nicotine content. The authors concluded that LNC and VLNC cigarettes may have reduced abuse liability in pregnant women (Heil et al., 2020).

Higgins and colleagues (2017) conducted a 14-session within-subject laboratory study to assess the abuse potential of VLNC cigarettes. Participants were 169 dependent smokers from one of three vulnerable populations (disadvantaged female smokers, smokers with opioid dependence, and smokers with affective disorders). During Sessions 1–5, subjective effects questionnaires and a Cigarette Purchase Task (CPT) were administered after participants smoked usual brand and each of four SPECTRUM® research cigarettes: 15.8 mg nicotine per g of total tobacco NNC cigarettes, 5.2 mg nicotine per g of total tobacco LNC cigarettes, 2.4 mg nicotine per g of total tobacco LNC cigarettes, and 0.4 mg nicotine per g of total tobacco VLNC cigarettes. During Sessions 6–11, participants could work to earn cigarette puffs by making 10 fixed-response mouse clicks to earn as many puffs from the cigarettes as they wanted during a 3-h period while choosing between two of the four variable nicotine content cigarettes. Sessions 12–14 compared only the VLNC and NNC cigarettes to assess whether preference could be shifted from the NNC cigarette by adjusting puff price such that puffs from the VLNC

cigarette were available contingent on 10 mouse clicks, while the number of clicks necessary to earn puffs from the NNC cigarette started at 10 and increased each time NNC cigarette puffs were chosen. With regard to the CPT, cigarette smoking decreased as a function of increasing price and decreasing nicotine content. Positive subjective effects decreased as a function of reducing the nicotine content in cigarettes. All cigarettes significantly reduced nicotine withdrawal symptoms and craving; however, the duration of these effects was greater with higher nicotine content cigarettes. There were no significant differences in smoking topography or breath CO levels as a function of nicotine content. When cigarettes were available at an equal response cost (Sessions 6-11), participants were more likely to choose the higher nicotine content cigarettes than the cigarettes containing lower nicotine content. When the response cost of the higher nicotine content cigarette increased (Sessions 12-14), participants chose to smoke the VLNC cigarette more frequently than the NNC cigarette. The authors concluded that VLNC cigarettes may have reduced abuse potential in vulnerable populations (Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017).

Davis and colleagues (2019) conducted a secondary analysis of choice task data collected during Sessions 12-14 of Higgins et al. (2017) to investigate whether unit price (calculated by dividing nicotine content by response requirement) determined shifts in preference from NNC to VLNC cigarettes. When the response requirement was the same for NNC and VLNC cigarettes, participants on average preferred the NNC cigarette. However, increasing the unit price for the NNC cigarette (i.e., by increasing the response requirement) shifted preference to the VLNC cigarette, which occurred immediately prior to the unit price of the NNC exceeding that of the VLNC cigarette. This shift was also accompanied by a reduction in total smoking choices made by participants (D. R. Davis, M. J. DeSarno, et al., 2019).

Davis and colleagues (2019) conducted a secondary analysis of data from Higgins et al. (2017) involving brief exposure to research cigarettes during Sessions 1-5 to determine if participants' menthol status (61 menthol smokers and 108 non-menthol smokers) was a moderator to their subjective and behavioral responses to LNC and VLNC cigarettes. No statistically significant effect of menthol status was observed on any of the outcomes of interest, including smoking topography, breath CO, withdrawal, craving, or CPT demand (Danielle R. Davis et al., 2019).

Davis and colleagues (2019) conducted a secondary analysis of data from Higgins et al. (2017) Sessions 1-14 to examine if age (28 young adults 18-24 years

of age versus 141 adults > 24 years of age) was a moderator of subjective and behavioral response to LNC and VLNC cigarettes. Young adults exhibited lower demand for LNC and VLNC cigarettes than adults > 24 on three of the five CPT indices. No other differences by age were observed across smoking topography, breath CO, cigarette puffs, craving, withdrawal, or smoking urge measures (D. R. Davis, M. A. Parker, et al., 2019).

Gaalema and colleagues (2019) conducted a secondary analysis of data from Higgins et al. (2017) Sessions 1-14 to examine if participants' psychiatric diagnosis status or anxiety and depression symptom severity moderated subjective and behavioral responses to LNC and VLNC cigarettes. Depression symptom severity was associated with higher smoking urges and greater desire to smoke. Those with both depression and anxiety disorders had higher reported smoking urges than those with depression alone or neither diagnosis. Higher withdrawal levels were present for those with both anxiety and depression diagnoses when compared to those with depression alone or with no diagnosis. Higher withdrawal levels were observed for those with more severe depression or anxiety symptoms compared to those with less severe symptoms, and consistent interactions were found between both diagnoses and symptom severity by time. Those with higher withdrawal scores had a less complete return to baseline withdrawal levels than those with lower baseline levels of withdrawal. There was no effect of diagnosis or symptom severity on the proportion of higher nicotine content choices. There was no significant interaction between psychiatric variables and nicotine content with respect to withdrawal. There was no effect of diagnosis or symptom severity on either breath CO boost or total puff volume, nor any significant interactions between nicotine content with diagnosis or symptom severity (Gaalema et al., 2019).

Higgins and colleagues (2018) conducted a secondary analysis of data from Higgins et al. (2017) to assess the influence of nicotine dependence severity on response to VLNC cigarettes. For this analysis, participants were retrospectively characterized by dependence severity based upon questions 1-4 of the FTND (range 0-6). Participants with scores of 0–2, 3, and 4–6 were categorized as mildly, moderately, and highly dependent, respectively. With regard to the CPT, demand Intensity and Omax were greater among more dependent smokers, and there was more intense and persistent demand for higher nicotine content cigarettes, but there were no interactions with dependence severity. Subjective effects increased as a function of nicotine

content, but there was no interaction with dependence. Dependence did not influence withdrawal. More dependent smokers reported greater urges to smoke than less dependent smokers, and reductions in smoking urge were dependent on nicotine content among smokers with high but not mild or moderate dependence. Higher nicotine content cigarettes were associated with larger, more intense, and a greater number of puffs than lower nicotine content cigarettes. Maximum flow rate increased as nicotine content increased among smokers with mild and moderate but not high levels of dependence. Participants were significantly more likely to choose the higher nicotine content cigarette during concurrent choice tests, with no significant differences in choice as a function of dependence severity, and participants chose the VLNC cigarette significantly more than the NNC cigarette, with no influence of dependence severity. The authors concluded that nicotine dependence severity does not influence the abuse liability of VLNC cigarettes (Higgins et al., 2018).

Parker and colleagues. (2018) conducted a secondary analysis of data from Higgins et al. (2017) to identify the effects of baseline cannabis use on the reinforcing effects of nicotine. Investigators found that cannabis use did not appear to have a significant impact on participants' choices during choice testing tasks, or on smoking topography. However, cannabis users did rate smoking satisfaction higher than non-users. Overall, this analysis concluded that cannabis use status did not correlate with a change in smoking addiction potential (Parker et al., 2018).

Streck and colleagues (2018) conducted a secondary analysis of data from Higgins et al. (2017) to compare the responses of participants with chronic health conditions to those of participants without chronic health conditions when given VLNC cigarettes. In concurrent choice tests, participants chose cigarettes with higher nicotine content across all cigarette pairings. In the cigarette purchase task, more intense demand was seen consistently with higher nicotine content cigarettes among all participants, regardless of the presence or absence of chronic health conditions (Parker et al., 2018).

Streck and colleagues (2018) conducted a secondary analysis of data from Higgins et al. (2017) to identify moderating effects of sex on the reinforcing effects of nicotine. The cigarette purchase task showed that cigarettes with higher nicotine content had higher reinforcing effects than did cigarettes with

lower nicotine content; this effect did not vary by sex. This study did not show that men and women differed significantly in sensitivity to changes in nicotine content (Streck et al., 2019).

Higgins et al. (2017) employed a within-subject design to investigate the acute effects of nicotine on cigarette preference, smoking behavior, and subjective effects in 26 adult smokers. Participants from three vulnerable populations (disadvantaged female smokers, smokers with opioid dependence, and smokers with affective disorders) attended multiple laboratory sessions. During Phase 1 (Sessions 1-5), participants used a puff topography device to smoke two usual brand cigarettes in Session 1 and two SPECTRUM® research cigarettes per session in Sessions 2-5. In Sessions 2-5, participants were exposed to one cigarette type per session (i.e., SPECTRUM® cigarettes containing 15.8, 5.2, 2.4, and 0.4 mg nicotine per g of total tobacco). No significant differences between cigarettes were observed in smoking topography, breath CO, craving, or withdrawal; however, smoking satisfaction ratings increased as a function of nicotine content, such that the cigarette with the highest nicotine content (i.e., an NNC cigarette) was rated as significantly more satisfying than the cigarette with the lowest nicotine content (i.e., a VLNC cigarette). A hypothetical cigarette purchase task was used to assess the price participants were willing to pay for research cigarettes. The price at which purchasing fell to zero was significantly lower in the VLNC cigarette condition, indicating participants valued the VLNC cigarette less than the higher nicotine content cigarettes. During Phase 2 (Sessions 6-11), a choice procedure was used to assess preference across the cigarettes used in the study. Participants had access to two types of research cigarettes in each session, and they were permitted to smoke as many of these cigarettes as they wanted during a 3-hour period under double-blind, *ad libitum* conditions, such that one of the possible six dose pairs was evaluated in each session. Puffs were contingent on computer mouse clicks, such that two puffs were awarded for 10 clicks. Research cigarettes were identified with the same letter codes in Phases 1 and 2, so participants were familiar with the cigarettes prior to the preference assessments in Phase 2. Participants chose the NNC cigarette significantly more than the two lowest nicotine content cigarettes, including the VLNC cigarette (Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017).

Arger and colleagues (2017) conducted a secondary analysis of data from Higgins et al. (2017) to evaluate the concurrence between subjective effects ratings and choice for cigarettes varying in nicotine content in 26 dependent smokers from three vulnerable populations (disadvantaged female smokers, smokers with opioid dependence, and smokers with affective disorders). Satisfaction and aversion scores independently predicted choice for NNC

research cigarettes over LNC and VLNC cigarettes. A one-point increase in satisfaction difference score was associated with a 7% increase in choice for the NNC cigarette. A one-point increase in aversion difference score was associated with a 10% decrease in choice for the NNC over the LNC and VLNC cigarettes. The results support the use of subjective effects measures as an indication of abuse liability of cigarettes varying in nicotine content (Arger et al., 2017).

Juliano et al. (2006) conducted a prospective study examining the effects of the nicotine content of cigarettes on relapse in 60 adult smokers. Participants who demonstrated 4 days of biochemically verified abstinence were randomly assigned to one of three conditions: 1) a lapse condition in which they smoked five Ultratech VLNC cigarettes, 2) a lapse condition in which they smoked five Ultratech LNC cigarettes, 3) or a no-lapse condition in which they smoked no cigarettes. Participants assigned to the lapse conditions smoked the first cigarette with a puff topography device in a laboratory setting and the remaining four study-assigned cigarettes in their natural environments over the next 4 hours. Participants in the no-lapse condition were instructed to remain abstinent that day. All participants were then instructed to remain abstinent during the next 6 days. Monetary incentives contingent on biochemically verified abstinence were available to increase the likelihood of abstinence, and smoking relapse was assessed during this 6-day period. No significant differences in CO boost, smoking time, or cigarette butt weight were observed between the two lapse conditions after smoking the first cigarette. However, heart rate was significantly higher in the LNC cigarette condition relative to the VLNC cigarette condition. Self-report, breath CO, and cigarette butt weight confirmed that participants in both lapse conditions complied with instructions to smoke four cigarettes in their natural environment. VLNC cigarettes produced significantly higher ratings on “harshness” and “tasting different from usual brand cigarettes;” however, there were no significant differences between cigarettes in ratings of craving, withdrawal or other subjective effects. During the next 6 days, no significant difference in rate of relapse was observed between the two lapse conditions; however, participants in the lapse conditions were more than twice as likely to smoke than participants in the no-lapse condition. As stated above, only participants who demonstrated 4 days of abstinence were randomized to study conditions. Therefore, the generalizability of study findings to smokers who may be unable to abstain from smoking is unclear (Juliano et al., 2006).

Juliano et al. (2011) investigated the effects of nicotine content and expectancy on various subjective measures in 148 adult smokers. Participants were randomly assigned to one of four conditions and attended one experimental session wherein they smoked a single study-assigned cigarette *ad libitum*. Half of participants were told they would receive a cigarette with a normal amount of nicotine, and the other half of participants were told they would receive a cigarette that contained no nicotine. Within each of these groups, half of participants received Quest 1 NNC cigarettes, and the other half received Quest 3 VLNC cigarettes. No significant differences in breath CO were observed between groups. Significant main effects of nicotine content were observed, such that participants who were given NNC cigarettes smoked their cigarette significantly longer than those who were given VLNC cigarettes. There was also a significant nicotine content and expectancy interaction effect on number of puffs. Among participants who were given NNC cigarettes, those who were told they received NNC cigarettes took more puffs than those who were told they received no nicotine. Among participants who were given VLNC cigarettes, those who were told they received NNC cigarettes took fewer puffs than those who were told they received no nicotine. In addition, there were main effects of nicotine content and nicotine expectancy on subjective ratings of cigarettes. Participants who were given NNC cigarettes rated the cigarettes more rewarding than those given VLNC cigarettes on all 11 subjective measures. Participants who were told they received NNC cigarettes rated the cigarettes more rewarding than those who were told they received no nicotine on 9 of 11 measures. Significant interaction effects were observed, such that participants who were told they received no nicotine and received VLNC cigarettes reported greater urge to smoke. Over 80% of participants reported that they believed they smoked a cigarette with nicotine content consistent with what they were told. The highest rate of disbelief (15%) was among participants who were given VLNC cigarettes but were told they received NNC cigarettes (Juliano et al., 2011).

Kamens and colleagues (2020) conducted a within-subject study aiming to characterize the pharmacokinetic profile of SPECTRUM® cigarettes among 12 adults following 12 hours of abstinence from smoking. Four experimental sessions were conducted, during which a usual-brand cigarette and three research cigarettes varying in nicotine content (SPECTRUM® NNC, LNC, and VLNC) were presented under double-blind conditions with order counterbalanced. At each session, blood nicotine, breath CO, and subjective effects were measured before and after smoking the session's assigned cigarette *ad libitum*. Blood-nicotine boost increased in a dose-dependent fashion, with the NNC research cigarette having a similar boost to usual-brand cigarettes. There was no influence of nicotine content on breath CO parameters, nor on self-reported measures of reinforcing effects. Participants took longer puffs on VLNC cigarettes and

smoked them more quickly. The NNC research cigarettes decreased withdrawal, the urge to smoke, and negative affect significantly more than other cigarette types, included usual-brand cigarettes (Kamens et al., 2020).

Kaplan and colleagues (2021) conducted a behavioral economics study in 151 regular smokers to evaluate tobacco product purchasing as a function of four varying regulatory scenarios. In this double-blind study, participants were randomized to one of five cigarette conditions that varied by nicotine content in the cigarettes: SPECTRUM® 15.8 (NNC), 5.2 (LNC), 2.4 (LNC), 1.3 (LNC), or 0.4 (VLNC) mg nicotine per g of total tobacco. Participants were provided with a 5-day budget and made real purchases for tobacco products in an Experimental Tobacco Marketplace where each session modeled a distinct regulatory scenario. In each regulatory scenario, the price of one product (either UB cigarette or assigned research cigarette) was manipulated across six independent pricing scenarios. The prices of all remaining products stayed constant across these scenarios. Participants received all the products they purchased during the session and were instructed to use these products over the next 5 days. Products in the ETM included: assigned research and UB cigarettes, electronic nicotine delivery devices, snus/dip, and nicotine replacement therapies. Research cigarette purchases were lowest when UB cigarettes were available and highest when research cigarettes were the only combusted product available. The concurrent availability of research cigarettes only minimally reduced UB cigarette purchasing. For all conditions except the 5.2 mg nicotine per g of total tobacco condition, non-combusted tobacco product purchasing was higher when research cigarettes were the only combusted product in the marketplace. Nicotine content of research cigarettes did not appear to influence results in the marketplace; however, the authors note that the study may not have been sufficiently powered to detect differences as a function of nicotine content (Kaplan et al., 2021).

Kaplan and colleagues (2022) investigated the association between blood plasma nicotine exposure and hypothetical behavioral economic demand for cigarettes differing in nicotine content. Using a within-subject design, participants smoked a single cigarette during each of six experimental sessions. Cigarettes varied across sessions, including a usual-brand cigarette and five types of SPECTRUM® research cigarettes ranging in nicotine content from 15.8 mg/g (NNC cigarettes) to 0.4 mg/g (VLNC cigarettes). During each session, blood plasma nicotine exposure was assessed at multiple timepoints (10, 15, 20, 30, 45, and 60 min into the session), and hypothetical behavioral economic demand was assessed via the Cigarette Purchase Task 20 minutes into the session. Both cigarette nicotine content and measures of blood plasma nicotine predicted changes in one measure of behavioral economic demand, elasticity (α), with α being significantly higher (indicating lower valuation and/or abuse liability)

for VLNC than NNC cigarettes. Results suggest blood plasma nicotine and cigarette nicotine content both predict changes in behavioral economic demand, with VLNC cigarettes producing the lowest behavioral economic demand (Kaplan et al., 2022).

Karelitz and Perkins (2021) conducted a five-session, within-subjects study in 37 adult dependent smokers to investigate the role of sensory perceptions as predictors of choice of cigarettes with varying nicotine content. Six SPECTRUM® research cigarettes, ranging from 0.4 mg nicotine per g of total tobacco (VLNC) to 17.4 mg nicotine per g of total tobacco nicotine (NNC), were used in the study. Each session, a VLNC cigarette was compared to another research cigarette, and the order was randomized across sessions on separate days. Subjective effects were measured immediately after initial sampling of each cigarette and followed by a puff-by-puff choice procedure to determine preference for each cigarette. Overall, subjective effects (e.g., "liking", "satisfying") and puff choices increased with increasing nicotine content, and menthol moderated associations between subjective effects and nicotine and between puff choices and nicotine. Subjective effects were predictive of puff choice, such that a greater magnitude of difference in subjective effects between VLNC and higher nicotine content cigarettes led to more puff choices from higher nicotine content cigarettes; however, there was no main effect of menthol or significant interaction of 'subjective effects' X 'nicotine condition' (Karelitz & Perkins, 2021).

Kassel et al. (2007) investigated smoking topography in 35 adolescent (15 – 18 years of age) light smokers (1 – 25 cigarettes per week). Participants attended one laboratory session wherein they received a single study cigarette. Half of participants were randomly assigned to receive an Ultratech VLNC cigarette, and the other half received an Ultratech LNC cigarette. Participants were blinded to the nicotine content of the cigarette. They were instructed to smoke as much or as little of the cigarette as they wanted using a smoking topography device. Participants took significantly more puffs from the VLNC cigarette than the LNC cigarette, and a non-significant trend emerged such that increases in breath CO were higher after smoking the VLNC cigarette. The LNC cigarette was rated as significantly more pleasant than the VLNC cigarette (Kassel, Greenstein, et al., 2007).

> In a follow-up study (Kassel, Evatt, et al., 2007), data from an additional 10 adolescent light smokers were combined with data analyzed in the previous report (Kassel, Greenstein, et al., 2007). Findings related to smoking topography, breath CO, and subjective effects were replicated in the follow-up study.

Kelemen and colleagues (2008) examined the effects of nicotine content on cognitive performance and response expectancy in 103 college smokers. The study employed a between-

subject design wherein participants were randomized to smoke either a Quest 1 NNC cigarette or a Quest 3 VLNC cigarette. They then completed assessments of subjective and cognitive effects and were instructed to guess whether the cigarette they received contained nicotine. Participants guessed the nicotine content of their cigarettes with a high level of accuracy, such that 71% of participants who received NNC cigarettes believed their cigarette contained nicotine, and 88% of those who received VLNC cigarettes believed their cigarette contained no nicotine. NNC cigarettes were associated with significantly less urge to smoke and greater positive subjective effects than VLNC cigarettes. As compared to those in the VLNC cigarette condition, participants in the NNC cigarette condition had significantly better cognitive performance scores on one of six measures. Participants who performed well were more likely to attribute their performance to the effects of the cigarette they smoked. In sum, participants preferred the NNC cigarettes; however, there was little effect of nicotine on cognitive performance (Kelemen, 2008).

King and colleagues (2009) examined the effects of alcohol on smoking behavior while participants smoked cigarettes that varied in nicotine content. Participants (n=42) were heavy social drinkers and light smokers (i.e., 1 – 50 cigarettes per week). The study employed a double-blind, between- and within-subject design wherein participants were randomly assigned to receive alcohol (0.8 g/kg) or placebo beverage (between-subject) and Quest 1 NNC or Quest 3 VLNC cigarettes (within-subject) during two sessions. Participants were first instructed to take standard puffs of the assigned cigarette with a puff topography device before and after beverage consumption. Then, 1 hour after beverage consumption, participants were provided the opportunity to smoke the assigned cigarettes over a 3-hour period. Regardless of beverage condition, NNC cigarettes increased positive subjective effects (e.g., satisfaction, enjoyable taste). Alcohol administration, compared to placebo, increased the urge to smoke and positive subjective effects for both NNC and VLNC cigarettes. In men, alcohol increased number of cigarettes chosen and smoking topography characteristics (i.e., puff count, volume, and duration), regardless of nicotine content. In women, however, no differences were observed in number of cigarettes chosen or smoking topography measures as a function of beverage condition (King et al., 2009).

Kuwabara and colleagues (2014) examined the effects of smoking on endogenous opioid release and reward in 10 smokers and 10 non-smokers. Participants abstained from smoking overnight and then received two PET scans, each on a separate day. Prior to PET scan, participants smoked either a Quest 1 NNC or Quest 3 VLNC cigarette. No significant differences in mu opioid receptor binding was observed between cigarette condition (i.e., VLNC versus NNC cigarette) or smoking status (i.e., smoker versus non-smoker) (Kuwabara et al., 2014).

Lindsey and colleagues (2013) examined the effects of cigarette nicotine content and abstinence state (i.e., abstinent versus non-abstinent) on subjective effects. The study employed a within-subject design wherein 14 smokers completed two sessions that differed by cigarette administered: Marlboro "Red" 100 NNC and Quest 3 VLNC cigarette. While in an fMRI machine, participants smoked one assigned cigarette following overnight abstinence and then again 25 minutes after smoking the first cigarette. Subjective effects were assessed repeatedly throughout the experimental sessions. Compared to VLNC cigarettes and non-abstinence, NNC cigarettes and being in a state of abstinence were associated with significantly greater positive subjective effects ratings (e.g., high, drug liking). In contrast, cigarette type was not associated with negative subjective effects (e.g., anxiety); however, craving was significantly reduced when participants were in a state of smoking abstinence, regardless of the nicotine content of the cigarette (Lindsey et al., 2013).

Macqueen and colleagues (2012) examined the effects of cigarette nicotine content on smoking topography in 67 adult smokers. In this two-session, within-subject study, participants were instructed to smoke a Quest 1 NNC or Quest 3 VLNC cigarette in a double-blind and counterbalanced manner following 12 hours of abstinence. Participants were provided the opportunity to smoke four cigarettes *ad libitum* (40-minute inter-cigarette interval) during each session while smoking topography and subjective effects were assessed. VLNC cigarettes were associated with elevated puff volume and duration, and a decrease in inter-puff interval compared to NNC cigarettes. However, differences in puff volume and duration appeared to be transient, as the effects dissipated across smoking bouts until differences were no longer observed between VLNC and NNC cigarette conditions. Participants rated VLNC cigarettes as more satisfying and indicated that they enjoyed the sensory aspects more than NNC cigarettes; however, these effects diminished across smoking trials. Finally, NNC cigarettes were associated with larger reductions in craving compared to VLNC cigarettes (Macqueen et al., 2012).

Naqvi and colleagues (2005) examined the effects of cigarette nicotine content on conditioned reinforcing effects and the airway sensory impact of cigarette puffs in 20 smokers. In this within-subject study, participants took cigarette puffs in six blocks. Each block included each puff type (Quest 1 NNC, Quest 3 VLNC, and unlit cigarettes) presented once per block in pseudo-random order. Heart rate, subjective effects, withdrawal and urge to smoke were measured both before and immediately after the controlled smoking. NNC cigarettes were rated as stronger and more rewarding than VLNC or unlit cigarettes. There were no pre- to post-smoking differences in heart rate, craving, withdrawal, or breath CO (Naqvi & Bechara, 2005).

Naqvi and colleagues (2006) assessed skin conductance responses elicited by the airway sensory effects of cigarettes with varying nicotine content in 15 adult smokers. In this within-subject study, participants took cigarette puffs in six blocks. Each block included each puff type (Quest 1 NNC, Quest 3 VLNC, and unlit cigarettes) presented once per block in pseudo-random order, while subjective effects and skin conductance were assessed. NNC cigarettes were rated as stronger, more desirable, and more pleasurable than VLNC cigarettes. Skin conductance responses did not differ between NNC and VLNC cigarette conditions, but were greater than the unlit cigarette condition. For VLNC cigarette puffs, the average skin conductance response was correlated with average positive subjective effects (Naqvi & Bechara, 2006).

Penetar and colleagues (2012) examined the effects of cigarette nicotine content on subjective and physiological effects in nine smokers. Participants were instructed to smoke four different cigarettes: usual brand, Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes in a counterbalanced order, each separated by 30 minutes. The VLNC cigarette was rated as significantly less satisfying than the LNC cigarette and less similar to participants' usual brand cigarette than the NNC and LNC cigarettes. The NNC and LNC cigarette, but not the VLNC cigarette, increased heart rate from baseline. Skin temperature did not vary throughout the study (Penetar et al., 2012).

Perkins and colleagues (2004) examined the influence of nicotine expectancy on the subjective and reinforcing effects of cigarettes in 96 smokers. The study employed a 2 x 2 design wherein nicotine instructional set (i.e., nicotine content descriptions) and nicotine content were manipulated such that participants were told they received normal nicotine cigarettes or told they received low nicotine cigarettes and they received Meridian NNC or Quest 3 VLNC cigarettes. Participants took two puffs of the study cigarette, rated the cigarette, then completed craving and withdrawal assessments. They then performed a progressive ratio task to assess demand for additional cigarette puffs. Participants who were told they received normal nicotine cigarettes had higher ratings for nicotine content and reward than those who were told they received low nicotine cigarettes. Similar effects were observed for participants who were given NNC versus VLNC cigarettes. Neither nicotine content nor instructional set influenced craving or withdrawal. Among participants given VLNC cigarettes, those who were told that they received NNC cigarettes earned a greater amount of puffs during the progressive ratio task than those who were told that they received VLNC cigarettes (Perkins et al., 2004).

Perkins and colleagues (2006) examined the role of sex and nicotine expectancy on the reinforcing effects of smoking in 120 adult smokers. In a 2 x 2 between-subjects design, half of participants received Quest 1 NNC cigarettes, and the other half received Quest 3 VLNC cigarettes. In addition, half of participants were accurately told about the nicotine content of

their cigarettes (i.e., “normal nicotine” or “no nicotine”), and the other half received no such instruction. Groups were stratified by sex, such that each condition had 15 men and 15 women. Participants completed a baseline assessment, took two puffs from the cigarette, and then completed additional assessments. Participants were then permitted to smoke the same cigarettes *ad libitum* over the next 30 minutes. The NNC cigarette was associated with increased reward and positive affect compared to the VLNC cigarette, but there was no difference in craving or smoking behavior. Instructions about the nicotine content of study cigarettes enhanced the effects of nicotine on smoking reward and reinforcement in women. These results are consistent with the results of other studies that suggest women may be more sensitive to the nonpharmacological effects of cigarettes than men (Perkins et al., 2006).

Perkins and colleagues (2008) examined the effects of mood induction, nicotine expectancy, and nicotine content on subjective measures. The study employed a 2 x 2 design, wherein 200 smokers were randomly assigned to one of five groups: (1) no smoking, (2) expected normal nicotine cigarettes and given Quest 1 NNC cigarettes, (3) expected normal nicotine cigarettes and given Quest 3 VLNC cigarettes, (4) expected no nicotine cigarettes and given NNC cigarettes, and (5) expected no nicotine cigarettes and given VLNC cigarettes. All participants completed two sessions, which differed in positive versus negative mood induction. Thus, nicotine content and expectancy manipulations were between subjects, and mood manipulation was within subjects. Smoking, as compared to not smoking, attenuated negative affect, withdrawal, and craving. Neither actual nor expected nicotine content influenced negative affect (Perkins, Ciccocioppo, et al., 2008).

Perkins and colleagues (2008) examined the effects of dopamine and opioid receptor gene variants on smoking reward and reinforcement. The study employed a two-session, within- and between-subjects design wherein 72 smokers of European ancestry were randomized to receive Quest 1 NNC cigarettes or Quest 3 VLNC cigarettes over both sessions. Nicotine expectancy was manipulated within each cigarette group such that half of the participants in each group were told that they would receive cigarettes with a normal amount of nicotine, and half were told that they would receive cigarettes with no nicotine. Mood induction was manipulated within-subject such that one session consisted of negative mood induction and the other consisted of positive mood induction. After mood induction and expectancy instructions, participants were asked to sample and rate the assigned cigarette, and then continued smoking additional cigarettes *ad libitum* during continued mood induction. Among study findings, female smokers with the A/A *OPRM1* genotype were more likely to choose NNC over VLNC cigarettes than females who carried the G allele (Perkins, Lerman, et al., 2008).

Perkins and colleagues (2010) examined the effects of smoking and cigarette nicotine content on affect. The study employed a within- and between-subjects design wherein 104 adult smokers were randomly assigned to one of three groups: Quest 1 NNC cigarettes, Quest 3 VLNC cigarettes, or no smoking. All participants completed five experimental sessions, which consisted of one neutral and four negative mood induction procedures. Participants were permitted to smoke their assigned cigarette *ad libitum* following the mood induction procedure. Affect, mood, craving, and withdrawal were assessed throughout each session. There was little variation in positive affect, negative affect, or withdrawal between the NNC and VLNC cigarette groups; however, smoking was more effective at relieving symptoms compared to abstinence. The NNC cigarette was associated with increased ratings of "liking" compared to the VLNC cigarette (Perkins et al., 2010).

Perkins and colleagues (2013) examined the positive and negative reinforcement-enhancing effects of nicotine in 25 dependent smokers (≥ 10 CPD and met diagnostic criteria for nicotine dependence) and 27 non-dependent smokers (reported never smoking more than five CPD and did not meet nicotine dependence diagnostic criteria). The study utilized a within-subject design wherein, following overnight abstinence, participants smoked a Quest 1 NNC cigarette, a Quest 3 VLNC cigarette, or remained abstinent. During each session, participants completed four separate progressive ratio reinforcement tasks with positive reinforcement (money and music), negative reinforcement (termination of noise), or no reinforcement. Relative to abstinence and VLNC cigarettes, the NNC cigarettes increased responding to music but not to other consequences. The reinforcement-enhancing effects of nicotine were similar across dependent and non-dependent smokers (Perkins & Karelitz, 2013).

Perkins and colleagues (2014) examined the reinforcement-enhancing effects of nicotine in 20 smokers. The study employed a three-session within-subject design wherein, following overnight abstinence, participants smoked a Quest 1 NNC cigarette, a Quest 3 VLNC cigarette, or remained abstinent. During each session, participants completed four separate progressive ratio reinforcement tasks, wherein the number of responses (i.e., button presses) required for money, music, a video, or no reward systematically increased. Relative to abstinence and the VLNC cigarette, the NNC cigarette significantly increased button presses when they were maintained by music and video rewards. These results suggest nicotine enhances the reinforcing value of sensory rewards, but may have less of an effect on the value of non-sensory rewards (Perkins & Karelitz, 2014).

Perkins and colleagues (2015) examined sex differences in withdrawal relief and negative affect as a function of cigarette nicotine content. The study employed a two-session, within-subject design wherein 44 smokers were asked to take 24 controlled puffs during a 2-

hour session, following overnight abstinence, from either a Quest 1 NNC or Quest 3 VLNC cigarette. Negative affect was assessed after every 6 puffs and withdrawal symptoms were assessed before and after smoking. There were no sex differences in baseline withdrawal or negative affect due to overnight abstinence. NNC cigarettes, as compared to VLNC cigarettes, were associated with greater decreases in withdrawal and negative affect in men, but not women. While women responded to the NNC cigarette with less negative affect relief compared to men, they reported significantly greater withdrawal relief from the VLNC cigarette compared to men. The authors concluded that women are more sensitive to non-nicotine stimuli, whereas men are more sensitive to the nicotine content of cigarettes (Perkins & Karelitz, 2015).

Perkins and colleagues (2016) assessed nicotine discrimination in 29 non-menthol smokers in a blinded, within-subject study. Participants were trained to discriminate between SPECTRUM® NNC and VLNC cigarettes with the instructions to "evaluate these cigarettes based on your overall subjective feelings" because it is "important that you learn how to tell the difference between the two cigarettes." Participants took 4 puffs of each cigarette, and each cigarette was separated by 15 minutes. Discrimination was then tested during 6 trials with similar smoking regimens in which participants were instructed to identify which cigarette they were smoking (i.e., “A” or “B”). Two choice trials then assessed reinforcement. Only 10 of the first 20 participants successfully discriminated between cigarettes. The researchers then increased the number of training trials from one trial per cigarette to two trials per cigarette. Eight of the remaining nine participants successfully discriminated between cigarettes. Data from these two groups were combined for subjective effects and choice analyses. Relative to those who were unable to discriminate between cigarettes, participants who could discriminate between cigarettes were significantly more likely to choose puffs from the NNC cigarette during the choice trials and rate the NNC cigarette higher on 7 of 8 subjective effects measures (e.g., liking, harsh) (Perkins, Kunkle, Michael, et al., 2016).

Perkins and colleagues (2018) examined associations between gender and subjective responses to VLNC cigarettes in 43 men and 31 women. SPECTRUM® cigarettes with two levels of nicotine (VLNC and NNC) were administered within-subject in one laboratory session following overnight abstinence such that five cigarettes of each type were administered randomly during the session under prescribed puffing conditions (four puffs per cigarette and15-m inter-cigarette intervals). Subjective effects were measured after each cigarette. A significant main effect of nicotine content on subjective effects was observed such that ratings of "nicotine," "flavor," "liking," "satisfying," "strong," and "similar to own brand" were significantly higher for NNC cigarettes than VLNC cigarettes. In addition, a significant main

effect of gender on "flavor" was observed such that women rated all cigarettes as more flavorful than men. A significant interaction effect of nicotine content and gender on "nicotine," "flavor," "satisfying," "strong," and "similar to own brand" was also observed, which showed that women demonstrated less sensitivity than men to the differential subjective effects of NNC and VLNC cigarettes (Perkins et al., 2018).

Perkins and colleagues (2018) investigated the effects of menthol on subjective and behavioral responses to VLNC cigarettes in 73 adult smokers. The menthol content of study cigarettes was matched to the menthol content of participants' self-reported usual brand cigarettes. Twenty-nine participants received non-menthol cigarettes, and 44 participants received menthol cigarettes. Study cigarettes were SPECTRUM® cigarettes with two levels of nicotine (VLNC and NNC). Cigarettes were administered within-subject in one laboratory session following overnight abstinence such that five cigarettes of each type were administered randomly during the session under prescribed puffing conditions (four puffs per cigarette and 15-m inter-cigarette intervals). Subjective effects were measured after each cigarette. Following these trials, participants were presented with two trials during which they could choose puffs between concurrently available VLNC and NNC cigarettes. There was a significant main effect of nicotine content on subjective effects such that ratings of "nicotine," "flavor," "liking," "satisfying," "strong," and "similar to own brand" were significantly higher for NNC cigarettes than VLNC cigarettes. Although a main effect of menthol on subjective effects was observed, no significant interaction effect of nicotine content and menthol on subjective effects was observed. Participants chose significantly more puffs from NNC cigarettes than VLNC cigarettes, with no significant differences due to menthol or due to interactions between menthol and nicotine content. Greater differences in subjective effects between NNC and VLNC cigarettes predicted choice for NNC cigarettes regardless of menthol content (Perkins et al., 2018).

Perkins and colleagues (2019) conducted a study that exposed 59 adult smokers to SPECTRUM® study cigarettes varying in nicotine content. The first portion of this study consisted of a discrimination task, wherein participants were presented with a VLNC cigarette with the lowest nicotine content (0.4 mg nicotine per g of total tobacco) and an NNC cigarette with the highest nicotine content (17 mg nicotine per g of total tobacco) and asked to take two puffs of each. VLNC cigarettes were then tested against additional NNC and LNC cigarettes with successively lower nicotine content in those participants who could successfully discriminate between the VLNC cigarette and the cigarette with higher nicotine content. The next portion of the study was a forced choice trial to identify nicotine preference: participants were presented with the VLNC cigarette and another cigarette of higher nicotine content and told they could

take four total puffs from the two cigarettes, in any combination they wanted. The number of puffs taken from the higher nicotine content cigarette versus the VLNC cigarette was determined to be that cigarette's reinforcing value. All participants found that higher nicotine content cigarettes were more reinforcing than the VLNC cigarettes. Although there was no significant difference in reinforcing effects between the higher nicotine content cigarettes, the reinforcing effects when compared to the VLNC cigarettes were significantly greater in LNC and NNC cigarettes with 5.3 mg nicotine per g of total tobacco nicotine or higher. Nondependent smokers also showed an ability to discriminate between cigarettes varying in nicotine content (Perkins & Karelitz, 2019).

Perkins and colleagues (2020) conducted a study with 17 adult dependent non-menthol smokers. Research cigarettes were SPECTRUM® NNC cigarettes (18.7 and 10.8 mg nicotine per g of total tobacco), LNC cigarettes (5.3, 2.3, and 1.3 mg nicotine per g of total tobacco), and VLNC cigarettes (0.4 mg nicotine per g of total tobacco). During the exposure phase, participants were blinded to the nicotine content of each cigarette, and first presented with four cigarettes: a VLNC cigarette, followed by two LNC or NNC cigarettes, followed by another VLNC cigarette. In the forced choice phase, participants were presented with one VLNC cigarette and one LNC or NNC cigarette and told to take a total of four puffs in any combination they desired. The number of puffs taken from the LNC or NNC cigarettes compared to the VLNC cigarettes was determined to be the reinforcing value of that cigarette. In the exposure phase, there was no difference in puff volume between the VLNC and the LNC or NNC cigarettes. Participants chose to puff from the LNC or NNC cigarettes significantly more than from the VLNC cigarettes in the forced choice phase. In addition, participants chose to puff from LNC or NNC cigarettes with greater than 5.3 mg nicotine per g of total tobacco significantly more than they chose to puff from the 1.3 mg nicotine per g of total tobacco LNC cigarettes (Perkins & Karelitz, 2020).

Pickworth and colleagues (1999) examined the effects of nicotine and tar on smoking-related outcomes in 20 smokers during four laboratory sessions. Participants were divided into two groups: Group 1 smoked full-tar Ultratech LNC and VLNC cigarettes, and Group 2 smoked reduced-tar Ultratech LNC and VLNC cigarettes. Participants attended two sessions following overnight abstinence and two sessions following 3-h abstinence. Thus, LNC and VLNC cigarettes were smoked following both durations of abstinence. Both reduced-tar and full-tar LNC cigarettes, but not VLNC cigarettes, increased plasma nicotine, heart rate, and blood pressure. However, methodological limitations, including nonabstinence at baseline and assay sensitivity, may have precluded an ability to observe small increases in plasma nicotine levels following VLNC cigarette use. No significant effects of nicotine content on breath CO, time to smoke, and

number of puffs were observed. Theta power decreased after smoking full-tar LNC cigarettes and increased after smoking full-tar VLNC cigarettes. All cigarettes reduced craving and withdrawal. Effects of nicotine content on some subjective measures (e.g., "bad effects") were observed (Pickworth, Nelson, et al., 1999).

Ray and colleagues (2006) examined the association of an opioid receptor variant (*OPRM1* A118G) on the relative reinforcing value of nicotine. In this within-subject study, 60 adult smokers (30 of each *OPRM1* genotype: A/A vs. A/G or G/G) completed two 4-day medication phases during which they received naltrexone or placebo. At the end of the medication phase, participants completed a 6-hour laboratory session. Participants sampled Quest 1 NNC and Quest 3 VLNC cigarettes, then completed subjective effects assessments. Thirty minutes later, participants completed a choice session in which they could choose puffs from either cigarette every 30 minutes for 3 hours. A significant genotype x gender interaction predicted the relative reinforcing value of nicotine. In women, but not men, the low activity G allele was associated with taking fewer puffs of the NNC cigarette. In addition, smokers with the A/A allele had increased difference scores in ratings of satisfaction, liking, and strength than those with the G allele. Successful discrimination between NNC versus VLNC cigarettes was decreased in smokers carrying a G allele. Naltrexone had no effect on nicotine reinforcement in any of the genotype or gender subgroups. Collectively, these results show that polymorphisms in *OPRM1* can change the relative reinforcing effects of nicotine in cigarettes (Ray et al., 2006).

Rose et al. (1999) investigated the role that peripheral nicotinic receptors play in cigarette reward. Twelve participants smoked Next VLNC cigarettes, Next VLNC cigarettes injected with nicotine, and usual brand cigarettes under the following two conditions: (1) after receiving intravenous (IV) saline, and (2) after receiving IV trimethaphan, a peripherally acting nicotinic antagonist. The VLNC cigarettes injected with nicotine were rated as the harshest of the three types of cigarettes. In the saline condition, usual brand cigarettes were rated as significantly more satisfying than VLNC cigarettes and VLNC cigarettes injected with nicotine. However, in the trimethaphan condition, there were no significant differences in ratings of satisfaction across cigarette type. Thus, the peripheral nicotinic antagonist decreased usual brand cigarette satisfaction. Under saline and trimethaphan conditions, VLNC cigarettes did not reduce craving as much as the other two types of cigarettes reduced craving (Rose et al., 1999).

Rose et al. (2000) investigated the pharmacological and sensorimotor effects of smoking in 80 participants. In a between-subjects design, three groups of participants (n = 20 per group) smoked Next VLNC cigarettes with either continuous IV nicotine, puff-sized pulses of IV nicotine, or saline injections, and a fourth group smoked usual brand cigarettes with IV saline. Although puff volume was controlled, it was tailored for each subject based on usual smoking

behavior. Overall, subjective ratings were similar between VLNC and usual brand cigarettes. The effects of IV nicotine on subjective ratings were minimal, but it did reduce craving when combined with VLNC cigarettes (Rose, Behm, Westman, & Johnson, 2000).

Rose and colleagues (2003) investigated the effects of smoking on brain function and subjective effects in smokers in two experiments. In the first experiment, 18 participants were exposed to three conditions in a single session: (1) usual brand cigarette plus IV saline, (2) Next VLNC cigarette plus IV saline, and (3) VLNC cigarette plus IV nicotine. In the second experiment, 16 participants smoked a usual brand cigarette and a VLNC cigarette in two sessions after receiving the nicotinic antagonist mecamylamine or placebo. Data from both experiments were pooled and showed that, in saline and placebo conditions, regional cerebral blood flow differed between usual brand and VLNC cigarette conditions, such that activation was greater in brain regions implicated in reward in usual brand cigarette conditions. Relations between subjective effects and regional blood flow were examined, but not relations between subjective effects and cigarette nicotine content (Rose, Behm, Westman, Mathew, et al., 2003).

Rose and colleagues (2003) investigated nicotine satiation in 18 dependent smokers. The study employed a seven-session, within-subject design, including a baseline session wherein participants smoked their usual brand cigarettes *ad libitum* and six additional sessions wherein they smoked usual brand, VLNC, or no cigarettes, while receiving IV saline, pulsed nicotine or slowly infused nicotine. After 1 hour of exposure to these conditions, participants were permitted to smoke their usual brand cigarettes *ad libitum* for 3 hours. Relative to the no cigarette conditions, VLNC cigarettes reduced the amount participants smoked in the *ad libitum* phase. However, the usual brand cigarette condition had reduced *ad libitum* smoking, indicating greater satiation, compared to the VLNC cigarette condition. VLNC cigarettes and IV nicotine had similar effects on craving reduction, but neither reduced craving to the extent of usual brand cigarettes (Rose, Behm, Westman, Bates, et al., 2003).

Rose and Behm (2004) investigated compensatory smoking in 16 smokers. During two 8-hour sessions, participants smoked Now highly-ventilated cigarettes (R. J. Reynolds Tobacco Co.) and LNC cigarettes[13] *ad libitum*. When compared to highly-ventilated cigarettes, the LNC cigarettes did not produce increases in smoking over the course of an 8-hour day or increases in puff volume as measured during the last cigarette of the day. Compared to the Now cigarette, the LNC cigarette was rated lower on "liking and satisfaction," but it was given comparable

[13] Although the LNC cigarette brand was not identified, the authors reported the nicotine content of these cigarettes as follows: "Following the method of Benowitz et al. (1983), we determined the total nicotine content of the tobacco to be approximately .1–.3 mg/cigarette" (p. 310).

ratings on “craving reduction” and “reward.” In sum, compared to highly-ventilated cigarettes, LNC cigarettes were not associated with compensatory smoking (Rose & Behm, 2004a).

Rose and colleagues (2004) investigated interactions between nicotine, ethanol, and mecamylamine in 48 dependent smokers who regularly consumed alcohol. Participants completed four sessions wherein they were randomized to an alcohol or placebo group and then ingested oral mecamylamine or placebo and smoked an NNC or VLNC cigarette. Subjective effects, withdrawal, and cognitive performance were assessed. NNC cigarettes were associated with significantly higher ratings of satisfaction, liking, enjoyment of respiratory tract sensations, reduction in craving, estimated nicotine delivery, similarity to usual brand, and strength compared to VLNC cigarettes. Alcohol administration increased NNC and decreased VLNC cigarette satisfaction. NNC cigarettes were more effective at reducing craving compared to VLNC cigarettes. NNC cigarettes were associated with significantly increased spatial processing speed in the cognitive tasks compared to VLNC cigarettes (Rose et al., 2004).

Rose and colleagues (2010) investigated how nicotine and non-nicotine components of cigarette smoke influence smoking reinforcement in 16 dependent smokers. The study employed a seven-session, within-subject design, including a baseline session wherein participants smoked their usual brand cigarettes *ad libitum*. Sessions 2-3 served as discrimination training sessions wherein participants learned to discriminate IV nicotine from IV saline and VLNC cigarette puffs from sham puffs. Sessions 4-7 were self-administration sessions wherein participants received either VLNC cigarettes or sham puffs plus either IV nicotine or IV saline. Participants were then given the opportunity to self-administer VLNC cigarettes, sham puffs, IV nicotine, or IV saline immediately after the programmed administration period. During the self-administration sessions, VLNC cigarettes were chosen more often than sham puffs, IV nicotine, or IV saline. VLNC cigarettes reduced craving and withdrawal and increased heart rate, but not blood pressure, compared to sham puffs. Smoke from VLNC cigarettes resulted in some subjective and physiological effects, and combining VLNC cigarette puffs and IV nicotine resulted in the greatest reductions in withdrawal symptoms. There were no direct comparisons with usual brand cigarettes (Rose et al., 2010).

Rose and colleagues (2010) investigated the effects of oral topical silver acetate solution on the sensory and reinforcing properties of VLNC and NNC cigarettes in 20 dependent smokers. The study employed a two-session, within-subject design wherein participants completed five puffing episodes at each visit after they rinsed their mouths with either silver acetate or placebo solution. The five puffing episodes included: usual brand cigarettes, NNC cigarettes, VLNC cigarettes, nicotine inhaler, and sham air puffs. Under placebo conditions, usual brand cigarettes were associated with qualitatively greater ratings of liking and

satisfaction compared to VLNC cigarettes. NNC cigarettes were associated with greater ratings of liking, but not satisfaction compared to VLNC cigarettes. Silver acetate reduced subjective effects rating of liking and satisfaction, irrespective of the nicotine content of the cigarettes (Rose, Behm, et al., 2010).

Rukstalis and colleagues (2005) conducted a within-subject laboratory study to evaluate the effects of naltrexone and bupropion on smoking in 26 dependent smokers. Participants completed three experimental sessions wherein they received pretreatment with either naltrexone (50 mg), bupropion (300 mg), or placebo and then took four double-blind puffs of Quest 1 NNC and Quest 3 VLNC cigarettes separated by 20 minutes. Subjective effects were assessed following this initial cigarette exposure. Thirty minutes later, participants completed a 2-hour choice procedure during which they were permitted to take four puffs from any combination of the two cigarettes. NNC cigarettes were associated with significantly higher subjective effects ratings of liking, satisfaction, and strength compared to VLNC cigarettes. Out of 12 choices, the NNC cigarette was chosen the majority of times: 10.9, 9.8, and 11.3 times in the bupropion, naltrexone, and placebo conditions, respectively. After naltrexone administration, fewer puffs were taken from the NNC cigarette compared to puffs taken from the NNC cigarette during the placebo condition. Bupropion had no effect on cigarette choice (Rukstalis et al., 2005).

Schlagintweit and colleagues (2016) conducted a laboratory study to assess the effects of nicotine content between subjects and nicotine expectancy within subjects in 30 dependent smokers. Participants completed two sessions wherein they smoked either Quest 1 NNC or Quest 3 VLNC cigarettes during both sessions. However, in a counter-balanced order across sessions, participants were informed that they would be smoking a nicotine-free and a nicotine-containing cigarette. Physiological responses, craving, and subjective effects were assessed after smoking. Participants were then exposed to neutral and smoking cues while physiological responses and craving were measured. Heart rate increased from baseline in both cigarette groups, but NNC cigarettes were associated with greater increases in heart rate than VLNC cigarettes. NNC cigarettes were also associated with increased ratings of liking compared to VLNC cigarettes. In addition, ratings of liking were higher when participants were told that they were smoking a nicotine-containing cigarette compared to when they were told they were smoking a nicotine-free cigarette. While both NNC and VLNC cigarettes reduced withdrawal-related craving, NNC cigarettes reduced craving more than VLNC cigarettes. Expectancy also influenced craving. Participants who were told that they received nicotine had reduced craving relative to those who were told that they received nicotine-free cigarettes. Smoking-associated stimuli increased craving regardless of nicotine expectancy (Schlagintweit & Barrett, 2016).

Schlagintweit and colleagues (2021) conducted a within-subject laboratory study to evaluate the influence of nicotine metabolism on response to VLNC cigarettes (Quest 3) in 33 regular smokers. Participants completed two sessions where they smoked an entire VLNC or took 10 sham puffs on an unlit cigarette. Participants then completed post-administration ratings of craving and withdrawal and the McKee Smoking Lapse Task. Slow metabolizers experienced greater VLNC-induced reduction in craving compared to normal metabolizers. Nicotine metabolism did not influence any other VLNC responses. Participants with high nicotine dependence levels administered increased puffs (VLNC and sham) during the ad lib session than participants with low levels of dependence (Schlagintweit et al., 2021).

Spinella and colleagues (2020) conducted a within-subject laboratory study to evaluate the influence of nicotine content on cigarette craving, withdrawal, and smoking behavior in a sample of dependent and nondependent smokers. Participants completed four randomized, double-blind sessions where they administered each of the four study products in a prescribed manner: NNC cigarettes (Yellow Light Natural American Spirit), VLNC cigarettes (Quest 3), nicotine inhalers (10 mg; 4 mg deliverable) and nicotine free inhalers (NFI). Participants completed the MNWS after administering their assigned product. Participants then completed the modified smoking lapse task, followed by a computerized progressive ratio task. Both the NNC and VLNC cigarettes significantly reduced craving and withdrawal scores after acute use. Nondependent smokers were more likely to abstain from smoking and administered fewer puffs than dependent smokers. There was a similar latency to smoke across study products; however, the VLNC, NNC, and the nicotine inhaler were associated with fewer puffs self-administered than the nicotine free inhaler (Spinella et al., 2020).

Spring and colleagues (2008) conducted a laboratory study to evaluate the influence of nicotine on positive and negative affect in 165 adult smokers. Participants were divided into three groups: smokers with no history of major depressive disorder (MDD) (n = 63), smokers with past but not current MDD (n = 61), and smokers with both current and past MDD (n = 41). Participants completed four sessions wherein they smoked a Lifetech LNC or VLNC cigarette after undergoing positive or negative mood induction, in a double-blind fashion. LNC cigarettes were associated with higher ratings of taste than VLNC cigarettes, but the cigarettes did not differ on ratings of harshness. Participants with past MDD had higher levels of positive affect following the positive mood induction after smoking an LNC cigarette compared to a VLNC cigarette. In addition, relative to participants with no history of MDD, participants with past or current MDD had increased positive affect following positive mood induction after smoking the NNC cigarette. Regardless of group, LNC as compared to VLNC cigarettes worsened negative affect responses to the negative mood induction (Spring et al., 2008).

Strasser et al. (2007) conducted a within-subject laboratory study to examine the influence of cigarette nicotine content on smoking in 50 adult smokers. Participants completed a single session wherein they smoked one of their usual brand cigarettes, followed by one each of Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes in random order. All cigarettes were smoked *ad libitum* through a CReSS smoking topography device, with a 30-minute inter-cigarette interval. The NNC cigarette was rated as stronger and more satisfying than the LNC and VLNC cigarettes. Total puff volume was greatest for the VLNC cigarette and breath CO boost was significantly greater after smoking the LNC compared to the NNC cigarette (Strasser et al., 2007).

Sweitzer and colleagues (2021) conducted a within-subject laboratory study to evaluate the subjective and behavioral effects of cigarettes varying in nicotine content among 87 young adult (ages 18-25) smokers. Participants completed a training session, followed by three fixed dose (FD) sessions, and a final choice session. During the FD sessions, participants took seven prescribed puffs of a SPECTRUM® research cigarette (15.8, 2.4, and 0.4 mg nicotine per g of total tobacco) to replicate smoking a single cigarette. Subjective effects and CO were assessed following each session. During the choice session, participants first sampled each of the three research cigarettes (double-blind) and were then instructed to choose the one cigarette they would most like to smoke during the session. In the FD sessions, post-cigarette CO was significantly greater in the VLNC condition compared with the NNC condition. HR and BP were significantly higher following the NNC cigarette compared to the VLNC and LNC cigarettes. NNC cigarettes were associated with significantly higher positive and negative subjective effects compared to VLNC and LNC cigarettes. The LNC cigarette was rated higher in positive subjective effects compared to the VLNC cigarette. During the choice session, 43% of participants chose the NNC cigarette, 25% chose the LNC cigarette, and 32% chose the VLNC cigarette (P=NS) (Sweitzer et al., 2021).

Tidey et al. (2013) conducted a within-subject laboratory study to assess the influence of nicotine and sensorimotor stimuli on craving, nicotine withdrawal, habit withdrawal, and subjective effects in 30 smokers with schizophrenia and 26 control smokers. Participants completed five counterbalanced experimental sessions: (1) Quest 3 VLNC cigarettes + 42 mg nicotine patch, (2) VLNC cigarettes + placebo patch, (3) no cigarettes + nicotine patch, (4) no cigarettes + placebo patch, and (5) usual brand cigarettes + no patches. In each 5-hour experimental session, participants were cued when to smoke through a CReSS smoking topography device such that their smoking rate and timing was similar to smoking patterns observed under baseline *ad libitum* smoking conditions. Following each 5-hour session, participants completed a 90-minute period of *ad libitum* usual brand cigarette smoking.

Smokers with schizophrenia had higher breath CO boost and total puff volume compared to control smokers. Among smokers with schizophrenia, VLNC cigarettes reduced habit withdrawal in the placebo patch conditions but not in the nicotine patch conditions; however, in control smokers, VLNC cigarettes reduced habit withdrawal in both patch conditions. In addition, smoking VLNC cigarettes during the 5-hour session reduced usual brand cigarette smoking during the 90-minute *ad libitum* sessions. Usual brand cigarettes were rated as more rewarding and satisfying than VLNC cigarettes across groups. Psychiatric symptoms were not affected by VLNC cigarette use (Tidey et al., 2013).

> Tidey and colleagues (2016) conducted a secondary analysis of Tidey et al. (2013) comparing puff topography from usual brand and Quest 3 VLNC cigarettes in 27 smokers with schizophrenia and 23 control smokers. Puff topography was measured during 5-hour *ad libitum* sessions while participants smoked either VLNC or usual brand cigarettes. Across the VLNC and usual brand cigarette sessions, participants with schizophrenia smoked more puffs per session and more puffs per cigarette, had higher cigarette volumes, and had shorter inter-puff intervals compared to control smokers. In addition, during the VLNC cigarette session, both groups increased puff duration and decreased inter-puff intervals, but because participants smoked fewer puffs, this resulted in a decrease of total session puff volume. Thus, the acute use of VLNC cigarettes did not increase smoking in schizophrenic participants (Tidey, Cassidy, et al., 2016).

Tucker and colleagues (2017) investigated cross-price elasticity and demand for VLNC cigarettes in 40 New Zealand smokers. Participants attended one laboratory session wherein they sampled one Magic brand VLNC cigarette following 12-h abstinence. They then completed subjective effects questionnaires and behavioral economics tasks. Participants rated their own brand cigarettes more favorably than VLNC cigarettes. Results from a demand task showed hypothetical CPD for usual brand and VLNC cigarettes was high at low prices (i.e., participants would smoke more CPD at low prices) and decreased sharply at high prices (i.e., participants would smoke very few CPD at high prices), a pattern that is characteristic of demand for inelastic commodities. Significant main effects of price and cigarette type were observed as well as an interaction between price and cigarette type such that, at lower prices, demand for usual brand cigarettes was much higher than demand for VLNC cigarettes, but, at higher prices, demand was equally low across both types of cigarettes. In a cross-price elasticity task, hypothetical price of VLNC cigarettes was held constant while price for usual brand cigarettes was manipulated. When usual brand cigarette price increased, demand for VLNC cigarettes

increased and demand for usual brand cigarettes decreased, indicating VLNC cigarettes are partially substitutable for usual brand cigarettes for some participants (Tucker et al., 2017).

Westman et al. (1996) conducted a within-subject laboratory study to evaluate the subjective and cardiovascular effects of nicotine and airway sensations in six male smokers. Participants completed six counterbalanced conditions: (1) continuous IV nicotine infusion (1 mg), (2) pulsed IV nicotine infusion, (3) IV saline infusion + Next VLNC cigarettes, (4) continuous IV nicotine infusion + VLNC cigarettes, (5) pulsed IV nicotine infusion + VLNC cigarettes, and (6) IV saline infusion + NNC cigarettes. Compared to VLNC cigarettes, NNC cigarettes increased venous nicotine boost. However, breath CO boost was higher after smoking VLNC cigarettes relative to NNC cigarettes. No differences in blood pressure or pulse were observed between cigarettes. Scores for satisfaction, liking, immediate craving reduction, chest sensation strength, chest sensation enjoyment, calming effect, and irritability reduction were comparable between cigarettes. However, ratings of exhilaration were lower after smoking VLNC compared to NNC cigarettes (Westman et al., 1996).

b. Individual Studies of Reduced Nicotine Content Cigarettes: Extended Exposure Studies

Addicott et al. (2015) investigated insula-based functional connectivity in 85 smokers interested in quitting. Participants were randomized into two groups for 30 days: one group was instructed to continue smoking their typical number of usual brand cigarettes each day, and another group was instructed to smoke an equivalent number of Quest 3 VLNC cigarettes and wear a standard 21 mg nicotine patch each day. Following the 30 days, all participants were instructed to stop smoking and underwent a graded nicotine patch regimen consisting of 21 mg nicotine per day for 6 weeks, 14 mg/day for 2 weeks, and 7 mg/day for 2 weeks. Relapse was defined as 7 consecutive days of smoking at least one CPD. There was no difference in relapse between experimental groups. Participants were then classified as relapsed or non-relapsed in subsequent analyses. At baseline, the non-relapsed group smoked fewer CPD and had lower dependence than the relapsed group. Some differences in insula-based functional connectivity were also noted between relapsed and non-relapsed participants (Addicott, Sweitzer, Froeliger, Rose, & McClernon, 2015).

Becker and colleagues (2008) investigated the effects of reduced nicotine content cigarettes on smoking cessation in 346 smokers interested in quitting. Participants were assigned to one of three conditions: (1) gradually reduced nicotine content cigarettes for 6 weeks (Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes, for 2 weeks each) plus 21 mg nicotine patch for 2 weeks before the quit date and gradually reduced nicotine patches for 10

weeks after the quit date, (2) gradually reduced nicotine content cigarettes for 6 weeks plus placebo patch for 2 weeks before the quit date and placebo patch for 10 weeks after the quit date, or (3) active control (NNC) cigarettes for 6 weeks plus placebo patch for 2 weeks before the quit date and gradually reduced nicotine patches for 10 weeks after the quit date. Results showed that gradually reduced nicotine content cigarettes plus nicotine patch were more effective than active control plus nicotine patch in achieving 4 weeks of continuous abstinence (32.8% vs. 21.9%). Participants who received reduced nicotine content cigarettes plus placebo patch had comparatively lower rates of abstinence (16.4%) (Becker et al., 2008).

Benowitz et al. (2007) investigated nicotine and carcinogen exposure in 20 smokers not interested in quitting. Unblinded participants were assigned to smoke usual brand cigarettes followed by Philip Morris gradually reduced nicotine content NNC, LNC, and VLNC cigarettes (10.3, 6.5, 3.9, 1.7 and 0.5 mg nicotine per cigarette) for 1 week each. Nicotine exposure declined as the nicotine content of the cigarettes was reduced, with little or no evidence of compensatory smoking. Polycyclic aromatic hydrocarbons (PAH), CO, and cardiovascular biomarkers remained stable, while urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) decreased. In addition, 25% of smokers spontaneously quit after using VLNC cigarettes (Benowitz et al., 2007).

Benowitz et al. (2012) followed 135 adult smokers not interested in quitting. Participants smoked usual brand cigarettes for two weeks during baseline and were then randomized into two groups. The control group smoked usual brand cigarettes throughout the study, while the experimental group smoked Philip Morris gradually reduced nicotine content NNC, LNC, and VLNC cigarettes (10.3, 6.5, 3.9, 1.7 and 0.5 mg nicotine per cigarette). Each type of reduced nicotine content cigarette was smoked for one month, except the final VLNC cigarette, which was smoked for 7 months. All participants were then followed for a subsequent year while they smoked usual brand cigarettes or quit smoking. However, this article only reported findings from the first 6 months of the study. Smokers in the experimental cigarette group had stable nicotine levels through Week 6, which then significantly declined from weeks 14 to 26 relative to baseline. In the experimental group, urinary NNAL declined significantly between baseline and weeks 14 to 26. Compensatory smoking, as estimated based on plasma cotinine levels and machine-smoke yields, was lowest while participants smoked VLNC cigarettes relative to other reduced nicotine content cigarettes. Participants who were noncompliant had higher rates of compensation. VLNC cigarettes were rated as milder, less satisfying, lower quality, and lower in nicotine compared to usual brand cigarettes. Two participants in the VLNC cigarette group quit smoking, and, relative to the control group, a

greater percentage of participants who smoked VLNC cigarettes reported considering quitting (Benowitz et al., 2012).

Bandeira and colleagues (2015) conducted a secondary analysis of data from Benowitz et al. (2012). This analysis involved data from 51 participants assigned to the experimental group. Regardless of the nicotine content of the gradually reduced nicotine content cigarettes, participants with higher levels of baseline dependence smoked more CPD and had higher levels of biomarkers of exposure (Bandiera et al., 2015).

Benowitz and colleagues (2015) conducted a secondary analysis of data from Benowitz et al. (2012). The present analysis evaluated two methods of determining VLNC cigarette compliance in participants who smoked usual brand cigarettes followed by gradually reduced nicotine content cigarettes over the course of 6 months. The first method was an analysis of changes in cotinine levels in comparison with expected changes based on changes in the nicotine content of cigarettes. Sixty percent of participants were estimated noncompliant using this method. The second method was a theoretical estimation of plasma cotinine concentration from the VLNC cigarettes based on known pharmacokinetics of nicotine and cotinine. Between 42% and 62% of participants were estimated noncompliant using this method. There was a high degree of concordance between the two methods of estimating noncompliance. In sum, the study illustrates two methods for measuring noncompliance with VLNC cigarettes and shows high levels of VLNC cigarette noncompliance over a 6-month gradual nicotine reduction clinical trial (Benowitz, Nardone, Hatsukami, et al., 2015).

In a follow-up to Benowitz et al. (2012), Benowitz and colleagues (2015) reported quit rates and toxicant exposure during the final months of the clinical trial and for 12 months after participants stopped smoking study cigarettes. During the 7 months of VLNC cigarette use, cotinine levels remained significantly lower than baseline, and there was no increase in CPD or nicotine withdrawal symptoms. During the next 12 months, cotinine levels of the VLNC cigarette group rose to baseline levels, and quit rates were low in both control and experimental groups. Thus, a temporary VLNC cigarette intervention did not increase quit rates in smokers uninterested in quitting (Benowitz, Nardone, Dains, et al., 2015).

Buchhalter et al. (2005) investigated the effects of VLNC cigarettes on subjective and physiological outcomes in 32 smokers during three 5-day within-subject *ad libitum* smoking conditions: (1) no smoking, (2) smoking Lifetech LNC cigarettes, and (3) smoking Lifetech VLNC cigarettes. Both LNC and VLNC cigarettes decreased intent and urge to smoke relative to the no smoking condition. Both the no smoking and the VLNC cigarette conditions increased difficulty concentrating and restlessness and decreased heart rates compared to the LNC cigarette condition. Participants liked the taste of VLNC cigarettes less over time, while other measures, including blood pressure and skin temperature, did not change (Buchhalter et al., 2005).

Denlinger and colleagues (2016) investigated the effects of VLNC cigarettes on biomarkers of exposure while participants were confined to a hotel for 5 days. One group of participants (n=23) received only SPECTRUM® VLNC cigarettes ("compliant group"), and the other group (n=7) received 10% usual brand cigarettes and 90% VLNC cigarettes ("noncompliant group"). Participants were provided with two packs of VLNC cigarettes per day, and they were instructed to smoke at least five of these each day. Participants in the noncompliant group smoked one usual brand cigarette at 10 am each day, and participants in this group who reported smoking more than 15 CPD at baseline were permitted to smoke a second usual brand cigarette at 2 pm. The study was not powered to compare outcomes between the compliant and noncompliant groups. In the compliant group, a 92% reduction in urinary total cotinine and a 94% reduction in TNE was observed (Denlinger et al., 2016).

Ding and colleagues (2014) examined whether VLNC cigarettes were associated with changes in exposure to nicotine and benzo[a]pyrene (BAP) levels in 72 smokers. The study employed a within-subject design wherein participants smoked usual brand cigarettes for 1 week during baseline, followed by Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes for 1 week each. Used cigarette filters were collected during each condition and compared to machine-smoked cigarettes to assess levels of BAP exposure. Mainstream smoke BAP was higher from usual brand cigarettes than all Quest cigarettes. Median total mouth-level BAP intake decreased as participants switched to Quest cigarettes, with statistically significant differences between each collection period. A similar decreasing trend was observed in median urinary cotinine levels. However, urinary 1-hydroxypyrene (1-HOP) and mean CPD were similar across conditions. Fifty-seven percent of usual brand cigarettes were smoked more intensely by participants than by the Canadian Intense machine-smoking regimen compared to only 4% of VLNC cigarettes. Minimal noncompliance was observed in the study. In sum, there was no evidence to suggest that VLNC cigarettes promoted compensatory smoking (Ding et al., 2014).

Donny and colleagues (2007) investigated the subjective, behavioral, and physiological effects of VLNC cigarettes in 30 participants who inhabited a residential research facility for 13

nights. During the first 2 days, participants smoked usual brand cigarettes. On Day 3, participants were randomly assigned to one of three conditions: 1) Quest 1 NNC cigarettes, 2) Quest 3 VLNC cigarettes, or 3) no smoking. Participants assigned to the NNC cigarette group smoked significantly more CPD than those assigned to the VLNC cigarette group. Relative to baseline, participants in the NNC cigarette group tended to increase CPD during the study, while those in the VLNC cigarette group significantly decreased CPD during the study. Participants took significantly more puffs per cigarette from NNC cigarettes than VLNC cigarettes, and latency to smoking the first cigarette of the day was significantly longer in the VLNC cigarette group than the NNC cigarette group. The NNC cigarette group had significantly higher breath CO than the VLNC cigarette group, and these differences increased over the course of each day. During a progressive ratio task that evaluated reinforcer efficacy, significantly fewer ratios were completed in the VLNC cigarette group than the NNC cigarette group, indicating that participants were willing to work harder to earn puffs from NNC cigarettes. Significantly higher ratings of negative subjective effects and lower ratings of positive subjective effects were observed in the VLNC cigarette group relative to the NNC cigarette group. In addition, relative to usual brand cigarettes smoked during baseline, positive subjective effects (e.g., "enjoyable") of VLNC cigarettes were lower and negative subjective effects (e.g., "unpleasant") were higher throughout the study. Similarly, relative to usual brand cigarettes during baseline, positive subjective effects of NNC cigarettes were lower and negative subjective effects were higher at the beginning of the study; however, these effects dissipated over time such that subjective ratings of NNC cigarettes were similar to usual brand cigarettes by the end of the study. Few differences in craving and withdrawal measures were observed between VLNC and NNC cigarette groups. Relative to no smoking, both types of cigarettes suppressed craving and withdrawal. NNC cigarettes produced greater increases in heart rate than VLNC cigarettes, and VLNC cigarettes produced small but significant increases in heart rate relative to no smoking. During an exit interview, participants' estimations of the nicotine content of their study cigarettes were not significantly different between NNC and VLNC cigarette groups (Donny et al., 2007).

Donny and Jones (2009) examined the behavioral and subjective effects of VLNC cigarettes with and without transdermal nicotine in a double-blind, placebo-controlled study of 68 adult smokers. Following 2 days of training and baseline assessment, participants were instructed to wear a transdermal patch and smoke only research cigarettes for 9 days in their natural environments, and they were randomized to one of four conditions: (1) Quest 1 NNC cigarettes and placebo patch, (2) Quest 3 VLNC cigarettes and placebo patch, (3) Quest 3 VLNC cigarettes and 7 mg nicotine patch, and (4) Quest 3 VLNC cigarettes and 21 mg nicotine patch.

Breath CO, CPD, salivary cotinine, subjective effects, and smoking topography were assessed daily. In the two placebo patch groups, no differences in CPD between NNC and VLNC cigarette groups were observed, but total puff volume was lower in the VLNC cigarette group. Cotinine levels were lowest in the group that received VLNC cigarettes and placebo patch. After overnight abstinence, no significant differences in ratings of withdrawal were observed between NNC and VLNC cigarette conditions. Subjective ratings of NNC and VLNC cigarettes were similar at the beginning of the study, but after extended exposure, VLNC cigarettes were rated lower on positive subjective effects and higher on negative subjective effects. Participants' ratings of the perceived nicotine content of cigarettes were lower for VLNC cigarettes than NNC cigarettes, but the ratings were not significantly different between groups. Effects of transdermal nicotine were also reported. In the 7 mg and 21 mg transdermal nicotine patch groups, CPD and puff volume were lower relative to the placebo patch groups. Relative to participants wearing a 21 mg nicotine patch, participants wearing a placebo patch demonstrated a significantly greater increase in breath CO after smoking. Ratings of withdrawal symptoms were lower in participants who received transdermal nicotine. In sum, participants smoked VLNC cigarettes at levels similar to NNC cigarettes despite subjective ratings indicating that VLNC cigarettes were less rewarding. Participants who received VLNC cigarettes did not demonstrate increased smoking to compensate for reduced nicotine content. Transdermal nicotine attenuated withdrawal and decreased smoking (Donny & Jones, 2009).

Donny and colleagues (2015) conducted a double-blind, parallel, randomized clinical trial of 839 non-treatment-seeking smokers at 10 sites. Participants were randomly assigned to smoke usual brand cigarettes or one of six types of SPECTRUM® research cigarettes, ranging in nicotine content from 15.8 mg nicotine per g of total tobacco (NNC cigarettes) to 0.4 mg nicotine per g of total tobacco (VLNC cigarettes) for 6 weeks. At the end of Week 6, participants abstained from tobacco use for 1 day to assess withdrawal and craving. Participants who received LNC or VLNC cigarettes with nicotine content ≤ 2.4 mg/g smoked significantly fewer cigarettes than those who received NNC or usual brand cigarettes. Participants who received LNC or VLNC cigarettes with nicotine content ≤ 5.2 mg/g were less compliant with instructions to only smoke study-assigned cigarettes than those who received NNC or usual brand cigarettes. Participants who received LNC or VLNC cigarettes with nicotine content ≤ 5.2 mg/g also had significantly lower urinary TNE than those who received NNC cigarettes; however, total NNAL and breath CO did not differ between these groups. Participants who received VLNC cigarettes were more likely to report a quit attempt than those who received NNC cigarettes. Total puff volume and measures of dependence at Week 6 were significantly lower among participants who smoked VLNC cigarettes compared to those who smoked NNC cigarettes.

Withdrawal during the abstinence session did not differ significantly across cigarette groups; however, craving was significantly reduced among participants who received LNC or VLNC cigarettes with nicotine content ≤ 2.4 mg/g. Participants' ratings of overall health, respiratory health, and depression did not vary significantly based on the nicotine content of the cigarettes they smoked (Donny et al., 2015).

Boatman and colleagues (2018) used data from Donny et al. (2015) to develop a new statistical method to model "casual effect" (i.e., the results of an intervention if every participant had perfect compliance). Using data from participants in the VLNC and usual brand cigarette groups of the Donny et al. (2015) study, outcomes from the final week of the trial (Week 6) were modeled with sample sizes of 225, 500, and 1,000. The model simulation showed that if all participants in the VLNC cigarette group were to comply with only smoking VLNC cigarettes, VLNC cigarette use would be associated with smoking approximately 14.98 cigarettes per day, compared to 22.18 cigarettes per day among those continuing to smoke usual brand cigarettes (Boatman, Vock, Koopmeiners, et al., 2018).

Boatman and colleagues (2018) conducted a secondary analysis of data from Donny et al. (2015). Reliance on self-reported compliance alone among participants who report smoking only research cigarettes may overestimate compliance and undermine estimates of response to research cigarettes. Therefore, the purpose of this study was to estimate the effect of VLNC relative to NNC cigarettes on changes in CPD using a combination of total TNE and self-reported compliance at Week 6 of the trial. Five different models involving various estimators of measurement error showed similar, statistically significant reductions in CPD for those in the VLNC condition relative to those in the NNC condition. Models "CURE", a linear regression model involving mixture distribution of TNE, and "A-CURE", a similar but more "efficient" model, estimated the greatest reductions in CPD for the VLNC group. Thus, these models may be best for estimating more precisely the effect of VLNC cigarettes on reducing CPD by bolstering self-reported compliance with total TNE (Boatman, Vock, & Koopmeiners, 2018).

Cassidy and colleagues (2018a) conducted a secondary analysis of data from Donny et al. (2015) to evaluate whether age influenced subjective effects and cigarette use in 716 of the 839 participants from the primary analysis. This

analysis used data from laboratory sessions that occurred after 2 and 6 weeks of research cigarette use. At each of these sessions, puff topography and subjective effects measures were collected while participants smoked one of their assigned cigarettes. Data from the 0.4-2.4 mg/g nicotine groups were combined into a VLNC/LNC cigarette group and compared to data from higher nicotine content cigarette groups. There was no effect of age on TNE levels or total puff volume. At week 2, younger adults (i.e., 18-24 years old) in the VLNC/LNC cigarette group had significantly lower subjective effects scores of smoking satisfaction, psychological reward, and enjoyment of respiratory tract sensations compared to older adults . However, these effects diminished over time. At Week 6, there was no influence of age on subjective effects, TNE levels, or puff volume in the VLNC/LNC group. Thus, the results suggest largely similar subjective and behavioral effects of LNC and VLNC cigarettes among younger and older adults (Cassidy, Colby, et al., 2018a).

Dermody and colleagues (2016) conducted a secondary analysis of data from Donny et al. (2015) to examine the effect of VLNC cigarettes on alcohol outcomes in 403 participants who reported recent alcohol use. No evidence of compensatory alcohol use or binge drinking was observed in response to nicotine reduction, even among higher risk subgroups of participants (Dermody et al., 2016).

Dermody and colleagues (2018) conducted a secondary analysis of data from Donny et al. (2015) to assess nicotine withdrawal as a function of nicotine content throughout the 6-week study. Participants in the high-tar VLNC cigarette group and 1.3 mg/g LNC cigarette group had increased anger, irritability, and frustration scores at Week 1 relative to those in the NNC cigarette group; however, there were no group differences in anger, irritability, or frustration during Weeks 2–6. Following a post-Week 6 overnight abstinence challenge, participants in the normal-tar VLNC cigarette group had significantly less anger, irritability, frustration and difficulty concentrating compared to those in the NNC cigarette group. In addition, participants in the 1.3 mg/g LNC cigarette group had significantly less desire to smoke than those in the NNC cigarette group. The authors concluded that withdrawal during and after VLNC cigarette use is relatively mild and transient (Dermody et al., 2018).

Kaizer and colleagues (2018) conducted a secondary analysis of data from Donny et al. (2015) to test a statistical model for integrating multiple supplemental data sources into the analysis of another primary data source. The primary analysis used multisource exchangeability models (MEMs) to measure the difference in the change in CPD from baseline between the VLNC and the NNC cigarette conditions. Data from Hastukami and colleagues (Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010) were used as supplementary data in the model. Changes in CPD were nearly identical among the Donny et al. (2015) high- and low-tar SPECTRUM® VLNC cigarette groups, but these results were different from the Hatsukami et al., which used Quest 3 VLNC cigarettes (Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010). The NNC and usual brand control groups resulted in similar CPD changes. MEMs resulted in approximately 2.2 times larger median effective supplemental sample size, a 56% reduction in bias, and 30% improvement in efficiency when using supplemental data. In addition, MEMs showed a decrease of .22 CPD from baseline among the treatment group, and an increase of between 6-6.5 CPD among the control group (Kaizer et al., 2018).

Kaizer and Koopmeiners (2020) conducted a secondary analysis of data from Donny et al. (2015) Reliance on self-reported compliance alone among participants who report smoking only research cigarettes may overestimate compliance and undermine measures of response to research cigarettes. The purpose of this study was to estimate compliance to research cigarettes of varying nicotine levels among those who self-reported compliance to research cigarettes at the end of the 6-week study. Kaizer and Koopmeiners used Bayesian mixture models incorporating TNE averaged within nicotine contents and found that their established cutoffs of TNE appeared appropriate for most nicotine-content levels, but not for one LNC (2.4 mg/g) cigarette, for which they noted an “improbable biological trend”. Thus, models involving both self-reported compliance and total TNE may be helpful for better estimating actual compliance to research cigarettes, but the precision of TNE estimates may be difficult to determine with LNC cigarettes, thus requiring further experimental investigation (Kaizer & Koopmeiners, 2020).

Nardone and colleagues (2016) performed a secondary analysis of data from Donny et al. (2015) to examine biochemical and self-reported rates of noncompliance at the end of the 6-week trial in 242 adult smokers assigned to

smoke either SPECTRUM® NNC or VLNC cigarettes. Self-reported noncompliance was assessed daily via interactive voice response calls during Week 6. Three biochemical techniques were used to assess noncompliance with study-assigned cigarettes (i.e., cotinine/CPD ratio, TNE/CPD ratio, absolute TNE). Each of the three biochemical approaches indicated that 75-78% of participants assigned to the VLNC cigarette group were noncompliant; however, only 39% of participants self-reported noncompliance during Week 6. The authors also noted that 57% of participants assigned to the NNC cigarette group reported noncompliance at some point during the study, suggesting difficulty with "brand-switching" regardless of nicotine content. Younger smokers, smokers with higher baseline CPD, and smokers who were less satisfied with the VLNC cigarettes were more likely to be noncompliant (Nardone et al., 2016).

Pacek and colleagues (2016) performed a secondary analysis of data from Donny et al. (2015) to examine whether cannabis use moderated VLNC cigarette effects. Data from the 0.4, 1.3, and 2.4 mg/g VLNC and LNC cigarette groups were compared to data from the usual brand and NNC cigarette groups. A total of 207 (29%) participants were cannabis users. Cannabis users and non-users assigned to the combined VLNC and LNC cigarette group demonstrated reductions in CPD, nicotine dependence, craving, and TNE compared to the combined usual brand and NNC cigarette group. At Week 6, the odds of cannabis use were not significantly different between the two groups. Although cannabis users experienced greater reductions in craving for positive reinforcing effects, the difference was likely of limited clinical significance (Pacek et al., 2016).

Pacek and colleagues (2017) conducted a secondary analysis of data from Donny et al. (2015) to examine relations between the actual and perceived nicotine content of cigarettes. At the end of the study, participants were asked, "What level of nicotine do you think was in your study cigarette?" Responses were "very high in nicotine," "high in nicotine," "moderate amount of nicotine," "low in nicotine," and "very low in nicotine." The results showed that 72% of participants assigned to VLNC and LNC cigarette groups (0.4 - 5.2 mg nicotine per g tobacco) perceived that they received very low or low nicotine cigarettes; whereas, only 54% of participants assigned to the NNC cigarette group (15.8 mg/g) perceived that they received very low or low nicotine cigarettes. No associations were observed between perceived nicotine content and CPD or quit attempts (Pacek, Joseph McClernon, et al., 2017).

Robinson and colleagues conducted a secondary analysis of data from Donny et al. (2015). Data were divided into two groups such that data from the NNC cigarette (15.8 mg nicotine per g of total tobacco) and usual brand cigarette groups were combined into an NNC cigarette group, and data from the VLNC cigarette (0.4 mg/g) and LNC cigarette (1.3 and 2.4 mg/g) groups were combined into a VLNC/LNC cigarette group. Data from participants assigned to the 5.2 mg/g group were excluded from this analysis. CPD was assessed weekly, while negative affect and cotinine were assessed at baseline, Week 3, and Week 6. CPD increased over time in the NNC cigarette group and decreased over time in the VLNC/LNC cigarette group. Negative affect was similar across groups and over time; however, a positive relationship was observed between change in negative affect over time and change in CPD over time in the NNC cigarette group. Such a relationship was not observed in the VLNC/LNC cigarette group. Thus, the authors concluded that smoking VLNC/LNC cigarettes disrupts the relationship between negative affect and smoking, which may help reduce dependence. No relations between positive affect and changes in CPD over time were observed in either group (Robinson et al., 2017).

Smith and colleagues (2017) conducted a secondary analysis of data from Donny et al. (2015) to examine the impact of 6 weeks of smoking VLNC cigarettes on future hypothetical consumption of VLNC and usual brand cigarettes. Participants completed a cigarette purchase task prior to study assignment and 6 weeks after being assigned to their study condition. Hypothetical purchasing was highly correlated with actual cigarette smoking throughout the 6-week trial. As price increased, hypothetical cigarette consumption decreased, and this decrease was systematically related to decreases in nicotine content. Compared to the NNC cigarette group, the VLNC cigarette group reported that they would smoke fewer cigarettes at a range of prices, spend a lower maximum amount of money on study cigarettes, and stop purchasing cigarettes at a lower price. VLNC cigarette smoking for 6 weeks, as compared to NNC cigarette smoking, was also associated with a lower maximum amount of money that participants would spend on usual brand cigarettes. Finally, relative to the NNC cigarette group, significantly more participants in the 5.2, 2.4, 1.3, and 0.4 mg/g LNC and VLNC cigarette groups said they would stop smoking in a year if the study cigarette was the only cigarette available for purchase (Smith et al., 2017).

Smith and colleagues (2020) conducted a secondary analysis of data from Donny et al. (2015) investigating solanesol levels as an indicator of mouth-level nicotine exposure and compensatory smoking behavior. Mouth level nicotine intake was found to be significantly lower for participants who smoked LNC cigarettes (5.2, 2.4, and 1.3 mg/g), or VLNC cigarettes (both high and normal tar) compared to those who smoked NNC cigarettes. Participants were not found to have changed their smoking intensity significantly in any of these conditions. Participants who smoked LNC cigarettes with 2.4 mg/g or less were found to smoke fewer cigarettes per day than those who smoked higher nicotine content cigarettes (Smith, Koopmeiners, Hatsukami, et al., 2020).

Tidey and colleagues (2017) conducted a secondary analysis of data from Donny et al. (2015) to examine whether baseline depressive symptoms influenced responses to cigarettes varying in nicotine content. Authors compared outcomes between the NNC cigarette groups (15.8 mg/g and usual brand cigarette groups) and LNC/VLNC cigarette groups (2.4, 1.3, and 0.4 mg/g cigarette groups). Participants were dichotomized into high (n = 109) or low (n = 608) depression groups based on their baseline Center for Epidemiologic Studies Depression Scale (CES-D) scores. At baseline, participants with higher baseline CES-D scores had higher nicotine withdrawal, craving, and smoking motives. CES-D scores did not moderate the effects of nicotine content on smoking rates, nicotine dependence, or cigarette craving throughout the 6-week trial. In participants with higher baseline CES-D scores, Week 6 CES-D scores were reduced in the LNC/VLNC cigarette groups relative to the NNC cigarette groups (Tidey, Pacek, et al., 2017).

Foulds and colleagues (2018) conducted a secondary analysis to estimate compliance with VLNC cigarettes in two randomized controlled trials of smokers with less than a college degree or with mood or anxiety disorders (N=100) (Allen et al., 2017; Krebs et al., 2017). Participants first completed a 1-week usual brand cigarette baseline, followed bya 2-week baseline wherein all participants were provided with SPECTRUM® NNC cigarettes. Participants were then randomized into a group in which they either continued smoking NNC cigarettes for 18 additional weeks or switched to progressively lower nicotine content cigarettes every 3 weeks, ending with 6 weeks of VLNC cigarettes. This study compares three methods of study compliance: 1) self-reported, 2) plasma cotinine/CPD ratio after smoking VLNC cigarettes compared to plasma cotinine/CPD ratio while smoking NNC cigarettes, 3) an adjustment to method 2 for environmental tobacco smoke (ETS) exposure by reducing both cotinine values in

the compliance ratio by 15 ng/ml. There were significant decreases in plasma cotinine, breath CO, and nicotine dependence in the VLNC cigarette group, but not the NNC cigarette group. At the 18-week visit, four participants in the VLNC group (8%) reported noncompliance in the prior 6 days compared to six participants in the NNC group (12%). Using method 2, 21 participants in the VLNC group (42%) were estimated to be noncompliant. Using method 3, controlling for ETS exposure, 18 participants in the VLNC group (36%) were estimated to be noncompliant. Both biochemical methods showed a high degree of agreement; however, the ETS-adjusted method suggested that three additional participants were compliant (Foulds et al., 2018).

Fraser and colleagues (2017) conducted a qualitative study to assess perspectives from key New Zealand stakeholders and smokers on a potential VLNC cigarette policy. Two focus groups, lasting approximately 20-60 minutes in duration, were held. One focus group included 21 daily smokers who were over age 16 and not pregnant. The second focus group included 17 key government or tobacco control stakeholders (e.g., politicians associated with health policy, tobacco control officials, smoking cessation experts). The focus groups consisted of guided interview questions on VLNC cigarette policy (e.g., potential benefits or risks; acceptibility; gradual versus immediate nicotine reduction). Following the interview, the smokers were provided with 15 Magic brand VLNC cigarettes to take home and sample. The smokers completed a 1-week follow-up on their opinions of the VLNC cigarettes. Both groups did not want a VLNC cigarette-only policy to be implemented in New Zealand. The groups expressed concern that the cigarettes would still be harmful, yet possibly perceived as safer. The groups also expressed concern that such a policy may be difficult to implement and might face resistance from the tobacco industry. After acute experience with VLNC cigarettes, most smokers rated the VLNC cigarettes negatively, most notably due to the unpleasant taste and smell (Fraser & Kira, 2017).

Hammond and O'Connor (2014) conducted an unblinded clinical trial in which 72 adult smokers received a free supply of their usual brand cigarettes during Week 1, followed by gradually reduced nicotine content cigarettes: Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes during Weeks 2, 3, and 4, respectively. At the end of each week, biological samples were collected, subjective assessments were administered, and participants smoked one cigarette of the type assigned to them that week using a puff topography device. No significant differences in CPD were observed between cigarette conditions. However, significantly more participants smoked non-study-assigned cigarettes while they were receiving VLNC cigarettes (44%) relative to while they were receiving NNC (28%) and LNC (31%) cigarettes. Participants took significantly more puffs on their usual brand cigarette relative to LNC and VLNC cigarettes. Although no significant differences in mean puff volume were observed between conditions,

total puff volume was significantly lower during the LNC cigarette condition relative to the usual brand cigarette condition. Increases in breath CO were significantly greater after smoking usual brand cigarettes and LNC cigarettes relative to the increases observed after smoking NNC and VLNC cigarettes. Urinary cotinine was not significantly different between NNC and usual brand cigarette conditions; however, it was significantly different across all three Quest cigarette conditions, and it was lowest in the VLNC cigarette condition. No significant differences in smoking urge or dependence measures were observed across cigarette conditions, with the exception that one dependence-related outcome, stereotypy (i.e., rigid patterns of tobacco use), was significantly higher for usual brand cigarettes relative to NNC and VLNC cigarettes (Hammond & O'Connor, 2014).

Hatsukami and colleagues (2010) examined the effects of VLNC cigarettes on smoking cessation, dependence, and toxicant exposure in 165 smokers who smoked “light” cigarettes and were interested in quitting. Following 2 weeks of smoking their usual brand cigarettes, participants were randomly assigned to one of three 6-week conditions: (1) Quest 2 LNC cigarettes, (2) Quest 3 VLNC cigarettes, and (3) 4 mg nicotine lozenges. Participants were instructed to use only study-assigned tobacco products for 6 weeks and then discontinue use of all products. Participants received similar smoking cessation counseling in all groups. Follow-up visits were conducted 1, 2, 4, and 6 weeks after the quit date. Subjective effects and biomarkers of tobacco exposure were assessed throughout the study. The number of study-assigned CPD was significantly different between LNC and VLNC cigarette groups and was significantly different from baseline, such that LNC CPD increased over the course of the 6-week intervention, while VLNC CPD decreased. Similarly, breath CO increased significantly in the LNC cigarette group and decreased significantly in the VLNC cigarette group. Thus, compensatory smoking was evident in the LNC cigarette group but not in the VLNC cigarette group. Urinary cotinine decreased significantly in all groups, with the greatest decrease observed in the VLNC cigarette group. For other biomarkers assessed [1-HOP, NNAL, N-Nitrosonornicotine (NNN), 3-hydroxypropyl mercapturic acid (3-HPMA), S-phenylmercapturic acid (S-PMA)], the greatest decreases relative to baseline were observed in the nicotine lozenge group; however, significant decreases were also observed in the LNC and VLNC cigarette groups. Measures of nicotine dependence decreased significantly over the course of the study in the VLNC cigarette group and nicotine lozenge group, with the lowest dependence scores in the lozenge group. No significant change in dependence was observed in the LNC cigarette group. Perceived risk of addiction decreased significantly in all three groups, with the greatest decrease observed in the lozenge group, followed by the VLNC cigarette group, and the LNC cigarette group. Ratings of withdrawal increased significantly in all three groups following cessation of usual brand

products. The smallest increase in withdrawal was observed in the VLNC cigarette group. Following cessation of study-assigned products at the end of the 6-week intervention, no significant changes in withdrawal ratings were observed in the nicotine lozenge or VLNC cigarette groups, but a significant increase in withdrawal was observed in the LNC cigarette group. A decreasing trend in craving was observed in all groups, but craving decreased the most over the course of the study in the VLNC cigarette group. Dropout rates were significantly different across groups: by the end of the 6-week intervention, dropout rates were 48% in the nicotine lozenge group, 40% in the LNC cigarette group, and 25% in the VLNC cigarette group. Thus, participants in the VLNC cigarette group were more likely to remain in the study relative to participants in the other groups. Abstinence rates were calculated using an intent-to-treat approach, such that dropouts were considered treatment failures. Biochemically-verified continuous abstinence rates (at least 4 weeks abstinent) were highest in the VLNC cigarette group during the study, but these group differences were not significant. However, biochemically-verified point prevalence abstinence rates (1 week abstinent) at the Week 6 follow-up visit were significantly higher in the VLNC cigarette group (47%) and nicotine lozenge group (37%) relative to the LNC cigarette group (23%). In sum, participants who smoked VLNC cigarettes demonstrated reductions in CPD; biomarkers of exposure; subjective measures of craving, withdrawal, and dependence; and increased rates of smoking cessation relative to participants who smoked LNC cigarettes (Hatsukami et al., 2010).

Hatsukami et al. (2013) examined the effects of VLNC cigarettes with and without a transdermal nicotine patch on smoking cessation in 235 smokers interested in quitting. Following 2 weeks of smoking their usual brand cigarettes, participants were randomly assigned to one of three 6-week conditions: (1) reduced nicotine content cigarettes, (2) 21 mg nicotine patch, or (3) reduced nicotine content cigarettes plus nicotine patch. Participants who were assigned to reduced nicotine content cigarette conditions initially received Quest 3 VLNC cigarettes. However, after 27% of participants were randomized, researchers switched to Xodus LNC cigarettes when Quest 3 cigarettes became unavailable. Participants were instructed to use only study-assigned nicotine or tobacco products for 6 weeks and then discontinue use of all products. They received behavioral counseling for smoking cessation weekly before the quit date and regularly for 6 weeks after the quit date. Follow-up visits occurred at 16, 24, and 36 weeks. Subjective effects and biomarkers of tobacco exposure were assessed throughout the study. Mean number of usual brand CPD was significantly different between groups. At week 6, 33% of participants in the VLNC/LNC cigarette group, 43% in the nicotine patch group, and 14% in the VLNC/LNC cigarette plus patch group reported using usual brand cigarettes. In addition, mean number of VLNC/LNC CPD was significantly lower in participants who received

transdermal nicotine. Mean breath CO was lowest in the nicotine patch group, highest in the VLNC/LNC cigarette group, and intermediate in the VLNC/LNC cigarette plus patch group. For all groups, total cotinine, TNE, and total NNAL were significantly lower at Week 6 compared to baseline. Participants assigned to the patch group had significantly higher TNE levels and lower NNAL levels at Week 6. All groups displayed comparable decreases in perceived health risk score for addiction. After one week of treatment, participants in all groups reported significant decreases in craving. All groups reported significant increases in withdrawal after Week 1, but the increase was significantly lower in the VLNC/LNC cigarette plus patch group relative to the patch only group. No differences were observed between groups in biochemically-verified abstinence rates at follow-up visits (Hatsukami, Hertsgaard, et al., 2013).

Dermody and colleagues (2015) conducted a secondary analysis of data from 112 treatment-seeking smokers who received Quest 3 VLNC cigarettes or Xodus LNC cigarettes for 6 weeks prior to a quit attempt while participating in Hatsukami et al. (2010) and Hatsukami et al. (2013). Greater reductions in nicotine exposure while smoking VLNC cigarettes predicted abstinence independent of individual differences in baseline variables. Nicotine reduction was larger among individuals who were assigned to smoke VLNC cigarettes compared to LNC cigarettes. The authors suggest that a reduced nicotine content cigarette with nicotine content above an addictive threshold may sustain nicotine exposure at a level that impedes cessation (Dermody et al., 2015).

Vogel et al. (2014) conducted a secondary analysis of data from Hatsukami et al. (2013) to evaluate sex differences in participants' responses to VLNC/LNC cigarettes. At baseline, males smoked more cigarettes on average than females, but there were no sex differences on nicotine dependence, number of quit attempts, or motivation to quit. Females also had higher baseline TNE and total NNAL compared to males, but cotinine was not different between sexes. After the 6-week intervention, VLNC/LNC cigarettes were equally effective in reducing smoking in females regardless of whether the cigarettes were combined with nicotine patch. However, males smoked fewer study cigarettes when nicotine patch was added to VLNC/LNC cigarettes. In both males and females, CO levels were lower when nicotine patch was combined with VLNC/LNC cigarettes compared to study cigarettes alone. Males also experienced greater suppression of withdrawal and increased ratings of product satisfaction when assigned to VLNC/LNC cigarettes plus patch than when

assigned to study cigarettes alone. In addition, males in the combination group had lower quit rates than males in the nicotine patch only group. Among females, those assigned to VLNC/LNC cigarettes alone had the highest rates of abstinence. The authors concluded that sex differences may impact response to reduced nicotine content cigarettes (Vogel et al., 2014).

Hatsukami et al. (2015) published a secondary analysis that examined the relationship between compensatory smoking and gradual versus immediate nicotine reduction in smokers who were not interested in quitting. Data from five clinical trials were analyzed. Two trials used gradual nicotine reduction, and three trials used immediate reduction. Data from participants assigned to the usual brand cigarette group and the VLNC cigarette group were analyzed in this report. In the VLNC cigarette group, significant decreases in CPD were observed relative to baseline, whereas in the usual brand cigarette group, significant increases in CPD were observed. A 5% decrease in CPD was observed in participants who received reduced nicotine content cigarettes in the gradual reduction studies, and an 11% decrease was observed in the immediate reduction studies. In contrast, a 12% increase in CPD was observed in the usual brand group. Significant changes in breath CO were not observed in any group. However, significant decreases in cotinine were observed in the VLNC cigarette group relative to baseline. No significant change in cotinine was observed in the usual brand cigarette group (Hatsukami et al., 2015).

Hatsukami and colleagues (2017) investigated tobacco use in 136 adult smokers not interested in quitting smoking. Participants were randomly assigned to one of three conditions and instructed to use only study-assigned tobacco products for 8 weeks. The “LNC1” group received SPECTRUM® LNC cigarettes containing 1.3 mg nicotine per g of total tobacco combined with non-combusted (i.e., smokeless tobacco, ENDS, NRT) and combusted non-cigarette tobacco products (i.e., cigars, cigarillos), the “LNC2” group received LNC cigarettes combined with non-combusted products, and the NNC cigarette group received SPECTRUM® NNC cigarettes combined with non-combusted and combusted non-cigarette products. Participants in the LNC cigarette groups smoked significantly fewer study-assigned cigarettes during the final few weeks of the intervention relative to participants in the NNC cigarette group. Although participants in both LNC cigarette groups smoked more non-study cigarettes than participants in the NNC cigarette group, the mean number of all combusted tobacco products used per day was significantly lower in the LNC cigarette groups relative to the NNC cigarette group during the last several weeks of the intervention. Participants in the LNC cigarette groups used more alternative tobacco products than participants in the NNC cigarette group, with participants in the LNC1 cigarette group using the most alternative products.

Participants in the LNC cigarette groups had significantly more 24-hour abstinence attempts than participants in the NNC cigarette group. In addition, TNE was significantly lower in the LNC cigarette groups relative to the NNC cigarette group, breath CO was significantly lower in the LNC2 cigarette group relative to the other two groups, and NNN and NNAL were significantly lower in the LNC2 cigarette group relative to the NNC cigarette group. In sum, participants who received LNC cigarettes smoked fewer combusted tobacco products, used more alternative tobacco products, had more quit attempts, and demonstrated less toxicant exposure than participants who received NNC cigarettes (Hatsukami et al., 2017).

In the largest study on this topic, Hatsukami and colleagues (2018) conducted a 10-site, randomized, double-blind clinical study to compare the effects of gradual versus immediate nicotine reduction on toxicant exposure in 1,250 adult smokers. Participants were randomly assigned to an immediate reduction group that received VLNC cigarettes for 20 weeks, a gradual reduction group that received cigarettes containing progressively decreased nicotine content every 4 weeks (15.5, 11.7, 5.2, 2.4, 0.4 mg nicotine per g of total tobacco) for 20 weeks, or a control group that received NNC cigarettes for 20 weeks. Completion rates were significantly lower for the immediate reduction group (68%) compared to the gradual reduction group (81%) and control group (86%). The immediate reduction group had significantly lower levels of the three primary biomarker outcomes (i.e., CO, 3-hydroxypropyl mercapturic acid [3-HPMA], and phenanthrene tetraol [PheT]) compared to the gradual reduction group, which did not differ from the control group. In addition, significantly lower levels of TNE, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 2-cyanoethylmercapturic acid (CEMA), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA), and S-phenylmercapturic acid (S-PMA), but not 2-HPMA, were observed in the immediate reduction group compared to the gradual reduction group. The immediate reduction group smoked cumulatively less CPD over the course of the 20-week study and had lower nicotine dependence scores compared to the gradual reduction group, with no differences in CPD or dependence among the gradual reduction versus control groups. While there was no difference between immediate and gradual reduction groups in the proportion of participants with any cigarette-free days during the study, the immediate reduction group had a significantly higher number of cigarette-free days compared to the gradual reduction group. The immediate reduction group had significantly higher withdrawal scores at Week 1 compared to the gradual reduction group; however, these differences dissipated after the first week. The immediate reduction group had higher rates of noncompliance with non-study cigarette use and an increased number of adverse events (predominantly related to withdrawal) compared to the gradual reduction group. This study provides further evidence that immediate nicotine reduction is associated with reduced

toxicant exposure and nicotine dependence and increased smoking abstinence compared to gradual nicotine reduction. While the immediate reduction group had increased levels of nicotine withdrawal, this effect was time-limited, dissipating after 1 week (Hatsukami et al., 2018).

Carroll and colleagues (2021) conducted a secondary analysis of Hatsukami et al. (2018) on the potential moderating effects of education, gender, and race on gradual versus immediate nicotine reduction. Regardless of education, gender, and race, all outcomes (e.g., CPD, CO, TNE) were lower in the immediate nicotine reduction group. The only moderating effect that was observed was that the magnitude of the effect of nicotine reduction on TNE varied by race (was lower in Black and White participants) (Carroll et al., 2021).

Cassidy and colleagues (2021) conducted a secondary analysis of Hatsukami et al. (2018) in which they analyzed the potential moderating effect of age (young adults, ages 18–24, or older adults, ages 25+) on the effects of gradual versus immediate nicotine reduction. For both age groups, CPD and TNE at Week 20 were lower in the immediate reduction group. The only moderating effect of age was observed with respect to positive subjective responses to cigarettes, which were lower among young adults relative to older adults in the immediate condition (Cassidy et al., 2021).

Denlinger-Apte and colleagues (2019) conducted a secondary analysis of data from Hatsukami et al. (2018) investigating the impact of menthol status on behavioral and physiological responses to VLNC cigarettes. At baseline, 752 adults were assigned to either SPECTRUM® VLNC or NNC cigarettes for 20 weeks (mentholated based on preference). Smokers in the VLNC cigarette condition significantly reduced CPD relative to participants in the NNC condition, regardless of menthol status. Those who smoked menthol cigarettes had less of a reduction in CPD and biochemically verified abstinence than those individuals who smoked non-menthol cigarettes; however, both menthol and non-menthol smokers in the VLNC group were more likely to report a cigarette-free day than those assigned to NNC cigarettes. Further, TNE was reduced for those in the VLNC cigarette condition relative to the NNC cigarette condition, but menthol smokers showed a smaller reduction in TNE than non-menthol smokers. In addition, there was a trend towards less of a reduction in breath CO exposure among menthol smokers. Craving and positive subjective ratings were lower for

the VLNC condition, with no interaction with menthol status. There was a trend towards a smaller treatment effect for craving reduction among menthol smokers (Denlinger-Apte, Kotlyar, et al., 2019).

Dermody et al. (2021) conducted a secondary analysis of Hatsukami et al. (2018) to evaluate the potential for unintended consequences of nicotine reduction on alcohol use. Although higher baseline alcohol use was associated with a smaller effect of VLNC cigarettes on urinary TNE at Week 20, no additional moderation was supported. Further, daily alcohol use and binge drinking was reduced during the study. Thus, the authors noted they found no evidence that a nicotine product standard would result in unintended consequences related to alcohol use (Dermody et al., 2021)

Robinson and colleagues (2019) conducted a secondary analysis of data from Hatsukami et al. (2018) to determine the association between affect and change in CPD. This analysis found that participants in the gradual nicotine reduction group initially demonstrated a slight increase in CPD, and then showed a slight decrease at Week 20. The NNC control group saw an increase in CPD compared to baseline until Week 8 of the study, which stayed constant until Week 20. The immediate reduction group saw a strong decrease in CPD at Week 4, which continued decreasing until Week 20 of the study. Furthermore, negative affect was positively associated with cigarette consumption and positive affect was negatively associated with cigarette consumption in the control group, but there was no significant association between affect and cigarette consumption in the gradual or immediate reduction groups (Robinson et al., 2019).

Smith and colleagues (2019) conducted a secondary analysis of data from Hatsukami et al. (2018) to determine the impact of gradual versus immediate nicotine reduction on subjective ratings of cigarettes. This analysis found that participants in the immediate nicotine reduction group rated cigarettes lower in measures of craving relief, satisfaction, psychological reward, and enjoyment of respiratory tract sensations. Participants in the gradual nicotine reduction group only rated study cigarettes lower at study Week 20. Furthermore, the immediate reduction group had higher levels of noncompliance with study cigarettes than did the gradual reduction group (Smith, Donny, et al., 2019).

Higgins and colleagues (2020) conducted a multi-site 12-week randomized clinical trial to assess smoking rates and dependence severity during extended use of NNC, LNC, and VLNC cigarettes among 775 individuals from one of three vulnerable populations (socioeconomically disadvantaged female smokers, smokers with opioid dependence, and smokers with affective disorders). Participants were assigned to one of three SPECTRUM® research cigarettes, which were provided for 12 weeks: NNC, LNC, or VLNC cigarettes. Overall, the total CPD decreased from baseline across weeks and during Week 12 among those assigned to the LNC and VLNC cigarettes, although nonstudy CPD was also higher for these groups. The CPD of those assigned to the LNC and VLNC differed from the NNC cigarettes, but not from each other. Several secondary outcomes were lower for those assigned to LNC and VLNC cigarettes relative to NNC cigarettes, including dependence severity and hypothetical demand for cigarettes. Finally, greater abstinence from smoking was observed for those assigned to LNC and VLNC cigarettes. The authors concluded that LNC and VLNC cigarettes may have reduced abuse potential in vulnerable populations (Higgins et al., 2020).

> In a secondary analysis of Higgins et al. (2020), Higgins and colleagues (2021) investigated cumulative vulnerabilities as a potential moderator of response to LNC and VLNC cigarettes. The authors categorized participants into three levels of cumulative-vulnerability severity based on the co-occurrence of 0–1, 2–3, or ≥ 4 of seven vulnerabilities to smoking: (1) rural residence, (2) a comorbid substance use disorder; (3) a current affective disorder; (4) low educational attainment; (5) poverty, (6) unemployment, and (7) physical disability. Overall, the authors reported that the total CPD at Week 12 increased as cumulative vulnerabilities increased and decreased as nicotine content decreased; there was no significant interaction of cumulative vulnerability and nicotine content. In general, the effects of LNC and VLNC cigarettes followed a similar patten for other outcomes (e.g., CPD across weeks, toxin exposure, dependence severity, craving/withdrawal). Thus, the authors reported little evidence that cumulative vulnerabilities moderate response to LNC and VLNC cigarettes (Higgins et al., 2021).

Klemperer and colleagues (2019) conducted a two-arm randomized trial in which 32 daily smokers were randomized to a CPD reduction arm and 36 daily smokers were randomized to a nicotine reduction arm. Participants in the CPD reduction arm were instructed to smoke 70%, 35%, 15%, and 3% of their baseline cigarette consumption during Weeks 1, 2, 3, and 4, respectively. Participants in the nicotine reduction arm were provided 100% of baseline CPD in the form of study cigarettes with systematically reduced nicotine content at percentages of

nicotine that were equivalent to the percentages of CPD in the CPD reduction arm. Participants in both groups also received 21 mg nicotine patches and were directed to use one patch per day. At the end of the study, participants in both arms had reduced measures of nicotine dependence, but participants in the CPD reduction arm were noncompliant (i.e., smoked non-study cigarettes) more often than those in the nicotine reduction arm. (Klemperer, Hughes, & Callas, 2019).

Klemperer and colleagues (2019) conducted a secondary analysis using data from Klemperer et al. (2019) to investigate quit attempts and quit intentions among individuals who were instructed to reduce cigarette smoking either by decreasing CPD or by using VLNC cigarettes. Significantly more participants in the CPD group (41%) made any quit attempt (including those < 24 hours) than those in the VLNC group (17%), but no significant difference in quit attempts ≥ 24 hours nor intentions to quit was observed between the two groups (Klemperer, Hughes, & Callas, 2019).

Nighbor and colleagues (2020) conducted a secondary analysis of Klemperer et al., (2019) to compare changes in the reinforcing efficacy of cigarettes following a reduction in CPD versus reducing nicotine exposure through use of VLNC cigarettes. All participants smoked NNC research cigarettes ad libitum for one week. Participants were then randomized to a 4-week phase where they either: continued smoking NNC content cigarettes and received a progressively fewer number of cigarettes each week (CPD group) or received cigarettes with progressively lower nicotine content each week (VLNC group). Participants completed the CPT for UB cigarettes at baseline, research cigarettes at each weekly session, and UB cigarettes at 1-month follow-up. At 1-month follow-up, UB cigarette demand was significantly reduced among both the CPD and VLNC groups compared to baseline UB cigarette demand, with no differences between the two groups. Among the VLNC group, several indices of demand decreased significantly throughout the 4-week study while they received progressively reduced nicotine content cigarettes. The CPD group did not experience significant changes in demand for research cigarettes throughout the 4-week study (Nighbor et al., 2020).

Krebs and colleagues (2021) conducted a 33-week, two-arm, double-blind, randomized clinical study to evaluate the effects of gradually reducing the nicotine content in cigarettes on ratings of acceptability, compliance, dependence, biomarkers, and cessation in 245 regular

smokers. Participants completed a 1-week UB cigarette baseline, followed by a two-week baseline of SPECTRUM® NNC research cigarettes. Participants were then randomized to continue smoking the NNC cigarettes or to receive progressively reduced nicotine content cigarettes (reduced every 3 weeks) for 18 weeks until they reached the VLNC cigarette level. Subsequently, participants chose to continue smoking their assigned NNC or VLNC study cigarettes, return to UB cigarettes, or make a quit attempt with counseling and NRT. The gradual reduction group was significantly more likely to drop out of the study compared to the NNC group. CPD, plasma cotinine, CO, and NNAL levels were significantly lower for the gradual reduction group compared to the NNC group at the end of the 18-week randomized phase. Measures of oxidative stress from tobacco smoke remained the same between groups. There were no significant differences in cigarette dependence or withdrawal as a function of group. Self-reported non-compliance was reported by 35% and 29% of participants in the NNC and gradual reduction groups, respectively. During the treatment choice phase, 69% of the NNC group and 44% of the gradual reduction group chose to continue receiving study cigarettes, 10% and 24% returned to UB, and 21% and 31% chose to make a quit attempt. Regardless of treatment choice, biochemically confirmed quit rates were 3% versus 9% at one month and 4% versus 7% at three months (p = NS) for the NNC and gradual reduction groups, respectively. There was no statistically significant difference in quit rates as a function of group among those who chose to make a quit attempt (Krebs et al., 2021).

Lin and colleagues (2020) conducted a secondary analysis of Krebs et al., (2021) to assess subjective effects of gradually reduced nicotine content cigarettes. Participants completed the mCEQ and Cigarette Liking Scale (CLS) from visits 3 to 9 (baseline to end of week 18). Cigarettes with a nicotine content of ≤ 2.4 mg nicotine per g of total tobacco were associated with lower ratings of satisfaction compared to NNC cigarettes. Cigarettes with a nicotine content of 0.4 mg nicotine per g of total tobacco were associated with lower ratings of psychological reward compared to NNC cigarettes. There were no differences in ratings of aversion as a function of nicotine content. Nicotine content cigarettes of 1.3 mg nicotine per g of total tobacco were associated with lower enjoyment of respiratory tract sensations compared to NNC cigarettes. Nicotine content cigarettes of 0.4 and 2.4 mg nicotine per g of total tobacco were associated with lower craving reduction compared to NNC cigarettes. For the cigarette liking scale, on average, positive subjective effects ratings were significantly lower for cigarettes containing ≤ 2.4 mg nicotine per g of total tobacco compared to NNC cigarettes (Lin et al., 2020).

McRobbie and colleagues (2016) conducted a randomized clinical trial of 200 treatment-seeking smokers. All participants received standard behavioral treatment and pharmacotherapy (varenicline or NRT) and were randomized on their quit day to receive a 2-week supply of Xodus LNC cigarettes or the standard treatment alone. When pharmacotherapy groups were combined, frequency, but not strength of urge to smoke, was significantly lower among participants who received LNC cigarettes. There were no significant differences in withdrawal as a function of pharmacotherapy or cigarette group. Participants who received LNC cigarettes had significantly higher rates of abstinence at Weeks 1 and 4, but these differences did not persist to Weeks 6 and 12. Sixty-six percent of participants reported that LNC cigarettes were moderately or very useful in their quit attempt: however, 62% said they would be unlikely to purchase them. In sum, supplementing standard smoking cessation treatment with LNC cigarettes for 2 weeks approximately doubled the odds of quitting smoking at Week 4, although the effect diminished by Week 12 (McRobbie et al., 2016).

Mercincavage and colleagues (2016) conducted a randomized, unblinded clinical trial of 158 non-treatment-seeking smokers. After a 5-day baseline period, participants were randomly assigned to an experimental condition in which they smoked gradually reduced nicotine content cigarettes (Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes) during three 10-day periods or a control group in which they smoked their usual brand cigarettes throughout the study. In the experimental group, there were significant increases in CPD relative to baseline during the Quest NNC and LNC cigarette phases, but not during the VLNC cigarette phase. The control group smoked significantly more CPD at the end of each of the three phases compared to baseline. Within the experimental group, total puff volume was significantly lower than baseline during all Quest phases. Fewer puffs of Quest cigarettes were taken relative to baseline. Compared to baseline, mean puff volume, duration, and peak velocity decreased during the Quest NNC and LNC cigarette phases and increased during the VLNC cigarette phase. In the control group, cotinine and NNAL levels were stable throughout the study; however, they were significantly reduced from baseline during each Quest phase in the experimental group. The experimental group rated all Quest cigarettes more negatively than usual brand cigarettes on subjective measures (Mercincavage et al., 2016).

Mercincavage and colleagues (2017) conducted a secondary analysis of data from Mercincavage et al. (2016) to examine the effects of a Quest cigarette advertisement on false beliefs about reduced nicotine content cigarettes. Only data from participants who were randomized to the Quest 1 NNC cigarette condition and completed the first 15 days of the study were analyzed in this report. Participants completed a Quest 1 cigarette beliefs questionnaire after

smoking their first Quest 1 cigarette. Following their second Quest 1 cigarette, participants viewed a Quest advertisement and again completed a beliefs questionnaire. Viewing a Quest advertisement increased the false belief that Quest cigarettes were healthier than regular cigarettes and decreased the false belief that they were less likely to cause cancer. Neither false beliefs nor subjective ratings of Quest cigarettes directly affected smoking behaviors (Mercincavage, Saddleson, Gup, et al., 2017). Although some interactions between false beliefs and subjective ratings were observed, it is unclear how relevant these findings are to VLNC cigarettes because the nicotine content of Quest 1 cigarettes (~12.7 mg nicotine per g of total tobacco) is much higher than VLNC cigarettes.

Mercincavage and colleagues (2017) conducted a secondary analysis of data from Mercincavage et al. (2016) and previously unpublished data to assess the acceptability of VLNC cigarettes. In addition to the two study conditions described in Mercincavage et al. (2016) wherein participants were assigned to a control group in which they smoked their usual brand cigarettes throughout the study or a "decreasing" nicotine group in which they smoked gradually reduced nicotine content cigarettes (Quest 1 NNC, Quest 2 LNC, and Quest 3 VLNC cigarettes) during three 10-day periods, some participants in the current study were also assigned to one of five "non-decreasing" nicotine content cigarette groups (i.e., NNC-VLNC-LNC, VLNC-LNC-NNC, VLNC-NNC-LNC, LNC-VLNC-NNC, LNC-NNC-VLNC). Study attrition was assessed as a proxy for VLNC cigarette acceptability. Seventy-seven of 246 participants dropped out of or were removed from the study (31.3% attrition). Attrition was greater in the non-decreasing nicotine groups (44.6%) than the decreasing nicotine group (25%) and control group (24.1%). Nicotine content significantly predicted study attrition, which was highest during the VLNC cigarette conditions (18%), followed by the LNC (9%) and NNC (7.8%) cigarette conditions. Across all groups, odds of attrition were 2.6 times higher when participants were using VLNC cigarettes compared to usual brand cigarettes. Compared to the control group, odds of attrition were greatest when participants switched from NNC to VLNC cigarettes (4.65) and from usual brand to VLNC cigarettes (4.48). Participants who provided more favorable ratings of study cigarettes were less likely to drop out (Mercincavage, Wileyto, et al., 2017).

Mercincavage and colleagues (2018) conducted a study with 100 daily smokers, 51 of whom were fast metabolizers of nicotine and 49 of whom were slow metabolizers of nicotine. During the first 5 days of the study, participants were instructed to smoke their own brand of cigarettes. At the end of Day 5, participants received SPECTRUM® LNC study cigarettes containing 5.2 mg/g (LNC1 phase.) On Day 20, participants were switched to SPECTRUM® LNC cigarettes containing 1.3 mg/g until Day 35 of the study (LNC2 phase). Participants were blinded to this switch. Investigators found that mean CPD was significantly higher during LNC1 than during baseline; however, cigarette consumption during LNC2 did not differ significantly from baseline consumption. The average total puff volume was lower during the LNC periods than during baseline; however, total puff volume was higher during LNC2 than during LNC1. Fast metabolizers had higher overall NNAL levels than slow metabolizers during the study. NNAL levels decreased significantly for both groups during the LNC periods. Overall, investigators concluded that fast metabolizers of nicotine were not at greater risk for compensatory smoking when exposed to LNC cigarettes (Mercincavage et al., 2018).

Rezaishiraz and colleagues (2007) investigated whether pretreatment with VLNC cigarettes plus NRT could reduce craving during a quit attempt. Participants were 98 adult heavy smokers (≥ 20 CPD) who received 2 weeks of Quest 3 VLNC cigarettes combined with 21 mg nicotine patch or 2 weeks of Quest 1 NNC cigarettes alone prior to their quit date. Following the quit date, all participants received counseling and NRT patches for up to 8 weeks. Participants in the VLNC cigarette plus patch group reported less frequent and less intense cravings before and during the quit attempt. However, withdrawal scores and quit rates did not significantly differ between groups (Rezaishiraz et al., 2007).

Rose and colleagues (2001) examined the relationship between smoking, cessation, and monoamine oxidase (MAO) activity in 16 adult smokers interested in quitting. Smoking cessation treatment included Next VLNC cigarettes for 2 weeks combined with nicotine replacement therapy (NRT), oral mecamylamine, and neostigmine before and after a quit date. Platelet MAO-B activity was measured before participants switched to VLNC cigarettes and again at 1 and 4 weeks post-cessation in six participants who quit smoking. MAO-B activity increased significantly after 4 weeks of cessation. The intensity of withdrawal symptoms after switching to VLNC cigarettes and after smoking cessation was significantly predicted by low baseline MAO-B activity. The authors concluded that smoking inhibits MAO activity and cessation reverses this effect. As VLNC cigarettes did not influence MAO activity, the authors speculated that non-nicotine agents in cigarettes are responsible for MAO inhibition (Rose et al., 2001).

Rose and Behm (2004b) examined the effects of several experimental manipulations on usual brand cigarette reinforcement. Participants were 233 adult smokers interested in quitting. During the 2-week study, participants received a placebo or 21 mg nicotine patch, mecamylamine or a placebo, and they switched to Next VLNC cigarettes, cigarettes with menthol content opposite of their usual brand (i.e., participants who usually smoked menthol cigarettes were switched to non-menthol cigarettes and vice versa), or ventilated low nicotine yield cigarettes. Usual brand cigarette reinforcement was assessed during three laboratory sessions, each separated by 1 week. All pharmacological treatments, as well as switching to VLNC cigarettes, reduced ratings of reward for usual brand cigarettes. The authors concluded that VLNC cigarettes could reduce the reinforcing effects of nicotine (Rose & Behm, 2004b).

Rose and colleagues (2006) examined the effects of NRT on smoking cessation in 96 adult smokers interested in quitting. Participants were randomly assigned to receive placebo or 21 mg nicotine patches (double-blind), and to smoke either usual brand cigarettes, ventilated low tar and nicotine yield cigarettes, or Next VLNC cigarettes for 2 weeks prior to their target quit date. After the quit date, participants continued to receive various combinations of pharmacotherapy (0, 21, or 42 mg nicotine patch and mecamylamine) for up to 6 weeks. Breath CO decreased from baseline to Week 2 in the low nicotine yield and VLNC cigarette conditions, but was relatively stable in the usual brand cigarette condition. Salivary cotinine was lowest in participants who received VLNC cigarettes and placebo patches. Compared to placebo patch, nicotine patch was associated with decreases in CPD in the low nicotine yield and VLNC cigarette conditions, but not in the usual brand cigarette condition. Nicotine patch increased compliance with study-assigned cigarettes (i.e., low nicotine yield and VLNC cigarettes), and nicotine patch pretreatment predicted continuous abstinence at 4 weeks post-cessation, irrespective of cigarette condition. (Rose et al., 2006).

Rose and colleagues (2007) studied regional brain activity associated with nicotine dependence in 15 dependent smokers. This study was funded by Philip Morris. Participants switched to Next or Quest 3 VLNC cigarettes plus 21 mg nicotine patches for 2 weeks, and then returned to smoking usual brand cigarettes for 2 weeks. PET scans assessed regional cerebral metabolic rate for glucose, and the FTND was used to assess dependence at baseline, following 2 weeks of VLNC cigarette plus patch exposure, and following 2 weeks of usual brand cigarette exposure. Participants had lower craving and dependence scores as well as decreased brain activity in the right hemisphere of the anterior cingulate cortex following the VLNC cigarette plus patch exposure period compared to baseline and usual brand cigarette exposure. Changes in craving scores across the three time points were negatively associated with changes in brain activity in several structures within the brain reward system, including the ventral striatum,

orbitofrontal cortex and pons. Differences in FTND scores were positively associated with thalamus activity (right hemisphere). Those who reported smoking for calming effects had a decrease in thalamus activity (bilaterally) and an increase in amygdala activity (left hemisphere) following VLNC cigarette plus patch exposure. However, those who reported smoking to enhance pleasurable relaxation had increased metabolic activity of the dorsal striatum following VLNC cigarette plus patch exposure (Rose et al., 2007).

Shiffman and colleagues (2018) conducted a randomized, double-blind clinical trial to investigate the effects of LNC cigarettes on smoking behavior in 238 adult nondaily smokers. Participants received usual brand cigarettes during a 2-week baseline period and were then randomized to receive SPECTRUM® 1.3 mg nicotine per gram of total tobacco LNC cigarettes or 15.8 mg nicotine per g of total tobacco NNC cigarettes for 10 weeks (SPECTRUM® cigarettes and usual brand cigarettes were provided for free). During baseline, mean CPD was 3.1. By Week 10, CPD decreased significantly more in the LNC cigarette group than in the NNC cigarette group (1.6 fewer CPD versus .05 fewer CPD, respectively). The percentage of days smoking also decreased more in the LNC cigarette group. However, measures of abstinence and intention to quit were not different between groups. Noncompliance was more common in the LNC cigarette group than the NNC cigarette group. Among participants who were not e-cigarette users at baseline, new use of e-cigarettes was significantly higher in the LNC cigarette group than the NNC cigarette group, especially among heavier smokers. At an exit interview, participants in the LNC cigarette group were more likely than those in the NNC cigarette group to correctly guess which type of study cigarette (i.e., NNC or LNC) they were assigned (Shiffman, Kurland, et al., 2018).

Shiffman and colleagues (2018) conducted a secondary analysis of data from Shiffman, Kurland, et al. (2018) and found that participants in the LNC cigarette group had a puff volume approximately 40% lower than participants in the NNC cigarette group, but CO boost did not differ significantly between the groups. Overall, participants in the LNC cigarette group burned on average 3% less tobacco mass than did participants in the NNC cigarette group; when stratified by age, participants over the age of 40 in the LNC cigarette group showed this decrease, but participants below the age of 40 did not. Filter optical density showed some decrease in the LNC cigarette group, and some increase in the NNC cigarette group, indicating that participants in in the VLNC group reduced their puffing intensity, while participants in the NNC group increased it when smoking study cigarettes (Shiffman, Mao, Kurland, & Scholl, 2018).

Shiffman and colleagues (2019) conducted a secondary analysis of data from Shiffman, Kurland, et al. (2018) and found that participants in the LNC cigarette group showed greater decreases in dependence after baseline than did participants in the NNC cigarette group. Baseline CPD numbers were the largest predictor of CPD during the study, regardless of study group. Furthermore, participants who were more dependent on cigarettes were not more likely to "cheat" with usual brand cigarettes if assigned to the LNC group compared to the NNC group (Shiffman et al., 2019).

Smith and colleagues (2019) conducted a study with 240 adult daily smokers who smoked more than five CPD. Participants were randomized in a 2 x 2 factorial design, to receive either NNC cigarettes, or VLNC cigarettes (blinded), and to receive or not receive a transdermal nicotine patch (open label). Participants were instructed to smoke only study cigarettes, and they were told to record the number of study and non-study cigarettes they smoked per day. In Week 7, participants were provided a daily descending monetary bonus for refraining from using any cigarettes. Participants randomized to receive NRT were encouraged to continue using their patches. Puff topography was measured from a single cigarette at a study visit. Participants assigned to VLNC cigarettes and NRT smoked significantly fewer CPD than did participants assigned to both the NNC alone and NNC+NRT groups. However, among participants in the VLNC groups, CPD did not differ significantly between those who received NRT and those who did not. Participants in the VLNC groups were more likely to report use of non-study cigarettes than participants in the NNC groups. During the abstinence period, the VLNC-only group trended towards more lapses than the NNC-only group; however, lapses between the groups did not differ significantly (Smith, Koopmeiners, et al., 2019).

Smith and colleagues (2020) conducted a crossover study with 16 adult daily smokers, who smoked more than five CPD. Participants checked into a hotel from Day 1 to Day 5 and were instructed not to bring any tobacco products; study participants completed a total of two such hotel stays. Participants were provided with SPECTRUM® VLNC cigarettes for one of their stays, and NNC cigarettes for the other stay. They were also given an "account balance" with which to purchase study cigarettes at a "cigarette store." Investigators found that the number of cigarettes smoked per day did not differ significantly between the VLNC-only and the NNC-only conditions. Breath CO was also not significantly different between the two conditions. The VLNC condition was associated with a significant decrease in total nicotine equivalents, indicating lower nicotine exposure from VLNC cigarettes than NNC cigarettes. Therefore, the investigators concluded that when presented with only VLNC cigarettes, smokers do not

significantly change their behavior to compensate for lowered nicotine content (Smith, Koopmeiners, White, et al., 2020).

> White and colleagues (2022) conducted a secondary analysis of data from Smith et al. (2020) investigating whether participants' puffing intensity increased with the use of VLNCs relative to their puffing intensity with NNC cigarettes. Mouth-level nicotine exposure indicated participants puffed VLNC cigarettes with greater intensity than NNC cigarettes in each respective 24-hour period; however, this effect diminished across sessions. Thus, the results of this study suggest individuals are unlikely to sustain compensatory puffing behavior over time (White et al., 2022).

Tidey and colleagues (2019) conducted a study with 58 adult smokers diagnosed with serious mental illness (i.e., schizophrenia, schizoaffective disorder, or bipolar disorder) who had no intention to quit smoking. Participants were randomized to receive either SPECTRUM® NNC or VLNC cigarettes. Participants attended laboratory sessions weekly to collect study cigarettes and were told only to smoke study cigarettes. Urine was collected to measure biomarkers of exposure. From post-randomization Week 6 to 7, participants were asked to abstain entirely from smoking for as long as possible in exchange for a financial incentive. During the abstinence week, participants provided measures of craving and breath CO values. By Week 6, participants in the VLNC group were smoking significantly fewer CPD than were participants in the NNC group. The VLNC cigarettes were also rated lower in measures of satisfaction. During the abstinence week, the median time abstinent and time to first lapse was longer in the VLNC group compared with the NNC group. No significant differences in psychiatric symptoms were measured (Tidey et al., 2019).

> Denlinger-Apte and colleagues (2019) conducted a secondary analysis of data from Tidey et al. (2019) on the effects of VLNC cigarettes on smoking topography. Following a 1-week baseline with the participants' usual-brand cigarettes, during which smoking topography was measured, participants were randomly assigned under double-blind conditions to receive either SPECTRUM® VLNC or NNC cigarettes for 6 weeks. Smoking topography measures were then collected again after 6 weeks. After controlling for baseline smoking topography, participants assigned to VLNC cigarettes smoked fewer puffs per cigarette and had shorter interpuff intervals relative to those assigned to NNC cigarettes at Week 6. No significant difference was observed between NNC and VLNC cigarettes with respect to cigarette volume, puff duration, puff volume, peak

flow rate, or breath CO boost, indicating no significant compensatory smoking behavior (Denlinger-Apte, Donny, et al., 2020).

Reed and colleagues (2022) conducted a secondary analysis of the data from participants assigned to use VLNC cigarettes (n=30) in Tidey et al. (2019) to identify predictors of non-compliance among individuals with serious mental illness. Noncompliance was estimated using the ratio of urinary TNE-6/self-report CPD at week 6 vs. baseline, and individuals with values greater than 0.1 were considered noncompliant. Subjective effects (measured with the Cigarette Evaluation Scale [CES]), dependence (FTCD, WISDM), and psychiatric symptoms (PANSS, BPRS, CDSS) were used as predictors of non-adherence in a regression model. Subjective ratings of enjoyment of respiratory tract sensations on the CES were the only significant predictor of non-adherence. Ratings were negatively associated with non-adherence such that lower ratings of enjoyment were associated with greater non-adherence (Reed et al., 2022).

Walker et al. (2012) evaluated the effects of VLNC cigarettes and standard Quitline care (8 weeks of NRT and behavioral support) on smoking abstinence in New Zealand smokers motivated to quit. A total of 1,410 callers to the Quitline were randomized to receive standard care alone or Quest 3 VLNC cigarettes for up to 6 weeks after their quit date along with standard care. The primary outcome was 7-day point-prevalence smoking abstinence at 6 months after the quit date. Abstinence rates were significantly greater in participants using VLNC cigarettes (33%) compared to standard care alone (28%). The continuous abstinence rate at 6 months was 23% for participants using VLNC cigarettes compared to 15% of participants receiving standard care alone. In the VLNC cigarette group, the average number of VLNC cigarettes smoked each week decreased throughout the study, and participants rated the cigarettes as “a little” to “moderately” satisfying. No significant differences were observed between groups in withdrawal, NRT use, or the occurrence of serious adverse events (Walker et al., 2012).

Walker and colleagues (2015) conducted a pilot clinical study in New Zealand to assess smoking behavior following 12 weeks of access to Magic VLNC cigarettes in 33 adult smokers unmotivated to quit. Participants were randomized to receive VLNC cigarettes for 12 weeks or continue smoking their usual brand cigarettes. There was a significant reduction in mean usual brand CPD from baseline to Week 6 among participants in the VLNC cigarette group, but not in the control group. This reduction was no longer significant at Week 12. VLNC cigarettes were associated with a decrease in dependence measures that was not observed in the control

group. Motivation to quit from baseline to Week 12 was not significantly different between groups; however, more participants in the VLNC cigarette group (n = 7) made a quit attempt compared to the control group (n = 1). Two participants in the VLNC cigarette group and one participant in the control group reported continual abstinence of usual brand cigarettes at Week 12. At baseline, participants in both groups were willing to pay the same price for VLNC cigarettes relative to usual brand cigarettes. After 12 weeks of access to VLNC cigarettes, participants were much less willing to pay for the VLNC cigarettes, unless there was a substantial price differential (Walker et al., 2015).

Table A.2: Reduced Nicotine Content Cigarettes

Nicotine Content Category	Cigarette Brand	Maximum Reported Nicotine Content (mg/cig)	Studies
VLNC	SPECTRUM® 0.4 mg [a] (NRC102, NRC103, NRC104, NRC105)	0.3*	(Arger et al., 2017; Boatman, Vock, Koopmeiners, et al., 2018; Cassidy, Colby, et al., 2018a; D. R. Davis, M. J. DeSarno, et al., 2019; Danielle R. Davis et al., 2019; D. R. Davis, M. A. Parker, et al., 2019; R. Denlinger-Apte et al., 2019; Denlinger-Apte, Cassidy, Colby, Sokolovsky, & Tidey, 2019b; R. L. Denlinger-Apte, E. C. Donny, et al., 2020; R. L. Denlinger-Apte, M. Kotlyar, et al., 2019; Denlinger et al., 2016; ; Dermody et al., 2018; Dermody et al., 2016; Donny et al., 2015; Faulkner et al., 2017; Faulkner et al., 2019; Faulkner et al., 2018; Foulds et al., 2018; Gaalema et al., 2019; Hatsukami et al., 2015; Higgins et al., 2018; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Kaizer & Koopmeiners, 2020; Kaizer et al., 2018; Kamens et al., 2020; Klemperer, Hughes, & Callas, 2019; Klemperer, Hughes, Callas, et al., 2019; Nardone et al., 2016; Pacek et al., 2016; Parker et al., 2018; Perkins & Karelitz, 2019, 2020; Perkins et al., 2017, 2018; Perkins, Kunkle, Michael, et al., 2016; Robinson et al., 2019; Smith, Donny, et al., 2019; Smith, Koopmeiners, Hatsukami, et al., 2020; Smith, Koopmeiners, et al., 2019; Smith, Koopmeiners, White, et al., 2020; Streck et al., 2019; Tidey et al., 2019)
	Next [b]	0.3*	(Baldinger et al., 1995a, 1995b, 1995c; Brauer et al., 1999; Brauer et al., 2001; Gross et al., 1997; Hasenfratz et al., 1993; Rose & Behm, 2004b; Rose et al., 2001; Rose et al., 2007; Rose, Behm, Westman, Bates, et al., 2003; Rose et al., 2000; Rose et al., 2006; Rose, Behm, Westman, Mathew, et al., 2003; Rose et al., 2004; Rose et al., 1999; Westman et al., 1996) [h]
	Ultratech/Lifetech "denicotinized" [c, d]	0.5	(Breland et al., 2002; Buchhalter et al., 2005; Buckley et al., 2007; Cook et al., 2007; Dallery et al., 2003; Eid et al., 2005; Greenstein et al., 2010; Juliano et al., 2006; Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007; Spring et al., 2008)
	Philip Morris 1 mg [e]	0.6	(Bandiera et al., 2015; Benowitz et al., 2012; Benowitz et al., 2007; Benowitz et al., 2006; Benowitz, Nardone, Dains, et al., 2015; Benowitz, Nardone, Hatsukami, et al., 2015; Hatsukami et al., 2015)
	Quest 3	0.6	(Adams et al., 2015; Addicott et al., 2014; Addicott et al., 2015; Attwood et al., 2012; Attwood et al., 2009; Barrett, 2010; Barrett et al., 2013; Barrett & Darredeau, 2012; Barrett et al., 2006; Becker et al., 2008; Brody, Mandelkern, Olmstead, et al., 2009; Chukwueke et al., 2020; Cobb et al., 2010; Darredeau et al., 2013; Dedert et al., 2012; Rachel L. Denlinger-Apte et al., 2017; Dermody et al., 2015; Ding et al., 2014; Donny et al., 2007; Donny & Jones, 2009; Hammond & O'Connor, 2014; Harrell & Juliano, 2012; Hatsukami et al., 2015; D. K. Hatsukami, L. A. Hertsgaard, et al., 2013; Hatsukami et al., 2010; Juliano et al., 2011; Kelemen, 2008; King et al., 2009; Kuwabara et al., 2014; Lindsey et al., 2013; Macqueen et al., 2012;

			Mercincavage et al., 2016; Naqvi & Bechara, 2005, 2006; Penetar et al., 2012; Perkins, Ciccocioppo, et al., 2008; Perkins et al., 2004; Perkins & Karelitz, 2013, 2014, 2015; Perkins et al., 2010; Perkins, Lerman, et al., 2008; Ray et al., 2006; Rezaishiraz et al., 2007; Rose, F. M. Behm, et al., 2010; Rose et al., 2007; Rukstalis et al., 2005; Schlagintweit & Barrett, 2016; Strasser et al., 2007; Tidey, Cassidy, et al., 2016; Tidey et al., 2013; Vogel et al., 2014; Walker et al., 2012; Walker et al., 2011)
	Magic [f]	0.7	(Fraser & Kira, 2017; Guillot et al., 2015; Tucker et al., 2017; Walker et al., 2015) [i]
LNC	SPECTRUM® 1.3 mg [a] (NRC200, NRC201)	0.9*	(Cassidy, Colby, et al., 2018a;; Dermody et al., 2018; Dermody et al., 2016; Donny et al., 2015 Foulds et al., 2018; Hatsukami et al., 2017; Kaizer & Koopmeiners, 2020; Mercincavage et al., 2018; Nardone et al., 2016; Pacek et al., 2016; Perkins & Karelitz, 2019, 2020; Shiffman, Kurland, et al., 2018; Shiffman, Mao, et al., 2018; Shiffman & Scholl, 2019; Shiffman et al., 2019; Smith, Koopmeiners, Hatsukami, et al., 2020)
	Xodus [g]	1.2	(Dermody et al., 2015; D. K. Hatsukami, L. A. Hertsgaard, et al., 2013; McRobbie et al., 2016; Vogel et al., 2014)
	SPECTRUM® 2.4 mg [a] (NRC300, NRC301)	1.7*	(Arger et al., 2017; Cassidy, Colby, et al., 2018a; Danielle R. Davis et al., 2019; D. R. Davis, M. A. Parker, et al., 2019;; Dermody et al., 2018; Dermody et al., 2016; Donny et al., 2015; Faulkner et al., 2017; Faulkner et al., 2019; Faulkner et al., 2018; Foulds et al., 2018; Gaalema et al., 2019; Higgins et al., 2018; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Kaizer & Koopmeiners, 2020; Kamens et al., 2020; Klemperer, Hughes, & Callas, 2019; Klemperer, Hughes, Callas, et al., 2019; Nardone et al., 2016; Pacek et al., 2016; Parker et al., 2018; Perkins & Karelitz, 2019, 2020; Robinson et al., 2019; Smith, Donny, et al., 2019; Smith, Koopmeiners, Hatsukami, et al., 2020; Streck et al., 2019)
	Philip Morris 2 mg [e]	1.7	(Bandiera et al., 2015; Benowitz et al., 2012; Benowitz et al., 2006; Benowitz, Nardone, Dains, et al., 2015; Benowitz, Nardone, Hatsukami, et al., 2015; Hatsukami et al., 2015)
	SPECTRUM® 5.2 mg [a] (NRC400, NRC401)	3.6*	(Arger et al., 2017; Cassidy, Colby, et al., 2018a; Danielle R. Davis et al., 2019; D. R. Davis, M. A. Parker, et al., 2019; Dermody et al., 2018; Dermody et al., 2016; Donny et al., 2015; Faulkner et al., 2017; Faulkner et al., 2019; Faulkner et al., 2018; Foulds et al., 2018; Gaalema et al., 2019; Higgins et al., 2018; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Kaizer & Koopmeiners, 2020; Kamens et al., 2020; Klemperer, Hughes, & Callas, 2019; Klemperer, Hughes, Callas, et al., 2019; Mercincavage et al., 2018; Parker et al., 2018; Robinson et al., 2019; Smith, Donny, et al., 2019; Smith, Koopmeiners, Hatsukami, et al., 2020; Streck et al., 2019)
	Philip Morris 4 mg [e]	3.9	(Bandiera et al., 2015; Benowitz et al., 2012; Benowitz et al., 2006; Benowitz, Nardone, Dains, et al., 2015; Benowitz, Nardone, Hatsukami, et al., 2015; Hatsukami et al., 2015)
	Quest 2	5.1	(Becker et al., 2008; Ding et al., 2014; Hammond & O'Connor, 2014; Hatsukami et al., 2015; Hatsukami et al., 2010; Mercincavage et al., 2016; Penetar et al., 2012; Strasser et al., 2007)
	SPECTRUM® (NRC500, NRC501)	7.0	(Foulds et al., 2018; Klemperer, Hughes, & Callas, 2019; Klemperer, Hughes, Callas, et al., 2019)
	Ultratech/Lifetech "nicotinized" [d]	7.2	(Buchhalter et al., 2005; Buckley et al., 2007; Cook et al., 2007; Dallery et al., 2003; Eid et al., 2005; Greenstein et al., 2010; Juliano et al., 2006; Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007; Pickworth, Nelson, et al., 1999; Spring et al., 2008)
	Philip Morris 8 mg [e]	7.4	(Bandiera et al., 2015; Benowitz et al., 2012; Benowitz et al., 2006; Benowitz, Nardone, Dains, et al., 2015; Benowitz, Nardone, Hatsukami, et al., 2015; Hatsukami et al., 2015)

NNC	Quest 1	8.9	(Adams et al., 2015; Attwood et al., 2012; Attwood et al., 2009; Barrett, 2010; Barrett et al., 2013; Becker et al., 2008; Chukwueke et al., 2020; Darredeau et al., 2013; Ding et al., 2014; Donny et al., 2007; Donny & Jones, 2009; Hammond & O'Connor, 2014; Harrell & Juliano, 2012; Juliano et al., 2011; Kelemen, 2008; King et al., 2009; Kuwabara et al., 2014; Macqueen et al., 2012; Mercincavage et al., 2016; Naqvi & Bechara, 2005, 2006; Penetar et al., 2012; Perkins, Ciccocioppo, et al., 2008; Perkins et al., 2004; Perkins & Karelitz, 2013, 2014, 2015; Perkins et al., 2010; Perkins, Lerman, et al., 2008; Ray et al., 2006; Rezaishiraz et al., 2007; Rose, F. M. Behm, et al., 2010; Rukstalis et al., 2005; Schlagintweit & Barrett, 2016; Strasser et al., 2007)
	Philip Morris 12 mg [e]	10.3	(Bandiera et al., 2015; Benowitz et al., 2012; Benowitz et al., 2006; Benowitz, Nardone, Dains, et al., 2015; Benowitz, Nardone, Hatsukami, et al., 2015; Hatsukami et al., 2015)
	SPECTRUM® 15.8 mg [a] (NRC600, NRC601)	11.4*	(Arger et al., 2017; Boatman, Vock, & Koopmeiners, 2018; Cassidy, Colby, et al., 2018a; Chukwueke et al., 2020; D. R. Davis, M. J. DeSarno, et al., 2019; Danielle R. Davis et al., 2019; D. R. Davis, M. A. Parker, et al., 2019; R. Denlinger-Apte et al., 2019; R. L. Denlinger-Apte, E. C. Donny, et al., 2020;; Dermody et al., 2018; Dermody et al., 2016; Donny et al., 2015; Faulkner et al., 2017; Faulkner et al., 2019; Faulkner et al., 2018; Foulds et al., 2018; Gaalema et al., 2019; Hatsukami et al., 2017; Higgins et al., 2018; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Kaizer & Koopmeiners, 2020; Kaizer et al., 2018; Kamens et al., 2020; Klemperer, Hughes, & Callas, 2019; Nardone et al., 2016; Pacek et al., 2016; Parker et al., 2018; Perkins & Karelitz, 2019, 2020; Perkins et al., 2018, 2018; Perkins, Kunkle, Michael, et al., 2016; Robinson et al., 2019; Shiffman, Kurland, et al., 2018; Shiffman, Mao, et al., 2018; Shiffman & Scholl, 2019; Shiffman et al., 2019; Smith, Donny, et al., 2019; Smith, Koopmeiners, Hatsukami, et al., 2020; Smith, Koopmeiners, et al., 2019; Smith, Koopmeiners, White, et al., 2020; Streck et al., 2019; Tidey et al., 2019)

*FDA used mg of nicotine per gram of total tobacco data to calculate mg of nicotine per cigarette based on an estimate of 0.7 g of tobacco per cigarette

[a] Nicotine content (mg/g) from CDC analysis and published studies, and nicotine yield from (National Institute on Drug Abuse, 2014).

[b] Nicotine content (mg/g) from Djordjevic et al., (1990), and nicotine yield from Baldinger et al., (Baldinger et al., 1995b).

[c] Nicotine content calculated by FDA based on nicotine yield data from Pickworth et al., (1999).

[d] Nicotine yield from Pickworth et al., (1999).

[e] Nicotine content (mg/cig) and nicotine yield from Benowitz et al., (2012) and Benowitz et al., (2006).

[f] Nicotine content (mg/cig) and nicotine yield from Walker et al., (2015).

[g] Nicotine content (mg/cig) and nicotine yield from Hatsukami et al., (2013).

[h] Brand not reported; however, supporting evidence suggests cigarettes used in Baldinger et al., (1995b) and Rose et al., (2003) were Next brand.

[i] Brand information for Guillot et al., (2015) obtained through personal communication with investigator.

D. Summary and Conclusions

a. Primary Outcomes

The primary aims of this RTD were to review and summarize findings related to the effects of VLNC cigarettes on addiction-related outcomes. Thus, all articles included in this RTD assessed self-reported or behavioral measures of reward (i.e., drug "liking," other subjective effects, choice), craving, withdrawal, dependence, or use (i.e., smoking topography, CPD). Findings related to these outcomes are discussed in this section.

i. Drug Liking and Other Subjective Effects

Self-reported subjective effects (e.g., drug "liking") are widely used measures of reinforcing efficacy and abuse liability of tobacco products. Several studies included in this RTD compared the subjective effects of VLNC, LNC, NNC or participants' usual brand cigarettes using self-reported measures of drug effects (e.g., Cigarette Evaluation Scale, Smoking Effects Questionnaire, Visual Analogue Scale items). Questions assessing drug "liking" have face validity and have been shown to be the most sensitive and reliable subjective effects measures of abuse liability (Carter & Griffiths, 2009).

Under conditions of brief exposure, several studies included in this RTD found that VLNC cigarettes were rated lower in cigarette "liking" compared to NNC cigarettes (e.g., Denlinger-Apte, Kotlyar, et al., 2019; Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013; Lindsey et al., 2013; Perkins, Ciccocioppo, et al., 2008; Perkins et al., 2006; Perkins et al., 2004; Perkins & Karelitz, 2019; Perkins et al., 2010; Perkins et al., 2017, 2018; Schlagintweit & Barrett, 2016) and usual brand cigarettes (e.g., Gross et al., 1997; Rose et al., 2004). However, other studies found no significant differences in "liking" as a function of nicotine content in cigarettes (e.g., Barrett et al., 2006; Dallery et al., 2003; Juliano et al., 2006; Westman et al., 1996). Other subjective effects (e.g., "good" or "positive" effects; "bad" or "negative" effects) co-vary with drug "liking." On average, VLNC cigarettes were rated lower on other positive subjective effects items (e.g., "satisfaction," "pleasure," "taste," "strength," "stimulation") compared to LNC cigarettes (e.g., Cook et al., 2007; Dallery et al., 2003; Greenstein et al., 2010; Hatsukami, Heishman, et al., 2013), NNC cigarettes (e.g., Darredeau et al., 2013; Hatsukami, Heishman, et al., 2013; Juliano et al., 2011; Macqueen et al., 2012; Perkins et al., 2010; Perkins et al., 2018, 2018) and usual brand cigarettes (e.g., Baldinger et al., 1995c; Brauer et al., 1999; Cobb et al., 2010; Gross et al., 1997; Hasenfratz et al., 1993). VLNC cigarettes were also rated lower on items such as "aversiveness," "sickness," and "dizziness" (e.g., Brauer et al., 2001; Chukwueke et al., 2020; Harrell & Juliano, 2012; Hasenfratz et al., 1993; Juliano et al., 2011; Kelemen, 2008), and higher on items such as "dislike" and "unpleasant" compared to NNC or usual brand cigarettes (e.g., Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013).

Notably, several factors have been shown to influence subjective effects ratings of VLNC and NNC cigarettes. These factors include participants' ability to discriminate the nicotine content of cigarettes. For example, NNC cigarettes have increased ratings of positive subjective effects when participants' are able to discriminate them from VLNC cigarettes (Perkins & Karelitz, 2020; Perkins, Kunkle, Michael, et al., 2016). In addition, positive subjective effects ratings increased when participants were told that they were receiving a nicotine-containing cigarette, regardless of the actual nicotine content of the cigarette (e.g., Denlinger-Apte et al.,

2017; Perkins, Ciccocioppo, et al., 2008; Perkins et al., 2006; Perkins et al., 2004; Schlagintweit & Barrett, 2016). Several studies included in this RTD assessed subjective effects of VLNC cigarettes following extended exposure. Findings from these studies were relatively similar to findings from brief exposure studies. On average, VLNC cigarettes were rated as less appealing (e.g., lower ratings of “liking”, “satisfaction”, and “pleasure”) compared to LNC and NNC cigarettes (e.g., Buchhalter et al., 2005; Denlinger-Apte et al., 2019; Mercincavage et al., 2016; Smith, Donny, et al., 2019). However, at least one study found no differences in subjective effects as a function of nicotine content in cigarettes (Benowitz et al., 2012). Positive subjective effects ratings for VLNC cigarettes were shown to remain constant or decrease over time (e.g., Buchhalter et al., 2005; Walker et al., 2012).

Donny and colleagues (2007) conducted a study that examined the effects of VLNC cigarettes on subjective effects in smokers who inhabited a residential research facility throughout the study. During 11 days of exposure to study cigarettes, participants assigned to the VLNC cigarette group rated positive subjective effects of cigarettes (e.g., "enjoyable") lower and negative subjective effects (e.g., "unpleasant") higher than baseline subjective effects of usual brand cigarettes. Similarly, during the first few days of exposure to study cigarettes, participants who received NNC study cigarettes rated positive subjective effects of cigarettes lower and negative subjective effects higher than baseline subjective effects of usual brand cigarettes; however, these effects dissipated over time such that subjective ratings of NNC cigarettes were similar to usual brand cigarettes by the end of the study (Donny et al., 2007).

Finally, some evidence suggests gender may influence differences in subjective effects. In one study, women rated all cigarettes as more flavorful than men, and an interaction was observed between gender and nicotine content such that women demonstrated less sensitivity than men to the differential subjective effects of NNC and VLNC cigarettes (Perkins et al., 2018). Another study found women reported increased satisfaction with VLNC or LNC cigarettes alone, while men reported greater satisfaction when these cigarettes were combined with NRT (Vogel et al., 2014). However, another study found that cigarettes with higher nicotine content had greater reinforcing effects than those with lower nicotine content, regardless of sex (Streck et al., 2019).

In sum, VLNC cigarettes are consistently shown to be of equal or lower abuse potential compared to NNC and usual brand cigarettes under conditions of brief and extended exposure. No studies reviewed in this RTD found that VLNC cigarettes were liked significantly more than NNC or usual brand cigarettes. Notably, knowledge of the actual nicotine content of cigarettes does not appear to be associated with increased abuse potential of VLNC cigarettes.

ii. Choice

Choice procedures have been used to evaluate the relative reinforcing effects of cigarettes varying in nicotine content. The results of studies included in this RTD show that when individuals were given the choice to smoke VLNC or NNC cigarettes, they reliably showed a preference for NNC cigarettes, indicating lower abuse liability for VLNC cigarettes (Chukwueke et al., 2020; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Perkins & Karelitz, 2019; Perkins et al., 2018; Perkins, Kunkle, Michael, et al., 2016). Research has also shown that this preference can be influenced. For example, Higgins and colleagues showed that when the effort required to obtain NNC cigarettes increases, some smokers will switch their preference from NNC cigarettes to VLNC cigarettes (Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017). In addition, Branstetter and colleagues (2019) used an escalating price structure, wherein puffs from VLNC cigarettes were least expensive, puffs from LNC cigarettes were priced intermediately, and puffs from NNC cigarettes were most expensive. Participants rated VLNC cigarettes as less satisfying than both LNC and NNC cigarettes, yet they purchased significantly more puffs of the VLNC cigarettes over the more expensive LNC and NNC cigarettes (Branstetter et al., 2019).

Rather than directly assessing choice between tobacco products, some studies evaluate how much smokers are willing to work to earn puffs from cigarettes when the number of responses required to earn a puff from a cigarette progressively increases (i.e., a progressive ratio task). Donny and colleagues (2007) found smokers assigned to an NNC cigarette group were willing to work significantly harder to earn puffs from their study-assigned cigarette than smokers assigned to a VLNC cigarette group (Donny et al., 2007). Additional behavioral studies assessed factors that may contribute to preference for cigarettes of varying nicotine content and found that various factors may impact preference. For example, participants self-administered more cigarettes when they were told the cigarettes contained nicotine versus when they were told the cigarettes were denicotinized (Darredeau et al., 2013); females with the OPRM1 G allele may be less sensitive to the reinforcing effects of nicotine (Ray et al., 2006); and naltrexone reduced the relative reinforcing effects of NNC cigarettes (Rukstalis et al., 2005).

Hypothetical choice tasks (e.g., Cigarette Purchase Task, Multiple Choice Questionnaire) are also used to characterize reinforcing efficacy by determining how changes in the cost of a commodity affect its consumption. These tasks typically involve prior experience with the product or brief laboratory exposure, followed by a series of questions asking participants to either (1) report how many cigarettes they would consume at a variety of escalating prices, or (2) choose between cigarettes or money at a variety of prices. Studies included in this RTD that used hypothetical choice tasks to assess VLNC cigarette reinforcement showed that participants

found VLNC cigarettes less reinforcing than NNC cigarettes (e.g., Hatsukami, Heishman, et al., 2013; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Kaplan et al., 2022; Parker et al., 2018; Smith et al., 2017; Tucker et al., 2017). In one study, Smith and colleagues (2017) examined the reinforcing efficacy of cigarettes varying in nicotine content following six weeks of access to the products. Compared to the NNC cigarette group, those in the VLNC cigarette group estimated that they would smoke fewer cigarettes if the cigarettes were free, spend less for the VLNC cigarettes, and quit smoking VLNC cigarettes at a lower price point (i.e., a price point at which participants would continue to pay for NNC cigarettes). Responses on the hypothetical choice task were highly correlated with the actual number of cigarettes smoked during Week 6 of the trial.

Hypothetical choice tasks can also be used to investigate the substitutability of tobacco products. For example, Tucker and colleagues (2017) employed a cross-price elasticity task in which the price of VLNC cigarettes was held constant while the price for usual brand cigarettes was manipulated. When usual brand cigarette price increased, demand for VLNC cigarettes increased and demand for usual brand cigarettes decreased, indicating VLNC cigarettes are partially substitutable for usual brand cigarettes (Tucker et al., 2017).

In sum, VLNC cigarettes are consistently shown to be of lower abuse potential compared to NNC cigarettes, as evidenced by responses to behavioral and hypothetical choice procedures. However, behavioral and hypothetical choice research has also shown that the choice between VLNC and NNC cigarettes can be influenced such that some smokers will switch their preference from NNC cigarettes to VLNC cigarettes when the price or effort required to obtain the products is manipulated.

iii. Smoking Topography

Smoking topography measures provide data on various aspects of smoking behavior, including number of puffs per cigarette, total time spent smoking, puff volume (i.e., puff size), puff velocity (i.e., puff intensity), puff duration, and inter-puff interval (i.e., length of time between puffs). Although some of these outcomes (e.g., puffs per cigarette) can be measured via direct observation, smoking topography is typically assessed with an electronic puff topography device attached directly to a cigarette.

Some studies reviewed in this RTD found no differences in smoking topography between VLNC and NNC or usual brand cigarette conditions (e.g., Brody, Mandelkern, Olmstead, et al., 2009; Faulkner et al., 2019; Hasenfratz et al., 1993; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017). However, many other studies found that smoking topography was different between cigarette conditions. Some of the more reliable findings

replicated across studies were the effects of VLNC cigarettes on total puff volume and number of puffs per cigarette. Both brief and extended exposure studies found total puff volume was lower (e.g., Donny et al., 2015; Donny & Jones, 2009; Mercincavage et al., 2016; Rose & Behm, 2004a; Tidey, Cassidy, et al., 2016) and number of puffs per cigarette was lower (e.g., Donny et al., 2007; Hammond & O'Connor, 2014; Mercincavage et al., 2016; Strasser et al., 2007; Tidey, Cassidy, et al., 2016) when participants smoked VLNC cigarettes relative to usual brand or NNC cigarettes. However, one brief exposure study showed higher puff volume and puff duration when participants smoked VLNC cigarettes, but these effects diminished within a single laboratory session (Macqueen et al., 2012). Another brief exposure study conducted in adolescents showed that VLNC cigarettes produced an increase in number of puffs relative to NNC cigarettes; however, additional measures were not collected to determine whether this was a transient or lasting effect (Kassel, Greenstein, et al., 2007).

One extended exposure study showed that participants smoking LNC cigarettes had a 40% decrease in puff volume and a 3% decrease in burned tobacco mass compared to those smoking NNC cigarettes (Shiffman, Mao, et al., 2018). Another extended exposure study showed initial decreases in puff volume when participants smoked VLNC cigarettes relative to NNC cigarettes, but these differences dissipated over the course of 7 days (Donny & Jones, 2009). Finally, some evidence suggests VLNC cigarettes are smoked faster (e.g., Benowitz et al., 2006; Juliano et al., 2011; Kamens et al., 2020), increase peak velocity (Mercincavage et al., 2016), and may decrease puffs per cigarette (Denlinger-Apte, Donny, et al., 2020) and inter-puff intervals when compared to NNC cigarettes (Tidey, Cassidy, et al., 2016).

One analysis of an extended exposure study by Donny and colleagues (2015) examined solanesol as a marker of mouth-level nicotine exposure. The results showed that participants did not significantly change their smoking intensity when smoking NNC, LNC, or VLNC cigarettes, indicating that decreasing the nicotine content of combusted cigarettes may not contribute to compensatory smoking behaviors (Smith, Koopmeiners, Hatsukami, et al., 2020).

Taken together, results of the studies reviewed in this RTD demonstrate somewhat mixed findings on the effects of VLNC cigarettes on smoking topography. However, the majority of studies show that individuals who smoke VLNC cigarettes demonstrate no differences in smoking topography relative to those who smoke usual brand or NNC cigarettes, or they demonstrate changes in smoking topography measures that are associated with reductions in tobacco smoke exposure (e.g., lower total puff volume).

iv. Cigarettes Per Day

Researchers typically assess CPD via participant self-report or by counting cigarette filters or packs returned by participants. By measuring CPD during an extended exposure trial, researchers can determine whether switching to VLNC cigarettes produces changes in the number of cigarettes smoked per day compared to usual brand or NNC cigarette conditions.

Many studies reviewed in this RTD measured VLNC CPD under conditions of extended exposure (e.g., several consecutive days or longer). These studies varied in sample size, duration of exposure, average CPD requirements to enter the study, participants' intentions to quit smoking, and the method by which participants transitioned from usual brand cigarettes to VLNC cigarettes (i.e., gradual versus immediate reduction in nicotine content). Despite these differences in study methods and participant characteristics, nearly all of the studies came to similar conclusions: relative to usual brand or NNC cigarette conditions, CPD was similar (e.g., Bandiera et al., 2015; Becker et al., 2008; Benowitz, Nardone, Dains, et al., 2015; Ding et al., 2014; Donny & Jones, 2009; Hammond & O'Connor, 2014; Mercincavage et al., 2016; Rose et al., 2001; Rose et al., 2006; Walker et al., 2015) or lower in VLNC cigarette conditions (e.g., Donny et al., 2015; Dermody et al., 2016; Donny et al., 2007; Hatsukami et al., 2015; Hatsukami, Heishman, et al., 2013; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010). One study found that in a gradual nicotine reduction condition (i.e., when participants were given cigarettes with gradually decreasing nicotine contents), participants showed an initial rise, then dip, in CPD; whereas, in an immediate nicotine reduction condition, CPD did not initially rise and then declined sharply (Robinson et al., 2019). Notably, studies that found lower CPD while participants smoked VLNC cigarettes tended to have larger sample sizes (e.g., Donny et al., 2015; Hatsukami et al., 2015), which may have had more statistical power to detect relatively small but consistent differences in CPD across conditions.

Importantly, the results summarized in the above paragraph involve comparisons between VLNC CPD and usual brand or NNC CPD, without accounting for the number of non-study cigarettes smoked per day in experimental conditions. Few studies have measured total CPD (e.g., the number of study-assigned VLNC cigarettes plus the number of usual brand or non-study cigarettes smoked by participants who were not fully compliant with study procedures) and compared these measures across conditions. One study found that, relative to usual brand and NNC cigarette conditions, the combination of study- and non-study-assigned CPD was lower in VLNC and LNC cigarette conditions when nicotine content was ≤ 2.4 mg per g of total tobacco (Donny et al., 2015). Another study found that fewer combusted tobacco products were smoked during LNC cigarette conditions relative to an NNC cigarette condition. Nevertheless, noncompliance with VLNC cigarettes is a concern discussed more thoroughly in

the Noncompliance section of this RTD. Briefly, the results of studies that examined VLNC cigarette noncompliance by measuring non-study CPD and biomarkers of exposure concluded that VLNC cigarette use does not increase overall exposure to combusted tobacco via compensatory smoking or use of alternative combusted tobacco products.

One study compared the effects of VLNC and NNC cigarettes on CPD in smokers who inhabited a residential research facility throughout the study. The results showed that when smokers had access to only VLNC cigarettes for 11 days, they smoked significantly fewer CPD than those who had access to only NNC cigarettes (Donny et al., 2007). In another study, participants checked into a hotel for two 4-night stays and were given access to only VLNC cigarettes or NNC cigarettes during each stay. CPD was not different between VLNC and NNC cigarette conditions during the 4 days that CPD was assessed (Smith, Donny, et al., 2019). Neither of these studies found that participants who received only VLNC cigarettes engaged in compensatory smoking behavior.

To determine whether speed of nicotine metabolism impacts smoking behavior, one study examined the effects of a two-step transition to LNC cigarettes in a group of 100 smokers, 51 of whom were fast metabolizers of nicotine. CPD increased in all participants when they switched to LNC cigarettes for 15 days. However, when participants transitioned to LNC cigarettes with even lower nicotine content for 15 days, this effect disappeared and CPD was found not to differ significantly from baseline CPD. Therefore, investigators determined that fast metabolizers were not at a greater risk for increasing CPD when presented with LNC cigarettes (Mercincavage et al., 2018).

Co-administration of an NRT product and VLNC cigarettes can also affect CPD. For example, in a 2x2 factorial study, participants were assigned to receive either NNC or VLNC cigarettes during the study, and to receive NRT in the form of a transdermal nicotine patch or no NRT. Participants who received VLNC cigarettes and NRT showed significantly lower CPD than participants who received either NNC cigarettes alone or NNC cigarettes with NRT; however, CPD did not differ significantly between participants who received VLNC cigarettes and NRT and participants who received VLNC cigarettes alone (Smith, Koopmeiners, et al., 2019).

In sum, results of studies reviewed in this RTD show that extended use of VLNC cigarettes does not produce increases in CPD. Rather, switching to LNC or VLNC cigarettes may produce modest decreases in CPD.

v. Dependence

Over the course of regular use, cigarette smoking can lead to symptoms of dependence, which may include tolerance to the effects of nicotine, withdrawal upon cessation of use, craving, and unsuccessful efforts to quit smoking. Because dependence takes time to develop or change, it is often measured under conditions of extended exposure. Studies reviewed in this RTD typically assessed dependence with the FTND, Fagerström Test for Cigarette Dependence (FTCD), Nicotine Dependence Syndrome Scale (NDSS), and Wisconsin Inventory of Smoking Dependence Motives (WISDM).

In a study that gradually reduced the nicotine content of cigarettes (NNC, LNC, and VLNC cigarettes) over the course of 4 weeks, there were few differences in dependence scores between conditions, but there was a trend towards significance (p= 0.06) in overall reduction of dependence scores across conditions (Hammond & O'Connor, 2014). Another gradual reduction study found no difference in dependence when comparing data from baseline to Week 26 in 135 participants who smoked either gradually reduced nicotine content cigarettes over the course of 6 months or their own brand cigarettes for the same duration. However, when comparing only data from Week 14 to Week 26, there was a significant decrease in dependence in the group that received gradually reduced nicotine content cigarettes (Benowitz et al., 2012). A secondary analysis of data from 51 smokers who participated in this study demonstrated that participants with higher FTND scores at baseline were more likely to demonstrate signs of dependence during the study, regardless of the nicotine content of their study cigarettes (Bandiera et al., 2015). In a follow-up study, participants assigned to receive gradually reduced nicotine content cigarettes were given VLNC cigarettes for an additional 6 months (Benowitz, Nardone, Dains, et al., 2015), and no significant changes in dependence were observed. However, a secondary analysis of data from a study conducted with non-daily smokers (Shiffman, Kurland, et al., 2018) showed that participants assigned to LNC cigarettes showed a greater decrease in dependence compared to those assigned to NNC cigarettes (Shiffman et al., 2019).

Immediate nicotine reduction from usual brand cigarettes to LNC or VLNC cigarettes resulted in reduced dependence in smokers compared to those who smoked NNC or usual brand cigarettes for 6 weeks (Donny et al., 2015) or 12 weeks (Walker et al., 2015) in participants not interested in quitting smoking. In smoking cessation studies in which participants endorsed wanting to quit, dependence also decreased over time (e.g., Hatsukami et al., 2010; Klemperer, Hughes, Callas, et al., 2019; Rose & Behm, 2004a; Rose et al., 2006).

The delay to smoking the first cigarette of the day is a strong predictor of dependence. In the only study to date that examined the effects of VLNC cigarettes on latency to smoke in smokers inhabiting a residential research facility, time to first cigarette was significantly longer among smokers who only had access to VLNC cigarettes for 11 days compared to those who only had access to NNC cigarettes (Donny et al., 2007).

In sum, limited evidence from studies reviewed in the RTD suggests that dependence may remain unchanged when smokers switch to VLNC cigarettes. However, more evidence suggests that switching to VLNC cigarettes decreases dependence.

vi. Craving and Withdrawal

Symptoms of tobacco withdrawal may include irritability, depression, insomnia, headache, or increased craving. Although craving is often characterized as a symptom of nicotine and tobacco withdrawal, it is also a symptom of dependence, and it can occur in the absence of other withdrawal symptoms. Thus, craving is usually measured and reported separately from withdrawal. Studies included in this RTD typically assessed craving and withdrawal with the Questionnaire of Smoking Urges (QSU), QSU-Brief, Minnesota Nicotine Withdrawal Scale (MNWS), Shiffman-Jarvik Withdrawal Scale, and Visual Analogue Scale items.

In brief exposure studies, VLNC cigarettes suppressed craving and withdrawal relative to baseline measures that were typically assessed following overnight abstinence (e.g., Adams et al., 2015; Addicott et al., 2014; Barrett, 2010; Barrett et al., 2013; Barrett & Darredeau, 2012; Brauer et al., 1999; Guillot et al., 2015; Rose, Salley, et al., 2010; Tidey et al., 2013). Furthermore, many studies showed that VLNC cigarettes can reduce craving and withdrawal as much as usual brand or NNC cigarettes (e.g., Baldinger et al., 1995a; Baldinger et al., 1995b; Breland et al., 2002; Buckley et al., 2007; Cobb et al., 2010; Dallery et al., 2003; Eid et al., 2005; Faulkner et al., 2019; Gross et al., 1997; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano et al., 2006; Perkins et al., 2006; Perkins & Karelitz, 2015; Perkins et al., 2010; Ray et al., 2006; Rose et al., 2000; Rukstalis et al., 2005). However, some studies observed that suppression of craving and withdrawal was lower after smoking VLNC cigarettes than usual brand or NNC cigarettes (e.g., Brauer et al., 2001; Dedert et al., 2012; Hatsukami, Heishman, et al., 2013; Juliano et al., 2011; Kamens et al., 2020; Kelemen, 2008; Rose, Behm, Westman, Bates, et al., 2003; Rose et al., 1999; Smith, Donny, et al., 2019; Tidey et al., 2019). In addition, results from a few studies suggest that VLNC cigarettes influence craving more than withdrawal. For example, one study found that VLNC cigarettes suppressed craving similarly to NNC cigarettes, but also produce an increase in other withdrawal symptoms (Attwood et al., 2009). Other studies have found no effects of VLNC cigarettes on withdrawal symptoms (e.g.,

Harrell & Juliano, 2012; Rose et al., 2004; Schlagintweit & Barrett, 2016). Notably, some of these brief exposure studies reported sex differences and generally found that female smokers experienced greater reductions in craving (e.g., Barrett et al., 2013; Barrett & Darredeau, 2012; Hatsukami, Heishman, et al., 2013) or withdrawal (e.g., Barrett, 2010; Perkins & Karelitz, 2015) compared to male smokers after smoking VLNC cigarettes. However, Perkins et al. (2006) found that, after smoking VLNC cigarettes, male smokers had greater reductions in craving compared to female smokers (Perkins et al., 2006).

During extended exposure studies, when participants smoked VLNC cigarettes from 4 days to 1 year, ratings of withdrawal (e.g., Benowitz et al., 2012; Buchhalter et al., 2005) and craving were generally similar compared to ratings observed in usual brand and NNC cigarette conditions (e.g., Buchhalter et al., 2005; Donny & Jones, 2009). One study found that, after switching to VLNC cigarettes from usual brand cigarettes for one week, withdrawal symptoms increased with no reported change in craving (Hatsukami et al., 2010). However, these effects were relatively brief; within 6 weeks, withdrawal symptoms returned to baseline levels, and craving score steadily decreased below baseline levels. Results from another study showed that VLNC cigarettes can produce persistent reductions in craving characterized by participants as "moderate" or "a lot" after 3 and 6 weeks exposure; however, some participants reported no relief from craving occurred during the 6-week study (Walker et al., 2012). Finally, one study demonstrated that 6 weeks of exposure to LNC and VLNC cigarettes containing 2.4 to 0.4 mg nicotine per g of total tobacco resulted in less craving and only transient and mild increases in other withdrawal symptoms compared to NNC cigarettes (Donny et al., 2015; Dermody et al., 2018).

Similar to brief exposure studies, female smokers experienced a reduction in craving after switching to LNC cigarettes for one week, whereas male smokers showed no change in craving upon switching. Overall, withdrawal symptoms increased in both male and female smokers after 1 week. However, these differences from baseline were short-lived. Ratings of both craving and withdrawal symptoms were no different than baseline over the remaining 6 weeks of the study (Vogel et al., 2014).

Craving and withdrawal were also assessed in several smoking cessation studies wherein participants were provided VLNC cigarettes along with NRT or other pharmacotherapies before a designated quit date. In these studies, participants who received VLNC cigarettes plus a nicotine patch experienced less severe cravings, with no difference in withdrawal (Rose et al., 2007), a greater reduction in craving and withdrawal (Rose et al., 2006), and less frequent and less intense cravings before and after quit date (Rezaishiraz et al., 2007) compared to those who received NNC cigarettes before the quit date. Another study found that LNC cigarettes plus

either varenicline or NRT resulted in decreases in craving compared to standard pharmacotherapy treatment alone, with no differences in withdrawal across groups (McRobbie et al., 2016).

In sum, VLNC cigarettes typically do not produce greater reports of craving or withdrawal compared to NNC cigarettes. Although findings from some brief exposure studies are mixed, the results of many studies suggest that brief exposure to VLNC cigarettes can suppress craving and withdrawal as well as NNC and usual brand cigarettes. Similar findings were observed in extended exposure studies. Notably, limited evidence suggests that VLNC cigarettes may suppress craving in females more than males.

b. Additional Outcomes

In addition to the primary addiction-related outcomes discussed above, articles included in this RTD also assessed other outcomes (e.g., biomarkers of exposure, physiological effects, and neurophysiological effects). These outcomes were secondary to the aims of this RTD. Therefore, selection criteria were not designed to capture every VLNC cigarette study that assessed these additional outcomes. Nevertheless, these outcomes are relevant to a product standard that would reduce the nicotine content of combusted cigarettes, so findings related to these outcomes are discussed in this section.

i. Biomarkers of Exposure

Some of the most commonly measured biomarkers of tobacco smoke exposure are CO (measured as breath CO or COHb), plasma nicotine, cotinine (collected through plasma, saliva, or urine), TNE (a combination of nicotine, cotinine, and other nicotine metabolites collected through plasma, saliva, or urine), and other harmful and potentially harmful constituents (HPHCs) or their metabolites (e.g., NNN, NNAL, BAP, 3-HPMA, S-PMA). Although nicotine and its metabolites would be expected to decrease in individuals who switch from NNC to VLNC cigarettes, other biomarkers of exposure would be expected to remain the same if smoking behavior remains unchanged. Thus, any changes in biomarker levels observed between NNC and VLNC cigarette conditions in clinical studies would indicate differences in smoking behavior (e.g., CPD, smoking topography) between these two groups. Notably, due to the short half-lives of some biomarkers (e.g., breath CO), decreases in smoking can produce decreases in these biomarkers during brief exposure studies. However, decreases in smoking may not produce decreases in some biomarkers (e.g., NNAL) under such conditions due to the prolonged half-lives of these biomarkers.

Most studies have found no differences in CO exposure between participants who smoke VLNC cigarettes and those who smoke usual brand or NNC cigarettes (e.g., Baldinger et

al., 1995c; Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Breland et al., 2002; Cobb et al., 2010; Denlinger-Apte, Donny, et al., 2020; Denlinger-Apte, Kotlyar, et al., 2019; Donny et al., 2015; Donny & Jones, 2009; Eid et al., 2005; Greenstein et al., 2010; Gross et al., 1997; Harrell & Juliano, 2012; Hasenfratz et al., 1993; Hatsukami et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano et al., 2006; Juliano et al., 2011; Kamens et al., 2020; Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007; Rose & Behm, 2004a; Rose et al., 2000; Smith, Koopmeiners, White, et al., 2020; Strasser et al., 2007). However, differences were observed in a few studies. Two brief exposure studies found increases in breath CO following VLNC cigarette use relative to NNC cigarette use (Dallery et al., 2003; Westman et al., 1996). In addition, an extended exposure study (35 days) showed that CO exposure initially increased when participants began smoking VLNC cigarettes and then dissipated over time (Mercincavage et al., 2016). As discussed in Section D.c.ii: *Compensatory Smoking* of Appendix A, these increases in CO exposure may be due to changes in smoking topography. Notably, at least one extended exposure study found decreases in CO boost after VLNC cigarette use compared to use of usual brand cigarettes (Hammond & O'Connor, 2014). Moreover, the only study to date that examined the effects of VLNC cigarettes on breath CO in smokers who inhabited a residential research facility found that when smokers only had access to study cigarettes for 11 days, those who were assigned NNC cigarettes had significantly higher breath CO than those who were assigned VLNC cigarettes. Further, these differences increased over the course of each day such that they were greater in the afternoon than in the morning (Donny et al., 2007).

The results of studies that examined nicotine, cotinine, or TNE levels had overwhelming concurrence regarding the effects of either brief or extended exposure to VLNC cigarettes compared to usual brand or NNC cigarettes. VLNC cigarettes produced substantially lower nicotine, cotinine, and TNE than usual brand or NNC cigarettes (e.g., Baldinger et al., 1995a; Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Branstetter et al., 2019; Breland et al., 2002; Cobb et al., 2010; Dallery et al., 2003; Denlinger-Apte, Kotlyar, et al., 2019; Ding et al., 2014; Donny et al., 2015; Donny & Jones, 2009; Gross et al., 1997; Hammond & O'Connor, 2014; Hasenfratz et al., 1993; Hatsukami et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2017; Kamens et al., 2020; Klemperer, Hughes, Callas, et al., 2019; Kuwabara et al., 2014; Mercincavage et al., 2016; Rose & Behm, 2004a; Rose et al., 2000; Rose, Behm, Westman, Mathew, et al., 2003; Westman et al., 1996).

The effects of VLNC cigarette exposure on other HPHCs were less reliable across studies. Nevertheless, studies reviewed in this RTD consistently found that VLNC cigarette exposure either reduced or did not change exposure to NNN, NNAL, 1-HOP, or BAP relative to NNC or

usual brand cigarettes (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Ding et al., 2014; Donny et al., 2015; Hammond & O'Connor, 2014; Hatsukami et al., 2010; Hatsukami et al., 2017; Mercincavage et al., 2018; Mercincavage et al., 2016). None of these studies found that VLNC cigarettes produced increases in any of these biomarkers. One study also examined 3-HPMA and S-PMA levels and found that these biomarkers decreased in VLNC cigarette conditions compared to LNC cigarette conditions (Hatsukami et al., 2010). The reductions in HPHCs that were observed in some of these studies following VLNC cigarette exposure were typically correlated with decreases in CPD or other smoking behaviors. Thus, as expected, fewer CPD resulted in overall reductions in HPHC exposure.

In sum, results from these studies demonstrate that biomarkers of exposure are typically similar or lower following extended use of VLNC cigarettes relative to NNC cigarettes. Biomarkers of exposure are rarely observed to be higher following VLNC cigarette use relative to NNC cigarette use.

ii. Physiological Effects

Physiological measures may be proxy measures for the stimulant effects of nicotine. Pharmacodynamic effects of nicotine include central and peripheral nervous system stimulation, arousal, and increased heart rate or blood pressure. Nicotine is a known stimulant, but physiological effects may occur in response to cigarettes even in the absence of nicotine due to conditioning or other psychoactive chemicals in tobacco smoke.

There is slight variability in the data assessing the physiological effects of VLNC cigarettes. Some studies included in this RTD show that, regardless of nicotine content, acute cigarette smoking is associated with an increase in baseline heart rate (e.g., Benowitz et al., 2006; Cobb et al., 2010; Dallery et al., 2003; Eid et al., 2005); however, these increases were either less pronounced following VLNC cigarette use compared to NNC cigarette use (e.g., Benowitz et al., 2006; Cobb et al., 2010) or were less consistent (i.e., observed at some but not all time points following use) (Eid et al., 2005). Some research has shown that escalations in heart rate dissipate after repeated exposure to VLNC cigarettes but not usual brand cigarettes (Cobb et al., 2010). In contrast, other studies did not observe increases in heart rate when participants smoked VLNC cigarettes (e.g., Gross et al., 1997; Penetar et al., 2012; Pickworth, Nelson, et al., 1999; Rose et al., 2000), and several studies showed significantly reduced escalations in heart rate compared to acute LNC, NNC, or usual brand cigarette administration (e.g., Baldinger et al., 1995c; Buchhalter et al., 2005; Donny et al., 2007; Hasenfratz et al., 1993; Hatsukami, Heishman, et al., 2013; Juliano et al., 2006; Rose et al., 1999; Schlagintweit & Barrett, 2016).

Some studies included in this RTD also investigated the effects of VLNC cigarettes on other physiological outcomes. Several studies found no differences in blood pressure after smoking a VLNC cigarette compared to an LNC cigarette (e.g., Buchhalter et al., 2005; Dallery et al., 2003), NNC cigarette (e.g., Benowitz et al., 2006), or usual brand cigarette (e.g., Benowitz et al., 2006). However, other studies showed significantly greater increases in blood pressure after smoking NNC or usual brand cigarettes relative to VLNC cigarettes (e.g., Hasenfratz et al., 1993; Hatsukami, Heishman, et al., 2013). While one study included in this RTD showed that skin temperature decreased to a greater extent with NNC cigarettes compared to VLNC cigarettes (Benowitz et al., 2006), other studies found no differences in skin temperature as a function of nicotine content in cigarettes (e.g., Penetar et al., 2012). Another study found no significant differences in skin conductance between VLNC and NNC cigarettes (Naqvi & Bechara, 2006).

In sum, while there is variability in the physiological effects data reviewed in this RTD, evidence suggests NNC cigarettes are associated with greater increases in physiological responses (e.g., heart rate, blood pressure) than VLNC cigarettes.

iii. Neurophysiological Effects

Drugs of abuse activate the mesocorticolimbic brain system. A key component of this system is the dopaminergic pathway from the ventral tegmental area to the nucleus accumbens, amygdala, and frontal cortex, which is associated with drug reinforcement. Both smoking behavior and nicotine administration have been shown to activate this reward pathway.

One study included in this RTD investigated the role of nicotine in ventral striatal dopamine release (Brody, Mandelkern, Olmstead, et al., 2009). Researchers found that dopamine release was associated with NNC cigarette smoking but not VLNC cigarette smoking.

Acute nicotine administration may induce endogenous opioid release and play a role in nicotine's rewarding effects. However, one study included in this RTD found that μ-opioid receptor binding did not differ as a function of nicotine content after participants smoked VLNC as compared to NNC cigarettes (Kuwabara et al., 2014).

Several studies included in this RTD measured regional cerebral blood flow to assess transient central nervous system actions of smoking and nicotine (e.g., Addicott et al., 2014; Rose, Behm, Westman, Mathew, et al., 2003). Unlike VLNC cigarettes, NNC cigarettes were associated with increases in regional cerebral blood flow in the thalamus, a region rich in nicotinic receptors; however, NNC cigarettes reduced blood flow in the amygdala (Rose, Behm, Westman, Mathew, et al., 2003). Addicott and colleagues (2014) showed increased activity in a fronto-temporo-cerebellar circuit that underlies craving. Activity in this circuit was suppressed

by the non-nicotine psychoactive and sensorimotor components of tobacco smoke (e.g., VLNC cigarette smoking) rather than by nicotine.

Studies have also examined the effects of cigarette nicotine content on electroencephalogram (EEG) measures. Within some frequency bands, studies have found differential effects of VLNC cigarettes on EEG power relative to usual brand (Baldinger et al., 1995c) and LNC cigarettes (Pickworth, Nelson, et al., 1999).

Taken together, results of studies reviewed in this RTD suggest that conditioned sensorimotor effects (e.g., like those resulting from VLNC cigarette smoking) can activate brain areas associated with cigarette reward and craving. However, nicotine is associated with more diverse brain activation, particularly in areas responsible for attention and reinforcement.

c. Special Topics for Consideration

A product standard that would reduce the nicotine content of combusted cigarettes will only be implemented if such a standard is found to be appropriate for the protection of public health. Consequently, the risks and benefits of the standard for the population as a whole must be considered prior to implementation. For example, the impact of a proposed nicotine standard on compensatory smoking, smoking cessation, product switching, noncompliance, and vulnerable populations must be considered. Furthermore, different approaches for implementing such a standard (i.e., gradual versus immediate nicotine reduction) should be considered. These topics are discussed in this section.

i. Noncompliance

Several studies assessed biochemical or self-reported measures of VLNC cigarette noncompliance (i.e., usual brand cigarette use). Studies that gradually reduced the nicotine content of cigarettes showed that noncompliance is high once participants reach the VLNC cigarette phase of the intervention (e.g., Benowitz, Nardone, Hatsukami, et al., 2015; Hammond & O'Connor, 2014; Smith, Donny, et al., 2019). For example, a within-subject, unblinded study wherein participants received three gradually reduced nicotine content cigarettes (i.e., NNC, LNC, and VLNC cigarettes) over the course of 3 weeks found that significantly more participants self-reported smoking at least one usual brand cigarette during the VLNC cigarette phase (44%) relative to the LNC cigarette phase (31%) and the NNC cigarette phase (28%) (Hammond & O'Connor, 2014). A secondary analysis of two gradual reduction studies in smokers with mood or anxiety disorders found that 36 - 42% of participants were biochemically confirmed to be noncompliant at the end of the 18-week studies (Foulds et al., 2018).

Notably, a secondary analysis of a study that compared gradual reduction and immediate reduction (Hatsukami et al., 2018) found that participants assigned to the immediate reduction group had higher rates of noncompliance than those assigned to the gradual reduction group (Smith, Donny, et al., 2019). Noncompliance may occur when participants immediately switch to reduced nicotine content cigarettes, regardless of the amount of nicotine in the reduced nicotine content cigarettes (e.g., LNC or VLNC cigarettes). However, noncompliance appears to be higher when smokers switch to lower nicotine content cigarettes. For example, Hatsukami and colleagues (2013) randomized 36 participants to receive VLNC, LNC, or NNC cigarettes for one week. Participants kept a daily diary of all experimental and usual brand cigarettes smoked. Participants in the NNC cigarette group smoked significantly more experimental cigarettes during the study than participants in the VLNC cigarette group. Noncompliance with study-assigned cigarettes was observed in all groups, such that 38% (n = 5), 36% (n = 4) and 17% (n = 2) of participants in the VLNC, LNC, and NNC cigarette groups, respectively, smoked at least one usual brand cigarette during the experimental week. These results are consistent with the largest analysis of VLNC cigarette noncompliance in a study that immediately switched participants to reduced nicotine content cigarettes (Nardone et al., 2016). This study showed that 39% of participants self-reported noncompliance during the last week of a 6-week intervention. However, biochemical methods used to assess noncompliance suggested 75 - 78% of participants may have been noncompliant with VLNC cigarettes. Notably, 57% of participants assigned to the NNC cigarette group reported noncompliance at some point during the study, suggesting difficulty with “brand-switching” regardless of nicotine content. Results from this study also showed higher rates of noncompliance among younger smokers, those less satisfied with VLNC cigarettes, and those with higher nicotine dependence scores (Nardone et al., 2016).

Two studies co-administered NRT while manipulating the amount of nicotine that participants were exposed to from their cigarettes. In one study, all participants were assigned transdermal nicotine patches, and participants were assigned to either a gradual nicotine reduction group (i.e., the nicotine content of their cigarettes decreased during the study) or a CPD reduction group (i.e., the number of their CPD decreased during the study). Participants in the CPD reduction group used more non-study cigarettes than did participants in the nicotine reduction group (Klemperer, Hughes, Callas, et al., 2019). In another study, participants were assigned to either an NNC cigarette group or a VLNC cigarette group, and all participants were also assigned to receive NRT (in the form of a transdermal patch) or not receive NRT. Participants assigned to receive VLNC cigarettes, with or without NRT, were more likely to use

non-study cigarettes than participants assigned to receive NNC cigarettes (Smith, Koopmeiners, et al., 2019).

Importantly, noncompliance with VLNC cigarettes does not appear to increase overall exposure to tobacco smoke when biomarkers of exposure are compared between control and VLNC cigarette conditions (see Section D.b.i: *Biomarkers of Exposure* and Section D.c.ii: *Compensatory Smoking* of Appendix A). In addition, compliance may improve over time. For example, Hatsukami and colleagues (2013) found improvements in compliance after 6 weeks of VLNC cigarette use compared to compliance at Week 1.

Notably, ancillary provision of NRT may improve compliance by reducing rates of usual brand cigarette smoking (e.g., Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2017). In the context of a smoking cessation study utilizing VLNC and LNC cigarettes, Hatsukami and colleagues (2013) found the highest rates of usual brand cigarette use among participants assigned to NRT alone (43%), followed by VLNC/LNC cigarettes alone (33%), and then among participants assigned to a combination of VLNC/LNC cigarettes plus NRT (14%). Similarly, when participants were provided the opportunity to use alternative nicotine and tobacco products in addition to LNC cigarettes, no differences were observed between LNC and NNC cigarette groups in the number of usual brand cigarettes smoked (Hatsukami et al., 2017).

In sum, studies have shown high levels of noncompliance to VLNC cigarettes, suggesting lower appeal and abuse potential compared to NNC cigarettes. Providing NRT to smokers using VLNC cigarettes may reduce rates of alternative tobacco use.

ii. Compensatory Smoking

One major concern associated with switching from usual brand or NNC cigarettes to VLNC cigarettes is the potential for compensatory smoking, which is a change in normal smoking behavior that would increase exposure to cigarette smoke to compensate for reduced nicotine intake. Compensation can occur by increasing the number of CPD or by changing the way in which cigarettes are smoked (e.g., increases in puff number, puff volume, puff duration etc.). In both brief and extended exposure studies with VLNC cigarettes, compensation was measured using CPD, puff topography measures, and biomarkers of CO exposure, such as breath CO or COHb. While CPD and puff topography can directly measure changes in smoking behavior, breath CO and COHb can help determine overall exposure to CO as a net effect of both CPD and puff topography.

When exposure to VLNC cigarettes is brief (e.g., limited to one or two exposures), transient compensatory smoking may occur. Changes in smoking topography (e.g., Kassel, Greenstein, et al., 2007; Macqueen et al., 2012; Strasser et al., 2007) and increases in CO have

been observed in such brief exposure studies (e.g., Eid et al., 2005; Strasser et al., 2007; Westman et al., 1996). For example, one study demonstrated the transient nature of compensatory smoking by showing increases in smoking topography and CO exposure during the first and second exposures to VLNC cigarettes, followed by the subsequent dissipation of these effects by the third and fourth exposures (Macqueen et al., 2012). Similarly, White and colleagues (2022) found that during a five-day study where participants checked into a hotel and were restricted to only study cigarettes, mouth-level nicotine exposure indicated that participants initially puffed VLNC cigarettes with greater intensity than NNC cigarettes; however, this effect diminished across sessions. However, results from the majority of studies reviewed in this RTD showed no compensatory smoking as a result of switching from usual brand or NNC cigarettes to VLNC cigarettes. Although not all studies examined every measure of compensatory smoking, most studies that examined these measures found no differences between control and VLNC cigarette conditions in CPD (e.g., Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Dermody et al., 2016; Hasenfratz et al., 1993; Hatsukami et al., 2015; Hatsukami, Heishman, et al., 2013; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; Hatsukami et al., 2017; Juliano et al., 2006; Juliano et al., 2011; Rose & Behm, 2004a; Smith, Donny, et al., 2019), CO exposure (e.g., Bandiera et al., 2015; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Denlinger-Apte, Donny, et al., 2020; Denlinger-Apte, Kotlyar, et al., 2019; Greenstein et al., 2010; Gross et al., 1997; Harrell & Juliano, 2012; Hasenfratz et al., 1993; Hatsukami, Heishman, et al., 2013; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; Hatsukami et al., 2017; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano et al., 2011; Kamens et al., 2020; Rose & Behm, 2004a; Smith, Koopmeiners, Hatsukami, et al., 2020; Tidey et al., 2013), smoking topography (e.g., Bandiera et al., 2015; Branstetter et al., 2019; Eid et al., 2005; Faulkner et al., 2019; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Juliano et al., 2006), or all three measures (e.g., Ding et al., 2014; Donny & Jones, 2009; Hammond & O'Connor, 2014; Mercincavage et al., 2016).

Notably, compensatory smoking has been observed with some reduced nicotine content cigarettes containing intermediate levels of nicotine (e.g., LNC cigarettes). For example, in a study of 165 smokers assigned to switch to LNC cigarettes or VLNC cigarettes, researchers found small but statistically significant differences in CPD between the LNC and VLNC cigarette conditions, such that LNC CPD increased over the course of the 6-week intervention, while VLNC CPD decreased (Hatsukami et al., 2010). However, one of the largest studies involving reduced nicotine content cigarettes found no compensatory smoking behavior for cigarettes containing intermediate levels of nicotine (Donny et al., 2015).

Taken together, the results of studies reviewed in this RTD suggest that some transient compensatory smoking may occur following initial VLNC cigarette exposure. However, after continued use of VLNC cigarettes, smokers stop compensating for reduced nicotine exposure.

iii. Smoking Cessation

A number of studies included in this RTD investigated the effects of VLNC or LNC cigarettes on smoking cessation among individuals interested in quitting smoking (e.g., Becker et al., 2008; Dermody et al., 2015; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2010; McRobbie et al., 2016; Rezaishiraz et al., 2007; Rose et al., 2006; Walker et al., 2012). In one of the only clinical trials to date that has examined the effects of VLNC cigarettes alone on smoking cessation in smokers who were interested in quitting, 165 smokers were randomized to LNC cigarettes, VLNC cigarettes, or 4 mg nicotine lozenges for 6 weeks (Hatsukami et al., 2010). Participants were instructed to discontinue use of all products at the end of the 6 weeks. Follow-up visits were conducted 1, 2, 4, and 6 weeks after the quit date. Biochemically-verified continuous (≥ 4 weeks) abstinence rates were highest in the VLNC cigarette group during the study, but group differences were not significant. However, biochemically-verified abstinence rates at the Week 6 follow-up visit were significantly higher in the VLNC cigarette group (47%) and nicotine lozenge group (37%) relative to the LNC cigarette group (23%).

Many smoking cessation studies investigated the effects of LNC or VLNC cigarettes when combined with NRT (e.g., Becker et al., 2008; Hatsukami, Hertsgaard, et al., 2013; Klemperer, Hughes, & Callas, 2019; McRobbie et al., 2016; Rezaishiraz et al., 2007; Rose et al., 2006; Smith, Koopmeiners, et al., 2019; Walker et al., 2012). In a study of 346 smokers interested in quitting, 32.8% quit after using a combination of VLNC cigarettes (nicotine was gradually reduced from NNC to LNC to VLNC cigarettes every two weeks) and nicotine patch, 21.9% quit after using NNC cigarettes and a placebo patch, and 16.4% quit after using VLNC cigarettes and a placebo patch (Becker et al., 2008). Thus, these results suggest that the combination of VLNC cigarettes and NRT is more effective at promoting continuous abstinence than VLNC cigarettes alone. In a study conducted in New Zealand, 1,410 callers to a Quitline were randomized to receive VLNC cigarettes with usual Quitline care (8 weeks of NRT and behavioral support) or usual care alone (Walker et al., 2012). Six months after the quit date, 7-day point-prevalence abstinence rates were significantly greater in participants using VLNC cigarettes (33%) compared to the usual care group (28%). Furthermore, continuous abstinence rates at Month 6 were significantly higher for participants who received VLNC cigarettes (23%) compared to those who received usual care (15%). In another study, 98 heavy smokers received either VLNC cigarettes and a 21 mg nicotine patch or NNC cigarettes for two weeks prior to quitting (Rezaishiraz et al., 2007). After the quit date, all participants wore nicotine patches for up to 8 weeks. Participants who

smoked VLNC cigarettes and received the patch reported less frequent and less intense cravings, but the self-reported quit rate did not differ significantly between groups.

Several other studies included in this RTD investigated the effects of VLNC or LNC cigarettes on smoking cessation among individuals uninterested in quitting (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015; Walker et al., 2015). Benowitz and colleagues conducted a series of studies wherein participants received gradually reduced nicotine content cigarettes over a period of 6 months, beginning with NNC cigarettes and ending with VLNC cigarettes (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Benowitz, Nardone, Dains, et al., 2015). A significantly greater proportion of participants who received reduced nicotine content cigarettes considered quitting at the end of the study, compared to those in a control group who smoked their usual brand cigarettes throughout the study (Benowitz et al., 2012). In a follow-up study in which a subset of participants was followed for 2 years, cotinine levels of the gradual nicotine reduction group rose to baseline levels or levels similar to those of the control group after 12 months wherein both groups could freely smoke usual brand cigarettes (Benowitz, Nardone, Dains, et al., 2015). Although 7% of participants in the gradual reduction group quit smoking, compared to only 3% of participants in the usual brand control group, this difference was not statistically significant (Benowitz, Nardone, Dains, et al., 2015). In another study, 33 participants were randomized to receive VLNC cigarettes or to continue to smoke their usual brand cigarettes for 12 weeks. The availability of VLNC cigarettes increased quit attempts in smokers who had no intention of quitting (Walker et al., 2015). A study among smokers with serious mental illness (i.e., schizophrenia, schizoaffective disorder, or bipolar disorder) assigned to receive either NNC or VLNC cigarettes showed that, when asked to abstain from smoking, participants in the VLNC group showed fewer lapses in abstinence and longer time to first lapse than those in the NNC group (Tidey et al., 2019). In contrast, another study where subjects were asked to abstain from smoking for one week after being assigned to receive either NNC cigarettes or VLNC cigarettes with or without NRT for 6 weeks showed that subjects in the VLNC groups trended towards more lapses in abstinence than those in the NNC groups. However, this difference was not statistically significant (Smith, Koopmeiners, et al., 2019).

Taken together, results from the studies reviewed in the RTD suggest that, regardless of interest in quitting smoking, smokers who are given VLNC cigarettes may be more likely to quit compared to those who continue to smoke usual brand or NNC cigarettes. Provision of NRT may further increase smoking cessation among individuals interested in quitting.

iv. Product Switching

One potential implication of a standard to reduce the nicotine content of cigarettes is that cigarette smokers may shift consumption toward other tobacco products. Indeed, as the evidence reviewed in this RTD suggests, smokers generally find LNC and VLNC cigarettes less reinforcing, less satisfying, and less enjoyable than usual brand or NNC cigarettes. Hatsukami and colleagues (2017) conducted a study to compare the use of alternative tobacco products and smoking behavior in 136 smokers unwilling to quit. Participants were randomly assigned to one of three conditions and instructed to use only study-assigned tobacco products for 8 weeks. The "LNC1" cigarette group received LNC cigarettes combined with non-combusted tobacco products (i.e., smokeless tobacco, ENDS, NRT) and combusted non-cigarette tobacco products (i.e., cigars, cigarillos), the "LNC2" cigarette group received LNC cigarettes combined with non-combusted products, and the NNC cigarette group received NNC cigarettes combined with non-combusted and combusted non-cigarette products. Participants who received LNC cigarettes used more alternative combusted and non-combusted tobacco products. However, these participants also smoked fewer total combusted tobacco products and had more quit attempts. Furthermore, tobacco toxicant levels in participants who received LNC cigarettes and only non-combusted products were significantly lower than those of participants who received NNC cigarettes, while toxicant levels in those who received LNC cigarettes and had access to both combusted and non-combusted products did not differ from the NNC cigarette group (Hatsukami et al., 2017). Additional evidence from a clinical trial that investigated LNC cigarette use in nondaily smokers showed that, among participants who were not e-cigarette users at baseline, new use of e-cigarettes was significantly higher during the study in the LNC cigarette group compared to the NNC cigarette group (Shiffman, Kurland, et al., 2018). More information about product switching can be found in the main document, "The Science of a Nicotine Standard for Combusted Tobacco Products," in Section V.C: *Potential for Non-Cigarette Combusted Tobacco Product Switching*.

v. Impact on Vulnerable Populations

1. *Adolescents*

Few studies have assessed the effects of VLNC cigarette use in adolescent and young adult smokers. A study comparing VLNC and LNC cigarette smoking topography in adolescent smokers found that participants took significantly more puffs from the VLNC cigarette compared to the LNC cigarette, and a non-significant trend emerged such that increases in breath CO were higher after smoking the VLNC cigarette compared to the LNC cigarette (e.g., Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007). However, the LNC cigarette was

rated as significantly more pleasant than the VLNC cigarette (Kassel, Greenstein, et al., 2007). Another laboratory study in adolescent smokers found no effect of nicotine content on withdrawal, negative affect, or CO boost; however, NNC cigarettes were associated with greater reductions in craving and increased smoking satisfaction relative to VLNC cigarettes (Cassidy, Colby, et al., 2018a). A similar laboratory study in young adults (ages 18 - 25) found no influence of nicotine content on total nicotine withdrawal score, affect, or smoking topography; however, NNC cigarettes were associated with increased subjective effects ratings compared to LNC and VLNC cigarettes (Faulkner et al., 2017). Notably, a secondary analysis of data from Donny et al. (2015) found that, at the end of the 6-week trial, there was no influence of age on subjective effects, TNE levels, or puff volume in participants who smoked LNC or VLNC cigarettes (Cassidy, Colby, et al., 2018a).

Another laboratory study on the effects of nicotine content and menthol preference among adolescent smokers (15-19 years of age) found VLNC cigarettes were rated significantly lower than NNC cigarettes, with no significant interaction of menthol status and nicotine content on subjective or behavioral measures (Denlinger-Apte, Cassidy, et al., 2019b) One study also found that young adult smokers (18-24 years of age) exhibited lower demand for LNC and VLNC cigarettes than adults > 24 on three of the five CPT indices, but there were no other differences between the two age groups in smoking topography, breath CO, cigarette puffs, craving, withdrawal, or smoking urge measures (Davis, Parker, et al., 2019). Finally, Faulkner and colleagues (2019) investigated how nicotine exposure contributes to relief of craving and negative affect among young adult smokers (18-25 years of age) and found that smoking reduced craving and negative affect regardless of nicotine content, and smoking topography did not vary as a function of nicotine content (Faulkner et al., 2019).

In sum, while existing data suggests adolescent smokers like VLNC cigarettes less than LNC cigarettes, and they may display compensatory smoking behaviors in response to VLNC cigarettes, these data are limited. As discussed in the Section D.c.ii: *Compensatory Smoking* of Appendix A, compensation typically dissipates after repeated exposure. Thus, in the absence of extended exposure studies, it is difficult to draw conclusions regarding the effects of VLNC cigarette use in adolescents and young adults.

2. Individuals with Symptoms of Mental Health Disorders

Cigarette smoking is overrepresented in individuals with symptoms of mental health disorders. Smokers with symptoms of mental health disorders have increased nicotine withdrawal symptoms (e.g., Breslau et al., 1992; Weinberger et al., 2010) and are more likely to

smoke to ameliorate negative mood (e.g., Marshall et al., 2008). As a result, this population has increased risk of tobacco-related mortality (e.g., Callaghan et al., 2014).

Several studies included in this RTD investigated the effects of VLNC cigarettes on mood following mood induction in smokers with symptoms of mental health disorders (e.g., Buckley et al., 2007; Cook et al., 2007; Spring et al., 2008). These studies found that, following positive mood induction, LNC cigarettes as compared to VLNC cigarettes were associated with an enhancement of positive mood among depression-prone or anhedonic smokers, but not control participants (e.g., Cook et al., 2007; Spring et al., 2008). In addition, LNC cigarettes, but not VLNC cigarettes, were associated with a worsening of negative mood in response to negative mood induction among smokers, regardless of baseline mental health status (Spring et al., 2008). Similarly, following an anxiety-eliciting mood induction, participants with PTSD reported greater relief of anxiety after smoking LNC cigarettes compared to VLNC cigarettes; however, LNC cigarettes increased autonomic arousal (e.g., skin conductance, heart rate) relative to VLNC cigarettes (Buckley et al., 2007).

A single extended exposure study assessed the effects of cigarettes varying in nicotine content on changes in psychiatric symptomatology among those with and without elevated depression symptoms (Tidey, Pacek, et al., 2017). Among participants with elevated depression symptoms, those assigned to smoke LNC or VLNC cigarettes for 6 weeks had lower depressive symptoms at the end of the study compared to those assigned to smoke NNC cigarettes. Another study that assigned participants with serious mental illness to receive either NNC or VLNC cigarettes saw no change in participants' psychiatric symptoms at the end of 6 weeks (Tidey et al., 2019).

Several studies included in this RTD assessed the effects of VLNC cigarettes on smoking rates, nicotine craving, dependence, withdrawal, and subjective effects among those with symptoms of mental health disorders (Buckley et al., 2007; Dedert et al., 2012; Denlinger-Apte, Donny, et al., 2020; Gaalema et al., 2019; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Tidey, Pacek, et al., 2017; Tidey et al., 2013). While some studies found no significant differences in craving or withdrawal as a function of nicotine content following brief smoking abstinence in these vulnerable populations (Buckley et al., 2007; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Tidey et al., 2013), others showed that usual brand cigarettes were associated with larger decreases in craving and withdrawal compared to VLNC cigarettes (e.g., Dedert et al., 2012). At least one extended exposure study found that relative to NNC cigarettes, LNC and VLNC cigarettes reduced smoking rates, nicotine dependence, and cigarette craving, and these effects were not moderated by baseline depressive symptoms (Tidey, Pacek, et al., 2017). In addition, similar to the general population, smokers with poor mental health

rate NNC cigarettes as more rewarding (e.g., taste, satisfaction) compared to VLNC cigarettes (Cook et al., 2007; Higgins, Heil, Sigmon, Tidey, Gaalema, Hughes, et al., 2017; Spring et al., 2008; Tidey et al., 2013).

Among studies that investigated the effects of reduced nicotine content cigarettes on smoking behavior in vulnerable populations, Higgins and colleagues (2017) found no significant differences in smoking topography or breath CO as a function of nicotine content in adult smokers from three vulnerable populations (opioid-dependent individuals, economically disadvantaged women, and individuals with affective disorders). Subsequent analyses of this study also found that cannabis use status, presence of chronic health conditions, and sex did not correlate with differences in smoking topography or the reinforcing effects of nicotine among smokers (Parker et al., 2018; Streck et al., 2019). In addition, Tidey and colleagues (2013) found that smokers with schizophrenia and control participants smoked fewer puffs and had lower total puff volumes, shorter inter-puff intervals, longer puff durations and marginally higher puff volumes when smoking VLNC cigarettes compared to usual brand cigarettes. However, these differences were not associated with subsequent increases in breath CO boost (Tidey, Cassidy, et al., 2016).

Several studies included in this RTD used laboratory paradigms to assess the effects of alcohol on specific components of smoking behavior for nicotine versus non-nicotine factors in heavy drinkers. One study included in this RTD found that alcohol increased smoking urge and subjective ratings of smoking for both NNC and VLNC cigarettes (King et al., 2009), while another study found that NNC cigarettes were associated with increases in subjective effects and a greater reduction in cigarette craving than VLNC cigarettes, and these effects were enhanced by ethanol self-administration. In addition, NNC cigarettes reduced craving and increased cognitive performance compared to VLNC cigarettes (Rose et al., 2004).

In sum, results of studies reviewed in this RTD provide little to no evidence that VLNC cigarettes increase risk of adverse effects (e.g., exacerbations of psychiatric symptomatology) in smokers with symptoms of mental health disorders.

vi. Gradual versus Immediate Nicotine Reduction

Two approaches have been suggested for enacting a nicotine product standard for combusted cigarettes. One approach is to gradually decrease the nicotine content in cigarettes over time until it reaches a minimally addictive level. The other approach is to immediately reduce the nicotine content to that level. Research on how these two approaches may affect compensatory smoking or other potential unintended consequences associated with nicotine

reduction could help inform the best policy for reducing the nicotine content of combusted cigarettes.

Several studies included in this RTD investigated the effects of gradual nicotine reduction on compensatory smoking (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Hammond & O'Connor, 2014; Mercincavage et al., 2018; Mercincavage et al., 2016). In these studies, participants were not interested in quitting and did not receive ancillary provision of NRT or alternative tobacco products. Benowitz and colleagues conducted a pilot study and a clinical trial investigating whether a gradual reduction in cigarette nicotine content would increase exposure to tobacco smoke toxins due to compensatory smoking (e.g., Benowitz et al., 2012; Benowitz et al., 2007). Participants smoked their usual brand cigarettes during baseline and were then switched from NNC to LNC to VLNC cigarettes containing 10.3, 6.5, 3.9, 1.7 and 0.5 mg nicotine per cigarette. In a 6-week pilot study, participants were switched weekly, and in a 6-month trial, participants were switched monthly. Little change in smoking behavior was observed; however, plasma cotinine concentration decreased as a function of cigarette nicotine content, such that cotinine was lowest while participants were smoking VLNC cigarettes. Compensation, calculated based on plasma cotinine levels, was higher while smoking LNC cigarettes compared to VLNC cigarettes (Benowitz et al., 2012). In addition, other studies have shown that compensatory smoking may increase when participants smoke reduced nicotine content cigarettes with intermediate levels of nicotine (e.g., LNC cigarettes) compared to usual brand cigarettes (Mercincavage et al., 2016). Furthermore, the results of other studies have shown that gradually reducing the nicotine content of cigarettes is associated with high levels of noncompliance when participants reach the VLNC cigarette phase of the intervention (e.g., Benowitz, Nardone, Hatsukami, et al., 2015; Hammond & O'Connor, 2014). Thus, some evidence suggests that, when the nicotine content of cigarettes is gradually reduced, compensatory smoking or use of alternative combusted tobacco products may increase at intermediate and lower nicotine levels.

Several extended-exposure studies investigated whether an immediate reduction in cigarette nicotine content would increase compensatory smoking (e.g., Donny et al., 2015; Walker et al., 2015). Like the gradual reduction studies discussed above, participants in these immediate reduction studies were not interested in quitting and did not receive ancillary provision of NRT or alternative tobacco products. In the most comprehensive study, Donny and colleagues (2015) randomized 839 smokers to one 6-week condition, during which they smoked their usual brand cigarettes or they were immediately switched to research cigarettes containing 15.8, 5.2, 2.4, 1.3, of 0.4 mg nicotine per g of total tobacco. Participants assigned to the LNC or VLNC cigarette groups who received cigarettes with nicotine content less than or

equal to 2.4 mg nicotine per g of total tobacco smoked significantly fewer cigarettes per day than participants assigned to the usual brand and NNC cigarette groups. Those who received LNC or VLNC cigarettes containing 5.2 mg nicotine per g of total tobacco or less had significantly lower urinary TNE than those who received NNC cigarettes. No differences in breath CO measures were observed between groups. The total puff volume at Week 6 was significantly lower among participants who smoked VLNC cigarettes compared to those who smoked NNC cigarettes. However, much like the gradual reduction studies, a secondary analysis showed that noncompliance was high in participants randomized to the VLNC cigarette group (Nardone et al., 2016). Walker et al. (2015) randomized 33 participants to receive VLNC cigarettes or to continue smoking their usual brand cigarettes for 12 weeks. Overall, participants in both groups smoked a similar total number of CPD, even though only the participants in the VLNC cigarette group received free cigarettes. These data demonstrate that an immediate decrease in cigarette nicotine content is unlikely to lead to significant compensation or increased toxicant exposure.

Finally, Hatsukami and colleagues (2015) conducted a secondary analysis pooling data from five clinical studies to examine relations between compensatory smoking and gradual versus immediate nicotine reduction. Two of the trials utilized a gradual reduction approach while three of the trials utilized an immediate reduction approach. CPD, breath CO, and cotinine levels were compared between the immediate reduction group, gradual reduction group, and a control group who received usual brand cigarettes. Relative to baseline, significant decreases in CPD were observed in participants in the gradual and immediate groups, whereas significant increases in CPD were observed in participants in the usual brand groups. In the gradual nicotine reduction studies, a 5% decrease in CPD was observed relative to baseline, and in the immediate nicotine reduction studies, an 11% decrease in CPD was observed. In contrast, a 12% increase in CPD was observed in participants who continued to smoke their usual brand cigarettes. Although significant changes in breath CO were not observed in any group, significant decreases in cotinine were observed in both the gradual and immediate groups, but not in the usual brand cigarette group. Results from this study suggest that compensatory smoking is relatively similar across the two nicotine reduction approaches (Hatsukami et al., 2015).

In sum, the results of several studies reviewed in this RTD suggest that neither gradual nor immediate reduction of nicotine in cigarettes leads to compensatory smoking; however, both approaches may increase the likelihood of smokers using alternative combusted tobacco products in addition to VLNC cigarettes. Limited evidence also suggests that gradual reduction

may lead to compensatory smoking during the intermediate steps of a gradual reduction approach when participants are smoking cigarettes with low to moderate nicotine content

vii. Menthol

Menthol cigarettes comprise over 30% of the combusted cigarette market share in the U.S. (U.S. Federal Trade Commission, 2019) and are used disproportionately by vulnerable populations (Villanti, Collins, Niaura, Gagosian, & Abrams, 2017; Villanti et al., 2016; Young-Wolff, Hickman, Kim, Gali, & Prochaska, 2014). Although there is evidence that menthol may increase the appeal of cigarettes (Kreslake, Wayne, & Connolly, 2008) and impact discrimination of nicotine content (Perkins, Kunkle, Karelitz, Michael, & Donny, 2016), there is little research on the extent to which menthol impacts response to VLNC cigarettes.

One brief exposure study found a main effect of menthol on subjective effects, but no significant interaction between nicotine content and menthol on subjective effects (Perkins et al., 2018). Further, the authors found no effect of menthol on choice or puffs for NNC over VLNC cigarettes. Another brief exposure study found no effect of menthol on smoking topography, breath CO, withdrawal, craving, or CPT demand (Davis et al., 2019). In another brief exposure study, menthol smokers of both NNC and VLNC cigarettes reported less craving reduction than non-menthol cigarette smokers, but there was no interaction between menthol and nicotine content (Denlinger-Apte, Cassidy, Colby, Sokolovsky, & Tidey, 2019).

Results from an extended exposure study that investigated the effects of menthol and nicotine content showed that smokers of menthol VLNC cigarettes had less of a reduction in CPD and biochemically verified abstinence than those who smoked non-menthol VNLC cigarettes (Denlinger-Apte, Kotlyar, et al., 2019). Results from this study also found that menthol VLNC cigarette smokers showed a smaller reduction in TNE than non-menthol VLNC smokers; craving and positive subjective ratings were lower in VLNC smokers, regardless of menthol status; and there was a trend towards a smaller difference in craving reduction and breath CO relative to baseline among VLNC menthol smokers.

In sum, although there are only a few studies on menthol reviewed in this RTD, brief exposure studies have found no effect of menthol on behavioral and subjective response to VLNC cigarettes. There is, however, some evidence that menthol may lessen reductions in CPD, craving, and some BOEs following extended exposure to VLNC cigarettes.

Appendix B: Social Science Literature Review: Reproducible, Transparent Review of the Extant Social Science Literature Relevant to Low Nicotine and Very Low Nicotine Tobacco Products

A. Executive Summary

In order to inform regulatory efforts related to a potential nicotine standard for combusted tobacco products, FDA conducted a reproducible, transparent review of the extant social science literature relevant to consumer knowledge, attitudes, perceptions, beliefs, and planned behavior regarding reduced nicotine tobacco products. FDA searched three electronic databases – PubMed, Web of Science, and Ebscohost – and identified 66 eligible articles for inclusion in this final report. This review reveals strong evidence[14] that a substantial majority of adult American consumers believe that nicotine is carcinogenic and that nicotine is a main cause of smoking related disease. There is strong evidence that the majority of the population believes that nicotine is the substance in cigarettes that maintains addiction. There is strong evidence that a significant minority (25%-35%) of consumers believe that reduced nicotine cigarettes are less harmful to health than normal nicotine content (NNC cigarettes), and a substantial minority of consumers believe that reduced nicotine cigarettes are less addictive than normal nicotine cigarettes. There is moderate evidence that between 45%-77% of adult American consumers support a nicotine product standard; however, there is evidence that misperceptions about nicotine and reduced nicotine products influence support for the nicotine product standard. Additionally, qualitative studies indicate that consumers are concerned that the proposed reduction in nicotine is not technically possible, do not understand why FDA wants to reduce nicotine levels in cigarettes, and have concerns about compensatory smoking if the standard is enacted. In addition to the findings about consumer perceptions of nicotine, RNC cigarettes, and a low nicotine product standard, this review found moderate evidence that there are messaging strategies that can be used to improve consumer understanding of nicotine, RNC cigarettes, and a low nicotine product standard.

[14] For the purposes of the social science review, the two social science reviewers used the following criteria to summarize the findings within each broad section: The qualifier "Very strong evidence" indicates that multiple high-quality studies report the same results, even across multiple study populations and research methodologies. The qualifier "strong evidence" indicates that there are multiple high-quality studies that report the same or very similar results. The qualifier "moderate evidence" indicates that there are some high-quality studies that report similar results, but those results have not been replicated consistently. Finally, the qualifier "weak evidence" indicates that the results are from low-quality studies, and/or that findings have not been replicated consistently across studies.

B. Methods

a. Eligibility Criteria

Relevant studies that were published in English in scholarly journals were eligible for potential inclusion. No limitation of the year of publication was imposed.

The following types of studies were excluded from this review: studies of chemistry or toxicology, epidemiologic studies of disease occurrence, biomedical/biomarker studies, genetic studies, studies of cannabis, studies not concerned with nicotine specifically and as a substance distinct from tar, studies employing exclusively animal models, studies utilizing only participants from outside the United States (US), studies utilizing participants from the US and other countries where data on US participants were not presented separately, studies that were published only in a language other than English, editorials, news briefs, commentaries, digests, unpublished dissertations, studies of behavioral or clinical pharmacology that did not assess knowledge, attitudes, perceptions, beliefs, or planned behavior respective to nicotine; and studies within the social science discipline that did not assess knowledge, attitudes, perceptions, beliefs, or planned behavior respective to nicotine RNC cigarettes, or a low nicotine product standard.

b. Information Sources, Search Strategy, and Data Extraction

The databases PubMed, Web of Science, and Ebscohost (Academic Search Complete, PsycInfo, and CINAHL) were selected for the literature search. These databases were first searched on September 21, 2017 using search strings tailored to each respective database. A second search using the same search strings was conducted on August 13, 2020. A third search using the same search strings was conducted on December 9, 2022. These search strings are listed below in Table B.1.

Table B.1. Search Strings Used to Identify Relevant Social Science Publications, by Database

Database	Search String	2017 Hits	2020 Hits
PubMed	("reduced nicotine" OR "nicotine reduction" OR "low nicotine" OR “lower nicotine” OR denicotinized OR denicotinised OR “nicotine free” OR VLNC OR “placebo cigarettes” OR "spectrum cigarettes" or "quest cigarettes" OR "nicotine infusion" OR “variable nicotine” OR “light cigarettes”) AND (cigar* OR “tobacco products”[Mesh]) AND (perception* OR perceive* OR belief* OR believe* OR attitude* OR expectanc*)	143	165

Web of Science	("reduced nicotine" OR "nicotine reduction" OR "low nicotine" OR "lower nicotine" OR denicotinized OR denicotinised OR "nicotine free" OR VLNC OR "placebo cigarettes" OR "spectrum cigarettes" or "quest cigarettes" OR "nicotine infusion" OR "variable nicotine" OR "light cigarettes") AND (cigar* OR tobacco) AND (perception* OR perceive* OR belief* OR believe* OR attitude* OR expectanc*	164	221
Ebscohost (Academic Search Complete, PsycInfo, and CINAHL)	("reduced nicotine" OR "nicotine reduction" OR "low nicotine" OR "lower nicotine" OR denicotinized OR denicotinised OR "nicotine free" OR VLNC OR "placebo cigarettes" OR "spectrum cigarettes" or "quest cigarettes" OR "nicotine infusion" OR "variable nicotine" OR "light cigarettes") AND (cigar* OR tobacco) AND (perception* OR perceive* OR belief* OR believe* OR attitude* OR expectanc*)	261	298

Note: Researchers searched the databases identified in the table on three dates (September 21, 2017; August 13, 2020; December 8, 2022), using the same search terms each time. [a]For the EbscoHost search in 2022, there were 472 hits before an automatic filter removed exact duplicates for export into EndNote 20 and 274 hits after automatic de-duplication.

Details of 2017 Search: One reviewer trained in conducting literature reviews conducted the search of databases and data extraction outlined above. The reviewer exported the identified publications into EndNote and de-duplicated the citations. The reviewer initially screened publications by reading each study's abstract. Articles that did not meet eligibility criteria and/or met exclusionary criteria were excluded. The reviewer then screened the remaining publications by reading the full text of the article. The reviewer also examined reference lists of included publications and the reference lists of excluded systematic or literature reviews to identify additional eligible articles that might not have been captured via the database search.

Details of 2020 Search: One reviewer trained in conducting literature reviews conducted the search of databases and data extraction outlined above. This search was an exact replication of the 2017 search and included a review of all relevant articles regardless of year of publication. The reviewer exported the identified publications into EndNote and de-duplicated the citations. The reviewer initially screened publications by reading each study's abstract. Articles that did not meet eligibility criteria and/or met exclusionary criteria were excluded. The reviewer then screened the remaining publications by reading the full text of the article. The reviewer also examined reference lists of included publications and the reference lists of excluded systematic or literature reviews to identify additional eligible articles that might not have been captured via the database search. External peer reviewers reviewed the findings from the first literature search and summary (September 2017) and identified three articles for inclusion in the review.

Details of 2022 Search: Two reviewers trained in literature reviews conducted a search of PubMed, Web of Science, and EbscoHost and identified publications published between 2020-2022 using the strategies outlined above. The reviewers exported identified citations to EndNote 20 and de-duplicated the citations. Reviewers completed an initial screening of publication abstracts for all studies; studies that did not meet eligibility criteria and/or met exclusionary criteria were excluded after a check for agreement between the two reviewers. One reviewer also identified additional articles for inclusion through SME (subject matter expert) recommendation and a backward literature search of the reference lists of the publications deemed eligible for inclusion, and through the reference lists of systematic or literature reviews. The reviewers then screened all publications that were eligible for inclusion by reading the full text of the publications selected for inclusion (N = 72; n = 45 from 2020 search and n = 27 from 2022 search). One additional publication recommended in the 2017 external peer review was selected for inclusion in the 2022 update.

c. Full-Text Screening of Publications

Reviewers coded each eligible publication using the following four criteria: relevance, risk of bias in methods and analysis, evaluation of results, and sufficiency of evidence. These criteria are described in more detail in section C below. In evaluating the body of evidence as a whole reviewers gave greater weight to studies that employed nationally representative sampling strategies or experimental designs, as these methodologies are more robust than alternative approaches.

C. Results

a. Study Selection

Details of 2020 Study Selection[15]: Prior to excluding duplicates, the searches of PubMed, Web of Science, and Ebscohost yielded 165, 221, and 298 citations, respectively (see Table B1). After de-duplication, 309 unique citations remained. Initial screening of abstracts resulted in the exclusion of 136 citations for the following reasons: language criterion (studies published only in languages other than English (3)); publication criterion (editorials/commentaries (11), news briefs or digests (4), systematic or literature reviews (11), and unpublished dissertations (4)); discipline criterion (animal studies (4), biomedical/biomarker studies (11), studies of chemistry

[15] The 2020 study selection was an exact replication of the 2017 study selection with the following exceptions: 1) any year of publication included content published through 2020, and 2) the 2020 study selection included a review of the articles recommended by external peer reviewers.

or toxicology (3), epidemiological studies (2), genetic studies (4)); topic criterion (studies of cannabis (5), studies of product science (4)); and participant criterion (studies of participants outside the United States or multi-country studies where data on US participants were not analyzed separately (71)). The full text of the remaining 173 publications was assessed for eligibility, resulting in the exclusion of a further 134 publications for the following reasons: studies not concerned with nicotine specifically and as a substance separate from tar (72), studies of pharmacological smoking behaviors without the assessment of knowledge, attitudes, beliefs, or perceptions regarding nicotine (32), studies within the social science discipline without the assessment of knowledge, attitudes, beliefs, or perceptions regarding nicotine (21), and studies of participants outside the US or multi-country studies where data on US participants were not analyzed separately (9). The remaining 39 publications were deemed to be eligible for inclusion. The reference lists of these publications were reviewed to identify potentially eligible publications that might not have been captured by the search strategy, yielding an additional three articles that were eligible for inclusion. These three articles were not captured by the search strategy due to slight differences in phrasing, e.g., "reducing nicotine" vs. "reduced nicotine." The reference lists of articles excluded for being systematic or literature reviews were likewise reviewed but did not yield additional publications that were eligible for inclusion. External peer reviewers reviewed the findings from the first literature search and summary conducted (September 2017) and identified three articles for inclusion in the review. A total of 45 publications were selected for inclusion in the review.

Details of 2022 Study Selection: Prior to excluding duplicates, the searches of PubMed, Web of Science, and Ebscohost yielded 195, 274, and 472 citations, respectively (see Table B1). After de-duplication, 468 unique citations remained. The two reviewers further excluded any studies published before 2020 (n = 403 excluded; n = 65 publications included). Of the 65 publications reviewed, 48 were removed for the following reasons: language criterion (0); publication criterion (9); discipline Criterion (8); topic Criterion (16); social science criterion (5); and participant Criterion (10). The remaining 17 publications were deemed to be eligible for inclusion. The reference lists of eligible publications from 2020-2022, including reference lists of articles excluded for being systematic or literature reviews, were reviewed to identify potentially eligible publications that might not have been captured by the search strategy. Additionally, one reviewer subject matter expert identified 11 articles for inclusion in the review. These strategies yielded 9 publications that were eligible for inclusion, plus an additional article that was identified by an external subject matter expert. Finally, the two reviewers screened the publications included from the 2020 review as a quality check and removed 4 articles.

b. Summary of Included Publications

A total of 66 publications were included in the final review after full text screening (a PRISMA diagram of the study selection process is provided in Section F: PRISMA diagram). Reviewers completed an initial coding of included publications, then summarized each publication with a particular focus on those results directly relevant to this review. These summaries are available in Section F: Article Summaries of Appendix B. An integrated summary of the body of evidence as a whole is presented below, organized into the following four categories: (1) reviews of industry documents; (2) studies of consumer knowledge, attitudes, beliefs, or perceptions about nicotine in general; (3) studies of consumer knowledge, attitudes, beliefs, or perceptions about reduced nicotine tobacco products; and (4) studies of consumer knowledge, attitudes, beliefs, and perceptions with respect to FDA regulation of tobacco. Publications that addressed multiple categories are discussed in each relevant section.

Within each broad category, results are organized by research methodology. Overall, the studies identified for inclusion in the review employed a range of research methodologies: experimental studies, cross-sectional survey studies using nationally representative data, cross-sectional survey studies using samples of convenience, and qualitative studies such as focus groups and interviews. Of the 66 studies included in this review, 6 used systematic review methods to examine industry documents, 23 used experimental designs, 24 used cross-sectional nationally representative surveys, eight used cross-sectional surveys with convenience sampling, six used qualitative methods, and one study included both an experiment and a nationally representative survey. Studies that employed nationally representative survey strategies or experimental designs were given more weight when evaluating the body of evidence because these methodologies are more robust than others for determining generalizability to the US population (nationally representative surveys) or causal relationships (experimental design). The two most common methodological challenges identified in the 2017 review were: 1) the use of convenience samples that were not nationally representative, limiting the generalizability of the results to the population of interest; and 2) the use of non-experimental designs, limiting the ability to detect causal relationships. However, multiple articles published between 2017 and 2022 have included nationally representative and experimental research that addresses the topic areas covered in this review. The two most common methodological challenges identified in the updated 2022 review were: 1) the use of stimuli and survey questions that are not specific to VLNC cigarettes but instead focus on a general reduction in the level of nicotine in cigarettes; and 2) the use of response options in surveys and experiments that are overly sensitive to survey ordering and wording effects. The published studies included in this review used a range of stimuli and survey questions to

measure consumers' understanding of nicotine, RNC and VLNC cigarettes, and a proposed reduction of nicotine. These studies provide useful data about consumer perceptions, attitudes, knowledge, beliefs, and intended behaviors toward RNC cigarettes and a potential reduced nicotine product standard. A larger pool of published studies that include stimuli and questions that measure consumer responses to VLNC cigarettes specifically would enable FDA to make more targeted predictions about consumer perceptions and behavior in a post-product standard marketplace.

c. Reviews of Industry Documents

Six narrative reviews (6/66, 9.09% of identified articles) examined tobacco industry documents to determine industry approaches to selecting nicotine content in cigarettes.

All six reviews found that the tobacco industry has a long history of adjusting cigarette components, including nicotine content, to maintain product appeal (Dunsby & Bero, 2004; Hsu & Grodal, 2015; Levy et al., 2021; Ling & Glantz, 2019; Pollay & Dewhirst, 2002; Yerger, 2011). Tobacco industry members conducted research on consumer perceptions of RNC cigarettes to determine the optimal amount of nicotine in cigarettes to maintain appeal. Industry documents indicate that poor taste, reduced throat sensations, and the potential inability for RNC cigarettes to create and sustain addiction are challenges to the profitability of these products (Dunsby & Bero, 2004; Hsu & Grodal, 2015; Levy et al., 2021; Pollay & Dewhirst, 2002; Yerger, 2011). Internal industry strategies to mitigate these issues and maintain RNC cigarette appeal to consumers included maintaining or increasing tar levels to improve taste (Dunsby & Bero, 2004), manipulating filter pH to enhance nicotine bioavailability in cigarettes (Pollay & Dewhirst, 2002), and adding menthol to enhance the flavor of reduced nicotine cigarettes (Yerger, 2011). Yerger (2011) noted that the interactive effect between nicotine and menthol allows consumers to perceive RNC cigarettes as similar in taste and throat hit to normal nicotine cigarettes. Furthermore, this interactive effect is so useful for maintaining appeal of cigarettes that some tobacco companies add small amounts of menthol to cigarettes not advertised as mentholated to increase the pleasurable and reinforcing aspects of nicotine.

The tobacco industry is also aware that consumers believe nicotine is harmful to health (Dunsby & Bero, 2004; Hsu & Grodal, 2015; Pollay & Dewhirst, 2002); to offset these concerns while maintaining a reinforcing level of nicotine in cigarettes, the tobacco industry has used advertising tactics in multiple communication channels to convey misleading information about nicotine. They identified women, older established smokers concerned with the health effects of smoking, and young new smokers as the consumer populations most receptive to RNC cigarettes that could be marketed as less harmful to health (Dunsby & Bero, 2004; Pollay &

Dewhirst, 2002). To meet demand for "healthier" products the tobacco industry used advertising cues such as red packaging (Pollay & Dewhirst, 2002) to imply cigarettes were "strong" and "satisfying" despite having reduced nicotine and they used product descriptors of "light" and "ultralight" (Hsu & Grodal, 2015) to convey to consumers that by selecting products with lower levels of nicotine and tar they could choose cigarettes that were less harmful. In addition to advertising, the tobacco industry used academic and popular media to present arguments that nicotine has potentially positive effects and that the addictiveness of nicotine is similar to the addictiveness of caffeine in coffee (Ling & Glantz, 2019).

Overall, reviews of industry documents reported that the tobacco industry can control the nicotine level in cigarettes and chooses levels that maintain consumer appeal and addiction. The tobacco industry explored changes to cigarettes to make them more appealing to consumers (including changes to nicotine levels and bioavailability of nicotine). These changes had a large impact on consumer perceptions and liking of the products, although the tobacco industry did not communicate these changes directly to consumers. Additionally, these reviews reported multiple marketing strategies industry used to affect consumer perceptions about the harms and hypothetical benefits of nicotine and RNC cigarettes. These marketing strategies perpetuated incorrect claims that some types of nicotine and cigarettes are healthier than others, and many consumers endorse belief in those incorrect claims.

d. Consumer Knowledge, Attitudes, Beliefs, or Perceptions About Nicotine

Twenty-seven articles (27/66, 40.91% of the included articles) examined consumer knowledge, attitudes, perceptions, or beliefs regarding nicotine as a specific substance in combusted cigarettes, not in the context of RNC cigarettes. There is strong evidence that a majority of US consumers incorrectly believe nicotine causes cancer, and strong evidence that a large majority of US consumers correctly believe nicotine is addictive. There is also strong evidence that the rate of incorrect beliefs about the harms of nicotine vary by smoking status; specifically, compared to people who do not smoke cigarettes, those that do had higher rates of correct beliefs about the harms of nicotine.

Studies Examining Knowledge, Attitudes, Beliefs, or Perceptions About the Harms of Nicotine

Many studies identified in this review reported that consumers believe nicotine causes cancer (Cummings et al., 2004; Borrelli & Novak, 2007; Kaufman et al., 2011; Mutti et al., 2011; Smith et al., 2011; Patel et al., 2013; Kim et al., 2017; Kemp et al. 2018; Villanti et al., 2019; Villanti et al., 2019; Yang et al., 2020; Villanti et al., 2020; Denlinger-Apte et al. 2021; Denlinger-Apte et al., 2021; Lin & Muscat 2021; Loud et al. 2021; Parker et al., 2021; Shi et al. 2021; Snell

et al. 2021; Steinberg et al. 2021; Differding et al. 2022; Jackson et al. 2022; Petersen et al. 2022; Weiger et al. 2022). In studies examining nicotine harm beliefs in the general population, the belief that nicotine causes cancer was endorsed by 40% to 78% of participants. Some studies examined rates of endorsement for this incorrect statement in different tobacco user populations; these studies found that around 46% of respondents that currently use ENDS, 52% to 61% of respondents that currently smoke cigarettes, and up to 84% of respondents who do not use tobacco products endorse the incorrect belief that nicotine causes cancer or that nicotine is the major component in cigarettes that leads to cancer.

Studies using nationally representative survey data found evidence of nicotine misperceptions in the general population. Kemp et al. (2018) reported that the majority of participants (83.2%) in a nationally representative survey characterized the amount of nicotine usually found in tobacco products as definitely harmful to children. Peterson et al. (2022) found a low prevalence of correct nicotine cancer harm perceptions across all years of HINTS data they analyzed (2015 = 27.1%, 2017 = 25.9%, 2019 = 22.0%). Snell et al. (2022) analyzed PATH data and found that Incorrect responses to a question about nicotine's harmfulness to health were reported by 68.9% of participants (SE: 0.56); 64.6% incorrectly reported that nicotine in cigarettes was very/extremely or not at all harmful to health (SE: 0.53), and 63.3% thought that nicotine was "probably" or "definitely" the main contributor to smoking-related cancers (SE: 0.63). Across these nationally representative studies, there was strong evidence that incorrect perceptions about nicotine harm vary by gender (females have more incorrect beliefs about nicotine harm than males), ethnicity (black and Hispanic individuals have more misperceptions than white individuals), education (less educated have more misperceptions than college educated), and age (older adults have more misperceptions about nicotine than younger adults).

Multiple nationally representative studies examined nicotine harm perceptions by tobacco use status. Lin and Muscat (2021) conducted a secondary analysis of the nationally representative Health Information National Trends Survey (HINTS) and reported that adults who dual used ENDS and cigarettes had the highest percentage of correct responses that nicotine did not cause cancer (40.40%) while adults who do not smoke had the lowest percentage of correct answers (15.75%). This study also found that 22.47% of adults who do not smoke did not know if nicotine caused cancer. Shi et al. (2021) asked participants to rate how much of the health risks of smoking are associated with nicotine on a scale from none to all. Over half of the people who currently used cigarettes incorrectly believed that nicotine caused "a relatively large part" (33.2%), a "very large part" (18.1%), or "all" (5.4%) of the health risks caused by smoking. Weiger et al. (2022) found that an estimated 61.2% of people who

were established cigarette users in the United States thought nicotine "definitely caused cancer", "probably caused cancer", or "did not know" if nicotine caused cancer.

Studies using convenience sampling also found evidence of nicotine misperceptions across sub-populations. Patel et al. (2013) conducted a cross-sectional survey among full-time faculty on two university campuses in the US and reported that 51% of all respondents ranked nicotine as high risk for general health. Pacek et al. (2017) used a cross-sectional survey to examine nicotine knowledge and beliefs in a convenience sample of HIV-positive people who smoke and reported that the majority of participants incorrectly identified nicotine as the cause of most smoking-related cancers and as a primary cause of lung cancer, asthma, heart disease, stroke, heart attack, and impotence. Villanti et al. (2019) surveyed young adults about harm perceptions of nicotine containing products and reported that respondents believed that a relatively or very large part of the health risks (66%) or cancer (60%) caused by smoking come from the nicotine. Borelli and Novak's (2007) survey of nurses found that a majority of participants endorsed the belief that nicotine is a cause of cancer. Bansal-Travers et al. (2010) conducted a study with adult smokers who wanted to quit smoking, and the majority of participants endorsed believing that nicotine is primarily responsible for smoking-related cancers. Finally, Loud et al. 2021 conducted qualitative focus groups with participants with different tobacco use histories; participants in all groups tended to incorrectly believe that nicotine causes some of the major health effects of smoking. Although these studies focused on incorrect beliefs about nicotine harms in specific sub-populations, demographic characteristics associated with rates of incorrect beliefs were similar to those in nationally representative surveys. Specifically, incorrect beliefs that nicotine is a cause of cancer or is responsible for the health risks caused by smoking are more prevalent for those that do not use tobacco products compared to those that do use tobacco products, for females compared to males, for blacks and Hispanics compared to whites), and for those with less than some college education (vs. at least some college), and for older respondents compared to younger respondents (compared to older respondents).

Studies Examining Knowledge, Attitudes, Beliefs, or Perceptions of the Addictiveness of Nicotine

Eleven studies reported consumer perceptions about the addictiveness of nicotine. These studies provide strong evidence that the majority of US consumers believe nicotine is addictive. However, these studies provide moderate evidence that consumers do not apply those correct perceptions to make accurate judgments about the absolute risks of using tobacco products or to make accurate judgements about the comparative risks of using different cigarette products.

Seven of the studies focused on consumer perceptions of the addictiveness of nicotine (Peterson 2022; Snell et al. 2022; Pacek et al. 2017; Loud et al 2021; Patel et al. 2019: Lin & Muscat 2021; Jackson et al. 2022). Peterson (2022) found a high prevalence of correct perceptions of nicotine's addictive properties across all years of HINTS data they analyzed, with a small but consistent increase in correct responses among all participants over time (2015 = 83.5%, 2017 = 84.7%, 2019 = 85.8%). In each HINTS cycle, an estimated 12% of adults living in the United States reported they do not know if nicotine is the main substance in tobacco that makes people want to smoke. Snell et al. (2022) reported that 82.9% (SE: 0.44) of participants agreed that nicotine was responsible for driving continued cigarette use, however only 13.1% (SE: 0.46) agreed that reducing nicotine would make cigarettes less addictive. Patel et al. (2019) examined the knowledge that people who currently smoke cigarettes have about the addictiveness of nicotine in a nationally representative study and reported that the majority of participants (63%) indicated that nicotine alone was the substance in cigarettes that caused addiction. Lin & Muscat (2021) found that 83% of people who do not use cigarettes and 97% of people who dual use e-cigarettes and cigarettes know that nicotine is addictive. Jackson et al. (2022) found that the majority of people who dual use cigarettes and ENDS agreed that nicotine is addictive and are concerned about nicotine addiction. Pacek et al. (2017) reported that the majority of participants in their study of HIV-positive people who use cigarettes correctly identified nicotine as the substance that makes cigarettes addictive. Loud et al. 2021 conducted qualitative focus groups with participants with different tobacco use histories; most participants understood that nicotine was addictive. This qualitative study reported that although consumers believe that nicotine is addictive, they also believe that an addiction to cigarettes comes from more than just nicotine.

Studies Examining Messaging Interventions to Correct Nicotine Misperceptions

Eleven studies that examined messaging interventions were identified in this review. These studies examined how different message formats and content corrected nicotine misperceptions. Overall, these studies reported that messaging increased endorsement of correct beliefs about the harms of nicotine (i.e., that nicotine does not cause cancer and that nicotine is the not the major source of health harms in cigarettes). Some studies found that messaging resulted in more accurate beliefs about the relative harm of RNC cigarettes. One experimental study (Villanti et al. 2019) examined the effect of a nicotine fact sheet on how people who smoke cigarettes rated the perceived risk and addictiveness of nicotine. Before exposure to the nicotine fact sheet, most people who smoke understood that nicotine is the main cause of tobacco addiction, but incorrectly believed that nicotine was the main cause of smoking-related health problems. However, viewing the nicotine fact sheet doubled the

probability of disagreeing that nicotine is the main cause of smoking-related disease. Another experimental study (Yang, Owusu, & Popova, 2020) examined the effect of nicotine educational messages on harm and risk beliefs about nicotine and reduced nicotine content cigarettes. Participants who viewed a message about nicotine had more correct responses to the statement that nicotine is a cause of cancer than participants in other conditions. Exposure to nicotine message was also associated with lower rates of false beliefs about nicotine and RNC cigarettes. A third experimental study (Shi et al. 2021) randomized subjects to view a control, or one of three messages designed to correct nicotine misconceptions (correction about nicotine only, correction about nicotine in NRT, and correction about nicotine in e-cigarettes). All three of these messages lowered subjects' perception of nicotine harm compared to the control. A fourth experimental study, Differding et al. (2022), randomized participants to view one of six messages designed to describe a low nicotine product standard and define VLNC cigarettes. Participants who viewed messages that included information about the addictiveness and harm of VLNC cigarettes were less likely to believe that nicotine caused cancer.

These studies identified in the review measured the short-term impact of the messaging interventions; it is unclear if messaging will increase correct perceptions of the harms and risks of nicotine in the long term. Additionally, these studies have not examined the impact of messaging on specific sub-populations; therefore, it is unclear whether the improvements produced by these messages will be similar for different audiences.

e. Consumer Knowledge, Attitudes, Beliefs, or Perceptions Regarding Reduced Nicotine Content Cigarettes

Thirty-one studies (31/66, 46.97%) focused on consumer perceptions and beliefs about the safety, harm, or addictiveness of RNC cigarettes. Fourteen used experimental or quasi-experiment research designs, ten used nationally representative cross-sectional data, five used cross-sectional samples of convenience, and two conducted qualitative studies. These studies provide very strong evidence that a significant minority of consumers (25-35%) believe that RNC cigarettes are less harmful and less carcinogenic than NNC cigarettes. Anywhere from 12% to 54% of people who smoke hold this misconception that RNC cigarettes are less harmful than NNC cigarettes. These studies also provide strong evidence 60-77% of consumers believe that RNC cigarettes are equally or more addictive than NNC cigarettes; people who smoke do not have significantly different rates of misperceptions about RNC cigarette addictiveness compared to the general population. Finally, studies that examined advertisements for RNC cigarettes identified messaging components that can be adjusted to decrease incorrect misperceptions of RNC cigarettes and improve message appeal. Although the studies included in this review did not identify a "gold-standard" message for correcting misconceptions about

the addictiveness and harm of RNC cigarettes, there is moderate evidence that messages that focus on how using RNC cigarettes can increase quitting efficacy tend to be the most appealing to people who use NNC cigarettes.

Perceived Relative Harm of Reduced Nicotine Cigarettes

Seventeen studies examined consumers' beliefs and perceptions about the relative harm of RNC cigarettes compared to NNC cigarettes. Four of these studies used experimental data, nine used nationally representative cross-sectional data, and four used cross-sectional samples of convenience. These studies provide strong evidence that a quarter or more of consumers believe that these RNC cigarettes are safer than NNC cigarettes, including a quarter or more of current tobacco users.

Four experimental studies assessed participants' perceptions of the safety of RNC or VLNC cigarettes after using them. All four studies found that participants perceive RNC or VLNC cigarettes to be significantly less harmful to health and less likely to cause cancer than NNC cigarettes (Pacek et al., 2018; Denlinger-Apte et al., 2017; Hatsukami et al., 2013; Denlinger-Apte et al. 2019a). Two of the studies (Pacek et al., 2018 and Denlinger-Apte et al., 2017) found that using RNC or VLNC cigarettes is unrelated to evaluations of their health harms. Pacek et al. (2018) conducted a double-blind randomized trial using a convenience sample to study the association between perceived nicotine content and health risks. They randomly assigned participants to smoke cigarettes of varying nicotine levels and found that participants who perceive the nicotine content of study cigarettes to be low, medium, or high/very high had significantly higher risk perceptions as compared to participants who perceive the nicotine content of the study cigarettes to be very low regardless of the actual nicotine content of the cigarettes they were assigned to smoke. Denlinger-Apte et al. (2017) conducted a within-subject experiment using a small convenience sample (N = 68). They asked participants to smoke two identical low nicotine cigarettes but told them that one had more nicotine than the other. Participants in their study rated the "very low" nicotine cigarette as significantly less risky than the "average" nicotine cigarette in terms of both overall health and specific disease risks including cancer risks although both cigarettes had identical levels of nicotine. The other two studies (Hatsukami et al., 2013 and Denlinger-Apte et al., 2019a) reported a correlation between the amount of nicotine present in study cigarettes and individuals' evaluations of the health harms from smoking. Hatsukami et al. (2013) conducted an experiment using a small convenience sample (N = 51) in which participants were asked to smoke cigarettes of varying nicotine contents. They found that participants perceived low nicotine cigarettes as being less likely to cause lung cancer and a variety of other diseases than high nicotine and intermediate nicotine cigarettes. Denlinger-Apte et al. (2019a) conducted an experiment where adolescents who smoke were assigned to smoke cigarettes with varying levels of nicotine across four

experimental sessions. They found that respondents who smoke VLNC cigarettes perceive them to be less likely to cause lung disease and cancer than those who smoke NNC cigarettes.

Four nationally representative studies examined consumer perceptions of the relative harm of RNC cigarettes in the general population without asking respondents to use a product. These studies reported that a significant minority (25%-35%) of consumers incorrectly believe that RNC cigarettes are safer and less carcinogenic than NNC cigarettes (O'Brien et al., 2017; Nguyen et al., 2018; Popova et al., 2019). O'Brian et al. (2017) used nationally representative HINTS data to assess US adults' beliefs about RNC cigarettes. They found that that 30% of respondents rate RNC cigarettes as less harmful than NNC cigarettes while 64% rate them as equally harmful. Nguyen et al. (2018) found that approximately 28% of US-born respondents in a nationally representative survey believe that RNC cigarettes are "slightly" or "much less" harmful than NNC cigarettes, and approximately 22% of US-born respondents believe they are "much" or "slightly less likely" to cause lung cancer. These percentages were significantly higher among the foreign-born population than the US-born population; approximately 32% of foreign-born respondents believe that RNC cigarettes are "slightly" or "much less" harmful than NNC cigarettes and approximately 28% believe that using NNC cigarettes would lead to a lower risk of lung cancer. Popova et al. (2019) analyzed nationally representative Tobacco products and Risk Perceptions Survey data and found that 35% of participants believed that RNCs were less harmful than regular cigarettes. O'Connor et al. (2005) measured beliefs about the harmfulness of RNCs in a slightly different way. They asked a nationally representative sample an open-ended question requiring them to identify a product that potentially reduced cigarette risk. Quest low nicotine cigarettes were the most cited product with 27% of respondents identifying them as a reduced risk product.

Five nationally representative cross-sectional studies and one study that used a convenience sample focused on people who smoke cigarettes and found that the proportion of people who smoke that believe RNCs are safer than NNC varies considerably across studies from a low of about 12% to a high of 54%. Cummings et al. (2004b) conducted a cross-sectional survey of adults who currently smoke cigarettes to assess their beliefs about the health risks of smoking and the safety of NRT. They found that approximately 54% of respondents believe that reducing nicotine in cigarettes makes them less dangerous. Cummings et al. (2004a), used the same sample and found that 46% percent of people who used "full-flavor" cigarettes believed that a reduction in nicotine makes cigarettes less dangerous, and a higher percentage of people who used "light" cigarettes believed that a reduction in nicotine makes cigarettes less dangerous (approximately 48% of those that smoke ultralight cigarettes, approximately 50% of people that smoke Marlboro light cigarettes, and approximately 50% of people who smoke other light cigarettes. Byron et al. (2018) analyzed a nationally representative survey and found

that 47.1% of all people who smoke believe that smoking RNC cigarettes over 30 years would reduce your cancer risk relative to smoking NNC cigarettes. Denlinger-Apte et al. (2021a) analyzed a subsample of people who currently exclusively smoke cigarettes from the PATH study to describe overall trends in risk perceptions of nicotine and RNC cigarettes across racial/ethnic, sexual orientation, and gender identity groups. They found that between 12.38% and 25.53% of respondents across racial categories have a misperception of the harmfulness of RNC cigarettes relative to NNC cigarettes. This rate was significantly higher for Asian respondents compared to white respondents. Jackson et al. (2022) used HINTS data and found that about 23% of people who use cigarettes and e-cigarettes believe that RNC cigarettes are less harmful than NNC cigarettes. In general, the misperception that RNC cigarettes are safer than NNC cigarettes was more common among non-white people who smoke relative to white people who smoke and among older compared to younger people who smoke (Mercincavage et al., 2019; Denlinger-Apte et al., 2021a; Byron et al., 2018). Mercincavage et al., (2019) analyzed baseline survey responses collected before two separate experiments to assess risk perceptions of RNC cigarettes. They found that non-White people who smoke are more likely than White people who smoke to incorrectly perceive RNC cigarettes as safer, healthier, and having less tar than regular cigarettes.

Three studies focused on subpopulations that may be of particular interest. Andersen et al. (2013) conducted a survey of a small convenience sample (N = 26) of patients in a perinatal substance abuse treatment program. They found that participants in the program believe that RNC cigarettes are as safe or safer for their babies than NNC cigarettes, and 60% would be somewhat or extremely likely to try RNC cigarettes if they might be safer for their baby. Borrelli and Novak (2007) conducted a survey using a convenience sample of nurses and found that approximately 38% believed that reducing nicotine in cigarettes makes them less dangerous to smokers. Finally, Smith et al. (2012) conducted an online survey using a convenience sample of college students (N = 579) and found that the majority of college students in their sample did not believe that reducing levels of nicotine in cigarettes makes them less dangerous to smokers.

Perceived Addictiveness of Reduced Nicotine Cigarettes

Eight studies described consumers' beliefs and perceptions about the addictiveness of RNC cigarettes relative to NNC cigarettes. Six nationally representative surveys and one survey that used a convenience sample reported that a majority of respondents believe that RNC cigarettes are equally or more addictive than NNC cigarettes; one experimental study on this topic found that consumers who use VLNC cigarettes believe that they are less addictive.

Six nationally representative surveys reported that 60% to 77% of consumers believe that RNC cigarettes are equally or more addictive than NNC cigarettes. O'Brien et al. (2017)

analyzed HINTS data and found that 65% of participants rate RNC cigarettes as equally addictive to NNC cigarettes and only 28% rate them as less addictive. Similarly, Nguyen et al. (2018) analyzed HINTS data and reported that 64% of respondents believe that RNC cigarettes are equally addictive to NNC cigarettes. Villanti et al. (2019a) analyzed the Truth Initiative Young Adult Cohort Study and found that 60% of young adult (aged 25-34) respondents do not believe the claim that low nicotine cigarettes are less addictive than NNC cigarettes. Lin and Muskat (2021) analyzed HINTS data and found that tobacco use status does not appear to significantly change misconceptions about the addictiveness of RNC cigarettes. People who do not smoke cigarettes, those that exclusively smoke cigarettes, and those that dual use cigarettes and e-cigarettes equally report believing that RNC cigarettes are equally addictive as regular cigarettes. Jackson et al. (2022) analyzed HINTS data to assess the relationship between beliefs about nicotine and nicotine containing products and use behavior. They found that around 77% of respondents that use cigarettes and e-cigarettes believe that RNC cigarettes are equally or more addictive than NNC cigarettes. Denlinger-Apte et al. (2021a) analyzed PATH data and reported that 80% of people who currently use cigarettes believe that RNC cigarettes are "equally addictive" or "more addictive" than NNC cigarettes. In addition to these six survey studies, Mercincavage et al. (2019) analyzed baseline survey responses for two separate experiments using convenience samples. They found that 63.4% of participants did not believe that RNC cigarettes were less addictive and would be easier to quit.

Only one study found that consumers understood that RNC cigarettes are less addictive than NNC cigarettes. Hatsukami at al. (2013) conducted an experiment where participants were randomly assigned to smoke cigarettes with varying levels of nicotine. They found that participants rated high nicotine cigarettes as having a significantly higher risk of addiction compared to low and intermediate nicotine cigarettes. This result suggests that using RNC cigarettes may affect perceptions of the addictiveness of these products relative to NNC cigarettes.

Studies Examining Advertising and Messaging Interventions to Correct Misperceptions of Reduced Nicotine Content Cigarettes

Fourteen studies focused on understanding the impact of advertising and messaging on misperceptions about the harm and addictiveness of RNC cigarettes. Eight used experimental data, two used quasi-experimental data, one used a convenience sample, and two conducted qualitative studies. Evidence from these studies suggest that advertising can lead to misperceptions of RNC cigarettes but that removing misleading text and adding corrective statements can help consumers better understand the relative harm and addictiveness of these products. Additionally, there is a challenge in identifying messages that correct both misperceptions about the addictiveness and health risks of RNC cigarettes simultaneously, and

that efficacy messages are the most appealing to smokers. One potential concern with these advertising and messaging studies is that they measured short term impacts, so it is unclear whether any changes in advertising or new message campaigns will have a long-term impact on reducing misperceptions of RNC cigarettes.

Four experimental studies, two quasi-experimental studies, and one study using a convenience sample found that advertisements can contribute to misperceptions of RNC cigarettes but can also be used to correct pre-existing misperceptions. Mercincavage et al. (2017) conducted a randomized controlled trial in which participants were exposed to an advertisement for Quest RNC cigarettes and then were asked to use them for 10 days. They found that after exposure to a Quest advertisement, participants believe that Quest cigarettes are lower in nicotine and healthier than NNC cigarettes. O'Connor et al. (2007) asked a convenience sample of college students to rate 12 advertisements for various tobacco products, including Quest cigarettes on a set of terms used to measure "positive expectancies" and "negative expectancies". They found that negative expectancies (including "hard to quit, cause cancer, dangerous, bad breath, stupid, addictive, make me cough, harsh, and make me nauseated") were lower for Quest compared to Marlboro Lights. The authors attributed the difference in negative expectancies to marketing that focused on the relative health benefits of Quest RNC cigarettes compared to NNCs, rather than their flavor. Shadel et al. (2006) conducted a quasi-experimental, post-test only study asking participants to view a single print Quest advertisement. They found that participants with both low perceived vulnerability and lower perceived need for cognition are significantly more likely to believe, falsely, that Quest cigarettes are safer and less addictive than NNC. Studies that examined message characteristics that might reduce misperceptions about RNC cigarettes removed misleading text or added corrective messages. For example, Lochbuehler et al. (2016) conducted an experimental study using a between-subjects design where participants were randomized to view one of four versions of a Quest product advertisement. They found that participants who were exposed to the corrective statement, "Nicotine free does not mean risk free. Quest contains as much tar as a light cigarette," are significantly less likely to endorse false beliefs about the harmfulness of the product. Strasser et al. (2008) conducted a quasi-experimental, post-test only study looking at US cigarette users' beliefs following exposure to three different Quest advertisements (a Quest advertisement created by the brand, a modified advertisement with no text, and an advertisement where the pack color was altered from its original blue to red). They found that participants in the no-text condition compared to all other conditions are significantly more likely to correctly believe that Quest cigarettes are not less addictive, not less likely to cause cancer, do not have fewer chemicals, are not healthier, and are not safer than regular cigarettes. Mercincavage et al. (2021) conducted an experiment in which participants were

randomized to view one of six RNC advertisements. They found that relative to an ad with no disclaimer at all, an industry-proposed disclaimer on RNC cigarettes that emphasizes that the products "contain nicotine" and that "less nicotine does not mean a safer cigarette" is associated with greater perceived health and addiction risk beliefs and fewer false beliefs about RNC products. Finally, Johnson et al. (2019) conducted an experiment that randomly assigned young adults who smoke cigarettes to view Quest advertisements that contained either implicit risk information (red vs. blue packaging), an explicit correct message, or both. They found that participants recalled more warning messages when they received both an explicit and implicit warning about risk.

Three experimental studies examined the impact of broader messaging strategies on consumer misperceptions of the safety and addictiveness of RNC cigarettes. Byron et al. (2019) used an experimental design in which respondents were randomly assigned to view one of seven descriptions of a potential FDA product standard. They found that compared to the control message, a message that described the policy as reducing 95% of the nicotine in cigarettes results in more accurate perceptions about nicotine content (76% vs. 49% accuracy) and addictiveness (44% vs. 34%), but less accurate perceptions about cancer risk (56% vs. 68%). Building on this study, Differding et al. (2022) conducted an experiment in which participants were randomized to view the 95% message that Byron et al. (2019) tested, or a variant of that message that added additional details about harm, addictiveness, or youth use. They found that people who view messages that include information about the addictiveness and harm of RNC cigarettes are less likely to believe that nicotine and RNC cigarettes cause cancer and that RNC cigarettes are safer than NNC cigarettes. Popova et al. (2019) also conducted an experimental study where participants were randomized to view one of five descriptions of a low nicotine product standard. They found that the treatment group that described VLNC cigarettes as "no longer relieved your cravings" had the lowest proportion of participants that believed that VLNC cigarettes are less harmful than regular cigarettes (26%).

One experimental study and two qualitative studies examined messaging about RNC cigarettes that appeal to current cigarette users and provided initial evidence that current cigarette users prefer messages that focus on quitting efficacy of RNC cigarettes. Duong et al. (2022) conducted a series of focus groups with people who use tobacco and people who do not use tobacco to examine the impact of messages about reducing nicotine in cigarettes. They found that for people who exclusively use cigarettes, efficacy messages about breaking addiction and messages about smoking risks are the most effective at encouraging attention, liking, and processing of message content. However, they also found that people who do not use tobacco felt that efficacy messages downplayed the risks of smoking. Ranney et al. (2022) conducted in-depth interviews to evaluate 18 different messages designed to counter

misperceptions of RNC cigarettes. They found that people who smoke prefer messages that promote self-efficacy for quitting rather than messages that invoke guilt or fear of using cigarettes. Finally, Reynolds et al. (2022), conducted a discrete choice experiment to estimate the impact of seven different messages on attitudes about a low nicotine product standard. They found that participants perceive messages that describe RNC cigarettes as products that increase quitting efficacy, as products that are less addictive, and as products that contain 95% less nicotine than NNC cigarettes to be the most positive.

f. Consumer Knowledge, Attitudes, Beliefs, Perceptions, or Planned Behavior Regarding FDA Regulation of Nicotine Levels in Cigarettes

Seventeen articles (17/66, 25.76% of articles identified) examined consumer knowledge, attitudes, beliefs, perceptions, or planned behavior regarding a potential low nicotine product standard. Five of the studies employed nationally representative cross-sectional data; six studies used experimental designs; one used a cross-sectional survey with a convenience sample; and five studies used qualitative approaches. Overall, these studies provide moderate evidence that support for a low nicotine product standard varies between 45% and 77%. There is also moderate evidence that support varies by smoking status with between two-thirds and three-quarters of people who smoke supporting a low nicotine product standard. However, these estimates of support may be out of date (based on data collected before 2019) or influenced by methodological concerns, including survey order effects. Additionally, several qualitative studies provide evidence that consumers may not fully understand the purpose, feasibility, and goals of a low nicotine product standard. Experimental and qualitative research identified in this review examined how to improve consumer understanding of the purpose and intended effects of a proposed product standard.

Three studies using nationally representative cross-sectional survey data examined US adults' attitudes towards a low nicotine product standard. Connolly et al. (2012) reported that approximately two-thirds of participants in a nationally representative phone survey would support the FDA reducing nicotine in cigarettes either immediately or gradually, and approximately 77% of participants would support reducing nicotine in cigarettes if it would result in fewer children becoming addicted to smoking. Pearson et al. (2013) reported that approximately 45% of participants in a nationally representative online survey support a low nicotine product standard. Approximately 20% disagreed that the government should regulate nicotine, approximately 28% were equivocal, and approximately 7% didn't know. People who currently used cigarettes were significantly less likely to support nicotine regulation compared to people who had never used tobacco products. Ali et al. (2019) reported that a majority of participants in their nationally representative survey favored a proposed regulation lowering

the nicotine content in cigarettes (52.4% Strongly Favor, 28.6% Somewhat Favor), while a minority opposed the proposed regulation (10.3% Somewhat Oppose, 8.7% Strongly Oppose).

Six additional studies focused on public opinion about a low nicotine product standard among people that currently use tobacco. Two of these studies used surveys with nationally representative samples, two used an experimental design, one used a survey with a convenience sample, and one used a qualitative research design. Fix et al. (2011) analyzed nationally representative data from the International Tobacco Control (ITC) United States Supplemental Survey and reported that approximately two-thirds of respondents who currently use cigarettes would support a law that reduces the nicotine content of cigarettes to make them less addictive. Patel et al. (2019) reported that in a nationally representative sample of people who use cigarettes, most participants (72%) support a policy that would reduce the level of nicotine in cigarettes. People who use cigarettes who endorse the misperception that nicotine itself is a major cause of the health harms associated with smoking have a greater adjusted odds of supporting a policy to reduce the nicotine content in cigarettes compared to those who do not endorse the misperception that nicotine causes the health harms of smoking. Delinger-Apte et al. (2019b) conducted a double-blind, randomized trial examining how using VLNC cigarettes for an extended period affects participant support for a proposed nicotine reduction, and what characteristics and responses to VLNC cigarettes were associated with support. They reported that after the 6-week trial there were no significant differences in support for a low nicotine product standard between people who used their usual brand of cigarettes and those who used VLNC cigarettes. For both cigarette-use conditions, about half of the sample support the policy (50% VLNC, 55% usual brand), about a quarter oppose it (26% VLNC, 20% usual brand), and about a quarter respond that they do not know whether they support the policy (24% VLNC, 25% usual brand). Delinger-Apte et al. (2021c) conducted a double-blind experiment where participants were assigned to use cigarettes that immediately or gradually reduced the amount of nicotine available to them. They found that 58% of all participants supported the policy at baseline and 60% supported it at week 20 of the experiment. The experimental condition (immediate or gradual reduction of nicotine in cigarettes) had no effect on support for the policy, but people who used cigarettes who were interested in quitting were more likely to support the policy. Pacek et al. (2019) conducted a cross-sectional survey using a convenience sample of young adults who use both cigarettes and e-cigarettes to examine responses to a hypothetical low nicotine policy. They found that participants tended to respond to a hypothetical low nicotine policy by planning to reduce or quit smoking while increasing their use of e-cigarettes. Finally, Pepper et al. (2020), conducted a survey of people who currently use cigarettes and those that currently use e-cigarettes in which

respondents were able to explain their response to a proposed low nicotine product standard using an open-ended question. Pepper et al. reported that the most common reasons that people who use tobacco strongly agreed with the standard are that they believe it would help smokers quit or cut down, and that it would reduce the perceived harms of smoking. The most common reason people who use tobacco strongly disagreed with the standard are that they believe it would hamper individual freedom and could possibly lead to compensatory smoking.

Multiple studies identified in this review reported that support for a low nicotine product standard varied by race, ethnicity, age, gender, and education. African American respondents tend to be more supportive of a low nicotine product standard than white, non-Hispanic respondents (Pearson et al., 2013; Ali et al., 2019; Kulak, Kamper-Demarco, and Kozlowski, 2020). Pearson et al. (2013) found that participants with a high school education or less, people who have never smoked, people who smoke and intend to quit, and more politically liberal participants were significantly more likely to support a low nicotine product standard. Ali et al. (2019) found that favorability was slightly lower among adults aged 25−64 years than those aged ≥65 years, and among adults with some college education than those with a college degree. They also found that favorability was higher for women than men, and for Hispanic participants than white, non-Hispanic participants. People who currently smoke cigarettes tended to be less supportive of a low-nicotine policy (Pearson et al., 2013; Ali et al., 2019; Kulak, Kamper-Demarco, and Kozlowski, 2020) and among those, men were significantly more likely to support the policy than women (Fix et al. 2011).

Although the evidence cited above indicates that support for a low nicotine product standard is high, additional studies indicate that survey effects and potential consumer confusion about the feasibility and purpose of a low nicotine product standard may be impacting the accuracy of the estimate of support for the low nicotine product standard. Kulak et al. (2020) conducted an experiment with a small convenience sample to assess the impact of ordering survey effects on estimates of support for a low nicotine policy. They found that support for the policy ranged from 46.2% to 61.8% depending on the order of survey response options. Four qualitative studies provide evidence that consumers may be confused about the purpose of a product standard, how it would work, and the impact it would have on public health. Denlinger-Apte et al. (2021b) conducted qualitative interviews with participants after they used VLNC cigarettes and reported that some participants were accurately able to describe the purpose of a reduced nicotine policy as reducing the addictiveness of smoking. However, some participants misunderstood nicotine's contribution to the health impacts of smoking and could not describe why FDA would propose reducing nicotine in cigarettes. Ranney et al. (2022) conducted 30 in-depth interviews with current smokers to study the impact of different

messages about a lower nicotine product standard. They found that confusion about whether RNC cigarettes are less addictive or harmful than NNC cigarettes impacted how different messages were interpreted. Some participants indicated confusion about why nicotine was being removed rather than other harmful chemicals, some participants did not believe that removing nicotine would eliminate the addictiveness of smoking, and some believed that a low nicotine policy might lead to compensatory smoking. Henderson et al. (2022) and Loud et al. (2022) conducted focus groups to examine consumer perceptions of a low nicotine policy. Henderson et al. (2022) reported that participants were concerned about the feasibility of removing nicotine from cigarettes, a potential overreach of government control, and the possibility that a reduced nicotine policy protects the tobacco industry. Loud et al. (2022) found that many participants believe that an addiction to cigarettes is based on more than just the amount of nicotine in the products and that a policy that reduces nicotine in cigarettes would not make them less addictive.

Preliminary experimental studies have explored how different messaging strategies can improve consumer understanding about a low nicotine product standard. Differding et al. (2022) conducted an experiment in which participants were randomized to view one of six messages to describe the product standard. They found that none of these messages impacted participants' support for a low nicotine product standard. Reynolds et al. (2022) conducted a discrete choice experiment to explore the impact of seven different messages on attitudes about a proposed reduction of nicotine. They found that messages focusing on the reduced addictiveness of RNCs, lower nicotine content, and increased quitting efficacy lead respondents to feel more positive about a low nicotine product standard, while messages focusing on chemicals in RNC cigarettes, and their harm led individuals to perceive a product standard more negatively. Further research about messaging strategies could support future communications regarding the low nicotine product standard.

D. Conclusion

Weighing the studies using robust designs and sampling methodologies more heavily along with the body of evidence as a whole, this review indicates that there is strong and consistent evidence that a substantial minority (25-35%) of American adults endorse the incorrect beliefs that RNC cigarettes are less harmful to health than NNC cigarettes and that their use is less likely to result in negative health outcomes. Compared to those who do not smoke, a larger proportion of people who smoke endorse the incorrect beliefs that RNC cigarettes are less harmful to health. In a likely related finding, there is strong and consistent evidence that the majority of American adults endorse the incorrect beliefs that nicotine is a carcinogen and a primary cause of smoking-related disease. These findings were consistent

across multiple study designs and study populations, although there is evidence that population characteristics such as ethnicity, gender, education, and smoking status are correlated with rates of incorrect beliefs about nicotine and VLNC cigarettes. Generally, studies that examined population subgroups reported that rates of incorrect beliefs about nicotine were higher among Black and Hispanic participants (compared to White participants), among women (compared to men), among people with less than a college education (compared to those with at least some college education), and among current tobacco users (compared to non-users). To ensure a positive net impact on population health from the nicotine product standard, it will be important to ensure that consumers understand that reduced nicotine cigarettes are just as harmful to health as cigarettes that contain higher amounts of nicotine. There is evidence that the majority of American adults believe that reduced nicotine cigarettes are equally addictive as NNC cigarettes. Overall, these findings provide evidence that consumers' beliefs about nicotine harm, nicotine addictiveness, RNC harms, and RNC addictiveness are related. Explicit messaging and information about nicotine in cigarettes affect beliefs about addictive properties of nicotine and VLNCs (compared to NNCs); additionally, experiences using NNC and VLNC cigarettes affect beliefs about the addictiveness of VLNCs without explicit messaging about nicotine content.

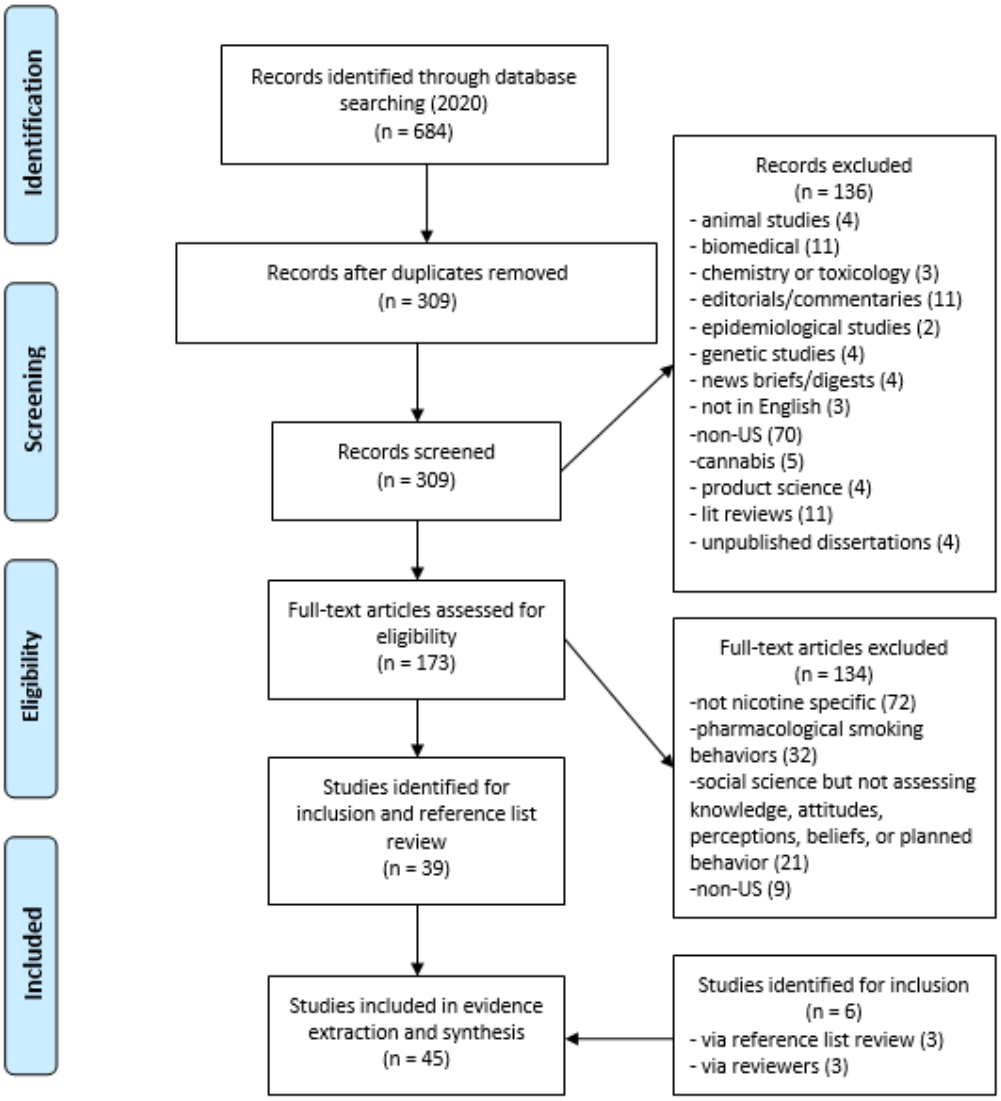
There is evidence that consumer-directed messaging can promote a more accurate understanding of nicotine harms and the proposed nicotine product standard while also communicating the risks of using RNC and VLNC cigarettes. To ensure a positive net impact on population health, it will be important to ensure that consumers understand that nicotine is not a carcinogen nor a primary cause of smoking-related disease. It may also be valuable to explicitly differentiate VLNC cigarettes from low yield/high ventilation light/low/mild cigarettes, as previous public health messaging campaigns have informed consumers that these products, which were sometimes marketed as being lower in nicotine, are not safer or less addictive. Public health messaging designed to educate consumers on actual risks of nicotine and VLNC cigarettes may be more effective if it communicates how a nicotine product standard improves population health while still emphasizing the harms associated with using combusted cigarettes. There may also be opportunities to improve understanding of nicotine and VLNC risks by tailoring information to specific population subgroups, although further research is necessary in this regard. There is insufficient evidence to identify important differences and needs that may exist in vulnerable subpopulations, such as racial/ethnic minorities, foreign-born populations, women, and sexual/gender minorities, among others. Although the current available evidence on public messaging about nicotine harms, RNC harms, and a low nicotine product standard has been conducted with effective research designs (experiments and focus

groups), these studies have limited generalizability to the US population or to specific sub-populations. Furthermore, it is important to note that while there is evidence that increasing correct harm perceptions for nicotine and emphasizing that reducing nicotine content may help people who smoke feel better able to quit smoking, there may be potential unintended effects in different tobacco user populations, including those who use other nicotine-containing products and those who do not use tobacco.

Finally, there is evidence that as many as 45%-77% of American consumers support a nicotine standard. Some studies found that people who smoke are less supportive of a product standard than those that do not; however, studies focused exclusively on people who use tobacco reported that 67% -75% of people who smoke support a proposed nicotine reduction. However, this support may partially be due to the misperception that nicotine is a major cause of smoking-related disease. These misperceptions may explain why consumers have such a wide range of reported behavioral intentions in response to lower nicotine products: consumers' reported behavioral intentions if a nicotine standard is put in place include quitting smoking combusted cigarettes, continuing to smoke VLNC cigarettes or other combusted tobacco products, or switching to non-combusted tobacco products. Additionally, there is evidence that consumers may not understand the purpose and feasibility a low nicotine product standard. Studies included in this review indicate that the content and framing of messaging about RNC cigarettes can impact consumers' behavioral intentions about tobacco product use if a reduced nicotine policy is put in place.

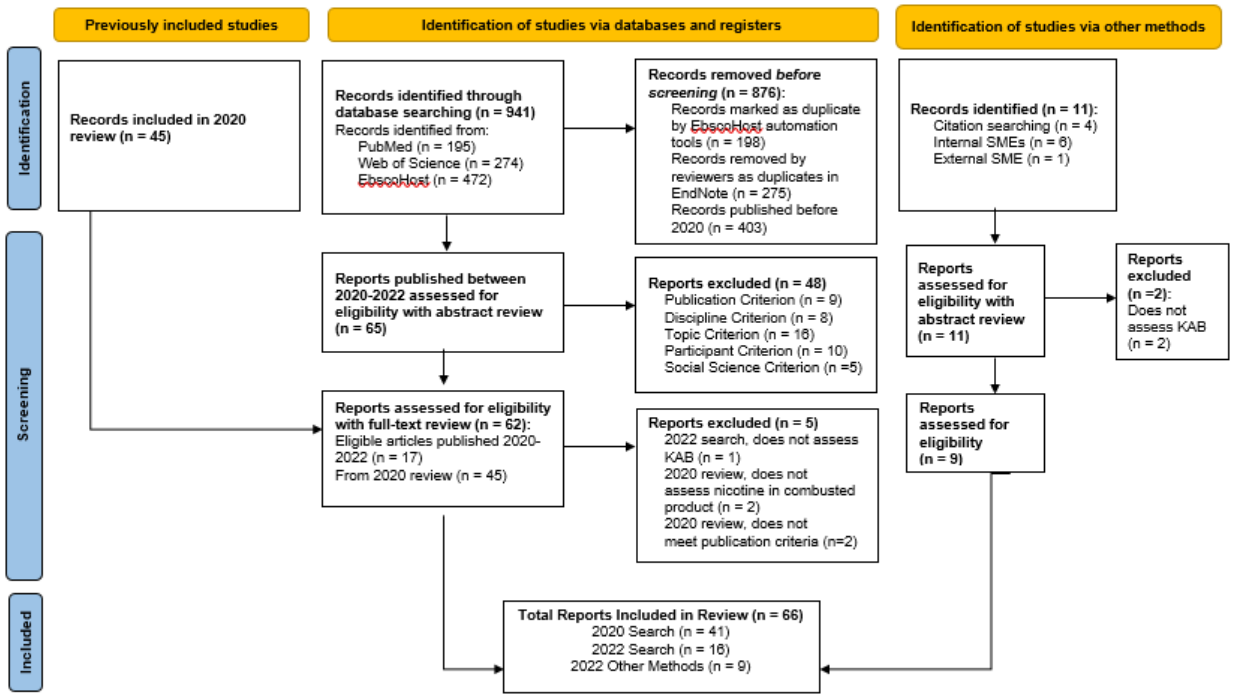
E. PRISMA diagram

Figure 1: PRISMA Diagram for 2020 Search



Note: This PRISMA diagram depicting the 2020 search was modified from the PRISMA 2020 diagram resource on www.prisma-statement.org. The phrase "studies identified for inclusion via reviewers" includes studies identified by external subject matter experts who conducted an external review of the original 2017 literature search and report.

Figure 2: PRISMA Diagram for 2022 Literature Search



Note: PRISMA 2020 diagram modified from resources on www.prisma-statement.org. SME = "Subject matter expert". KAB = "Knowledge, attitudes, and beliefs". Publication Criterion means that the report was removed because it was not a peer-reviewed article with original research or a review of industry documents. Discipline Criterion means that the report was removed because it was not related to social science (disciplines excluded were Chemistry/Toxicology, Epidemiologic studies of disease occurrence, Biomedical/biomarker studies, Genetic studies, or studies employing exclusively animal models). Topic Criterion means that the report was removed because it was not concerned with nicotine specifically and as a substance distinct from tar. Participant Criterion means the report was removed because it did not utilize participants from the US only or did not present US data separately when examining both participants from the US and other countries. Does not assess KAB means the report was excluded because it did not assess knowledge, attitudes, perceptions, beliefs, or planned behavior respective to nicotine

F. Article Summaries

Ali et al. (2019) conducted a secondary data analysis of a nationally representative survey (2018 SummerStyles survey) to examine the prevalence and correlates of favorability ratings for lowering nicotine levels in cigarettes. Participant data (N = 4037) were collected with the web-based panel survey, and data were weighted to be nationally representative. Ali et al. reported that a majority of participants indicated that they favored the proposed regulation (52.4% Strongly Favor, 28.6% Somewhat Favor, 10.3% Somewhat Oppose, 8.7% Strongly Oppose). Responses differed by gender, ethnic group, age, education, and smoking status. Following adjustment, favorability was slightly higher among women than men (APR = 1.06, 95% CI=1.03, 1.10), and higher among Hispanics than white non-Hispanics (APR = 1.07, 95% CI=1.01, 1.13). Favorability was slightly lower among adults aged 25−44 years (APR = 0.87, 95% CI=0.84, 0.91) and 45−64 years (APR = 0.95, 95% CI = 0.92, 0.98) than those aged ≥ 65 years, among adults with some college education than those with a college degree (APR = 0.93, 95% CI = 0.89, 0.97), and among current noncigarette tobacco product users (APR = 0.88, 95% CI = 0.81, 0.96) than nonusers. Limitations of this study include that they used a relatively smaller sample from the web-based panel survey.

Andersen et al. (2013) conducted a cross-sectional study assessing smoking behavior and knowledge, attitudes, and practices regarding reduced nicotine cigarettes among patients in a perinatal substance abuse treatment program. Participants (N = 26) were recruited from those patients of the program who self-identified as smokers. The measures of interest were assessed via a self-administered, bespoke paper questionnaire. Approximately 85% of participants reported current pregnancy and approximately 92% reported current opioid agonist therapy. Participants reported smoking an average of 12.3 cigarettes per day. Approximately 88% reported being at least somewhat interested in quitting, while approximately 42% reported previous use of a pharmacological smoking cessation method. One participant reported having previously tried reduced nicotine cigarettes. Approximately 68% reported believing that reduced nicotine cigarettes are at least as safe or safer for their baby as compared to regular cigarettes. Approximately 60% of participants reported being somewhat or extremely likely to try reduced nicotine cigarettes if they knew that reduced nicotine cigarettes would not cause increased craving or smoking and might be safer for their baby. Limitations include inability to generalize to the wider population of interest due to convenience sampling, small sample size, and the inability to assess for causal relationships when using cross-sectional study designs.

Bansal-Travers, Cummings, Hyland, Brown, and Celestino (2010) conducted a survey assessing smoking and nicotine knowledge, and associations between knowledge and quitting

behavior, among adult smokers in New York State, known as the CEASE (CEssation After Smoking Education) Study. A post-test only control group design was employed, with one group of participants receiving novel educational materials and another receiving standard educational materials. Participants (N = 682) were recruited from adult cigarette users who contacted the New York State Smokers' Quitline from December 2004 to February 2005. Participants were randomized to receive either the novel or control educational materials via mail, as well as a nicotine medication 2-week starter kit. One month later, participants (n = 515) completed a telephone survey assessing knowledge, use of nicotine replacement therapy, and current smoking status. Approximately 71% of participants in the control group and approximately 68% of participants in the treatment group reported believing, incorrectly, that nicotine is the component in cigarettes that is primarily responsible for cancer in smokers. Approximately 84% of the control group and approximately 86% of the treatment group reported believing, correctly, that switching to a low nicotine cigarettes does not improve one's chances of quitting smoking. These differences in response rates between groups were not statistically significant. The authors did not report on any associations between knowledge and use of nicotine replacement therapy or smoking status at follow-up. Limitations include an inability to generalize to the wider population of interest due to convenience sampling and the inability to assess for causal relationships.

Borelli and Novak (2007) conducted a cross-sectional study of perceptions of harm reduction tobacco products and behaviors among nurses. A convenience sample of participants (N = 178) were recruited from a hospital and a home health care agency in Providence, Rhode Island. Participants completed a self-administered questionnaire assessing beliefs regarding risk reduction behaviors and products, nicotine replacement products, potential reduced exposure products, health beliefs, and demographics. The measures were either adapted from existing measures or developed by the authors. Approximately 38% of participants reported believing, incorrectly, that reducing nicotine in cigarettes makes them less dangerous to smokers. Approximately 28% of participants reported believing that nicotine patches are not at all likely to cause heart attacks. Approximately 60% of participants reported somewhat agreeing or strongly agreeing with the statement that "Nicotine is a cause of cancer." The majority of participants correctly believed that nicotine replacement therapy is less likely to cause addiction than cigarettes. Limitations include an inability to generalize to the wider population of interest due to convenience sampling, small sample size, and the inability to assess for causal relationships when using cross-sectional study designs.

Byron et al. (2018) analyzed results of a nationally representative survey to examine the prevalence and demographic correlates of the misperception that VLNC cigarettes are less

carcinogenic than current cigarettes. The survey introduced the concept of VLNC cigarettes and asked about perceived cancer risk from smoking these cigarettes. Most of the participants (N =1758; n = 650 smokers; mean age of participants was 43.1 years) were white (78.5%) or black (14.9%). Half the smokers were male, and 6.5% were gay, lesbian, or bisexual. Almost half (46.7%) had not attended college, and 29.7% lived below the federal poverty level. Overall, 47.1% of smokers believed that smoking VLNC cigarettes for 30 years was less likely to cause cancer than smoking current cigarettes for 30 years. The misperception was more common among smokers aged 55 or older than among smokers aged 18–34 (56.6% vs 42.0%, adjusted OR (AOR) 1.90; 95% CI 1.14 to 3.15) and more common in black than white smokers (57.4% vs 45.1%, AOR 1.67; 95% CI 1.00 to 2.79). The authors did not find significant differences in prevalence of misperceptions about VLNC across education level, sex, income, Hispanic ethnicity and sexual orientation. Additionally, 23.9% of smokers reported that they would be less likely to quit smoking if the government required tobacco companies to remove most of the nicotine from cigarettes. Compared to smokers who believed VLNC cigarettes were equally or more harmful than normal nicotine content cigarettes, smokers who believed VLNC cigarettes were less harmful were more likely to report that they would be less likely to quit smoking if a nicotine standard was put in place (32.0% vs 15.8%, $p < 0.01$). Limitations of this study are that the authors used a hypothetical situation to frame the questions about VLNC use; predicting behaviors in hypothetical situations may not provide an accurate representation of actual behaviors.

Byron et al. (2019) conducted a between-subjects online experiment to examine how different ways of describing VLNC cigarettes affect ratings of perceived nicotine content, perceived addictiveness, and perceived risk. Participants (N= 1353) were randomly assigned to view one of seven descriptions of a potential FDA product standard mandating lower nicotine levels. The control description used language from FDA's wording in press releases to describe VLNC ("Imagine if tobacco companies were required to lower the nicotine in cigarettes to a minimally or non-addictive level."); the other six descriptions varied different message characteristics, including amount and type of information included in the description. Participants were recruited via Mturk; inclusion criteria included over age 18 who resided in the US. The majority of the participants were white (81%) and were not current smokers (78%). Compared to the control message, the percentage description resulted in more accurate perceptions about nicotine content (76% vs. 49% accuracy) and addictiveness (44% vs. 34%), but less accurate perceptions about cancer risk (56% vs. 68%). Messages that included additional information such as images or explanation to the percentage description did not significantly improve accuracy in nicotine content, perceptions of addictiveness, or perceptions of cancer risk for VLNC. Compared to the control message, the concise language description reduced accuracy of perceived nicotine content and addictiveness but increased accuracy of

cancer risk perceptions. One limitation is the inability to generalize to a wider population due to convenience sampling procedures.

Connolly, Behm, Healton, and Alpert (2012) conducted a cross-sectional survey of US adults regarding their opinions on the FDA's regulation of cigarettes and nicotine. Random-digit dialing was used to recruit a sample of American adults who were representative of the contiguous United States. Participants (N = 1021) completed a telephone survey that included measures of demographics and degree of support of several hypothetical tobacco policies. Cigarette users were oversampled and represented approximately half of participants. Approximately 42% of participants either agreed or strongly agreed that cigarettes should be banned in the US in the next decade. Approximately 43% of participants supported the FDA in immediately decreasing nicotine in all cigarettes, approximately 22% supported the FDA in gradually decreasing nicotine in all cigarettes over fifteen years, approximately 13% felt the FDA should conduct further research before deciding whether to decrease nicotine in cigarettes, and 22% felt that the FDA should take no action regarding nicotine in cigarettes. Approximately 77% of participants would support the FDA in reducing nicotine in cigarettes if the policy would result in fewer children being addicted to smoking. Participants who did not use tobacco were more likely than participants who used cigarettes to support reducing nicotine in cigarettes (OR 1.94; 95% CI 1.35, 2.79), and were more likely than cigarette users to support reducing nicotine in cigarettes if it could cause fewer children to become addicted (OR 1.55; 95% CI 1.02, 2.35). Limitations include the inability to assess for causal relationships when using cross-sectional study designs.

Cummings et al. (2004) conducted a supplementary analysis of their nationally representative, cross-sectional survey of adult current cigarette uers to assess whether there were significant differences in beliefs about nicotine harms between cigarette users who smoked Marlboro Lights and those who smoked other brands. A nationally representative sample of participants (N = 1046) were recruited via random digit dialing. Data were gathered via a questionnaire administered over the telephone and were weighted to the demographic distribution of adult smokers in the US as per the US Department of Commerce. Analyses were restricted to measures related to knowledge and beliefs about low tar cigarettes for Marlboro Lights users (n = 192), other ultralight cigarettes users (n = 142), other light cigarettes users (n = 205), and full-flavor cigarette users (n = 490). Approximately 50% of Marlboro lights users reported believing, incorrectly, that reduction of nicotine makes cigarettes less dangerous to smokers, as compared to approximately 48% of ultralight users, approximately 50% of other light cigarette users, and approximately 46% of full-flavor cigarette users. None of these

differences were statistically significant. Limitations include the inability to assess for causal relationships when using cross-sectional study designs.

Cummings et al. (2004) conducted a cross-sectional survey of adult current cigarette smokers to assess smoking history, beliefs about the health risks of smoking, and the safety and effectiveness of nicotine replacement therapy. A nationally representative sample of participants (N = 1046) were recruited via random digit dialing. Data were gathered via a questionnaire administered over the telephone and were weighted to the demographic distribution of adult cigarette users in the US as per the US Census Bureau. Approximately 40% of participants reported having ever used any smoking cessation medication. Approximately 92% of participants correctly identified that nicotine is present in cigarette smoke. Approximately 54% of participants reported believing, incorrectly, that the reduction of nicotine makes cigarettes less dangerous to smokers. Approximately 67% of participants endorsed the incorrect statement that nicotine causes cancer and approximately 37% endorsed the incorrect belief that low nicotine cigarettes are less addictive. Fewer than half of participants correctly identified that nicotine patches and gum are less likely to cause addiction than cigarettes, while 65% reported incorrectly believing that nicotine is either as likely or more likely than cigarettes to cause heart attacks. Approximately 73% of participants endorsed the statement that it is easy to get addicted to nicotine gum. Limitations include the inability to assess for causal relationships when using cross-sectional study designs.

Denlinger-Apte, Joel, Strasser, and Donny (2017) conducted a within-subject experiment to assess adult daily cigarette users' perceptions of the health risks of very low nicotine cigarettes and their predicted future behavior if only very low nicotine cigarettes were available. Participants (N = 68) were recruited from the Pittsburgh community. The sampling frame and method of recruitment were not specified by the authors. Inclusion criteria included being at least 18 years of age, smoking at least 10 CPD, and an expired carbon monoxide level of at least 8 ppm or a urine cotinine level > 100 ng/mL. Exclusion criteria included significant medical changes in the precious week, currently seeking smoking cessation treatment, alcohol intoxication at time of visit, and current pregnancy or breastfeeding. Participants completed baseline questionnaires and then smoked two Quest 3 cigarettes with identical nicotine yields (0.05 mg), but were informed that one cigarette had an average level of nicotine and the other a very low level of nicotine. Participants reported smoking a mean of 16.53 CPD, with a mean of 21.95 years of daily smoking. The cigarette participants were told had very low nicotine, was rated as having significantly lower nicotine than the other identical cigarette that was described as having an average level of nicotine. Participants rated the "very low" cigarette as being significantly less risky than the "average" cigarette in terms of both overall health and every

specific disease risk assessed, including risk for lung cancer, other cancer, heart disease, stroke, emphysema, chronic bronchitis, and addiction. No significant interactions were observed between nicotine content expectancy and gender or menthol preference and any of the health risks assessed. Participants rated the "very low" cigarette as being less satisfying, rewarding, and enjoyable than the "average" cigarette; however, no interaction was observed between nicotine content expectancy and craving reduction. A significant interaction was observed between nicotine content expectancy and gender in terms of respiratory enjoyment, with males enjoying the "average" cigarette significantly more than females. In terms of future behavior, participants were significantly more likely to predict being abstinent from cigarettes in one month and five years if only very low nicotine cigarettes were available. Limitations include the possibility that expectancies may be short-lived or may change with ongoing exposure to very low nicotine products; the lack of cigarette packaging stimuli in the study, which may modify consumer experience; and the imprecision of asking participants to predict their own behavior in five years.

Delinger-Apte et al. (2019) examined how using VLNC cigarettes for an extended period (6 weeks) affected participant support for a nicotine reduction policy, and what characteristics and responses to VLNC cigarettes were associated with support. Data were collected during a double-blind, randomized trial that included a baseline usual-brand (UB) smoking phase followed by randomization to 6 weeks of use of usual brand cigarettes or one of six SPECTRUM® research cigarette conditions varying in nicotine content, which were mentholated or non-mentholated according to preference. At baseline and week 6, the authors measured support for a nicotine reduction policy, perceived risks of developing seven tobacco-related diseases using the Perceived Health Risk Scale (PHRS). At baseline (N = 360), 59% of participants supported a nicotine reduction policy, 18% opposed and 23% responded Don't Know. At week 6 (n = 333), 50% of participants in the VLNC condition supported the policy, 26% opposed and 24% responded Don't Know, whereas 55% the usual brand condition supported the policy, 20% opposed and 25% responded Don't Know. Responses at week 6 did not differ by condition. Among those in the VLNC condition who had supported the policy at baseline, 69% continued to support the policy, 15% opposed and 16% indicated Don't Know at week 6. Among those in the usual brand condition who had supported the policy at baseline, 78% continued to support the policy, 6% opposed and 16% responded Don't Know at week 6. Support at week 6 was lower among non-adherent VLNC smokers (71 out of 163; 44%) compared with adherent smokers (37 out of 57; 65%). Support was higher among those adherent to smoking only VLNC cigarettes (65%) compared with those who were non-adherent to smoking only VLNC cigarettes (44%). Older participants and those interested in quitting smoking were more likely to support VLNC. No other covariates were significantly associated with supporting the proposed nicotine policy. Limitations include possible bias because participants were told at the time of recruitment that the study was designed to examine VLNC cigarettes; therefore, people with

existing attitudes and knowledge of VLNC cigarettes may have been oversampled. Additionally, adherence to the VLNC cigarette treatment was low; therefore, people in that condition may systematically differ from those who did not maintain the VLNC regimen. The VLNC sample was relatively small and was not nationally representative.

Denlinger-Apte et al. (2019a) conducted an experiment to examine how smoking cigarettes with different nicotine and menthol contents affected cigarette users' perceived likelihood of developing tobacco-related diseases and cigarette liking. Participants were adolescent cigarette users aged 15–19 (N = 50; Mean age= 17.7 years; 50% of sample female; Mean cigarettes per day = 8.3, SD= 4.6). During each of four experimental sessions, participants smoked one unlabeled research cigarette with 0.4, 1.3, 5.2, or 15.8 mg nicotine per g of total tobacco. Immediately after smoking the research cigarette, participants completed a Perceived Health Risk Scale (PHRS) and Cigarette Evaluation Scale (CES) to rate their perceived likelihood of developing tobacco-related diseases and subjective cigarette effects.. The authors reported statistical comparisons between the 0.4 mg (VLNC) and 15.8 mg (normal nicotine content) nicotine per g of total tobacco. Participants reported significantly lower perceived risk of lung related diseases and cancer for VLNC cigarette compared to the NNC cigarette; the difference between perceived risk of VLNC and NNC for addiction and stroke was not significant. Participants reported significantly reduced CES scores for VLNC cigarettes compared to NNC cigarettes. Overall, adolescent cigarette users have inaccurate perceptions that VLNC cigarettes are lower in risk for developing tobacco-related diseases when they are introduced to VLNC cigarettes under double-blind conditions. Limitations include concerns about generalizing to the general population of adolescents in the US and a small sample size that prevented researchers from testing potential interactions of menthol preference or gender.

Denlinger-Apte et al. (2021a) conducted a secondary analysis of wave 4 of the PATH study (2016-17) to describe overall trends in risk perceptions of nicotine, VLNC cigarettes, and alternative nicotine delivery systems (ANDs including NRT, and e-cigarettes) as well as examining trends by racial/ethnic, sexual orientation, and gender identity groups. They restricted their sample to respondents who reported current established cigarette use, but no established non-combustible tobacco product use (n = 8340). The majority of participants perceived nicotine to be "somewhat" or "extremely" harmful, with 63.83% reporting that it "probably" or "definitely" causes cancer and 81.89% believing that it is "probably" or "definitely" addictive. The majority of participants believed that VLNC cigarettes had about the same level of addictiveness as a regular cigarette. Between 12.38% and 25.53% of respondents across racial categories had a misperception of the harmfulness of VLNC cigarettes relative to regular nicotine cigarettes. This rate was significantly higher for Asian respondents compared to white respondents. Misperceptions related to nicotine causing cancer were higher among Black (78.41%), Asian (69.53%) and Hispanic/Latino (60.18%) respondents compared to white respondents. They also found evidence of misperceptions by sexual orientation. Gay and Lesbian respondents had fewer misperceptions about the addictiveness of VLNC cigarettes

compared to straight respondents. Bisexual respondents had fewer misperceptions about nicotine and cancer but a higher rate of misperceptions about nicotine and addiction. Limits of this study include its cross-sectional design that limits the ability to draw causal conclusions and does not allow for an exploration of trends over time.

Denlinger-Apte et al. (2021)b conducted a qualitative interview study to explore participants' perceptions, beliefs, and attitudes about VLNC and FDA nicotine reduction policy after using very low nicotine content (VLNC) cigarettes. Participants (N = 16) were first assigned to exclusively smoke NNC cigarettes (Spectrum cigarettes containing 15.5 mg nicotine/g tobacco) for one week and were told that the NNC cigarettes had nicotine levels similar to commercially available cigarettes. Then participants were assigned to exclusively smoke VLNC cigarettes (Spectrum cigarettes containing 0.4 mg nicotine/g tobacco) for one week and were told that the VLNC cigarettes had 97% less nicotine compared to the NNC cigarettes. Participants anticipated that they would have compensatory smoking when using the VLNC cigarettes; however, the majority of participants reported that they smoked the same amount or less when using VLNC cigarettes compared to when they were using NNC cigarettes. A few participants attempted to compensate for the lower nicotine levels by increasing their smoking early in the VLNC week but reported tapering down over time. Some participants believed that FDA is interested in limiting the allowable nicotine content in cigarettes because nicotine is the primary addictive constituent in cigarettes; however, others had inaccurate comprehension regarding nicotine as a harmful constituent in cigarettes, independent of its addictive properties. When presented with the hypothetical scenario that only VLNC cigarettes were available to purchase in the US, most participants said they would smoke VLNC cigarettes, several predicted they would use VLNC cigarettes to reduce their smoking over time until to eventually quit, some participants discussed both combusted and non-combusted products as potential substitutes, and a few participants discussed purchasing conventional cigarettes from potentially illicit sources. Limitations include a design that depended on self-report to confirm cigarette use in the NNC vs VLNC conditions, lack of double-blinding cigarette conditions that may have introduced demand characteristics, and a small sample size that limits generalizability.

Denlinger-Apte et al. (2021)c conducted a double-blind experiment to determine whether the immediate or gradual reduction of nicotine influences support for a low nicotine policy among cigarette users. They recruited a convenience sample (N = 1250) current daily cigarette users from the communities surrounding 10 US academic institutions. Their sample was 44% female, had an average age of 45.1, was majority white (61%), and used an average 17.1 cigarettes per day. Participants were randomly assigned into three groups; one that immediately started smoking VLNC cigarettes, one that smoked cigarettes that gradually reduced their level of nicotine intake over a 20-week period, and a control group smoking NNC cigarettes. Individuals were asked about their support for a low nicotine policy at baseline and at week 20. Denlinger-Apte et al. found that 58% of participants supported a low nicotine policy

at baseline while 60% supported it at week 20. There was no difference in policy support across the treatment or control groups. Over 80% of respondents that supported the policy at baseline continued to support it at week 20 and 23% of respondents that initially opposed the policy supported it by week 20. While the treatment showed no effect, cigarette users that were interested in quitting and those with higher cigarette risk perceptions were more likely to support the policy. Younger participants and males with higher cigarette dependence scores were less likely to support it. Limitations of this study include the fact that it uses a convenience sample that may not be representative of all US cigarette users. Additionally, attrition was higher in the immediate reduction condition relative to the gradual and control conditions, which may have affected the causal effects estimate.

Differding et al. (2022) conducted an experiment in which they randomized participants to view one of six messages designed to describe the nicotine product standard. Participants (N = 1200) were recruited from MTurk and were stratified by cigarette use status (smoking/nonsmoking) and education (college degree/no college degree) such that each treatment group received an equal number of smokers with a high level of education, smokers with a low level of education, and nonsmokers with both levels of education. Each participant was randomly assigned to view one of six messages describing a low nicotine policy. The control condition stated that manufacturers would be required to remove 95% of nicotine from cigarettes. The other message conditions added information about the addictiveness of nicotine, the addictiveness of VLNC cigarettes, the harm of VLNC cigarettes, the impact of the standard on youth experimentation, or a combination of these pieces of information. They found that participants who viewed messages that included information about the addictiveness and harm of VLNC cigarettes were less likely to believe that nicotine and VLNC cigarettes caused cancer and that VLNC cigarettes were safer than NNC cigarettes. However, interest in using VLNC cigarettes, support for low nicotine policies, and the proportion of cigarette users that would quit under a low nicotine standard did not vary across the different message treatment groups. The limitations of this study include that it used an online sample of convenience which limits its external validity. It also did not use a general control message so we cannot get a sense of how these different messaging strategies compare to a group that receives no message at all.

Dunsby and Bero (2004) conducted a review of internal tobacco industry documents to understand the industry's perspective regarding the marketability of low nicotine tobacco products. Documents were retrieved from the Legacy Tobacco Documents Library, Tobacco Documents Online, industry websites, Lexis-Nexis, and PubMed between 2002 and 2004. Results yielded industry documents indicating that consumers associate nicotine content with the perceived harmfulness of the product and conflate the health effects of tar and nicotine. Furthermore, industry documents indicated that reduced nicotine cigarettes would be marketable to consumers seeking a less harmful cigarette or to quit smoking, potentially

creating a new market segment and expanding sales. Older female smokers and young adults who smoke occasionally were identified as the populations most likely to be receptive to reduced nicotine cigarettes. Industry identified poor taste, reduced throat sensations, and the potential for smokers to no longer be addicted to nicotine and quit smoking as challenges to the profitability of reduced nicotine cigarettes. Maintaining or increasing tar yield was identified as a strategy to improve the negative effect on taste caused by nicotine reduction.

Duong et al. (2022) conducted 16 focus groups to examine effective message strategies to communicate about VLNC cigarettes across four key target audiences: exclusive cigarette users (n = 27), dual cigarette/e-cigarette users (n = 25), former cigarette users (n = 32), and young adult (18-30 y.o.) non-users (n = 31). All participants viewed eight messages that fell into four categories: efficacy messages that were positively framed to increase perceptions of quitting efficacy, risk messages that addressed the misunderstanding that VLNCs are less harmful than regular cigarettes, messages about alternative sources of nicotine for those who find it hard to quit nicotine, and a compensation message that addressed beliefs about compensatory smoking. Two coders analyzed focus group transcripts and extracted themes related to ratings of message effectiveness, attitudes toward the message, and behavioral intentions after viewing the message. Exclusive cigarette users viewed the risk messages and efficacy messages as the most effective, and dual users were the only group that was receptive to the message about alternative sources of nicotine. Former cigarette users and non-users were critical of messages emphasizing positive aspects of VLNC cigarettes that seemed to encourage relapse for former cigarette users or smoking initiation among youth, and messaging that might increase incorrect beliefs that alternative tobacco products are harmless. Limitations include a small sample size with limited generalizability.

Fix et al. (2011) analyzed baseline data from the International Tobacco Control (ITC) United States Supplemental Survey to assess US cigarette users' knowledge and attitudes towards tobacco regulation by the FDA. The ITC is a longitudinal, nationally representative telephone survey. Participants (N = 678) were recruited via random digit dialing. Individuals who were at least 18 years of age, reported being daily smokers of at least 10 cigarettes per day, and reported the variety of cigarette they used and type of location where they purchased these products were eligible for inclusion in the study. Data were gathered via a questionnaire administered by telephone. Three measures were specifically focused on the regulation of nicotine. Approximately 67% of participants reported that they would support a law that reduced the amount of nicotine in cigarettes in order to make cigarettes less addictive, provided that nicotine was made easily available in a non-cigarette form. Males were significantly more likely to support this law than females. Approximately 30% of participants

reported that they would support banning cigarettes altogether if nicotine were made easily available in non-cigarette form. Approximately 19% of participants reported that they would support a law that banned tobacco products completely if nicotine were made easily available in non-cigarette form. Low income participants were significantly more likely than moderate or high income participants to support this law. Limitations include the inability to assess for causal relationships and the imprecision of asking participants to predict their own attitudes towards future, hypothetical regulatory action.

Hatsukami et al. (2013) conducted two experimental studies that primarily examined whether cigarettes of varying nicotine contents produce dose-response effects. The first study is relevant to this review because it examined how participants perceived the health risk posed by low, intermediate, and high nicotine cigarettes, respectively. Participants (N = 51) were recruited at three sites – University of Minnesota, University of Pittsburgh, and NIDA Intramural Research Program – via convenience sampling using advertisements and recruitment of participants from previous studies. Eligibility criteria included being 18-64 years of age, smoking at least 10 CPD, an expired CO of at more than 10 ppm, inhaling when smoking, using non-cigarette forms of tobacco less than 10 of the last 30 days, not planning to quit or reduce smoking, not using nicotine replacement therapy, bupropion, or varenicline in the last three months, being in good health, not being pregnant, and not taking certain medications or illicit drugs more than twice a week for the last month. Participants rated the high nicotine cigarettes (0.6 mg yield) as having a significantly higher risk of addiction as compared to the low (<0.04 mg yield) and intermediate nicotine (0.3 mg yield) cigarettes. Participants perceived low nicotine cigarettes as being significantly less likely to cause lung cancer, emphysema, bronchitis, other cancers, heart disease, and stroke as compared to high nicotine cigarettes. Participants perceived low nicotine cigarettes as being significantly less likely to cause lung cancer as compared to intermediate nicotine cigarettes. Limitations include inability to generalize to the wider population of interest due to convenience sampling, as well as small sample size.

Henderson et al. (2022) reported the results of a focus group study conducted in 2020 (see Loud et al. 2020 for methods) that examined people's perceptions of the reduced nicotine policy, beliefs about nicotine, and responses to messages about VLNCs and nicotine reduction policy. Henderson et al. focuses on focus-group participants' perceptions the nicotine reduction policy, which were recorded either after exposure to a specific message or during the final part of the focus group. Positive reactions to the policy included hope that it would help current cigarette users quit smoking by taking away the addictive components of cigarettes. Negative or neutral reactions to the policy included concerns about the intent behind the policy, concerns about the feasibility and adoption/ implementation of the policy; and concerns about

the effectiveness of the policy in reducing cigarette consumption. Concerns about the intent behind the policy included fears that the policy represented too much government control and that the actual goal was to protect the tobacco industry. Concerns about the feasibility of the policy included beliefs that it is not possible to remove nicotine from cigarettes or confusion about why the policy would remove nicotine but not other harmful chemicals. Concerns about the effectiveness of the policy included perceptions that VLNC cigarettes would still be addictive, that VLNC cigarettes would encourage people who smoke to smoke more to compensate for the reduction in nicotine; and that VLNC cigarettes would encourage people who quit to relapse and people who don't smoke to initiate smoking. Limitations of this study include those inherent in qualitative study designs (small convenience sample that reduces the generalizability of findings) and lack of detailed reporting about the prevalence of each theme in the focus group sample.

Hsu and Grodal (2015) examined industry documents, including product advertisements, to understand how industry perceived and sought to influence consumer perceptions of light cigarettes. Documents dated from 1964 through 1993 were retrieved from the Legacy Tobacco Documents Library. Results yielded evidence indicating industry was aware that consumers associated both tar and nicotine with harm, and conflated the health effects of these two substances. Reduction of both tar and nicotine had negative effects on taste, and industry was concerned that too great a reduction in nicotine would result in smoking cessation among consumers. In response to this, industry compensated the poor taste resulting from tar reduction by increasing nicotine content in light and ultralight products. Industry also sought to differentiate tar and nicotine in the minds of consumers, increasing marketing information about tar reduction while decreasing marketing information about nicotine. As light cigarettes began claiming an increasing market share, industry became aware that consumers viewed nicotine and tar as categorical rather than continuous variables, i.e., light vs. regular, and that these categories were a cognitive shorthand for healthier vs. less healthy, respectively. In response, companies competed to have the highest tar and nicotine contents within the light and ultralight product categories in order to provide consumers with maximum taste and satisfaction while still maintaining consumer perceptions that the products were less harmful.

Jackson et al. (2022) conducted a secondary analysis of the cross-sectional and nationally representative health information national trends survey (HINTS) to assess the relationship between beliefs about nicotine, VLNC cigarettes, and e-cigarettes on cigarette and e-cigarette use behavior. They explored this in the larger population, by tobacco use status, and by cancer survivor status. Respondents were asked to evaluate their beliefs about the addictiveness, cancer causing potential, and concerns about nicotine as well as their

perceptions of how harmful and addictive VLNC cigarettes are compared to NNC cigarettes. Jackson et al. found that 52% of cigarette users and 46% of e-cigarette users think nicotine causes cancer. The overwhelming majority in both groups agreed that nicotine is addictive and are concerned about nicotine addiction. Additionally, 77% of cigarette and e-cigarette users believed that low nicotine cigarettes were just as harmful or more harmful than conventional cigarettes, and a similar proportion believed that they were equally or more addictive. Cancer status did not change these proportions much across either tobacco use group. Those that believe nicotine causes cancer were 70% less likely to be ever users of NNC cigarettes than never cigarette users. However, concerns about nicotine addiction, and beliefs that LNCs are addictive were associated with a higher odds of ever smoking. Concerns about nicotine addiction and beliefs that LNCs are addictive were associated with a higher odds of using e-cigarettes. Beliefs about e-cigarette harm were associated with a lower odds of use. The results for cancer survivors were very similar for those of the overall population. Individuals with a cancer history who believe that nicotine causes cancer were 51% less likely to be ever cigarette users than never cigarette users. Limitations of this study include that it is a cross-sectional analysis and thus cannot be used to determine causal relationships. In particular, it is difficult to determine whether attitudes about nicotine, VLNC cigarettes, and e-cigarettes cause tobacco use behavior rather than the other way around.

Johnson et al. (2019) conducted a between-subjects experiment to examine how explicit risk message content (e.g., warning labels) and implicit risk message content (e.g., package color) affected advertisement content recall, product beliefs, and use intentions for previously commercially available reduced nicotine cigarettes (Quest cigarettes). Young adult cigarette users aged 18–30 years (N= 426) completed a brief online survey that randomly assigned participants to view cigarette advertisements that varied in (1) implicit product risk information (red packaging, blue packaging) and (2) presence of explicit corrective message about nicotine-free products (yes, no). After exposure to the cigarette advertisement and prior to answering additional questions, participants responded to an open-ended prompt asking them to recall characteristics of the product they had just viewed. Recall scores were higher for red packs compared to blue packs; participants had more correct responses to recall questions, had greater recall for warning messages, and were more likely to remember that cigarettes contained nicotine in the red pack condition with a corrective message. However, there was no main or interaction effects of package color or the corrective message on product beliefs or use intentions. Limitations includes concerns about generalizability due to small convenience sample that was not nationally representative; the sample size was small enough in each experimental condition to merit caution when interpreting these results.

Kaufman et al. (2011) conducted a cross-sectional survey assessing potential relationships between believing that the FDA evaluates cigarettes for safety and smoking risk perceptions. A nationally representative sample of adult current cigarette users (N = 1046) was recruited via random digit dialing. Data were weighted to align to the age, race, and gender distribution of adult smokers in the US as per the Tobacco Use Supplement to the Current Population Survey. Approximately 46% of participants did not believe that FDA evaluates cigarettes for safety before they can be sold to consumers, 10% of participants did not know if FDA evaluates cigarettes for safety, and 44% of participants believed that the FDA evaluates cigarettes for safety. Participants who were unsure or endorsed this belief that FDA evaluated cigarettes for safety were significantly more likely to endorse inaccurate health beliefs about cigarettes, to express lower intentions to quit, and to expect to be able to avoid harm to their health as a result of smoking as compared to participants who did not believe that the FDA evaluates cigarettes for safety. Approximately 67% of participants reported believing that nicotine causes cancer; this belief was not significantly associated with beliefs about whether the FDA evaluates cigarettes for safety. Mediational analyses found that FDA evaluation belief may influence risk perceptions rather than vice versa. Limitations include the inability to assess for causal relationships when using cross-sectional study designs and the imprecision of asking participants to predict their own future quitting behavior.

Kemp et al. (2018) analyzed results from a nationally representative cross-sectional survey to understand adults' perceptions of the harms of nicotine to children and to identify sociodemographic factors related to inaccurate risk perceptions. Participants who responded to all survey questions (Tobacco Products and Risk Perceptions Survey, 2015, 2016; n = 11948) were included in the analysis. The majority (83.2%; 95% CI: 82.3%–84.1%) of adults characterized the amount of nicotine usually found in tobacco products as definitely harmful to children; (6.2% (95% CI: 5.7%–6.8%)), as maybe harmful, 1.7% (95% CI: 1.3%–2.0%) as unlikely harmful, 0.6% (95% CI: 0.4%–0.8%) as not harmful, and 8.3% (95% CI: 7.6%–9.0%) responded that they don't know how harmful nicotine is to children. Race and/or ethnicity, education, sex, and tobacco use status were associated with significant variation in perceptions of nicotine harm to children. For example, African American non-Hispanic individuals, Hispanic individuals, and "other" non-Hispanic individuals had significantly lower odds of endorsing "definitely harmful" or "maybe harmful" than white individuals. In addition, respondents with either less than a high school diploma, a high school diploma, or some college were significantly less likely to perceive nicotine as being definitely harmful to children compared with those with a bachelor's degree or higher. Compared with women, men had significantly lower odds of characterizing nicotine as definitely harmful to children. In addition, adults who use tobacco

products were significantly less likely to state that nicotine is harmful to children compared with adults who did not use tobacco products. Limitations for this study include that the questions assessed harm perceptions of nicotine for children under 13 years old but did not examine how harm perceptions varied by nicotine product type. Therefore, it is unclear whether participants' responses can be generalized across different modes of nicotine exposure that are inherent in different nicotine products.

Kulak et al. (2020) conducted an experiment to study question framing and order effects when estimating support for a low-nicotine policy. They used Prime Panels to recruit a sample of 540 US adults who were asked two questions measuring their support for a policy that would reduce the level of nicotine in cigarettes. The first used a Likert-scale (one more general and one more specific) asking them to evaluate their support on a scale from strongly oppose to strongly support. They were also asked to indicate their preferred policy from a discreet list of four options ranging from a system in which low and no-nicotine cigarettes would be available along with conventional cigarettes to one in which cigarettes would contain no nicotine at all. To determine ordering and question type effects participants were randomized such that some viewed more supportive options first, while others viewed opposing options first. Although it had no impact, respondents were also randomized to view a more general or specific Likert-scale question. They found that response order mattered when estimating support for a low-nicotine policy and 61.8% of respondents strongly supported the policy when support options were presented first, while only 46.2% strongly supported the policy when opposing options were presented first. They used responses to these two questions to create an overall measure of support (despite respondents viewing different versions of the two questions) and they found that support for a low-nicotine policy varied by smoking status and race/ethnicity. Current cigarette users were significantly less likely to support the policy than others, while Black, Non-Hispanic participants were significantly more likely to support the policy. Limitations of this study include an inability to generalize to the wider US population due to convenience sampling, as well as small sample size particularly for some racial/ethnic categories.

Levy et al. (2021) conducted a search of public patents and industry documents to examine when cigarette manufacturers first had the technical capability to reduce the nicotine of cigarettes they produced and to quantify what impact cigarette manufacturers had on public health by choosing to produce and market highly addictive cigarettes rather than switch production to VLNC cigarettes. The authors conducted a systematic search of internal tobacco industry document electronic archives Truth Tobacco Document Library using a keyword search and a snowball search. The authors identified patents and internal company documents that describe methods to extract nicotine from tobacco dating back to the 1920s and 1930s. Additionally, the authors identified internal company documents that describe the design

objective of ensuring a minimum amount of nicotine in cigarettes to ensure that cigarettes could create and sustain nicotine dependence from the 1960s to 1980s. The authors conclude that the industry did not use internal information about the harms of cigarettes and the ability to lower nicotine content to start producing very low nicotine, less addictive cigarettes; instead, companies chose to produce and market cigarettes designed to show reduced nicotine and tar yields via smoking machines but engineered in ways that allowed cigarette users to easily compensate to obtain enough nicotine. These choices were made so that cigarettes on the market would remain addictive and difficult to quit, thus ensuring more sales for companies.

Lin and Muscat (2021) conducted a secondary analysis of the nationally representative health information national trends survey (HINTS) to assess knowledge and beliefs about nicotine, VLNC cigarettes, and e-cigarettes by tobacco user type. They used data from Cycle 3 of HINTS collected between January and April 2019 (N = 5,438). They excluded former cigarette users and exclusive e-cigarette users to reach a final sample of 3113 people who did not use cigarettes, 302 exclusive cigarette users, and 77 dual users. They found that more than 83% of people who did not use cigarettes, more than 83% of exclusive cigarette users, and 97% of dual users know that nicotine is addictive. The dual user group had the highest percentage of respondents that correctly responded that nicotine did not cause cancer (40.40%) while the non-user group had the lowest percentage of correct answers (15.75%). Additionally, 22.47% of non-users reported that they did not know if nicotine caused cancer. Researchers also found that all three user groups equally report believing that VLNC cigarettes are equally addictive to regular cigarettes. Limitations of the study include that data are cross-sectional in nature and do not permit causal inferences.

Ling and Glantz (2019) conducted a search of the industry documents to examine strategies tobacco companies have used to fund and conduct scientific research related to potential benefits of nicotine, and to use their findings to promote nicotine. The authors conducted a systematic search of internal tobacco industry document electronic archives Truth (formerly Legacy) Tobacco Document Library between June 2013 and December 2017, using a keyword search, a snowball search, and triangulating with PubMed research studies. They reported that tobacco companies and their industry-funded scientific collaborators have consistently implemented strategies to promote benefits of nicotine to scientific and general audiences while minimizing its health risks. RJR and other major cigarette companies worked to shift the debate on tobacco from the addictive qualities of nicotine and the adverse health effects of smoking to purported physiological benefits from nicotine, which RJR believed would counter declining cigarette sales and improve the industry's image. Strategies for promoting benefits of nicotine included explicitly comparing it to caffeine and coffee in terms of risk to health and in its utility as a stimulant and aid to cognition and mood. The review also reported

that messages highlighting positive aspects of nicotine similar to messaging promoted by the tobacco industry in the 1980s and 1990s, continued to appear in popular media in the 2000s.

Lochbuehler et al. (2016) conducted an experimental study utilizing a between-subjects design to assess whether alterations in explicit and implicit claims in a cigarette advertisement results in changes in knowledge and risk beliefs in consumers. Participants (N = 203) were recruited via advertisements and were eligible for inclusion if they were smoking a minimum of 10 non-menthol CPD for a minimum of five years, not currently trying to quit or intending to do so in the next two months, had a breath carbon monoxide level of at least 5 ppm, were aged 21-65, were fluent speakers of English, were not currently abusing other substances, and had no visual impairments. Participants were assigned to one of four conditions, each a version of a Quest product advertisement. Eye movements were measured via an eye tracking device while participants were viewing stimuli. Risk beliefs and recall measures were assessed following viewing of stimuli. Participants who were exposed to the corrective statement, "Nicotine free does not mean risk free. Quest contains as much tar as a light cigarette," were significantly less likely to endorse false beliefs about the harmfulness of the product. Limitations include the inability to generalize to the wider population of interest due to convenience sampling and the use of a single print advertisement, which may not replicate the diversity of ways in which consumers may interact with product advertising outside of a study setting.

Mercincavage et al. (2017) conducted a randomized controlled trial in which participants' advertisement beliefs, subjective ratings, and smoking behaviors were assessed before and after exposure to Quest 1 (0.6 mg nicotine) cigarette advertisements and a 10-day period of Quest 1 use. Participants (N = 77) were recruited from the Philadelphia area via digital and print advertisements or were former participants of previous studies. Eligibility criteria included being at least 21 years of age, exclusively smoking at least 15 non-menthol filtered CPD, a regular smoking history of at least five years, and no plans to quit within the next two months. Exclusion criteria included drinking at least 25 alcoholic drinks per week, current use of marijuana or nicotine containing products other than cigarettes, a self-reported history of any psychiatric condition except depression, a myocardial infarction in the last year, a substance use disorder in the past five years, current pregnancy or lactation, or an initial CO level of less than 10 ppm. After exposure to a Quest advertisement, participants reported significantly higher mean ratings in support of the beliefs that Quest cigarettes are lower in nicotine and are healthier than regular cigarettes, as well as significantly lower mean ratings in support of the belief that Quest cigarettes are less likely to cause cancer. Subjective ratings for Quest cigarette strength and taste were significantly positively associated with inaccurate health beliefs, including that Quest cigarettes are safer, healthier, less likely to cause cancer, and help people

quit smoking, counter to study hypotheses. Limitations include the inability to generalize to the wider population of interest, given the use of convenience sampling, the small sample size, and, as noted by the researchers, the failure to correct for family-wise error when making multiple comparisons.

Mercincavage et al. (2019) analyzed baseline survey responses collected before two separate experiments to assess risk perceptions of reduced nicotine content (RNC) cigarette and their correlates of those perceptions. Participants included in this analysis were cigarette users naïve to RNC cigarettes (mean age 43.44 years old, who participated in either a study of cigarette packaging (n = 177) or a study on warning labels (n = 323) unrelated to RNC cigarettes). The majority were male (63.0%) and non-Hispanic (96.4%); 48.4% identified as White and 51.8% had completed some college or technical training as their highest level of education. Prior to completing the risk perception questionnaire, participants received no preamble or background information related to a federal nicotine reduction policy to avoid influencing their subsequent responses. Most participants endorsed correct responses for risk perception items; however, participants endorsed the perception items that RNC cigarettes are less addictive and make it easier to quit as incorrect (63.4% and 51.0% respectively). Race was associated with incorrect perceptions of multiple RNC cigarette risks: Non-White cigarette users were more likely than White cigarette users to incorrectly perceive RNC cigarettes as safer, healthier, and having less tar than regular cigarettes, and safer than high nicotine cigarettes even if you do not quit. Men were more likely than women to be unsure about the perception that RNC cigarettes have less tar than regular cigarettes. Older age was associated with greater likelihood of being incorrect about the less addictive and less tar items. Education and nicotine dependence were not associated with any RNC risk perception items. Limitations include that the sample was small and not nationally representative; this may decrease the generalizability of these findings.

Mutti et al. (2011) conducted a cross-sectional survey utilizing data from Wave 5 of the International Tobacco Control Policy Four-Country Survey (ITC-4) to assess adult cigarette users' perceptions of risk of different types of cigarettes. Results were provided separately for each country. The ITC-4 recruits a representative, population-based sample of cigarette users via random digit dialing, with N = 2,034 participants from the US included in this study. Approximately 23% of US participants endorsed believing that it is possible for some cigarettes to be less harmful than others, and approximately 40% of US participants endorsed believing that nicotine is the cause of most cancer from using cigarettes. Limitations include the inability to assess for causal relationships when using cross-sectional study designs.

Nguyen et al. (2018) conducted a secondary analysis of the cross-sectional and nationally-representative health information national trends survey (HINTS) to examine tobacco harm and addiction beliefs held by US born and foreign-born respondents. They also examined

the role of race/ethnicity and acculturation in nicotine and addiction beliefs among the foreign-born. Participants in the HINTS-FDA 2015 and HINTS-FDA 2017 cycles (total N = 5474) aged 18 years or older answered self-administered mail surveys. Of the sample, 486 (14%) were foreign-born. Survey items assessed general nicotine beliefs, perception of cigarette addiction, and low nicotine cigarette beliefs. Additionally, respondents rated whether a cigarette advertised as "low nicotine" would: (1) be more or less harmful than a typical cigarette; (2) have lower or higher risk of causing lung cancer than a typical cigarette; (3) be more or less addictive than a typical cigarette; and (4) be believable. Compared to US-born respondents, a higher proportion of those who are foreign-born believed low nicotine cigarettes would have much lower risk (18% foreign-born vs. 2% US-born) of causing lung cancer than a typical cigarette. Among the foreign-born, compared to Non Hispanic-White respondents, Non Hispanic-Black and Hispanic respondents were more likely to believe that an LNC would be more harmful; Non Hispanic-Black and Hispanic respondents were also more likely to believe that LNC would be more addictive than a regular cigarette. In addition, Non Hispanic-Black respondents were less likely to believe that cigarette could be "low nicotine" compared to Non Hispanic-White respondents. Among the foreign-born, those who spoke English "well" were more likely to believe that the nicotine in cigarettes is the substance that causes most of the cancer caused by smoking compared to those who spoke English "very well." Limitations of the study include that data are cross-sectional in nature and do not permit causal inferences. Additionally, the authors excluded "don't know responses" in their analysis of nicotine and addiction belief items; because never cigarette users were more likely to answer don't know responses compared to former and current smokers, never cigarette users may be underrepresented in this analysis.

O'Brien et al. (2017) conducted a cross-sectional study by analyzing a single round of data from the Health Information National Trends Survey (HINTS) to assess US adults' beliefs about LNC cigarettes. HINTS is a nationally representative, probability-based, longitudinal, observational study on American adults' knowledge, attitudes, and use of health information. Participants (N = 3738) were recruited by mailings sent to a random sample of non-vacant residential addresses. Data were gathered via self-administered paper questionnaires. Approximately 83% of participants correctly identified nicotine as the main substance that makes people want to smoke. Approximately 49% of participants incorrectly identified nicotine as the substance that causes most smoking-related cancers. Participants who were 65 years of age or older, identified as black, Hispanic, or other race, who had a high school education or less, and who had never smoked had significantly higher odds of endorsing this incorrect belief. Approximately 64% of participants rated LNC cigarettes as equally harmful to regular cigarettes, while 30% of participants rated LNC cigarettes as less harmful. Participants who were black or quit smokers were significantly more likely to rate LNC cigarettes as more harmful compared to their counterparts. Approximately 65% of participants rated LNC cigarettes as equally addictive as regular cigarettes, while 28% rated LNC cigarettes as less addictive. Compared to white

participants, Hispanic participants perceived LNC cigarettes to be significantly more addictive . Participants with a college or postgraduate education believed the LNC cigarettes were significantly less addictive as compared to participants with a high school education or less. Limitations include the inability to assess for causal relationships when using cross-sectional study designs and a low response rate of 33%.

O'Connor et al. (2005) conducted a cross-sectional survey utilizing data from the US arm of the International Tobacco Control Policy Four-Country Survey (ITC-4) to assess adult cigarette users' knowledge, use, and beliefs of cigarettes that are marketed as being less harmful. The ITC-4 recruits a representative, population-based sample of smokers via random digit dialing. Participants (n = 2028) completed a telephone survey in 2003 comprising measures about knowledge, beliefs, and use of supposedly less-harmful products and smokeless products, as well as demographic information. In response to an open-ended question asking participants if they were able to name a potentially reduced risk cigarette, Quest was the product most commonly named by participants, with 27% of participants identifying it. In terms of use, two participants reported currently using Quest. As Quest is a reduced nicotine product, the researchers argued that this indicates that smokers consider nicotine to be a source of harm. Limitations include the inability to assess for causal relationships when using cross-sectional study designs

O'Connor et al. (2007) conducted a cross-sectional, web-based survey to assess how college students perceive light cigarettes and potentially reduced exposure products (PREPs). Participants (N = 424) were recruited from the psychology department subject pool at the University of Buffalo. Enrollment in an introductory psychology course in the current semester was the sole eligibility criterion. Participants completed a questionnaire that included advertising stimuli for 12 cigarette brands and measures of 28 positive and negative expectancies derived from two validated questionnaires and the relevant literature. Data analyses pooled expectancies into two groups, positive ("satisfying, fun, exciting, interesting, smell good, taste good, friends would like, stimulating, good with a drink, sophisticated, mature, mild, and low tar") and negative ("hard to quit, cause cancer, dangerous, bad breath, stupid, addictive, make me cough, harsh, and make me nauseated"). Participants rated the two PREPs (Quest and Eclipse) as significantly lower in both positive expectancies and negative expectancies than Marlboro Light. Positive expectancies for Eclipse were significantly higher as compared to Quest; no significant differences were observed between the two PREPs in terms of negative expectancies. Limitations include the inability to assess for causal relationships when using cross-sectional study designs, the inability to generalize to the wider population of

interest due to the use of convenience sampling, and the inability to parse out differences for each expectancy measured due to the pooling of variables.

Pacek et al. (2018) examined associations between perceived nicotine content and perceived health risks and smoking outcomes, employing data from a double-blind, randomized trial wherein participants were randomly assigned to smoke cigarettes of varying nicotine contents. Participants (N = 780) were recruited via advertisements in print, TV, radio, and web media. Inclusion criteria included being at least 18 years of age, smoking at least five CPD, and having an expired CO of greater than 8 ppm or urinary cotinine of more than 100 ng/mL. Exclusion criteria included intention to quit smoking in the next 30 days, use of non-cigarette tobacco products on more than nine of the last 30 days, frequent binge drinking, significant or unstable mental conditions, positive illicit drug screen for at least one substance other than cannabis, current pregnancy or breastfeeding, or exclusive use of RYO tobacco. Data on perceived health risks were assessed via questionnaire at baseline and endline, while smoking outcome measures were assessed via an interactive voice response system that automatically called participants daily. Perceived nicotine content was significantly positively associated with perceived health risks of all the diseases assessed, regardless of the actual nicotine content of the cigarettes assigned to participants. Participants who perceived the nicotine content of the study cigarettes assigned to them to be low, medium, or high/very high had significantly higher risk perceptions as compared to participants who perceived the nicotine content of the study cigarettes to be very low. Participants who perceived the nicotine content of the study cigarettes to be very low were significantly more likely to report that they would quit smoking in one year if only the study cigarettes were available as compared to participants who perceived the study cigarettes assigned to them to be low or moderate in nicotine. Limitations include the inability to generalize to the wider population of interest, given the use of convenience sampling, and the imprecision of asking participants to predict their own future quitting behavior.

Pacek et al. (2017) conducted a cross-sectional survey to examine knowledge and beliefs related to smoking and nicotine among adult cigarette users living with HIV. Participants (n = 271) were recruited via Amazon Mechanical Turk (MTurk). Inclusion criteria included having at least a 95% approval rating on MTurk, being at least 18 years of age, residing in the US, ever receiving an HIV diagnosis, having smoked at least 100 cigarettes in their lifetime, and having smoked at least one cigarette in the last month. Data were gathered via a questionnaire that measured demographics, HIV disease history, and smoking characteristics using measures adapted from validated instruments and the relevant literature. The sample was majority male and Caucasian. The majority of participants correctly identified smoking as a cause of lung

cancer, asthma, heart disease, stroke, heart attack, and impotence. The majority of participants also incorrectly identified nicotine as a primary cause of each of these health conditions. Approximately 93% of participants correctly identified nicotine as the substance that makes cigarettes addictive. Approximately 56% of participants incorrectly identified nicotine as the cause of most smoking-related cancers. Participants who were older and those who had higher income levels demonstrated significantly less knowledge of the health risks of nicotine. A significant positive association was observed between the number of cigarettes smoked per day and the knowledge of health risks of nicotine. A significant inverse association was observed between the number of cigarettes smoked per day and the knowledge of the health risks of smoking. Limitations include the inability to generalize to the wider population of interest, given the use of convenience sampling, and the inability to assess for causal relationships when using cross-sectional study designs.

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Pacek et al. (2019) conducted a cross-sectional study using data from Amazon's Mechanical Turk to evaluate how young adult dual users of cigarettes and e-cigarettes may respond to a hypothetical very low nicotine product standard and menthol ban on cigarettes. Participants (N = 240) were US young adults (18-29) who had use cigarettes and e-cigarettes for at least 3 months and at least one day in the past week. Participants were presented with two

hypothetical regulations in which all cigarettes would have very low nicotine content, and only non-menthol cigarettes would be available. They were then given the following options to respond to each of these hypothetical policy scenarios: stop using cigarettes or e-cigarettes, use them a lot less often, use them a little less option, use them the same amount, use them a little more often, or use them a lot more often. They found some evidence that in response to a hypothetical low nicotine policy dual cigarette and e-cigarette users would be likely to reduce or quit smoking while increasing e-cigarette use. They also found some evidence that for menthol cigarette users, a menthol ban would lead dual users to increase their use of e-cigarettes. Limitations of this study include the fact that the sample is not representative of the general US population, that data is self-reported, that policies were hypothetical, and they do not evaluate use of other tobacco products.

Parker et al. (2022) conducted an online cross-sectional experiment with adult opioid users to examine how nicotine messaging impacted beliefs about nicotine. Participants over age 18 with opioid use in the past 30 day (N = 543) were randomized to see nicotine messaging (n = 362) or no messaging (control, n = 181). Those in the nicotine messaging condition were exposed to six educational messages (developed by Villanti et al., 2019) prior to completing outcome measures. Those in the control condition completed outcome measures without exposure to any messages. Participants responded to multiple questions about nicotine beliefs, nicotine replacement therapy beliefs, and e-cigarette beliefs. Nicotine belief questions included the claim "Nicotine is a cause of cancer" (True, Don't Know, False); "In your opinion, how large a part of the health risks of cigarette smoking comes from the nicotine itself?" (None/small part, Large/very large part); and "In your opinion, how large a part of the cancer caused by cigarette smoking comes from the nicotine itself?" (None/small part, Large/very large part). Participants in the messaging condition had more correct responses than participants in the control condition that the claim "Nicotine is the cause of cancer" was false (Messaging condition correct response = 62.5%, control condition correct response = 35.9%). Exposure to nicotine messaging also increased correct responses about how large a part of the cancer caused by cigarette smoking comes from the nicotine itself (messaging condition correct response = 69.4%, control condition correct response = 59.1%). Limitations were that this study employed a cross-sectional online survey; this approach is affected by selection bias that limits generalizability.

Patel et al. (2013) conducted a survey to examine the perception of risks related to smoking and nicotine among a population of full-time faculty on two university campuses in the US; one of these campuses included faculty in the health sciences and the other campus included faculty from other disciplines. Approximately 585 participants completed all survey items, including questions about their perception of harm resulting from four exposures (cigarettes, second-hand smoke, smokeless tobacco, and nicotine) with respect to four health domains (general health, heart attack/stroke, all cancer, and oral cancer). Perception of harm

was scored for each exposure on a seven-point Likert scale with one being ‘‘not at all harmful’’ and seven being ‘‘extremely harmful.’’ Difference scores (difference of nicotine scores from cigarette scores) were also placed into three categories: higher risk perception of nicotine than cigarettes (a negative value); no difference in risk perception between nicotine and cigarettes (zero); and higher risk perception of cigarettes than nicotine (a positive value). This study reports findings for cigarettes and nicotine, while details of the other comparisons are included in other published articles. Ninety-seven percent of all respondents ranked cigarettes as high risk for general health, and 51% of all respondents ranked nicotine as high risk for general health (cigarettes mean risk rating 6.7; nicotine mean risk rating 5.3). The majority of respondents incorrectly categorized nicotine as moderate or high risk for specific health domains (heart attack/stroke, all cancer, and oral cancer). The results from a logistic regression indicate that health sciences faculty were significantly more likely than other faculty to answer that cigarettes are riskier than nicotine for general health; that younger respondents were more likely to perceive cigarettes as riskier than nicotine than older respondents; that White respondents were more likely than respondents of other races/ ethnicities to perceive cigarettes as riskier than nicotine; and that respondents who smoked were significantly more likely than respondents who never smoked to answer that cigarettes are riskier than nicotine. Limitations to this study include using a convenience sample of university faculty with a small sample size. Because the survey respondents included health professionals, responses may not be representative of the general population. The authors argue that health professionals are the segment of the population most likely to have accurate perceptions of nicotine’s health risks, but this study does not provide the data to support that claim.

Patel et al. (2019) used data from a nationally representative sample of cigarette users to examine nicotine addiction knowledge, nicotine health beliefs, low-nicotine cigarette policy support, and behavioral intentions regarding low-nicotine cigarettes. Survey participants were English- or Spanish-speaking adults between 18 and 54 years old (N = 1261). More than half of the participants indicated that nicotine alone was the substance in cigarettes that caused addiction (63%). About half of smokers indicated that a relatively large or a very large/all of the cancer risk (49%) or health risks more generally (56%) caused by cigarette smoking comes from the nicotine itself. The majority of participants (72%) supported a policy that would reduce the level of nicotine in cigarettes. Cigarette users who inaccurately believed that nicotine itself was a major cause of the health harms associated with smoking had greater adjusted odds of supporting a policy to reduce nicotine content in cigarettes (adjusted OR = 1.66, $p < .05$). Limitations include asking participants to provide ratings of their support and behavioral intentions in response to a hypothetical policy scenario; predictions of behavior in hypothetical situations may not align with actual behaviors. Respondents were not provided with a full

explanation of lower nicotine cigarettes or the implications of a policy intended to lower nicotine amounts to sub-addictive levels before indicating their responses; therefore, there may be variation in responses due to differences in prior knowledge and understanding of the policy questions.

Pearson et al. (2013) conducted a cross-sectional study to assess public support among American adults for a potential FDA product standard that would reduce nicotine in cigarettes. Participants (n = 2,649) were recruited from KnowledgePanel, a probability-based online research cohort. The larger cohort was recruited via address-based sampling and random digit dialing. Participants were randomly sampled from the cohort, oversampling African Americans, Hispanics, and smokers. Demographics, smoking status, political ideology, and support for a nicotine standard were assessed via an online, self-administered questionnaire employing measures adapted from the 2010 Tobacco Use Supplement to the Current Population Survey and Pew Research Center. In terms of demographics, the sample was roughly split evenly between males and females, with approximately 49% current smokers, 25% former smokers, and 26% never smokers. Approximately 72% of participants identified as white, approximately 11% as African American, approximately 11% as Hispanic, and approximately 6% as other race/ethnicity. The mean age was 49.1 years and approximately 45% of the sample had a high school education or less. Mean political ideology, measured on an 11-pont scale with 0 = very liberal and 11=very conservative, was 6.5. Approximately 45% of participants agreed that government should regulate nicotine while approximately 20% disagreed, approximately 28% were equivocal, and approximately 7% didn't know. African Americans were significantly more likely to support nicotine regulation as compared to white participants, as were participants with a high school education or less as compared to those with a college degree. An inverse relationship was observed between support for nicotine regulation and political ideology, with support decreasing 11% with every 1 unit increase from liberal to conservative. Current cigarette users were significantly less likely to support nicotine regulation as compared to never cigarette users. Cigarette users with intentions to quit in the next 30 days or in the next 6 months were significantly more likely to support nicotine regulation as compared to their counterparts who did not report such quit intentions. Limitations include the inability to generalize to the wider population of interest, given the use of convenience sampling, and the inability to assess for causal relationships when using cross-sectional study designs.

Pepper et al. (2020) conducted an online survey of current adult tobacco users (N = 2508; participants either used cigarettes or vape products) to examine reasons for supporting or opposing the FDA nicotine product standard. Participants read a short explanation of a potential product standard ("The Food and Drug Administration (FDA) recently announced that

it wants to reduce the amount of nicotine in cigarettes to make them less addictive."), then rated whether they agreed with the standard and explained why in a short open-ended response. The researchers focused on analyzing responses from those who strongly agreed (n = 1000) or strongly disagreed (n = 285) with the proposed standard. Compared to those who agreed with the standard, those who disagreed with the standard 1) anticipated more compensatory smoking (agreed = 0.6%; disagreed = 25.1%), 2) were less likely to anticipate that the standard would support quitting in themselves or others (agreed = 24.2%, disagreed = 2.5%), 3) had less belief that the standard would prevent or reduce addiction (agreed = 9.9%, disagreed = 1.2%) and 4) had more belief that the change would not prevent or reduce addiction (agreed = 0.7%, disagreed = 6.2%). Compared to those who agreed with the standard, those who disagreed were less likely to say that smoking was bad for health (agreed 18.3%, disagreed = 3.3%) and that nicotine is harmful or addictive (agreed = 13.8%, disagreed = 6.2%); additionally, they were more likely to say that nicotine is not harmful/is less harmful than other chemicals (agreed = 1.6%, disagreed = 10.3%). The most common reasons for strongly disagreeing were believing that such a policy would hamper individual freedom to choose or would represent government overreach (27.6%) or that the decision would cause compensatory smoking (25.1%). The most cited reason (24.2%) for strongly agreeing was believing that a reduced nicotine standard would help smokers quit or cut down. More cigarette users than non-users believed that low nicotine cigarettes would cause compensatory smoking; however, cigarette users were also more likely to believe that low nicotine cigarettes could help with smoking cessation and reduction. Limitations include the use of a non-representative sample and the coding of responses only from those who "strongly agreed" or "strongly disagreed" with the standard; these choices reduce the generalizability of findings to the larger population of current tobacco users.

Peterson et al. (2022) conducted a secondary analysis of the nationally representative HINTS data to evaluate changes in nicotine misperceptions across time and subpopulations. Their data came from three HINTS cycles conducted in 2015, 2017, and 2019. They used two questions that ask respondents whether they believed nicotine was the main substance in cigarettes that makes people want to smoke, and whether nicotine was the chemical most responsible for causing cancers from smoking. They determined the odds of responding accurately, inaccurately, or with a "don't know" to these questions over time and across socioeconomic and demographic subgroups. They found that a large proportion of respondents correctly perceive nicotine to be addictive and this percentage increased over time from 83.5% in 2015 to 85.8% in 2019. There was no change over time in the proportion of respondents that did not know if nicotine was addictive. There was also little to know difference across

subgroups except for e-cigarette users who had 2 times higher odds of providing an incorrect response about the addictiveness of nicotine. Incorrect responses about the role of nicotine in causing cancer was significantly higher and increased over time from 48.61% in 2015 to 58.01% in 2019. The percentage of respondents providing a don't know response to this question decreased over time. Those with the highest level of education and younger age groups had the lowest odds of an incorrect response while African Americans had the highest odds of an incorrect response. The limitations of this study include that it is cross-sectional which limits causal inference.

Pollay and Dewhirst (2002) conducted a chronological review of industry documents to understand industry's intent and approach to developing and marketing light cigarettes. Documents were retrieved from the KBM Group, Physicians for a Smoke-Free Canada, Roswell Park Cancer Institute, and Anne Landman's Daily Document service. Results yielded evidence indicating that industry was aware that consumers perceived nicotine to be harmful to health. Industry concerns regarding reduced nicotine cigarettes included the potential inability of such cigarettes to create or sustain addiction, thereby reducing the consumer market. To meet market demand for less harmful cigarettes, industry reduced tar levels while maintaining or increasing nicotine levels. The latter strategy mitigated the negative taste impact of reducing tar levels and was in one case achieved via manipulating filter pH to enhance nicotine bioavailability. Women, highly-educated individuals, older established adult smokers, and young newly-established smokers were identified by industry as the consumer populations most receptive to using reduced nicotine cigarettes, and to perceive such use as an alternative to quitting. Package color was identified by industry as a factor affecting consumers' subjective assessment of the strength of a cigarette, with reduced nicotine cigarettes in red packages being perceived by consumers as stronger and more satisfying than the same product in another package color.

Popova et al. (2019) analyzed data drawn from a nationally representative sample (2018 Tobacco Products and Risk Perceptions Survey) to measure perceived relative harm of VLNC cigarettes and anticipated behavioral intentions to use tobacco products after viewing different framings of the nicotine tobacco product standard. Participants (N = 1185) were adult current cigarette users aged 18 and older. Participants were randomly assigned one of five versions of a nicotine reduction question, questions that contained either a literal description of VLNCs ("nicotine levels were reduced by 95%"), a mention of the government's role in using the standard, a statement about reduced addictiveness, a statement about the negative outcome of cigarettes no longer being able to relieve cravings, or a statement about the benefit of being able to quit more easily. Following the framing exposure, participants selected their most probable tobacco use intentions: intention to quit using all tobacco products, intention to

switch to non-combusted tobacco products, or intention to continue using combusted tobacco. Participants then rated the perceived risk of VLNCs: less harmful than regular cigarettes, equally/more harmful, or "do not know". Overall, 30.5% of the participants indicated they would quit using all tobacco products, 61.0% indicated they would smoke VLNCs or other combusted tobacco, and 5.8% intended to switch to non-combusted tobacco products if a nicotine standard was put in place. The proportion of participants intending to quit all tobacco products was highest (43.9%) and intentions to use combusted tobacco were lowest (45.3%) when nicotine reduction was framed as creating cigarettes that "no longer relieved your cravings". Pairwise comparisons of the frames showed that all frames were similar to one another in their effects on anticipated tobacco use intentions, except the question framed as "no longer relieved your cravings.". Overall, 35% of participants believed that VLNCs were less harmful than regular cigarettes, and the proportion was lowest in the "no longer relieved your cravings" group. Participants in the "no longer relieved your cravings" condition had the lowest proportion believing that VLNCS are less harmful than regular cigarettes (26%). Limitations include asking cigarette users to rate risk perceptions and intentions for using VLNCs, without considering their current or actual use of VLNCs, and asking for ratings of self-reported anticipated behavioral intentions that may over- or under-estimate actual behavior.

Ranney et al. (2022) conducted in-depth interviews to evaluate 18 different messages designed to counter misperceptions of VLNC cigarettes. They used a convenience sample of current cigarette users aged 18-65 (N = 30), with a median age of 42.5 years. Each participant was shown six of 18 messages designed around six larger themes derived from cognitive science. These messages did one of the following six things: provided truthful information only, provided truthful information followed by negating misinformation, included an emotive component, provided an alternative account, affirmed popular values, or explained the logical fallacy in the misperception. Three central themes emerged from the qualitative interviews. First, there was confusion about the proposed VLNC cigarette policy and this confusion affected how messages were interpreted. Confusion centered around the fact that VLNC cigarettes were less addictive and not less harmful, and some respondents were confused about why toxins in cigarettes were not reduced. Second, messages that promote self-efficacy for quitting rather than guilt or fear were better received. Third, direct and succinct messages were seen as better able to grab attention and inform people who smoke. Limitations include the inability to assess for causal relationships or generalize to the wider population of interest in qualitative studies.

Reynolds et al. (2022) conducted a discrete choice experiment (DCE) to estimate the impact of seven different messages on attitudes toward a reduced nicotine policy, the perceived harm of VLNC cigarettes, and behavioral intentions to quit or initiate smoking. Their data comes from a 2021 Ipsos KnowledgePanel which they report as representative of US adults. Their sample (N = 1483) consisted of four groups; young adult (18-29) non-users (n =

351), adults who currently use cigarettes but do not use e-cigarettes (n = 590), adult former cigarette users (n = 443), and adult dual users of cigarettes and e-cigarettes (n = 99). They used a within subject fractional factorial design to study seven message attributes with two levels each. These attributes focused on the presence or absence of content about the following characteristics of VLNC cigarettes: addictiveness, chemicals, curbing satisfaction, level of nicotine reduction, harmfulness, and quitting efficacy. They also varied whether a message contained the FDA logo as an indication of message source. Subjects were asked to complete two of three DCE tasks evaluating which messages made participants feel most positive and negative about a reduced nicotine policy, which messages made them think that VLNC cigarettes were most and least harmful, and which messages made them most and least likely to either quite (current cigarette users) or initiate (never cigarette users) cigarette use. Participants perceived messages that focused on quitting efficacy, reduced addictiveness, and lower nicotine to be the most positive, while those related to chemicals and harm were perceived to be negative. Messages about the chemicals in, and harm from VLNC cigarettes increased perceptions of harmfulness, decreased the likelihood of initiation, and increased the likelihood of quit intentions. Messages that focused on the reduced addictiveness of VLNC cigarettes, and greater quit efficacy when using them led to increasing motivations to initiate smoking. The limitations of this study include the fact that it is cross-sectional and cannot tell us about changes over time, and that it involves hypothetical scenarios that may not reflect participants' actual behavior.

Shadel et al. (2006) conducted a quasi-experimental, post-test only study of what current cigarette users in the US believe about Quest cigarettes following exposure to a single print Quest advertisement. Participants (N = 200) were recruited via interceptions in shopping malls in 14 states where Quest cigarettes were not marketed at the time of the study. Regular smoking status was the only inclusion criterion referenced by the researchers. Participants first viewed the Quest advertisement and then answered questions regarding demographics, smoking and quitting history, beliefs about Quest cigarettes, need for cognition (i.e., desire to think about complex issues), and perceived vulnerability to the health effects of smoking. In terms of demographics, the sample was roughly evenly split between male and female, with an average age of 33.8 years. The sample was 87.5% Caucasian and 56% had a high school education or GED. Participants with both low perceived vulnerability and lower perceived need for cognition were significantly more likely to believe, falsely, that Quest cigarettes are safer and less addictive. An interaction was observed between these two variables, with need for cognition becoming a significant variable when perceived vulnerability was low. Limitations include the lack of a control group; the inability to assess changes in beliefs as a result of ad

exposure due to the use of a post-test only design; the inability to generalize to the wider population of interest, given the use of convenience sampling; and the inability to assess for causal relationships when using cross-sectional study designs.

Shi et al. (2021) conducted two studies addressing misperceptions of nicotine and how they can be corrected. The first was a cross-sectional study using an online sample of current cigarette users (N = 371) recruited using the SSRS online probability panel, and they reported this sample is nationally representative. They asked participants to rate how much of the health risks in smoking are associated with nicotine on a scale from none to all. They also assessed participants' attitudes and intentions to use e-cigarettes and NRT, as well as their intentions to quit smoking. They reported that over half of the people who use cigarettes incorrectly believe that nicotine causes a "relatively large part" (33.2%), a "very large part" (18.1%), or "all" (5.4%) of the health risks caused by smoking. They found that perceptions of nicotine harm were not associated with attitudes towards or intention to use nicotine replacement therapy (NRT) but that they led to an increase in harm perceptions of e-cigarettes and a decrease in the likelihood of using those products. Limitations of this first study include a small sample size and the fact that it is cross-sectional limiting its ability for causal inference. For their second study, Shi et al. conducted an experiment using a post-only between-subject design to explore the impact of different messages designed to correct misperceptions about nicotine. They used an online convenience sample (N = 1008) designed to recruit an equal number of tobacco users and non-tobacco users. They randomized subjects to view a control, or one of three messages designed to correct nicotine misconceptions (one additional message was not discussed in this paper). These messages provided a general correction of nicotine misconceptions, a correction focused specifically on NRT, and a correction focused on e-cigarettes. They found that all three of these messages lowered subjects' perception of nicotine harm, while the e-cigarette correction message led to less favorable attitudes about e-cigarette use. Finally, they found that none of the messages impacted attitudes about NRT. Limits of this second study include the use of a convenience sample meaning that it was not representative of the entire US population.

Smith et al. (2011) conducted a cross-sectional experiment with a convenience sample of adult cigarette users (N = 239) to compare the effects of five different versions of corrective statements about cigarette harms to health. Of these messages, one proposed by the DOJ included an explicit statement about nicotine; the rest of the messages were created by Philip Morris, an independent group of public health experts, or by the study investigators. Data were collected before, immediately after, and 1-week after exposure to stimuli. Before exposure to corrective statements, 48% either agreed or strongly agreed with the statement "nicotine is only a minor factor in whether a person can stop smoking." All statements created by DOJ,

public health experts, and study investigators elicited a stronger affective response and were rated by respondents as significantly more persuasive ($p < 0.05$) that the industry created message. Smith et al. reported a significant time effect for all belief outcome measures; in every case, an increase in scores was observed immediately after participants viewed the corrective statements, followed by a slight decline one week later. Limitations of this study include that this was conducted with a convenience sample of self-reported cigarette users and that the article does not report detailed information about the measures used to examine participant beliefs about nicotine.

Smith et al. (2012) conducted an exploratory, cross-sectional online survey of college students regarding smoking behavior, quit intentions, and perceptions of regular, light, and ultralight cigarettes. Participants (N = 579) were recruited via convenience sampling at a large public university in the southwestern United States. Being a college student was the only inclusion criterion referenced by the researchers. In terms of demographics, Caucasian and Hispanic students were overrepresented at 74%, and 17%, respectively, while African American students were underrepresented at approximately 3%. Approximately 76% of participants were business majors. Data were gathered via an online survey comprising items the researchers described as being drawn from "prior research." Results showed that participants' perceptions about the tar and nicotine content of light and ultralight cigarettes were not significantly different from each other, which the researchers indicated may suggest that participants were not able to distinguish between these two substances. As compared to never cigarette users, former cigarette users disagreed significantly more strongly with the statements that ultralights and lights contain reduced levels of nicotine. The majority of participants reported they did not believe that reduced levels of nicotine make cigarettes safer. Limitations include the use of non-validated survey measures; the inability to generalize to the wider population of interest, given the use of convenience sampling; and the inability to assess for causal relationships when using cross-sectional study designs.

Snell et al. (2022) conducted an analysis of PATH data to determine generalizable estimates characterizing the current state of knowledge about nicotine addictiveness and harm among a large sample of current cigarette users. Their analytical sample included adults (n = 9140) who reported past 30-day cigarette smoking in Wave 1 of the PATH Study (2013–2014) and who participated in all four publicly available waves of data (2013–2018). Adults in the study sample were predominantly male (54%), between the ages of 25 and 54 (65%), reported race and ethnicity as non-Hispanic White (67%), earned a high school degree or GED equivalent or less (54%), and reported annual household income less than $50 000 (60%). Incorrect responses to a question about nicotine's harmfulness to health were reported by 68.9% of participants (SE: 0.56); 64.6% incorrectly reported that nicotine in cigarettes was

very/extremely or not at all harmful to health (SE: 0.53), and 63.3% thought that nicotine was "probably" or "definitely" the main contributor to smoking-related cancers (SE: 0.63). Conversely, only 12.5% (SE: 0.41) agreed that reducing nicotine in cigarettes would make them less harmful. In terms of nicotine's addictive properties, 82.9% (SE: 0.44) of participants agreed that nicotine was responsible for driving continued cigarette use, however only 13.1% (SE: 0.46) agreed that reducing nicotine would make cigarettes less addictive. Older adults, participants who were non-White, and those with lower levels of income or education tended to be more likely to hold misperceptions about nicotine. Significant inconsistencies across knowledge aspects were noted within subpopulations. Older adults were more likely to agree with the statement that nicotine drives tobacco use, while being less likely to agree that lowering nicotine would make cigarettes less addictive. Those with higher educational attainment also exhibited inconsistent views about nicotine and health harm: these groups had greater odds of correctly disagreeing with the statement that nicotine in cigarettes causes cancer, but greater odds of incorrectly agreeing that reducing nicotine would make cigarettes less harmful. Key findings from longitudinal models suggested that misperceptions about nicotine-attributable health harm may, in fact, motivate a desirable behavioral outcome among cigarette users (quit attempts), but this potential benefit did not translate to increased odds of successfully achieving cessation, and of using an effective, evidence-based support tool such as nicotine replacement therapy. Limitations of this study include those inherent in survey designs (including disagreement between actual and reported behavior, issues of self-report) and analysis choices that limited ability to control for unobservable characteristics that may influence tobacco use behavior.

Steinberg et al. (2021) conducted a cross-sectional survey of U.S. physician's (N = 1020) beliefs about harm reduction, tobacco/e-cigarette knowledge, and beliefs about health effects of nicotine. Physicians represented six specialties: family medicine, internal medicine, OB/GYN, cardiology, pulmonary/critical care, and hematology/oncology. The majority of physicians "strongly agreed" that nicotine directly contributes to the development of cardiovascular disease (83.2%), COPD (80.9%), and cancer (80.5%). Comparatively fewer "strongly agreed" that nicotine directly contributes to the development of birth defects (32.9%) and 30.2% did not answer this question—a potential indicator of "do not know." Females were more likely than males to correctly perceive nicotine risks for birth defects (APR 1.28, 95%CI 1.07–1.54). Younger physicians were also more likely to correctly perceive the impact on birth defects. Pulmonologists were less likely than most other specialties to misperceive nicotine as a direct contributor to COPD. Additionally, family physicians were more likely than oncologists to misperceive nicotine as a carcinogen. Paradoxically, OB/GYNs misidentified risk related to birth defects more than other specialties. Limitations include sampling bias due to low response rate and self-selection into the study, as well as concerns with generalizability.

Strasser et al. (2008) conducted a quasi-experimental, post-test only study of what smokers in the US believe about the harmfulness of Quest cigarettes following exposure to three different Quest advertisements. Participants (N = 500) were recruited from an online panel. Inclusion criteria were being aged 18-65, having access to a computer, smoking at least five CPD, and having smoked at least 100 cigarettes in their lifetime. Exclusion criteria were having ever been exposed to a Quest advertisement, having ever used a Quest cigarette, and experiencing difficulty viewing advertisements on their television. Participants provided demographic information via an online questionnaire and then were randomized to one of three advertisement conditions: the original, unaltered Quest advertisement, an advertisement with no text, and an advertisement where the pack color was altered from its original blue to red. Following 30 seconds of exposure to the assigned condition, participants completed a questionnaire regarding their beliefs about Quest's tar and nicotine content, addictiveness, chemical content, potential to harm health, relative safety, and utility as a cessation aid. Participants with a college education were significantly more likely than their counterparts to correctly believe that Quest cigarettes are lower in nicotine than regular cigarettes. As compared to participants in the other two conditions, participants in the no-text condition were significantly more likely to correctly believe that Quest cigarettes are not less addictive, not less likely to cause cancer, do not have fewer chemicals, are not healthier, and are not safer than regular cigarettes. No significant differences were observed between participants assigned to the three conditions regarding beliefs on whether Quest is an effective cessation aid. Limitations include the use of non-validated measures; the inability to assess changes in beliefs as a result of ad exposure due to the use of a post-test only design; the inability to generalize to the wider population of interest, given the non-representative sample; and the inability to assess for causal relationships when using cross-sectional study designs.

Villanti, Naud, et al. (2019) analyzed the results of a nationally representative cross-sectional survey to determine the prevalence and correlates of nicotine and nicotine product perceptions in a nationally representative sample of U.S. young adults. Survey items included questions about nicotine's role in causing disease; the perceived addictiveness of RNC cigarettes, and the likelihood of addiction to these products compared to cigarettes; and rankings of harm for different nicotine delivery products. Participants (N = 4,091) completed the Truth Initiative Young Adult Cohort Study Wave 10 (Fall 2016). The study sample was composed of young adults aged 18-40, of which 23% were aged 18-24, 57% were aged 25-34, and 20% were aged 35-40. Over half of the sample was non-Hispanic white (56%), 13% was non-Hispanic black, 22% was Hispanic, and 9% reported other race. Approximately half were female (51%) and the majority had completed at least some college education (67%). Overall, 55% of young adults believed that nicotine is a cause of cancer, with an additional 24% reporting that they did not know. More than 60% of respondents believed that a relatively or

very large part of the health risks (66%) or cancer (60%) caused by smoking come from the nicotine. Approximately 60% of participants reported that the claim that a cigarette brand is low in nicotine means that it is less addictive was false; 23% of the sample responded "don't know" to this statement and 17% of the sample responded that the claim was true. Nicotine beliefs significantly varied by tobacco use status, sex, ethnicity, and education. Compared to non-past 30-day tobacco users, past 30-day tobacco users were more likely to incorrectly believe that nicotine is a cause of cancer, that nicotine is responsible for a large part of the health risks caused by smoking. Females (vs Males) and non-Hispanic blacks and Hispanics (vs white), and those with less than a college education (vs some college education or higher) had higher odds of endorsing the incorrect beliefs that nicotine is a cause of cancer and that a large part of the health risks caused by smoking comes from the nicotine. Limitations include a low cumulative response rate and the inconsistent inclusion of a "don't know" option across all items; it is unclear whether participants would have responded differently to relative harm items without the "don't know" option.

Villanti, West, et al. (2019) conducted a cross-sectional experimental study to test the effect nicotine educational messages on harm and risk beliefs about nicotine, NRT, E-cigarettes, and RNC cigarettes. They administered the survey on Amazon Mechanical Turk (N = 521) and randomly assigned participants to either nicotine messaging (n = 263), sun safety messaging (n = 128), or no message control (n = 130). The sample was majority white (80%) and had at least some college education (87%). Approximately half of participants were male (52%), were aged 25−34 years (46%); 40% reported past 30−day tobacco or E-cigarette use In the nicotine messaging condition, participants viewed 6 tested messages: 1) nicotine is the addictive substance in tobacco products, 2) nicotine makes it easier for people to start smoking regularly, 3) nicotine makes it harder for people to quit smoking, 4) nicotine does not cause cancer, 5) chemicals in cigarette smoke, not nicotine, largely cause cancer, heart disease, and other health problems related to smoking, and 6) nicotine can be used safely long-term in quit smoking products like nicotine patches, gum, or lozenges. Participants in the nicotine messaging condition had more correct responses to the statement that nicotine is a cause of cancer than participants in other conditions (78.3% of nicotine condition said false vs 36.8% in other conditions) and were less likely to respond "Don't know" to this item (5.3% of nicotine condition vs 26.0% of other conditions). After controlling for past 30−day tobacco use, exposure to nicotine messaging was associated with lower level of false beliefs about nicotine ($b = 1.82$, $p < 0.001$) compared with the control conditions; nicotine messaging was also associated with reduced RNC cigarette false beliefs ($b = -1.13$, $p = 0.054$). Brief exposure to nicotine messages did not impact norms about nicotine, behavioral control, or intention to use tobacco or nicotine products. Limitations include potential issues with generalizability of findings due to using an online convenience sample and brief exposure to sample nicotine education messages instead of repeated exposures that are more similar to public education messaging.

Villanti et al. (2020) conducted a secondary analysis of two waves of the Truth Initiative Young Adult Cohort study conducted in the spring and fall of 2016 (N = 3122). They categorized respondents' beliefs about nicotine and analyzed whether these beliefs were related to susceptibility, curiosity, and use of tobacco products. Participants, aged 18 to 40, were asked three items assessing their beliefs about the role of nicotine in cancer and disease. Villanti et al. used these items to classify individuals into one of four latent classes of belief. A majority of respondents (51%) believed that nicotine plays a large role in health risks including cancer (class 1). A much smaller share (9.4%) believed that nicotine plays a large role in causing health harms but are not sure about its role in causing cancer (class 2). The second largest group (32.5%) believed that nicotine plays a small role in health risks including cancer (class 3). Finally, the smallest group (7.5%) believed that nicotine plays no role in health effects or a small role in causing cancer (class 4). They found that these latent nicotine belief classes were highly correlated with susceptibility to and curiosity about various tobacco products in the same survey wave but were not predictive of future susceptibility and curiosity in a follow-up wave. Respondents in classes 3 and 4 who believed that nicotine played a small or no role in health effects had the highest prevalence of ever or past 30-day tobacco use in the same wave. Individuals in class 4 had an 86% higher odds of increased e-cigarette use in a future wave, but this effect did not hold across other tobacco products or for class 3 respondents. Limitations of this study include issues of causality particularly for the findings using a single wave of data.

Weiger et al. (2022) conducted a secondary analysis of PATH data to describe the proportion of adult cigarette users who incorrectly believe that nicotine causes cancer and to explore potential factors to consider in future messaging strategies to correct this misperception. They explored the impact of race, ethnicity, sex, age, education, income, and sexual orientation; tobacco product use behavior; perceived harm related to tobacco; exposure to pro- or anti-tobacco messaging; and normative influences on misperceptions about the role of nicotine in cancer. They found that the majority of cigarette users had the misperception that nicotine is the chemical that causes most of the cancer caused by smoking cigarettes (61.2% answered "definitely yes", "probably yes", or "don't know" in response to that survey item on the PATH study Wave 3). This rate was higher for racial and ethnic minority respondents, women, people with a lower socioeconomic status and older respondents. Those that use ENDS or smokeless tobacco products have a lower-than-average prevalence for this misconception. Individuals with a higher overall risk perception of tobacco were more likely to have this misperception. There was no difference by exposure to pro-tobacco advertising. Participants who reported injunctive norms against smoking having higher misperceptions of nicotine. Limitations of this study include that it is cross-sectional, which limits causal inference.

Yang et al. (2020) conducted an online experiment with convenience sample of US adults to examine perceived risk and addictiveness of nicotine, perceived e-cigarette risk, and behavioral intentions to switch to e-cigarette or dual use. Participants completed a pre-test survey to assess baseline measures of nicotine and e-cigarette perceptions, then were

randomly assigned to view a nicotine fact sheet or bottled water ad (control); change in correct responses to nicotine questions and post-test harm perceptions were analyzed. Participants (N = 1906; nicotine fact sheet condition n = 378 and control condition n = 378) were current adult cigarette users and recent former cigarette users. Results of the logistic regression analysis indicated that most cigarette users understand that nicotine is the main cause of tobacco addiction, but most incorrectly believe that nicotine is the main cause of smoking-related health problems. Yang et al. reported that exposure to information about nicotine can change beliefs about nicotine health risks; compared to the control, exposure to the nicotine fact sheet doubled the probability of disagreeing that nicotine is the main cause of smoking-related disease (26.2% vs. 12.7%, 95% CI = 1.51, 2.82, $p < 0.001$). However, there were no significant differences between pretest and posttest in perceived addictiveness of nicotine or perceived comparative risk of e-cigarettes in the nicotine fact sheet condition. Limitations of this study include that the sample was not nationally representative and only examined responses from current and former cigarette users; the findings from this study may not generalize to those who have never used cigarettes.

Yerger (2011) conducted a review of industry documents to understand the industry perspective on menthol and nicotine dependence. Documents were retrieved from the Legacy Tobacco Documents Library in 2010. The analysis of documents found that industry conducted research to examine interactive effects of nicotine and menthol levels in cigarettes. Internal research concluded that the addition of menthol improved the taste and sensory experience of reduced nicotine cigarettes, making them more acceptable to consumers. Industry research also found that menthol, in addition to being a flavor, has nicotine-like effects. This industry research identified an optimal level of menthol that made consumers perceive reduced nicotine cigarettes to be similar in taste and throat hit to full-flavor cigarettes. This review also indicated that some tobacco companies are aware of the synergistic effects of menthol and nicotine and add small amounts of menthol to normal nicotine cigarettes not advertised as mentholated to increase the pleasurable and reinforcing aspects of use.

Appendix C: History of the Document

- Originally drafted in 2014.

- Substantial revisions were made in 2017 after the Reproducible Transparent Document Review of Clinical Research Related to the Abuse Liability of VLNC Cigarettes (Round 1) and the Reproducible Transparent Document Review of the Extant Social Science Literature Relevant to Low Nicotine and Very Low Nicotine Tobacco Products (Round 1) were conducted.

- Updated in 2018 after the Reproducible Transparent Document Review of Clinical Research Related to the Abuse Liability of VLNC Cigarettes (Round 2) was conducted.

- Updated in 2020 after the Reproducible Transparent Document Review of Clinical Research Related to the Abuse Liability of VLNC Cigarettes (Round 3) was conducted.

- Revised in response to reviewer comments in 2020 after the document was peer reviewed by a panel of outside experts (Requisition No. 1223340 under Contract No. HHSF223201700015B with Versar, Inc.).

- Updated in 2021 after the Reproducible Transparent Document Review of Clinical Research Related to the Abuse Liability of VLNC Cigarettes (Round 4) and the Reproducible Transparent Document Review of the Extant Social Science Literature Relevant to Low Nicotine and Very Low Nicotine Tobacco Products (Round 2) were conducted.

- Updated in 2022 after the Reproducible Transparent Document Review of Clinical Research Related to the Abuse Liability of VLNC Cigarettes (Round 5) and the Reproducible Transparent Document Review of the Extant Social Science Literature Relevant to Low Nicotine and Very Low Nicotine Tobacco Products (Round 3) were conducted.

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