REVIEW

# Nicotine Reduction: Strategic Research Plan

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## ABSTRACT

**Background:** Reducing nicotine content in cigarettes and other combustible products to levels that are not reinforcing or addictive has the potential to substantially reduce tobacco-related morbidity and mortality. The authority to reduce nicotine levels as a regulatory measure is provided in the U.S. Family Smoking Prevention and Tobacco Control Act and is consistent with the general regulatory powers envisioned under the relevant articles of the World Health Organization's Framework Convention on Tobacco Control. Many experts have considered reducing nicotine in cigarettes to be a feasible national policy approach, but more research is necessary.

**Purpose:** This article describes proceedings from a conference that had the goals of identifying specific research gaps, describing methods and measures to consider for addressing these gaps, and considering ways to foster collaboration.

**Results and Conclusion:** Identified research gaps included determining the dose of nicotine that would be optimal for reducing and extinguishing cigarette use, examining approaches for reducing nicotine levels in the general and special populations of smokers, understanding how constituents other than nicotine may contribute to the reinforcing effects of tobacco, and identifying unintended consequences to determine ways to mitigate them. Methods that can be used ranged from brain imaging to large human clinical trials. The development and availability of valid biomarkers of exposure and effect are important. Infrastructures to facilitate collaboration need to be established.

## INTRODUCTION

Cigarettes and other tobacco products that are burned are among the most toxic products sold for human consumption. Eliminating or significantly decreasing the use of combustible tobacco products would substantially reduce tobacco-caused morbidity and mortality (Zeller, Hatsukami, & Strategic Dialogue on Tobacco Harm Reduction Group, 2009). One way to achieve this goal is to reduce levels of nicotine in combusted tobacco products to nonreinforcing levels. Such reductions should not be driven by filter ventilation or other changes in cigarette design that can be easily countered by the user, but instead by reducing nicotine exposure. In this review, we emphasize reductions in the nicotine content of the tobacco itself below a threshold level of reinforcement, which would likely substantially decrease the development and level of tobacco dependence and facilitate cessation. This is in contrast to approaches that set upper limits on machine-delivered nicotine yields but which were intended to remain capable of sustaining addiction (O'Connor, Cummings, Giovino, McNeill, & Kozlowski, 2006).

In the United States, a nationwide gradual reduction of the nicotine content in cigarettes was proposed by Benowitz and Henningfield (1994) almost two decades ago. Subsequently, the conclusions by several predominantly U.S. researchers, organizations of scientists, and health professionals concurred that reduction of cigarette nicotine content to nonaddictive levels could have a significant and positive impact on public health (cf. American Medical Association, 1998; Gray et al., 2005; Henningfield et al., 1998; Tengs, Ahmad, Savage, Moore, & Gage, 2005; Zeller, Hatsukami, & Strategic Dialogue on Tobacco Harm Reduction Group, 2009). With the enactment of the Family Smoking Prevention and Tobacco Control Act, the U.S. Food and Drug Administration (FDA) now has the authority to reduce nicotine to levels that are nonaddictive, although not to zero, if FDA concludes such a measure "is appropriate for the protection of the public health." Similarly, the World Health Organization Framework Convention on Tobacco Control (FCTC) includes articles that allow governmental agencies to establish standards for nicotine.

In meetings held in 2007 and 2009, scientists, tobacco control policy experts, and representatives of U.S. government agencies examined the scientific knowledge and feasibility of this approach. The scientific literature since 1994 was reviewed, presented, and discussed. Based on this discussion, the meeting

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participants came to the conclusion that actively pursuing research on nicotine reduction would be a highly worthwhile endeavor (Hatsukami, Perkins, et al., 2010). The potential feasibility of this approach is particularly supported by studies conducted by Benowitz et al. (2007), Hatsukami, Kotlyar, et al., (2010), and most recently Benowitz et al. (2012). These studies showed substantial reduction in smoking, no significant compensatory smoking, and reduced toxicant exposure at very low doses of nicotine. Furthermore, smoking cessation is facilitated with the use of very low nicotine content cigarettes in a population of smokers, from both the United States and New Zealand, interested in quitting (Hatsukami, Kotlyar, et al., 2010; Walker et al., 2012).

A subsequent meeting was convened in 2011 to develop a strategic research plan to examine the effects of reducing nicotine content of tobacco products, focusing on cigarettes. Meeting presenters were asked to consider critical research questions, potential measures and methods, and indicators of outcome success. Topics discussed ranged from the neurobiology of nicotine addiction to how consumers may perceive reduced nicotine cigarettes (Table 1).

The aims of this article are to describe the proceedings from the 2011 meeting and to identify specific research questions that would move the science of nicotine reduction forward. These questions go beyond the general research questions described in this article based on preceding meetings (Hatsukami, Perkins, et al., 2010). The contents of this article do not represent a consensus opinion of all the participants although it was circulated among the presenters to obtain their feedback. The hope for this meeting was to provide a strategic research approach, to motivate more scientists to be interested in this area of research, and to develop a collaborative network of researchers. Although this meeting was United States focused, we believe the description of the meeting proceedings are relevant internationally because various nicotine control strategies are being considered under tobacco regulation in other nations and under the FCTC (World Health Organization, 2012).

## MAIN POINTS OF DISCUSSION

The general framework to explore the impact of reduced nicotine content (RNC) cigarettes is one that was described in an article by Hatsukami, Biener, Leischow, and Zeller (2012) and the Institute of Medicine report *Clearing the Smoke* (Stratton, Shetty, Wallace, & Bondurant, 2001). In this framework, population harm was described as being associated with toxicity of the product, the extent of product use, and finally the uptake and continued use of the product. Toxicant exposure is a function of the toxicity of the product itself and use of other tobacco products. The extent of product use, uptake, and continued use are related to the abuse liability or addiction potential and appeal of the product. Addiction potential is largely determined by nicotine and the rate of nicotine absorption. One method for reducing population harm would be to reduce nicotine in the most highly addictive and toxic product so that extent of use, uptake, and continued use of the product would be substantially reduced. Factors that might moderate the impact of the reduced nicotine product include both individual differences in response to the product and environmental influences (e.g., tobacco control policies).

In order to assess the impact of RNC cigarettes, a schema described for tobacco product evaluation can be used (Hatsukami, Biener, Leischow, & Zeller, 2012; Institute of Medicine, 2012). Preclinical tests in animals can be conducted to assess the abuse liability of different levels of nicotine in cigarettes, particularly in the area of acquisition of nicotine self-administration in both adolescent and adult animals. In addition, neurophysiological changes that affect function resulting from exposure to different nicotine doses can be explored. Human imaging, laboratory, and clinical trial studies can examine the abuse liability and effects of varying levels of nicotine content in cigarettes and their impact on tobacco use behaviors, toxicant exposure, and potential health risk in general population of smokers and in vulnerable populations. Moderating factors to consider in use of the product include how the consumer perceives the product and its appeal, such as the way it is packaged, priced, and promoted. Finally, once the product is out in the market, then implementation of a comprehensive surveillance system and risk management program is essential.

Using this framework and schema, key issues that were covered in this meeting included (a) simulation or forecasting models for estimating the population-level effects of RNC cigarettes; (b) specific high priority areas of research (from preclinical to clinical) and different methodological approaches, considerations, and tools (e.g., biomarkers) for evaluating RNC cigarettes; (c) the role of other tobacco- or nicotine-containing products in a world of RNC cigarette products; (d) research in children, adolescents, and vulnerable populations; (e) consumer perception and product appeal; (f) influence of other constituents of tobacco and product design features; and (g) potential unintended marketplace consequences. Although the primary focus was on cigarettes, determining how these issues are relevant to all combustible products was recognized.

### The Importance of Modeling

Use of simulation or forecasting models to predict the impact of a policy on public health can be an extremely valuable exercise because often population benefits and risks can only be estimated (see Tengs et al., 2005). Core inputs should be considered when prioritizing questions and measures driving research on nicotine reduction. As examples, these could include (a) effects of RNC cigarettes on initiation and cessation rates, (b) compensatory smoking behavior and toxicant exposure, (c) probability of switching to other tobacco products and medicinal nicotine, (d) toxicity of alternative tobacco products and medicinal nicotine and potential polyproduct use, (e) consumer perception and response to reducing nicotine in cigarettes as a policy measure, and (f) use and toxicity of black market products. The modeling approach makes it easier to analyze multiple dimensions of a specific policy and the potential impact of a policy or policies (including unintended consequences) before they are implemented. Modeling also helps to assess the complex array of factors that modulate overall impact.

### Tools for Assessing the Effects of Reduced Nicotine

Tools for assessing the impact of RNC cigarettes include imaging studies, animal and human laboratory studies, clinical trials, and measurement of biomarkers of exposure and harm. The following describes the types of studies that are likely to contribute to the science base for reducing nicotine in cigarettes and other combustible products.

**Table 1. Program for the Nicotine Reduction: Establishing a Research and Plan and Collaboration Meeting**

| Topic | Presenter | Facility |
|---|---|---|
| Introduction | | |
| Overview | Dorothy Hatsukami, Ph.D. | University of Minnesota |
| | Mitch Zeller, J.D. | PinneyAssociates |
| Public health impact modeling | David Mendez, Ph.D. | University of Michigan |
| Dose–response effects of nicotine: measures and methods | | |
| Neurobiology (CNS and trigeminal nerve effects) | William Corrigall, Ph.D. | Corrigall Consulting |
| Animal laboratory | Mark LeSage, Ph.D. | University of Minnesota |
| Human laboratory (abuse liability) | | |
| Adults | Robert Balster, Ph.D. | Virginia Commonwealth University |
| Adolescents | Joseph DiFranza, M.D. | University of Massachusetts |
| Imaging | Edythe London, Ph.D. | University of California, Los Angeles |
| Moderators of dose–response effect: methods for assessment | | |
| Drug related: rate of drug delivery, other constituents, additives | Jack Henningfield, Ph.D. | Pinney Associates |
| Individual differences | Neal Benowitz, M.D. | University of California, San Francisco |
| Environmental cues | Eric Donny, Ph.D. | University of Pittsburgh |
| | Saul Shiffman, Ph.D. | University of Pittsburgh |
| Reduction approaches and outcome variables (i.e., initiation, dependence, and cessation) | | |
| Biomarkers to detect and assess effects of compensation | Stephen Hecht, Ph.D. | University of Minnesota |
| | Neal Benowitz, M.D. | University of California, San Francisco |
| Adult trials (initiates vs. established smokers) | Dorothy Hatsukami, Ph.D. | University of Minnesota |
| Adolescent trials (initiates vs. established smokers) | Suchitra Krishnan-Sarin, Ph.D. | Yale University |
| Vulnerable populations (e.g., substance abuse and mental illness) | Jennifer Tidey, Ph.D. | Brown University |
| Other critical issues: research measurement and designs | | |
| Cigarette design (no ventilation)/restricting or limiting other constituents or additives | David Ashley, Ph.D. | Food and Drug Administration |
| Role of other nicotine products (NRT, oral tobacco) | Jonathan Foulds, Ph.D. | Penn State University |
| Consumer perception and response | Richard O'Connor, Ph.D. | Roswell Park Cancer Institute |
| Summary comments | | |
| Discussion | Kenneth Warner, Ph.D. | University of Michigan |
| Developing an infrastructure for collaboration/logistics for funding | | |
| | Cathy Backinger, Ph.D. | Food and Drug Administration |
| | Timothy McAfee, M.D., M.P.H. | Centers for Disease Control and Prevention |
| | Michele Bloch, M.D., Ph.D. | National Cancer Institute |
| | David Shurtleff, Ph.D. | National Institute on Drug Abuse |
| Consensus and wrap-up | Dorothy Hatsukami, Ph.D. | University of Minnesota |
| | Mitch Zeller, J.D. | PinneyAssociates |

*Preclinical Animal Models*

Understanding the neurobiology of nicotine addiction has advanced significantly (D'Souza & Markou, 2011; Gotti, Zoli, & Clementi, 2006; Kuryatov, Berrettini, & Lindstrom, 2011; Saccone et al., 2009; Thorgeirsson et al., 2008; Tuesta, Fowler, & Kenny, 2011). However, there is little knowledge regarding how reducing the levels of nicotine in cigarettes would affect the developing brain or a brain that has been altered by chronic exposure to nicotine. Animal models allow investigation in these areas, and such basic research will be important to continue regardless of whether or not a nicotine reduction policy is implemented (Donny et al., 2012; Hatsukami, Perkins, et al., 2010).

Animal studies on nicotine reduction also allow for controlled analysis of factors that might alter the functional relationship between nicotine reduction and outcomes of interest. The FDA and the Drug Enforcement Agency recognize that specific animal models are particularly informative when assessing abuse liability (Food and Drug Administration, 2010). The following animal models and techniques would be particularly useful in evaluating effects of reducing levels of nicotine: (a) Drug self-administration models that provide estimates of threshold reinforcing nicotine doses in adolescents and adults and factors that moderate them; (b) demand curve analysis and growth-curve analysis that provide quantitative techniques to facilitate detection of factors that moderate reduction and acquisition of self-administration, respectively (Greenwald & Hursh, 2006; Hursh, Galuska, Winger, & Woods, 2005; Hursh & Silberberg, 2008; Lanza, Donny, Collins, & Balster, 2004); (c) drug discrimination models that can be used to screen understudied or novel constituents for their own abuse potential or capability of enhancing nicotine's effects (Smith & Stolerman, 2009); (d) withdrawal models that allow for further delineation of the mechanisms underlying possible adverse consequences of reduction (e.g., Harris, Pentel, Burroughs, Staley, & Lesage, 2011); and (e) methods incorporating tobacco smoke, tobacco extracts, or other known tobacco constituents to facilitate research on the aggregate contribution of constituents to abuse liability (e.g., Harris, Stepanov, Pentel, & Lesage, 2012).

*Human Testing: Brain Imaging*

Brain imaging is one method of obtaining insight into the effects of RNC cigarettes that may serve as an indicator of abuse liability. Several imaging techniques can be applied to study RNC cigarettes. Positron emission tomography (PET) can be used to determine the extent of occupancy of specific nicotinic receptor subtypes and the extent of dopamine release in certain regions of the brain in response to nicotine. For example, a β2 PET ligand has been developed to determine the extent of occupancy and saturation of α4β2 nicotinic cholinergic receptor (the receptor associated with the reinforcing effects of nicotine) in response to use of tobacco products. Interestingly, studies have shown almost complete saturation of α4β2 nicotinic acetylcholine receptors after smoking a single cigarette (Brody et al., 2006), whereas cigarettes with yields as low as 0.05 mg nicotine have been found to occupy about 25% of the α4β2 receptors (Brody, Mandelkern, Costello, et al., 2009). Likewise, studies have shown less striatal dopamine release when smoking 0.05-mg nicotine-yield cigarettes compared with normal nicotine-yield cigarettes (Brody, Mandelkern, Olmstead, et al., 2009).

PET and MRI imaging techniques can be used to measure the effects of nicotine reduction on cerebral blood flow (Rose et al., 2003), activation in specific regions of the brain in response to tasks that assess cognition, craving, or mood states (Azizian, Monterosso, O'Neill, & London, 2009; Brody et al., 2002; Ernst et al., 2001; Tang et al., 2012; Wang et al., 2007), and brain connectivity (e.g., greater connectivity of the insula in nonsmokers vs. smokers; Ghahremani et al., 2011). However, research linking these brain effects to clinical features of nicotine addiction or reinforcement is needed. To date, little is known about the relationship between these brain measures and behavioral or subjective measures of nicotine addiction.

*Human Testing: Laboratory Models*

Accurate predictions of the effects of nicotine reduction is facilitated by a fundamental understanding of dose-effect relationships between unit dose and outcomes such as the physiological and subjective effects of smoking, symptoms of nicotine withdrawal, smoking topography, and pattern of smoking over time. Methods for examining dose-effect relationships have been developed for both drugs (Carter & Griffiths, 2009) and tobacco products (Carter et al., 2009). Researchers have already used similar techniques for assessing RNC products including measures of the following: (a) pharmacokinetics, subjective (e.g., drug liking), behavioral, and other responses (Benowitz, Jacob, & Herrera, 2006); (b) self-administration and puff topography (Kassel, Greenstein, et al., 2007; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999); (c) behavioral economics (Donny, Houtsmuller, & Stitzer, 2007; Shahan, Bickel, Badger, & Giordano, 2001; Shahan, Bickel, Madden, & Badger, 1999); (d) drug discrimination (e.g., Perkins, Fonte, Sanders, Meeker, & Wilson, 2001); (e) drug choice (e.g., Hatsukami et al., 2011); and (f) withdrawal suppression (e.g., Breland, Buchhalter, Evans, & Eissenberg, 2002; Buchhalter, Schrinel, & Eissenberg, 2001).

Several factors are important to consider in collecting and interpreting dose–response data. First, chronic dosing with RNC cigarettes may be required to allow for changes in effects to emerge over time (e.g., extinction, changes in dependence, changes in tolerance, or resulting increased sensitivity to nicotine). Second, the context in which cigarettes are evaluated may have a significant impact on outcomes. For example, extinction of self-administration may unfold more rapidly in the laboratory (Donny, Houtsmuller, & Stitzer, 2007) than the real world (Donny & Jones, 2009). Thus, laboratory studies of RNC products should be complemented by clinical trials under more naturalistic conditions.

*Human Testing: Clinical Trials*

Clinical trials can help to explore the dose–response effects of RNC cigarettes to determine the threshold dose for nicotine self-administration, addiction, and extinction or cessation. These trials can also help to determine the best approach to reducing levels of nicotine in cigarettes and how different populations may respond to these different approaches. Finally, clinical trials can assess negative or unintended consequences from RNC cigarettes and methods to mitigate such adverse effects.

In principle, guidelines for conducting clinical pharmaceutical trials can be used to determine the threshold dose for nicotine reinforcement or addiction, but there may be design issues that are specific to tobacco-product evaluation. These

include recruiting a sample of subjects that varies in demographic and smoking history characteristics and that is large enough to examine data by potential moderator variables such as sex, race/ethnicity, age, social economic status, extent (light and heavy), and pattern (intermittent and daily) of smoking, level of dependence (e.g., FTND, cigarettes per day, time to first cigarette), extent of nicotine exposure (e.g., levels of total nicotine equivalents), rate of nicotine metabolism (e.g., trans-3'hydroxycotinine to cotinine ratio), psychiatric comorbidity including substance abuse, and possibly genotype (CYP2A6 genetic polymorphism, α5 nicotinic receptor genotype).

Depending on the research question that is being addressed, the trials may utilize a double-blind, randomized study design or they may be more reflective of "real world" use and not be blinded. Short-term inpatient or laboratory components can be added to clinical trials to further assess biomarkers of exposure and harm under highly controlled conditions and to capitalize on a population of smokers who have longer exposures to RNC cigarettes. Although trials of prolonged exposure to RNC cigarettes would be optimal, conducting studies for many months or years may not be feasible or necessary. Trials attempting to provide an understanding of potential long-term effects should minimally be 1 month in duration to allow adequate time for behavior change.

The primary outcome measures can be considered in three major categories: (a) beneficial impact, (b) acceptability, and (c) adverse consequences. Beneficial impact examines the effects of RNC cigarettes on (a) pattern and rate of tobacco use, (b) toxicant exposure, (c) dependence or trajectory of dependence of smoking experimenters, (d) number of quit attempts, and (e) cessation. Acceptability of the nicotine product involves measurement of (a) dropout rates and reasons for dropping out, (b) extent of compliance with product use, and (c) extent of experience with discomfort (e.g., withdrawal symptoms, craving, negative affect). Adverse negative consequences would include assessment of (a) compensatory smoking and toxicant exposure and effect, (b) mental, physical, and cognitive effects (e.g., manifestation of psychiatric disorder, fatigue, or cognitive impairment that may affect quality of life or performance), (c) uptake of alcohol, other drugs, or other high risk and unhealthy behaviors, and (d) potentially use of other tobacco products if used conjointly with RNC cigarettes, or product tampering. The primary challenge will be determining how to weigh the beneficial impact with acceptability and potential adverse consequences. Another challenge would be extrapolating results from short-term trials to long-term effects. Assessing the feasibility of RNC cigarettes will be strengthened by convergence of data and modeling public health effects using these data.

*Biomarkers as Outcomes*

Use of biomarkers for assessing exposure levels and the risk for nicotine addiction, cancer, and cardiovascular and pulmonary diseases are essential in examining the effects of RNC cigarettes. These following biomarkers are suggested based on prior studies showing sensitivity to change in smoking status, differences across tobacco products and/or predictive validity (Carmella et al., 2009; Hatsukami, Benowitz, Rennard, Oncken, & Hecht, 2006; Hecht, Yuan, & Hatsukami, 2010; Yuan et al., 2011, 2012), and targeting different pathophysiological mechanisms associated with disease (Hatsukami et al., 2006),

- Nicotine exposure: plasma or saliva cotinine, urinary total nicotine equivalents
- Carbon monoxide
- Carcinogen biomarkers: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides, *N*'-nitrosonornicotine and its glucuronide, phenanthrene-tetraol, and possibly the mercapturic acid metabolites of acrolein, benzene, and other toxic volatile organic chemicals
- Cardiovascular disease: exposure biomarkers—oxidants (e.g., 8-epi-PGF2), carbon monoxide, cotinine or urinary nicotine equivalents, acrolein (HPMA), and metabolites of butadiene (MHBMA); effect biomarkers—endothelial function, thrombosis, inflammation, glucose, lipid, and hemodynamic measures
- Pulmonary function tests

*Role of Other Tobacco and Medicinal/Pharmaceutical Products*

When examining the effects of RNC cigarettes, the potential interplay with other nicotine delivery products such as cigars, roll-your-own tobacco, various forms of smokeless tobacco, electronic cigarettes, and medicinal or pharmaceutical products, should be considered. A logical consideration would be to reduce nicotine levels in all products intended to be burned and smoked, while excluding other potentially less harmful products. Two types of studies would be of interest in this regard while individuals are switched to RNC cigarettes. One type of study would assess the extent of use of other tobacco and medicinal products. The other type of study would examine the effects of prescribing specific tobacco or medicinal products to mitigate any negative consequences to switching to RNC cigarettes (e.g., withdrawal symptoms). These types of studies might attempt to ascertain whether access to other products led to better or worse compliance with the ongoing use of RNC cigarettes and the resulting toxicity from dual- or poly-tobacco use. Another type of study would look at factors that might moderate the extent of use of other tobacco products (e.g., relative price, varying levels of access across products, product information).

*Considerations of Special Populations*

The majority of human laboratory or clinical trial studies have been conducted in adults. To date, only two laboratory studies on RNC cigarettes in adolescents were identified (Kassel, Evatt, et al., 2007; Kassel, Greenstein, et al., 2007). Yet, predicting the likely effects of RNC cigarettes in adolescents is of interest to determine their potential effects on uptake and continued use of cigarettes. Even results observed in young adults aged 18 to 25 may not be sufficient because of differences in reasons for initiation of tobacco use, brain development, psychosocial development, and sensitivity to nicotine (U.S. Department of Health and Human Services, 2012). Research with adolescents must be conducted with appropriate attention to ethical and confidentiality concerns, inclusion of appropriate education and behavioral interventions, and inclusion of short- and long-term monitoring.

Vulnerable populations such as those individuals who have mental illness also require special consideration, in large part, because of the high prevalence of comorbid disorders in smokers (Lasser et al., 2000). Mental illness is also predictive of persistent smoking (Goodwin, Pagura, Spiwak, Lemeshow, &

Sareen, 2011), suggesting greater difficulty with RNC cigarettes in this population. Despite barriers to quitting, a significant number of smokers with comorbid disorders report wanting to quit (Weinberger, Desai, & McKee, 2010). RNC cigarettes have been administered to smokers with schizophrenia in short-term laboratory studies. Surprisingly, these studies have observed no increase in withdrawal symptoms, psychiatric symptoms, and cognitive dysfunction when smokers switch to very low nicotine content cigarettes (Tidey, Rohsenow, Kaplan, Swift, & AhnAllen, 2012). Longer clinical trials will help advance understanding of the full impact of RNC cigarettes in this population.

### Consumer Perception and Response

Consumer attitudes, beliefs, and affective reactions toward a product will affect their behavioral responses to the product (Rees et al., 2009). Factors that contribute to consumer perception and use of a product include the product itself and its price, promotion, and placement. Therefore, examining RNC cigarettes must involve not only the assessment of the product, but also consumer responses to what is said about the product, how much it costs relative to other products, the marketing messages, claims, and labels associated with the product and its accessibility. These responses will also be affected by the availability and knowledge of other tobacco products and medicinal nicotine. For example, a recent survey showed a high level of support for decreasing levels of nicotine in cigarettes if nicotine was made easily available in non-cigarette forms (Fix et al., 2011). The best approach for this area of research would include both laboratory and survey studies that involve assessing experience with the product and manipulating how the product is priced, packaged, labeled, and promoted. Subjective measures would include expectancies regarding the product, affective responses to the product, subjective responses to the product, and amount of money they are willing to pay for the product. Potential successful outcomes could include increased desire to quit and decreased desire to initiate smoking. These outcomes will depend on how consumers perceive the benefits of reducing nicotine in cigarettes to themselves and public health.

### Other Constituents and Design Features

The initial primary target for reducing the addictiveness of a tobacco product is reducing nicotine exposure. Nevertheless, other factors that may contribute to the addiction potential of tobacco products should be considered. First, the magnitude of nicotine's effects is related to dose and speed of absorption, which are controlled by the product's formulation (U.S. Department of Health and Human Services, 2010). For example, physical design (e.g., filter ventilation, filter efficiency) and modulators of pH (e.g., addition of ammonia) can increase the unionized nicotine to total nicotine ratio, which could contribute to product addictiveness. Second, other chemicals may function alone or interact with nicotine to alter the addictive properties of smoking. Finally, other compounds may modulate the sensory effects of smoke. Examples of constituents and design features that could be studied are described in Table 2.

**Table 2. Constituents and Design Features Contributing to Addictiveness of Tobacco**

| Constituent/design | Methods/measures |
|---|---|
| Acetaldehyde and monamine oxidase inhibitors (MAOIs) | These ingredients produce synergistic addictive effects; acetaldehyde binds to biogenic amines forming MAOIs that can enhance the reinforcing effects of nicotine (Talhout, Opperhuizen, & van Amsterdam, 2007). |
| Diammonium phosphate, ammonia, urea, and organic salts | These ingredients and additives can increase the speed and efficiency of nicotine absorption by modifying smoke pH (Gordon, 1992). |
| Leaf position | Use of tobacco from lower stalk positions results in mainstream smoke with lower pH (Creighton, 1988). |
| Menthol and related additives | Certain additives to cigarettes at specific doses can produce cooling, smoothing, and conditioning effects reducing the irritation of smoke, which may alter users' smoking behavior (Yerger & McCandless, 2011). |
| Physical engineering | The size of the aerosol particles in smoke can change with different cigarette design features, puffing behavior, and the length of the remaining tobacco rod. Aerosol particle size could impact lung deposition and delivery of constituents and absorption of nicotine and toxins (Adam, McAughey, McGrath, Mocker, & Zimmermann, 2009). |
| Ventilation holes | Studies have shown that differences in tip ventilation can significantly impact the chemical and physical properties of smoke as it exits the cigarette (Watson, Trommel, & Ashley, 2004). |
| Cigarette elasticity | The elasticity of cigarettes contributes to the addiction potential by allowing smokers to obtain higher levels of constituents without having to change how they smoke (Anonymous, 1999). Cigarette elasticity can be a function of the cigarette paper, tipping paper, tobacco filler, and cellulose acetate filter. |
| Nicotine analogues | Tobacco industry documents indicate significant industry effort to identify or develop analogues of nicotine, which would have the same or enhanced biological activity (Neumann, 1988). It is important to evaluate how the presence of these analogues might negate any reduction in the addictive properties of tobacco resulting from a significant decrease in the level of nicotine. |

**Table 3. Research Priorities and Types of Studies to Address Priorities**

| Research topic | Type of studies |
|---|---|
| What is the nicotine content of combustible product that will prevent addiction and facilitate cessation? | • Animal studies to determine (a) the threshold dose for acquisition of nicotine self-administration in adolescent rats and the dose for maintenance in adolescent and adult rats, (b) the similarity or differences in the maintenance or extinction dose for adolescent rats compared with adult rats, (c) changes in sensitivity to nicotine dose during the extinction curve, and (d) differences in threshold dose for nicotine self-administration in pregnant vs. nonpregnant females.<br>• Human laboratory studies to (a) characterize rates and levels of nicotine absorption of varying RNC cigarettes, (b) examine comparative abuse liability of varying RNC cigarettes and moderating variables related to product regulation that may affect abuse liability (e.g., price, packaging, messaging), (c) determine change in the level of tolerance from prolonged use of RNC cigarettes that results in change in sensitivity to nicotine, and (d) examine individual differences in nicotine dose discrimination (age, race/ethnicity, sex, rate of metabolism).<br>• Human clinical studies to examine (a) dose–response effects from reduced nicotine cigarettes/combustible products, especially at low doses, (b) variability in responses, and (c) factors (e.g., sex, age, pattern of smoking, race/ethnicity) that may moderate these effects. |
| Is gradual or immediate reduction in nicotine the best approach to reducing nicotine in combustible products (greatest benefit and least risk) and how do different populations of smokers respond to these approaches? | • Human clinical studies to determine (a) the effects of the two approaches to reducing levels of nicotine in cigarettes in large-scale, multisite studies and (b) how different populations respond to reduced nicotine content cigarettes. |
| What are the optimal gradations for a gradual reduction strategy? What should be the length of time for each gradation? | • Human clinical studies to examine (a) responses to reduced nicotine cigarettes/combustible products across varying doses and factors (e.g., sex, age, pattern of smoking, race/ethnicity) that may moderate these effects and (b) length of time to achieve stability of responses to each dose |
| What are potential negative consequences and how do we minimize them? | • Human clinical studies and surveillance to identify (a) potential negative or unintended consequences and (b) methods that would minimize any negative consequences from nicotine reduction, including minimizing compensatory smoking behavior. Potential methods aimed at maximizing benefits include use of medicinal nicotine or other medications, availability of and access to cessation programs, availability of other tobacco products, educational campaigns including those aimed at health professionals, media campaigns targeted toward youth, and capitalizing on the impact of social networks. The role of other (nonsmoked) tobacco products and medicinal nicotine in a policy measure for reducing nicotine in cigarettes is of particular interest. Studies can prescribe the use of these products or allow open access to them to determine pattern of use and extent of toxicant exposure. Tobacco industry strategies in response to nicotine reduction must be anticipated. |
| Other studies | • Communication and educational approaches that examine (a) role of packaging, messaging, and marketing on product acceptance and perception and (b) product perception among adolescents including risks for addiction, personal danger of addiction, and susceptibility in trying a first cigarette.<br>• Assessing product characteristics that identify (a) additives to the tobacco product (e.g., acetylaldehyde, nornicotine, harman and norharmon), nicotine analogues, or design features (including elasticity) that enhance addictiveness of a product or encourage compensation; (b) nonpharmacological elements that enhance addictiveness of a product (flavorants); and (c) effective ways to reduce these product characteristics.<br>• Post RNC cigarette surveillance that monitors (a) adolescent and young adults responses to the RNC cigarette; (b) proportion of adolescents or young adults with negative reactions to their first cigarette; (c) rate of experimentation; (d) trajectory toward addiction among initiators (e.g., rate of continuation of smoking and dependence, rate of quitting, speed of progression to dependence); (e) rate of cessation among established users; (f) pattern of all tobacco use; and (g) anticipated unintended consequences. |

*Note.* RNC = reduced nicotine content.

### Unintended Consequences on the Marketplace

A market place where consumers had no access to addictive cigarettes may result in unintended consequences. Identification of these unintended consequences through specifically designed laboratory research studies, clinical trials, surveys, and postmarket surveillance will inform the development of risk management plans and help to minimize their impact. Below are the major unintended consequences that were described at the meeting and elsewhere (Henningfield et al., 1998):

- Increased availability of black market products, which do not meet the reduced nicotine level
- Use of other unregulated tobacco in roll-your-own cigarettes
- pH modification strategies or addition of other additives by the consumer or manufacturers
- Product tampering (e.g., addition of nicotine to product)

There may be effective ways to minimize unintended consequences by anticipating the needs of current users. One option to consider is whether a slow change in lowering nicotine levels in tobacco would minimize market pressure for unregulated products. A second approach could be encouragement of the use of products that are relatively nontoxic but deliver nicotine in an equivalent dose to cigarettes, including the use of products that come closer to matching the speed with which cigarettes deliver nicotine to the lungs and the brain. Certain products have already been developed that might meet this need, but they need to be properly evaluated and regulated. A third (and not exclusive) approach is to investigate the potential for more effective enforcement policies to discourage the development of black markets. The advantages and disadvantages of each of these approaches warrant discussion.

### Research Priorities and Types of Studies to Address Priorities

Table 3 summarizes and further describes the four research priorities that were identified from the meeting and additional studies that might contribute to understanding moderating factors and surveillance needs. Types of studies that can be conducted to address these priorities are described next to each research question. These questions are more easily addressed now that research cigarettes with varying nicotine content are available through the U.S. National Institute on Drug Abuse.

Regulatory bodies will be responsible for determining how much evidence is needed to support a policy of reducing the levels of nicotine in cigarettes as a mandated regulatory measure. That is, our research recommendations should not be construed as proposing that all of the questions need to be answered prior to adoption of such a policy. In fact, public health policies are often adopted on the basis of initial findings that support such an effort, even though key issues remain to be resolved, for example, public health policies to control the spread of malaria, HIV AIDS, and influenza. Similarly, it is conceivable that in light of current projections of unacceptable rates of tobacco-attributable morbidity and mortality for decades to come, a clinical trial of sufficient size and duration to better understand the risks and benefits of nicotine reduction would be sufficient to support implementation of such a policy. In fact, it is common in public health to address serious problems with approaches that are grounded in science, knowing that some additional evaluation and supporting research may also be needed to evaluate the impact of the policy (Centers for Disease Control and Prevention, 2011, 2012; Schlipkoter & Flahault, 2010; World Health Organization, 2012).

### Next Steps and Forming Collaborations

Some of the research questions that have been described are already being addressed by some investigators (e.g., optimal threshold dose for reducing cigarette/nicotine self-administration, gradual vs. immediate reduction in nicotine), whereas others (e.g., impact on light or experimental smokers) should be of high priorities for new research, which emphasizes the need for complementary collaboration. Several mechanisms can be used to move the science more efficiently forward and develop strategic collaborations: (a) Formation of working groups on: modeling to determine public health impacts of reducing levels of nicotine in cigarettes and to determine parameters that should be included in this model, animal and human research to discuss common measures and methods within and across species, and surveillance and risk management to identify items for surveillance including negative consequences and to discuss plans for risk management; and (b) creation of a coordinating center or an interactive Web site to ensure use of common measures, integration and sharing of data, and the capability of comparing across animal, human laboratory, and clinical studies.

In conclusion, legislative changes now make it possible for governments to specifically control the nicotine content of tobacco products. This provides a tremendous opportunity to explore new ways to reduce the prevalence of tobacco use and its toll on public health. The WHO Tobacco Regulation Study Group has concluded that nicotine regulation is vital to prevent dependence in new tobacco users and achieve abstinence in current users (World Health Organization, 2012). Although the regulation of tobacco products cannot be considered in isolation or as a higher priority than other tobacco control measures, it is an inescapable fact that nicotine in cigarettes is what sustains smoking. Analysis of tobacco industry documents highlights the concept that nicotine is essential to causing and sustaining tobacco use and addiction and was recognized by the tobacco industry before it was generally accepted among public health researchers. This was candidly stated in an R.J. Reynolds document in 1972: "*If, as proposed above, nicotine is the sine qua non of smoking, and if we meekly accept the allegations of our critics and move toward reduction or elimination of nicotine from our products, then we shall eventually liquidate our business*" (Teague, 1972). Reducing nicotine to levels that are not reinforcing will provide individuals a greater choice for whether they want to continue use of an extremely toxic product or quit.

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## DECLARATION OF INTERESTS

*Dorothy Hatsukami was funded by Nabi Biopharmaceuticals and NIDA to be a site for a nicotine immunotherapy trial. Neal Benowitz serves as consultant to several pharmaceutical companies that market smoking cessation medications and has been a paid expert witness in litigation against tobacco companies. Jack Henningfield and Mitch Zeller are employed by Pinney Associates, which provides consulting services to GlaxoSmithKline Consumer Healthcare on issues related to the treatment of tobacco dependence. Jack Henningfield also shares an interest on a potential oral nicotine gum replacement product and serves as an expert witness in litigation against the tobacco industry.*

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## REFERENCES

Adam, T., McAughey, J., McGrath, C., Mocker, C., & Zimmermann, R. (2009). Simultaneous on-line size and chemical analysis of gas phase and particulate phase of cigarette mainstream smoke. *Analytical and Bioanalytical Chemistry*, *394*(4), 1193–1203. doi:10.1007/s00216-009-2784-y

American Medical Association. (1998). *1998 annual meeting of the American Medical Association, reports of the Council on Scientific Affairs*. Retrieved from http://www.ama-assn.org/resources/doc/csaph/csaa-98.pdf

Anonymous. (1999). *The engineering of Canadian cigarettes: Legacy Tobacco Documents Library*. Retrieved from http://legacy.library.ucsf.edu/tid/tae73a99/pdf

Azizian, A., Monterosso, J., O'Neill, J., & London, E. D. (2009). Magnetic resonance imaging studies of cigarette smoking. *Handbook of Experimental Pharmacology*, *192*, 113–143. doi:10.1007/978-3-540-69248-5_5

Benowitz, N. L., Dains, K. M., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D., & Jacob, P., 3rd. (2012). Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiology, Biomarkers & Prevention*, *21*(5), 761–769. doi:10.1158/1055–9965.EPI-11–0644

Benowitz, N. L., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D., & Jacob, P., 3rd. (2007). Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology, Biomarkers & Prevention*, *16*(11), 2479–2485. doi:10.1158/1055–9965.EPI-07-0393

Benowitz, N. L., & Henningfield, J. E. (1994). Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *New England Journal of Medicine*, *331*(2), 123–125.

Benowitz, N. L., Jacob, P., 3rd, & Herrera, B. (2006). Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clinical Pharmacology and Therapeutics*, *80*(6), 703–714. doi:10.1016/j.clpt.2006.09.007

Breland, A. B., Buchhalter, A. R., Evans, S. E., & Eissenberg, T. (2002). Evaluating acute effects of potential reduced-exposure products for smokers: Clinical laboratory methodology. *Nicotine & Tobacco Research*, *4*(Suppl. 2), 131–140. doi:10.1080/1462220021000032780

Brody, A. L., Mandelkern, M. A., Costello, M. R., Abrams, A. L., Scheibal, D., Farahi, J., . . . Mukhin, A. G. (2009). Brain nicotinic acetylcholine receptor occupancy: Effect of smoking a denicotinized cigarette. *International Journal of Neuropsychopharmacology*, *12*(3), 305–316. doi:10.1017/S146114570800922X

Brody, A. L., Mandelkern, M. A., London, E. D., Childress, A. R., Lee, G. S., Bota, R. G., . . . Jarvik, M. E. (2002). Brain metabolic changes during cigarette craving. *Archives of General Psychiatry*, *59*(12), 1162–1172.

Brody, A. L., Mandelkern, M. A., London, E. D., Olmstead, R. E., Farahi, J., Scheibal, D., . . . Mukhin, A. G. (2006). Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. *Archives of General Psychiatry*, *63*(8), 907–915. doi:10.1001/archpsyc.63.8.907

Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Allen-Martinez, Z., Scheibal, D., Abrams, A. L., . . . London, E. D. (2009). Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. *Neuropsychopharmacology*, *34*(2), 282–289. doi:10.1038/npp.2008.87

Buchhalter, A. R., Schrinel, L., & Eissenberg, T. (2001). Withdrawal-suppressing effects of a novel smoking system: Comparison with own brand, not own brand, and denicotinized cigarettes. *Nicotine & Tobacco Research*, *3*(2), 111–118. doi:10.1080/14622200110042636

Carmella, S. G., Chen, M., Han, S., Briggs, A., Jensen, J., Hatsukami, D. K., & Hecht, S. S. (2009). Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. *Chemical Research in Toxicology*, *22*(4), 734–741. doi:10.1021/tx800479s

Carter, L. P., & Griffiths, R. R. (2009). Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug and Alcohol Dependence*, *105*(Suppl. 1), S14–S25. doi:10.1016/j.drugalcdep.2009.04.003

Carter, L. P., Stitzer, M. L., Henningfield, J. E., O'Connor, R. J., Cummings, K. M., & Hatsukami, D. K. (2009). Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiology, Biomarkers and Prevention*, *18*(12), 3241–3262. doi:10.1158/1055–9965.EPI-09-0948

Centers for Disease Control and Prevention. (2011). Ten great public health achievements—Worldwide, 2001–2010. *MMWR Morbidity & Mortality Weekly Report*, *60*(24), 814–818.

Centers for Disease Control and Prevention. (2012). *Global health—Global health initiatives*. Atlanta, GA: Author. Retrieved from http://www.cdc.gov/globalhealth/ghi/countries/countries.htm

Creighton, D. E. (1988). *The significance of pH in tobacco and tobacco smoke: Legacy Tobacco Documents Library*. Retrieved from http://legacy.library.ucsf.edu/tid/kjz02i00/pdf

D'Souza, M. S., & Markou, A. (2011). Neuronal mechanisms underlying development of nicotine dependence: Implications for novel smoking-cessation treatments. *Addiction Science & Clinical Practice*, *6*(1), 4–16.

Donny, E. C., Houtsmuller, E., & Stitzer, M. L. (2007). Smoking in the absence of nicotine: Behavioral, subjective and physiological effects over 11 days. *Addiction*, *102*(2), 324–334. doi:10.1111/j.1360-0443.2006.01670.x

Donny, E. C., & Jones, M. (2009). Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug and Alcohol Dependence*, *104*(1–2), 23–33. doi:10.1016/j.drugalcdep.2009.01.021

Donny, E. C., Taylor, T. G., LeSage, M. G., Levin, M., Buffalari, D. M., Joel, D., . . . Sved, A. F. (2012). The impact of tobacco regulation on animal research: New perspectives

and opportunities. *Nicotine & Tobacco Research*. Advance online publication. doi:10.1093/ntr/nts162

Ernst, M., Matochik, J. A., Heishman, S. J., Van Horn, J. D., Jons, P. H., Henningfield, J. E., . . . London, E. D. (2001). Effect of nicotine on brain activation during performance of a working memory task. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(8), 4728–4733. doi:10.1073/pnas.061369098

Fix, B. V., O'Connor, R. J., Fong, G. T., Borland, R., Cummings, K. M., & Hyland, A. (2011). Smokers' reactions to FDA regulation of tobacco products: Findings from the 2009 ITC United States survey. *BMC Public Health*, *11*, 941. doi:10.1186/1471-2458-11-941

Food and Drug Administration. (2010). *Draft guidance for industry: Assessment of abuse of potential of drugs*. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

Ghahremani, D. G., Galvan, A., Baker, C. M., McGlennen, K. M., Poldrack, R. A., & London, E. D. (2011, June 18–23). *Functional connectivity of insula cortex in human adolescent smokers and non-smokers*. Oral presentation at the College on Problems of Drug Dependence Annual Meeting, Hollywood, FL.

Goodwin, R. D., Pagura, J., Spiwak, R., Lemeshow, A. R., & Sareen, J. (2011). Predictors of persistent nicotine dependence among adults in the United States. *Drug and Alcohol Dependence*, *118*(2–3), 127–133. doi:10.1016/j.drugalcdep.2011.03.010

Gordon, D. L. (1992). *PM's global strategy: Marlboro product technology*. San Francisco: Legacy Tobacco Documents Library, University of California, San Francisco. Retrieved from http://legacy.library.ucsf.edu/tid/uft21f00

Gotti, C., Zoli, M., & Clementi, F. (2006). Brain nicotinic acetylcholine receptors: Native subtypes and their relevance. *Trends in Pharmacological Sciences*, *27*(9), 482–491. doi:10.1016/j.tips.2006.07.004

Gray, N., Henningfield, J. E., Benowitz, N. L., Connolly, G. N., Dresler, C., Fagerstrom, K., . . . Boyle, P. (2005). Toward a comprehensive long term nicotine policy. *Tobacco Control*, *14*(3), 161–165. doi:10.1136/tc.2004.010272

Greenwald, M. K., & Hursh, S. R. (2006). Behavioral economic analysis of opioid consumption in heroin-dependent individuals: Effects of unit price and pre-session drug supply. *Drug and Alcohol Dependence*, *85*(1), 35–48. doi:10.1016/j.drugalcdep.2006.03.007

Harris, A. C., Pentel, P. R., Burroughs, D., Staley, M. D., & Lesage, M. G. (2011). A lack of association between severity of nicotine withdrawal and individual differences in compensatory nicotine self-administration in rats. *Psychopharmacology (Berl)*, *217*(2), 153–166. doi:10.1007/s00213-011-2273-9

Harris, A. C., Stepanov, I., Pentel, P. R., & Lesage, M. G. (2012). Delivery of nicotine in an extract of a smokeless tobacco product reduces its reinforcement-attenuating and discriminative stimulus effects in rats. *Psychopharmacology (Berl), 220*(3), 565–576. doi:10.1007/s00213-011-2514-y

Hatsukami, D., Benowitz, N. L., Rennard, S. I., Oncken, C., & Hecht, S. S. (2006). Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine & Tobacco Research*, *8*(4), 600–622. doi:10.1080/14622200600858166

Hatsukami, D., Biener, L., Leischow, S. J., & Zeller, M. R. (2012). Tobacco and nicotine product testing. *Nicotine & Tobacco Research*, *14*(1), 7–17. doi:10.1093/ntr/ntr027

Hatsukami, D., Jensen, J., Anderson, A., Broadbent, B., Allen, S., Zhang, Y., & Severson, H. (2011). Oral tobacco products: Preference and effects among smokers. *Drug and Alcohol Dependence*, *118*(2–3), 230–236. doi:10.1016/j.drugalcdep.2011.03.026

Hatsukami, D., Kotlyar, M., Hertsgaard, L. A., Zhang, Y., Carmella, S. G., Jensen, J. A., . . . Hecht, S. S. (2010). Reduced nicotine content cigarettes: Effects on toxicant exposure, dependence and cessation. *Addiction*, *105*(2), 343–355. doi:10.1111/j.1360-0443.2009.02780.x

Hatsukami, D., Perkins, K. A., Lesage, M. G., Ashley, D. L., Henningfield, J. E., Benowitz, N. L., . . . Zeller, M. (2010). Nicotine reduction revisited: Science and future directions. *Tobacco Control*, *19*(5), e1–e10. doi:10.1136/tc.2009.035584

Hecht, S. S., Yuan, J. M., & Hatsukami, D. (2010). Applying tobacco carcinogen and toxicant biomarkers in product regulation and cancer prevention. *Chemical Research in Toxicology*, *23*(6), 1001–1008. doi:10.1021/tx100056m

Henningfield, J., Benowitz, N. L., Slade, J., Houston, T. P., Davis, R. M., & Deitchman, S. D. (1998). Reducing the addictiveness of cigarettes. Council on Scientific Affairs, American Medical Association. *Tobacco Control*, *7*(3), 281–293. doi:10.1136/tc.7.3.281

Hursh, S. R., Galuska, C. M., Winger, G., & Woods, J. H. (2005). The economics of drug abuse: A quantitative assessment of drug demand. *Molecular Interventions*, *5*(1), 20–28. doi:10.1124/mi.5.1.6

Hursh, S. R., & Silberberg, A. (2008). Economic demand and essential value. *Psychological Review*, *115*(1), 186–198. doi:10.1037/0033-295X.115.1.186

Institute of Medicine. (2012). *Scientific standards for studies on modified risk tobacco products*. Washington, DC: National Academies Press.

Kassel, J. D., Evatt, D. P., Greenstein, J. E., Wardle, M. C., Yates, M. C., & Veilleux, J. C. (2007). The acute effects of nicotine on positive and negative affect in adolescent smokers. *Journal of Abnormal Psychology*, *116*(3), 543–553. doi:10.1037/0021-843X.116.3.543

Kassel, J. D., Greenstein, J. E., Evatt, D. P., Wardle, M. C., Yates, M. C., Veilleux, J. C., & Elssenberg, T. (2007). Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers. *Journal of Adolescent Health*, *40*(1), 54–60. doi:10.1016/j.jadohealth.2006.08.006

Kuryatov, A., Berrettini, W., & Lindstrom, J. (2011). Acetylcholine receptor (AChR) alpha5 subunit variant associated with risk for nicotine dependence and lung cancer reduces (alpha4beta2)alpha5 AChR function. *Molecular Pharmacology*, *79*(1), 119–125. doi:10.1124/mol.110.066357

Lanza, S. T., Donny, E. C., Collins, L. M., & Balster, R. L. (2004). Analyzing the acquisition of drug self-administration using growth curve models. *Drug and Alcohol Dependence*, *75*(1), 11–21. doi:10.1016/j.drugalcdep.2004.02.006

Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D., & Bor, D. H. (2000). Smoking and mental illness. *Journal of American Medical Association*, *284*(20), 2606–2610. doi:10.1001/jama.284.20.2606

Neumann, C. L. (1988). *Nicotine analogs: Known compounds: Legacy Tobacco Documents Library*. Retrieved from http://legacy.library.ucsf.edu/tid/huv46b00/pdf

O'Connor, R. J., Cummings, K. M., Giovino, G. A., McNeill, A., & Kozlowski, L. T. (2006). How did UK cigarette makers reduce tar to 10 mg or less? *British Medical Journal*, *332*(7536), 302. doi:10.1136/bmj.332.7536.302

Perkins, K. A., Fonte, C., Sanders, M., Meeker, J., & Wilson, A. (2001). Threshold doses for nicotine discrimination in smokers and non-smokers. *Psychopharmacology (Berl)*, *155*(2), 163–170. doi:10.1007/s002130000660

Pickworth, W. B., Fant, R. V., Nelson, R. A., Rohrer, M. S., & Henningfield, J. E. (1999). Pharmacodynamic effects of new de-nicotinized cigarttes. *Nicotine & Tobacco Research*, *1*, 357–364. doi:10.1080/14622299050011491

Rees, V. W., Kreslake, J. M., Cummings, K. M., O'Connor, R. J., Hatsukami, D. K., Parascandola, M., . . . Connolly, G. N. (2009). Assessing consumer responses to potential reduced-exposure tobacco products: A review of tobacco industry and independent research methods. *Cancer Epidemiology, Biomarkers and Prevention*, *18*(12), 3225–3240. doi:10.1158/1055–9965.EPI-09-0946

Rose, J. E., Behm, F. M., Westman, E. C., Mathew, R. J., London, E. D., Hawk, T. C., . . . Coleman, R. E. (2003). PET studies of the influences of nicotine on neural systems in cigarette smokers. *American Journal of Psychiatry*, *160*(2), 323–333. doi:10.1176/appi.ajp.160.2.323

Saccone, N. L., Saccone, S. F., Hinrichs, A. L., Stitzel, J. A., Duan, W., Pergadia, M. L., . . . Bierut, L. J. (2009). Multiple distinct risk loci for nicotine dependence identified by dense coverage of the complete family of nicotinic receptor subunit (CHRN) genes. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *150B*(4), 453–466. doi:10.1002/ajmg.b.30828

Schlipkoter, U., & Flahault, A. (2010). Communicable diseases: Achievements and challenges for public health. *Public Health Reviews*, *32*(1), 90–119.

Shahan, T. A., Bickel, W. K., Badger, G. J., & Giordano, L. A. (2001). Sensitivity of nicotine-containing and de-nicotinized cigarette consumption to alternative non-drug reinforcement: A behavioral economic analysis. *Behavioural Pharmacology*, *12*(4), 277–284.

Shahan, T. A., Bickel, W. K., Madden, G. J., & Badger, G. J. (1999). Comparing the reinforcing efficacy of nicotine containing and de-nicotinized cigarettes: A behavioral economic analysis. *Psychopharmacology (Berl)*, *147*(2), 210–216. doi:10.1007/s002130051162

Smith, J. W., & Stolerman, I. P. (2009). Recognising nicotine: The neurobiological basis of nicotine discrimination. *Handbook of Experimental Pharmacology*, *192*, 295–333. doi:10.1007/978-3-540-69248-5_11

Stratton, K., Shetty, P., Wallace, R., & Bondurant, S. (Eds.). (2001). *Clearing the smoke: Assessing the science base for tobacco harm reduction*. Washington, DC: National Academy Press.

Talhout, R., Opperhuizen, A., & van Amsterdam, J. G. (2007). Role of acetaldehyde in tobacco smoke addiction. *European Neuropsychopharmacology*, *17*(10), 627–636. doi:10.1016/j.euroneuro.2007.02.013

Tang, D. W., Hello, B., Mroziewicz, M., Fellows, L. K., Tyndale, R. F., & Dagher, A. (2012). Genetic variation in CYP2A6 predicts neural reactivity to smoking cues as measured using fMRI. *Neuroimage*, *60*(4), 2136–2143. doi:10.1016/j.neuroimage.2012.01.119

Teague, C., Jr. (1972). R.J. Reynolds confidential research planning memorandum on the nature of the tobacco business and the crucial role of Nicotine therein. Winston-Salem, NC: R.J. Reynolds.

Tengs, T. O., Ahmad, S., Savage, J. M., Moore, R., & Gage, E. (2005). The AMA proposal to mandate nicotine reduction in cigarettes: A simulation of the population health impacts. *Preventive Medicine*, *40*(2), 170–180. doi:10.1016/j.ypmed.2004.05.017

Thorgeirsson, T. E., Geller, F., Sulem, P., Rafnar, T., Wiste, A., Magnusson, K. P., . . . Stefansson, K. (2008). A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature*, *452*(7187), 638–642. doi:10.1038/nature06846

Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., Swift, R. M., & AhnAllen, C. G. (2012). Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schoziphrenia and controls. *Nicotine & Tobacco Research*, 15(1), 121–129. doi:10.1093/ntr/nts098

Tuesta, L. M., Fowler, C. D., & Kenny, P. J. (2011). Recent advances in understanding nicotinic receptor signaling mechanisms that regulate drug self-administration behavior. *Biochemical Pharmacology*, *82*(8), 984–995. doi:10.1016/j.bcp.2011.06.026

U.S. Department of Health and Human Services. (2010). *How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease. A report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

U.S. Department of Health and Human Services. (2012). *Preventing tobacco use among youth and young adults: A report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services. Retrieved from http://www.surgeongeneral.gov/library/preventing-youth-tobacco-use/index.html

Walker, N., Howe, C., Bullen, C., Grigg, M., Glover, M., McRobbie, H., . . . Whittaker, R. (2012). The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: A randomized controlled trial. *Addiction*. Advance online publication. doi:10.1111/j.1360-0443.2012.03906.x

Wang, Z., Faith, M., Patterson, F., Tang, K., Kerrin, K., Wileyto, E. P., . . . Lerman, C. (2007). Neural substrates of abstinence-induced cigarette cravings in chronic smokers. *Journal of Neuroscience*, *27*(51), 14035–14040. doi:10.1523/JNEUROSCI.2966-07.2007

Watson, C. H., Trommel, J. S., & Ashley, D. L. (2004). Solid-phase microextraction-based approach to determine free-base nicotine in trapped mainstream cigarette smoke total particulate matter. *Journal of Agricultural and Food Chemistry*, *52*(24), 7240–7245. doi:10.1021/jf049455o

Weinberger, A. H., Desai, R. A., & McKee, S. A. (2010). Nicotine withdrawal in U.S. smokers with current mood, anxiety, alcohol use, and substance use disorders. *Drug and Alcohol Dependence*, *108*(1–2), 7–12. doi:10.1016/j.drugalcdep.2009.11.004

World Health Organization. (2012). *WHO study group on tobacco product regulation. Report on the scientific basis of tobacco product regulation (Vol. WHO Technical Report Series, no. 967).* Geneva, Switzerland: Author. Retrieved from http://www.who.int/tobacco/publications/prod_regulation/trs_967/en/index.html

Yerger, V. B., & McCandless, P. M. (2011). Menthol sensory qualities and smoking topography: A review of tobacco industry documents. *Tobacco Control*, *20*(Suppl. 2), ii37–ii43. doi:10.1136/tc.2010.041988

Yuan, J. M., Gao, Y. T., Murphy, S. E., Carmella, S. G., Wang, R., Zhong, Y., . . . Hecht, S. S. (2011). Urinary levels of cigarette smoke constituent metabolites are prospectively associated with lung cancer development in smokers. *Cancer Research*, *71*(21), 6749–6757. doi:10.1158/0008-5472.CAN-11–0209

Yuan, J. M., Gao, Y. T., Wang, R., Chen, M., Carmella, S. G., & Hecht, S. S. (2012). Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers. *Carcinogenesis*, *33*(4), 804–809. doi:10.1093/carcin/bgs026

Zeller, M., Hatsukami, D., & Strategic Dialogue on Tobacco Harm Reduction Group. (2009). The Strategic Dialogue on Tobacco Harm Reduction: A vision and blueprint for action in the US. *Tobacco Control*, *18*(4), 324–332. doi:10.1136/tc.2008.027318