Dear [Name],

Please find the paper on nicotine reduction and the ENDS documents attached. Kindly let me know if there is anything else you need.

Regards,

[Name]

---

From: [Name]@ec.europa.eu
Sent: 06 November 2013 12:59
To: [Name]@ec.europa.eu; [Name]
Subject: RE: Background Documents

Dear [Name],

I think you are missing the ENDS document and another paper on nicotine reduction.

I will ask my colleague, [Name] to send to you.

Regards,

[Name]

---

From: [Name]@ec.europa.eu
Sent: 06 November 2013 12:19
To: [Name]
Subject: Background Documents

Dear [Name],

Looking through the topics that will be discussed at TobReg and the documents I have received, it seems that I am missing some papers. I have for the moment only the following 4: modified risk products, nicotine reduction, smokeless tobacco and ammonia rebuttal.

Could you possibly check and resend me whatever is missing?

Thank you very much and best regards,

[Name]
From: **********
Sent: Wednesday, November 06, 2013 11:59 AM
To: **********
Subject: RE: my coordinates

Excellent! ;)

From: ec.europa.eu
Sent: 06 November 2013 11:59
To: **********
Subject: RE: my coordinates

Dear **********,

Thanks a lot. By the way, it looks good for the flight, there seems to be a later flight out of Rio (short before midnight) which would still bring me back on Saturday (I have to be back Sunday by all means).

Thanks a lot again,

best,

From: **********
Sent: Wednesday, November 06, 2013 11:56 AM
To: **********
Subject: my coordinates

Hello **********,

Here is my signature.
Reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction

Geoff Ferris Wayne
Report to World Health Organization/ SacTob
Oct 16, 2013
DRAFT

I. Introduction
II. Tobacco addictiveness model
III. Establishing a threshold for addiction
IV. Feasibility of nicotine reduction
V. Potential behavioral and population outcomes
VI. Policy approaches to nicotine reduction
VII. Conclusions
VIII. Recommendations
I. Introduction

Nearly two decades ago, Benowitz and Henningfield (1994) proposed a gradual reduction of nicotine in cigarettes as a potential strategy for harm reduction. A number of health scientists have since concluded that such an approach could have a significant and positive impact on public health (Benowitz and Henningfield 2013; Gray et al. 2005; Hatsukami et al. 2013a; Henningfield et al. 1998; Smith et al. 2013; Tengs et al. 2005; Zeller et al. 2009). The goals of a nicotine reduction policy are to reduce pharmacologic addiction in smokers, making it easier for them to quit, or encouraging them to transition to less harmful sources of nicotine, while preventing novice smokers from transitioning from experimental or occasional smoking to cigarette addiction (Benowitz and Henningfield 2013; Henningfield et al. 1998). This strategy is consistent with Article 9 of the Framework Convention on Tobacco Control (FCTC), which addresses the need to develop guidelines for regulating the contents and emissions of tobacco products (World Health Organization 2003; World Health Organization 2012).

A nicotine reduction strategy is premised on the assumption that nicotine is primarily responsible for supporting cigarette use, and that a threshold level of nicotine can be identified below which the acquisition and maintenance of cigarette dependence will be substantially reduced (Henningfield et al. 1998). Thus, there are both theoretical and practical questions which must be addressed in evaluating the likely outcomes of this approach: the role of nicotine in initiating and sustaining tobacco addiction, the amount of nicotine necessary for addiction, differences due to the chemical form or delivery mechanisms of nicotine, the degree of variation in response to nicotine among individuals or key populations such as children and those with mental illness, processes for reducing nicotine in tobacco and their potential effects, behavioral responses to reduced nicotine cigarettes such as compensatory or increased smoking in nicotine addicted smokers, and relative toxicity of reduced nicotine cigarettes.
An early obstacle to evaluating the potential outcomes of a nicotine reduction strategy was the lack of an existing science base. For example, an initial concern was the potential for reduced nicotine products to increase the toxicity of cigarette use as a result of more intense or more frequent smoking (Jarvis and Bates 1999; Shatenstein 1999). More recent clinical studies appear to address this concern, demonstrating substantial reductions in smoking and reduced exposure to toxins with little compensation even at very low doses of nicotine (Benowitz et al. 2012; Benowitz et al. 2007; Hatsukami et al. 2010a). This report will review the state of the science with respect to tobacco and nicotine addiction (section II), the concept of a threshold for nicotine addiction (section III), and the practical feasibility of reducing nicotine in cigarettes below the threshold for addiction (section IV).

Environmental factors are also known to affect adoption and use of tobacco products, and would likely play a critical role in the outcome of a nicotine reduction strategy. Factors to be considered include the relative availability of alternate sources of nicotine, the degree of regulation of alternative products, potential growth of illicit sales of high nicotine cigarettes, availability of treatment for dependence, education of smokers and potential smokers regarding use, withdrawal, and treatment, and public support for regulation of nicotine. For example, lack of accessibility or appeal of less toxic nicotine delivery systems and treatment medications are more likely to spur illicit sales or drive smokers to other potentially harmful tobacco product (Henningfield et al. 2004b). This report will review population outcomes that may be anticipated as a result of a nicotine reduction strategy (section V), and policy approaches necessary to support this strategy and minimize unintended or negative health consequences to nicotine reduction (section VI).

The Institute of Medicine report “Clearing the Smoke” (Stratton et al. 2001) provides a useful framework for assessing tobacco product harm in relation both to a product’s toxicity as well as those factors that encourage experimentation and use (see also (Hatsukami et al. 2012; Zeller et al. 2009). Cigarettes and other burned tobacco are not only highly toxic in comparison to alternatives such as medicinal nicotine, but have
unmatched potential for harm due to their greater availability, addictiveness, and appeal. A nicotine reduction strategy could substantially reduce population harm, even in the absence of reducing toxicity, by decreasing incentives to begin or continue use of these deadly products (Zeller et al. 2009). This report assesses the likelihood of such an outcome based on the available science base, and identifies those areas in which additional research is needed (section VII).

II. Tobacco addictiveness model

Early efforts to reduce the disease burden of smoking relied on product-driven reductions in cigarette smoke delivery. This was achieved primarily through the introduction of filter ventilation to dilute the smoke, alongside use of expanded tobacco and other product changes (Hoffmann and Hoffmann 1997). However, smokers simply compensated for reduced delivery by altering their smoking behavior, puffing longer and more frequently, or increasing the number of cigarettes smoked per day, maintaining their exposure to both nicotine and toxins (Benowitz et al. 2005; National Cancer Institute 2001).

In a historical analysis, Parascandola (2011) observed that the failure of past tobacco harm reduction efforts resulted from an incomplete understanding within the public health community of the factors controlling smoking behavior, and in particular, the role of nicotine in driving that behavior. A nicotine reduction strategy follows directly from the assumption that nicotine is the primary psychoactive drug in tobacco and the key to ongoing tobacco use. However, the state of the science on nicotine addiction and tobacco use is evolving. Anticipating the consequences of product regulation—both intended and unintended—requires a clear and complete understanding of nicotine and tobacco dependence.

II.a. Nicotine addiction
Nicotine is a highly addictive and potent drug, generating psychoactive and rewarding effects at acutely administered doses of less than 1 mg (Benowitz 2008). Low doses of nicotine produce central or peripheral nervous system stimulation, arousal, enhanced mood, and increase in heart rate or blood pressure, while high doses may result in bradycardia, hypotension, and depressed mental status. Nicotine also improves motor reflex and cognitive performance including attention and memory (Heishman et al. 2010). Tolerance to the behavioral and cardiovascular effects of nicotine develops rapidly with repeated exposure. Thus, the pharmacologic basis of nicotine addiction combines positive reinforcements (arousal, mood, performance) alongside the avoidance of withdrawal symptoms that arise in the absence of nicotine (Benowitz 2008; DiFranza et al. 2010a).

The addiction potential of a nicotine delivery system varies as a function of its dosing mechanism, including the speed with which it can deliver nicotine and the ease with which nicotine can be extracted (Henningfield et al. 2011; Wayne and Carpenter 2009). Cigarettes provide a particularly effective form of delivery. When an individual inhales smoke from a cigarette, nicotine from the tobacco is carried in smoke particles into the lungs, where it is rapidly absorbed and carried to the brain. Nicotine diffuses readily into brain tissue, binding to nicotinic cholinergic receptors (nAChRs). The gradual absence of nicotine following extinction of smoking results in subnormal release of dopamine and other neurotransmitters, experienced as malaise and inability to experience pleasure. Other symptoms of nicotine withdrawal include irritability, restlessness, anxiety, difficulty concentrating, decreased heart rate, increased appetite, and inability to sleep (Benowitz 2008).

Cigarette addiction is maintained through repeated behaviors. The first cigarette of the day produces substantial pharmacologic effect and enhanced mood. With subsequent smoking, there is an accumulation of nicotine in the body, resulting in a greater level of tolerance, and withdrawal symptoms become more pronounced between successive cigarettes. Most smokers tend to take in the same amount of nicotine from day to day. Smokers adjust their smoking behavior to compensate for changes in the availability of
nicotine or in the rate of elimination of nicotine from the body in order to regulate the body levels of nicotine (Benowitz 2008).

Compulsion is a core feature of tobacco addiction, characterized by wanting, craving or needing to smoke that recurs after each cigarette (DiFranza et al. 2010b). When defined to include withdrawal symptoms, compulsion has 99% sensitivity in identifying which novice smokers will progress to established smoking (DiFranza et al. 2007a; DiFranza et al. 2007b; Wellman et al. 2004).

II.b. Individual variability in response to nicotine

Most tobacco use begins in adolescence. While many youth try cigarette smoking, only 20–25% of those who experiment with cigarettes become addicted adult smokers (Institute of Medicine 1994). Genetic vulnerability to nicotine dependence may explain the transition to tobacco use for some. Twin studies indicate greater than 50% heritability in prevalence of cigarette smoking, number of cigarettes smoked per day, ability to quit smoking, and nature of withdrawal symptoms experienced at quitting (Lessov-Schlaggar et al. 2008). Other risk factors for smoking include peer and parental influence and individual personality traits such as depression or anxiety (Institute of Medicine 1994).

Early exposure to nicotine is associated with more severe nicotine dependence and increased smoking behaviors among adult smokers (Benowitz and Henningfield 1994; Breslau and Peterson 1996; Cui et al. 2006; Lando et al. 1999; Taioli and Wynder 1991). These findings mirror animal studies, in which exposure during adolescence produces both increased reward and higher levels of self-administration (Adriani et al. 2002; Adriani et al. 2003; Kota et al. 2008; Levin et al. 2007; Trauth et al. 1999; Trauth et al. 2000; Vastola et al. 2002). These findings suggest that the developing brain may be more susceptible to permanent changes caused by nicotine exposure that support addiction (Benowitz 2008; Hatsukami et al. 2010b).
A high (approximately fourfold) individual variability has been observed in rate of metabolism of nicotine (Hatsukami et al. 2010b; Hukkanen et al. 2005). Women metabolize nicotine faster than men (Benowitz 2008; Benowitz et al. 2006b), which could contribute to a higher level of addiction. Women have greater sensitivity to nicotine than men (Sofuoglu and Mooney 2009), and more difficulty quitting smoking (Eissenberg et al. 1999; Fant et al. 1996; Gritz et al. 1996; Perkins et al. 1999; Wetter et al. 1999). Smoking behavior in women is more highly influenced by conditioned cues and by negative affect, while men are more likely to smoke in response to pharmacologic cues and regulation of nicotine intake (Bevins and Caggiula 2009; Carpenter et al. 2005; Perkins et al. 2006; Perkins et al. 1997).

Individuals with psychiatric and/or substance abuse disorders have much higher rates of nicotine dependence, smoke more cigarettes per day, and have more difficulty quitting (Lasser et al. 2000; Lawrence et al. 2010; McClave et al. 2010; Williams and Ziedonis 2004; Ziedonis et al. 2008). Nicotine use may function as a form of self-medication for some disorders (Schroeder and Morris 2010), particularly schizophrenia, where nicotine can improve deficient sensory gating (Leonard and Adams 2006; Leonard et al. 2001), and depression, where nicotine may desensitize nicotinic receptors in a manner functionally similar to many antidepressant drugs (Mineur and Picciotto 2009; Mineur and Picciotto 2010). In addition, smoking (but not nicotine) inhibits brain monoamine oxidase, which could contribute to antidepressant actions (Lewis et al. 2007). Smokers with mental illness constitute more than a third of all smokers and more than half of nicotine-dependent smokers (Grant et al. 2004; Lasser et al. 2000; Lawrence and Mitrou 2009).

A subset of light or occasional smokers consumes five or fewer cigarettes per day or nondaily, and appears to smoke primarily for the positive reinforcing effects of nicotine (Benowitz 2008). These smokers use cigarettes primarily in association with specific activities, such as after meals or with alcohol, and less in response to negative affect, and may be more reactive to smoking cues (Watson et al. 2010). Although they experience minimal or no withdrawal symptoms, many of these occasional smokers
have difficulty quitting, suggesting dependence but in a form distinct from that of everyday smokers.

II.c. Tobacco delivered nicotine

Tobacco smoke is a complex mixture containing several thousand individual compounds (Hoffmann and Hoffmann 1997; Wayne and Carpenter 2009), that may contribute to a cigarette’s addictive properties either independently (Plescia et al. 2013) or in combination with nicotine (Talhout et al. 2007; Villegier et al. 2007).

Nicotine in its unprotonated or free-base form may be readily absorbed through the oral mucosa and upper respiratory tract, as in the case of smokeless tobaccos or cigars. When inhaled in this form, nicotine is characterized by a stinging sensation or “bite” in the upper respiratory tract, which may be considered too irritating or unpalatable to be acceptable to smokers. Alternately, in cigarette smoke, a large percentage of nicotine remains in the protonated or bound form, where nicotine is more easily inhaled and carried deep within the respiratory tract. However, bound nicotine may not be absorbed as quickly or readily, and it does not provide the same sensory stimulus of unprotonated nicotine (Pankow 2001; Wayne and Carpenter 2009).

Modern cigarette construction seeks to provide an ideal balance between efficiency and palatability of nicotine delivery. For example, high ammonia content tobacco can increase the proportion of unprotonated nicotine in cigarette smoke, supporting more rapid or efficient absorption of nicotine (Henningfield et al. 2004a). Sugars or other additives may then be employed to offset the harshness of unprotonated nicotine and facilitate deeper inhalation (Wayne and Carpenter 2009).

The sensory characteristics (taste, aroma, tracheobronchial sensations) of tobacco smoke provide direct cues for the smoker, guiding smoking behaviors at the level of the individual puff (Carpenter et al. 2007; Rose 2006). Motoric components of cigarette use (handling, puffing, inhaling) are not capable of eliciting a significant degree of
Nicotine reduction satisfaction among smokers in the absence of sensory components, as indicated by smoking studies conducted using unlit cigarettes (Brelan et al. 2002). On the other hand, variations in sensory components such as taste and impact may have significant effects on measures of smoking reward (Perkins et al. 2001b; Rose 2006). For example, attenuating olfactory and taste cues diminishes both enjoyment and behaviorally reinforcing effects of cigarette smoke, particularly among female smokers (Rose 2006; Rose and Behm 2004b).

Nicotine plays a central role in the sensory composition of cigarette smoke. Nicotine-containing cigarettes are consistently rated as stronger than denicotinized cigarettes in terms of perceived respiratory tract sensations (Rose and Behm 2004a; Rose and Behm 2004b). Nicotine aerosol inhalation elicits strong irritant effects (Lee et al. 1993) and even IV nicotine infusions can elicit respiratory tract sensations (Henningfield and Goldberg 1983; Rose et al. 2000).

Some balance of smoke constituents is necessary to offset the excessive harshness of nicotine and make tobacco smoke palatable. “Tar” is a common measure of the total particulates in smoke excluding nicotine; the ratio of tar/nicotine has been found to be a key determinant of the overall harshness of smoke (Rose 2006; Rose et al. 1999). Alternately, some tobacco constituents may provide additional stimulus either alongside of or in place of nicotine (Wayne and Carpenter 2009). Menthol is a common tobacco additive with strong sensory stimulant properties, and has been used to compensate for reduced nicotine in extremely low delivery products (Celebucki et al. 2005; Ferris Wayne and Connolly 2004). Menthol may also attenuate some of the irritant effects of nicotine by virtue of its local anesthetic properties (Galeotti et al. 2001), and increases the permeability of biological membranes (Shojaei et al. 1999), which could conceivably influence nicotine absorption.

Some non-nicotine smoke components may have direct pharmacologic effects on the brain or interact with nicotine’s reinforcing effects. Brody et al. (2009) demonstrated significant α4β2* nAChR occupancy from smoking a denicotinized cigarette, suggesting
that even in the absence of nicotine, tobacco smoke may produce measurable pharmacologic effects. Various minor tobacco alkaloids are reinforcing either on their own (nornicotine) or by potentiating the effects of nicotine (anabasine, nornicotine, anatabine, cotinine and myosmine) (Bardo et al. 1999; Clemens et al. 2009). Acetaldehyde is self-administered by animals (Plescia et al. 2013), and has been shown to potentiate the reinforcing effects of nicotine, especially in adolescence (Belluzzi et al. 2005; Cao et al. 2007; Rodd-Henricks et al. 2002; Talhout et al. 2007).

Harman and salsolinol are condensation products of acetaldehyde that inhibit monoamine oxidase (MAO) (Talhout et al. 2007). MAO inhibitors increase response rates substantially when given to rats self-administering nicotine (Guillem et al. 2005; Guillem et al. 2008; Villégier et al. 2007) (Guillem et al. 2005; Villégier et al., 2007), possibly by exerting antidepressant effects on their own, or by potentiating the reinforcing effects of nicotine by increasing the lifetime of neurotransmitters such as dopamine after their release is evoked by nicotine (Rose et al. 2001).

II.d. Dual-reinforcement model of addiction

Although the addictive properties of tobacco are often attributed exclusively to nicotine (USDHHS 1988) the reinforcing effects of nicotine in the absence of tobacco have not been conclusively shown using blinded protocols (Dar and Frenk 2004; Fulton and Barrett 2008). As with other psychostimulant drugs, nicotine produces unconditioned effects that increase the ability of non-drug stimuli to serve as conditioned reinforcers, independently of any direct association between nicotine administration and stimulus presentation (Caggiula et al. 2002; Chaudhri et al. 2007; Chaudhri et al. 2006; Olausson et al. 2003; Olausson et al. 2004; Palmatier et al. 2007a; Palmatier et al. 2007b).

The critical role played by non-drug stimuli has been demonstrated in rodent studies, where discontinuing environmental stimuli associated with intravenous nicotine injection decreases self-administration behavior almost as effectively as the removal of nicotine itself (Caggiula et al. 2002; Le Foll and Goldberg 2005). In experiments with rats
(Cohen et al. 2005) and squirrel monkeys (Le Foll et al. 2007) the response rate maintained by nicotine-associated light stimuli is equal to the responding maintained by nicotine. By contrast, the use of behavioral procedures without environmental stimuli directly paired with nicotine delivery result in very low levels of drug-taking behavior (Donny et al. 2003).

An emerging hypothesis proposes that nicotine addiction, whether characterized by high rates of self-administration exhibited in laboratory animals, or by cigarette smoking in humans, is supported by the reinforcing stimuli that accompany nicotine intake, and the capacity of nicotine to enhance the reinforcing effects of such stimuli. In this dual-reinforcement model, nicotine acts first as a primary reinforcer, establishing a concurrent neutral stimulus as a conditioned reinforcer by association. Secondly, nicotine acts as a reinforcement enhancer, magnifying the incentive value of the nicotine-associated, conditioned reinforce (Caggiula et al. 2009).

As the effects of nicotine become associated with various non-nicotine stimuli, these stimuli acquire conditional value or serve as cues for future nicotine delivery. As a result, the conditional stimuli for tobacco can alter behavior in a manner that maintains smoking or results in lapse/relapse after sustained abstinence. Thus, proximal stimuli normally associated with smoking, such as a lit cigarette, can induce reports of craving in smokers but not in non-smokers (Carter and Tiffany 1999). This hypothesis serves to explain the importance of sensory stimuli relative to nicotine in determining subjective responses to tobacco smoke (Rose 2006; Rose et al. 2000) as well as the reduction in subjective reports of tobacco craving, desire to smoke, and tobacco withdrawal that are produced by placebo cigarettes (Donny et al. 2007).

Rees et al. (2012) observe that sensory cues can be highly characteristic for individual tobacco products, and suggest that these brand-specific cues may acquire incentive salience, reinforcing use at the level of brand characteristics. They suggest that the limited commercial appeal of denicotinized cigarettes such as Quest may be due in part to disruptions to the established chemosensory cue-nicotine dosing contingency. While
nicotine administration increases the salience of sensory cues, it does not alter their palatability (Palmatier et al. 2013). Thus, the incentive amplifying effects of nicotine may be most effective for familiar sensory stimuli that already have positive associations, such as flavors like cocoa or menthol.

**II.e. Drug expectancy**

Drug expectancy plays an important role in smoker response (Darredeau and Barrett 2010; Juliano et al. 2011; Perkins et al. 2008; Perkins et al. 2004), particularly in women (Perkins et al. 2006). According to expectancy theory, a smoker will experience urge reduction in response to smoking a placebo cigarette, if the smoker has the stimulus (or dose) expectancy that he or she is smoking an active nicotine cigarette and has the response expectancy that nicotine reduces urges to smoke (Kirsch and Lynn 1999; Perkins et al. 2003). The expectation that an individual is receiving nicotine increases the likeability and clinical efficacy of nicotine replacement products, and this expectation interacts with pharmacological factors to produce overall subjective and behavioral responses (Darredeau and Barrett 2010; Hughes et al. 1989; Perkins et al. 2009a).

In a balanced placebo design, smokers who expect smoking to relieve negative affect (following an anxious mood induction) experience improved mood, even when they smoke a placebo cigarette (Juliano and Brandon 2002). Telling smokers they are smoking nicotine attenuates urge to smoke in the context of smoking a placebo cigarette, but has little effect in the context of nicotine administration, indicating that either nicotine or the belief that one is smoking a nicotine cigarette is sufficient to attenuate smoking urges, but that dose expectancies are not additive with the effects of nicotine (Juliano et al. 2011).

Drug expectancy may be informed by sensory stimuli that indicate to a smoker the likelihood of a given nicotine dose through conditioned associations. These cues may be articulated by the smoker as “strength” of the cigarette and reflect some combination of the nicotine-derived impact and other smoke compounds that interact with oral,
trigeminal, or other receptors (Megerdichian et al. 2007; Wayne and Carpenter 2009; Wayne et al. 2004).

Expectancy effects are also separable from nonpharmacological stimuli. For example, the same denicotinized cigarettes smoked under different dose expectancy sets produce different effects (Darredeau et al. 2013). Nicotine content information plays a role in smokers' subjective responses to nicotine inhalers, particularly with respect to craving associated with positive reinforcement (i.e., intention to smoke) though not on craving associated with negative reinforcement (i.e., withdrawal relief) (Darredeau and Barrett 2010; Perkins et al. 2009b). Although smokers have expectancies for pleasurable effects from smoking, they show reduced expectancy of positive effects from less familiar formulations (Perkins et al. 2003).

II.f. Social/ contextual factors

Dependence is not limited to the physiological experience of nicotine exposure, but also shaped by acquisition practices and consumption behaviors that are product specific, and set within unique cultural contexts. The social context of tobacco use is clearly relevant to understand patterns of use of various tobacco products, as is the extent of external pressure to abstain or quit. De Leon et al. (2013) identify the need for tobacco use measures which account for contextual factors that help to determine smoking behaviors and dependence. These would include: where it is permissible to use tobacco products (both legally and in terms of social norms); the cost of tobacco use both individually and to one’s family; and, how stigmatized tobacco use is among subpopulations (eg, with respect to gender, religious affiliation, and social status). These factors may prove particularly useful in understanding the process of experimentation with tobacco prior to transitioning to tobacco dependence, the processes that lead to the choice to quit, and quitting outcomes.

II.g. Summary of findings on tobacco addictiveness
1) Tobacco addiction is maintained by nicotine. Cigarettes that do not deliver nicotine do not sustain addiction.

2) Nicotine addiction is supported both by positive reinforcements (e.g. mood, performance) and the avoidance of withdrawal symptoms.

3) There is considerable individual variability in response to nicotine. Women differ from men in metabolism of nicotine and are more responsive to conditioned cues.

4) Nicotine dependence initiated in adolescence has implications for dependence in adulthood.

5) Nicotine delivered by tobacco smoke is distinct from other forms of nicotine.

6) Key factors in the determination of addictiveness of tobacco delivered nicotine include the form of nicotine, ease of inhalation, related sensory stimulus, and the potential addictive or reinforcing effects of other smoke compounds.

7) Denicotinized tobacco is more successful at reducing craving and producing pleasure in smokers than nicotine without tobacco.

8) The weight of evidence supports the dual-reinforcement model of addiction, in which the conditioned stimulus (tobacco smoke) strengthens dependence beyond that produced by unconditioned nicotine.

9) Drug expectancy alters response to nicotine and non-nicotine cigarettes. Expectancy may reflect cues housed within the delivery mechanism (sensory stimuli) as well as information received through advertising, packaging, or other communication.

10) Development of dependence is informed by social context and environmental factors that determine product access and appeal.
III. Establishing a threshold for addiction

The concept of a nicotine addiction threshold implies that there is a minimum amount of nicotine intake required for acquisition and maintenance of nicotine addiction. In their original proposal, Benowitz and Henningfield (1994) proposed 5 mg/day (associated with plasma cotinine levels of approximately 50-70 ng/ml/day) as an estimate of the addiction threshold for nicotine. This estimate was based on observational data from experienced smokers, rather than empirical studies that manipulated nicotine exposure, and was intended primarily as a starting point for more critical research and discussion.

Since this initial proposal, the widespread clinical availability of denicotinized cigarettes has led to a significant body of research exploring the effects of reduced nicotine exposure on smoking behaviors and subjective measures (Hatsukami et al. 2007; Hatsukami et al. 2010b). At the same time, growing interest has led to a range of animal studies on nicotine self-administration and related behaviors (Caggiula et al. 2009; Donny et al. 2012; Palmatier et al. 2012; Smith et al. 2013). These studies provide insight regarding the potential reinforcing effects of cigarettes at extremely low levels of nicotine.

III.a. Nicotine self-administration

Henningfield and colleagues (Henningfield and Goldberg 1983; Henningfield et al. 1983) conducted early studies of intravenous (IV) nicotine self-administration by smokers. Although nicotine responses tended to be more regularly spaced than responses to saline, the overall response rates for nicotine did not reliably exceed those for saline. Therefore, the evidence for nicotine serving as a reinforcer was unclear. In a 2004 study, IV nicotine (.75, 1.5, and 3 mg/injection) and saline were available concurrently for abstinent male cigarette smokers during 3-hour sessions. Smokers preferred nicotine injections compared with saline administration for all 3 nicotine doses (Harvey
et al. 2004). These doses were higher than the usual nicotine intake of a smoker, which is on average 1–2 cigarettes/hour or 1–4 mg nicotine/hour (Benowitz and Jacob 1990).

A more recent study examined self-administration of nicotine using doses within the range of average intake by smokers (Sofuoglu et al. 2008). A choice procedure was used in which male and female smokers were able to select among various IV nicotine doses (0.1, 0.4, 0.7 mg) or saline, where the 0.1 mg dose represented approximately half the amount of nicotine inhaled from a typical cigarette puff. Both the 0.4 and 0.7 mg, but not the 0.1 mg, doses were preferred over placebo. These findings provide a preliminary estimate for the reinforcing threshold of nicotine in smokers as between 0.1 and 0.4 mg.

The findings are consistent with research on discrimination, which indicates that threshold levels for nicotine discrimination are well below the typical nicotine delivery of most cigarette brands, and does not differ between smokers and non-smokers, with median thresholds of 3 μg/kg vs 2 μg/kg, respectively (i.e. around .23 and .15 mg) (Perkins et al. 2001b). However, as noted by Hatsukami et al. (2010b), a more than hundred fold variability of nicotine discrimination is reported among individuals.

Animal studies of nicotine self-administration are more numerous than human studies and support similar conclusions with respect to a nicotine threshold. Smith et al. (2013) reported significant decreases in nicotine self-administration among rats when nicotine dose was reduced to 3.75 μg/kg/infusion or below. In contrast, doses at or above 7.5 μg/kg/infusion produced similar or greater rates of self-administration relative to maintenance at 60 μg/kg. In this study nicotine was administered alongside a cocktail of other tobacco constituents, in order to more accurately mirror the effects of tobacco use.

Donny et al. (2012) examined dose–response curves across a range of studies both for acquisition and maintenance of nicotine self-administration. They placed the peak of the acquisition curve at around 20–30 μg/kg, with similar results observed over several
species, including rats, dogs, monkeys, and humans (Harvey et al. 2004; Matta et al. 2007). At lower unit doses (3.75–10 µg/kg) mean response rates increased with dose, showing considerable individual variability in response rates in this range, and a lower proportion of subjects acquiring nicotine self-administration compared to saline control (Cox et al. 1984; Shram et al. 2008b).

During maintenance of nicotine self-administration, the peak of the dose-response curve was typically found between 10–30 µg/kg (Brower et al. 2002; Corrigall and Coen 1989; DeNoble and Mele 2006; Donny et al. 1995; Shoaib et al. 1997; Watkins et al. 1999). Again, nicotine self-administration decreased and variability increased when unit doses less than 10 µg/kg were substituted. The authors observed that the threshold reinforcing dose at the low end of the dose range was rarely determined. However, doses as low as 3 µg/kg have been shown to maintain nicotine self-administration rates above those for saline in both limited and extended access studies (Brower et al. 2002; Corrigall and Coen 1989; Cox et al. 1984; Shoaib et al. 1997; Watkins et al. 1999).

The findings suggest that a nicotine reinforcement threshold for maintenance of nicotine self-administration in adult animals might lie between 3 and 7.5 µg/kg nicotine (0.23 and .56 mg), consistent with although marginally higher than those indicated by human studies. However, the number and range of doses has been small in most studies, limiting accuracy. Moreover, some studies manipulated doses between subjects, which would not be analogous to the within-subject change in doses that would occur following the implementation of a nicotine reduction policy (Donny et al. 2012)

Research conducted on nicotine self-administration has relied for the most part on rapid infusions of high unit doses of nicotine (15-30 µg/kg/infusion). Sorge and Clarke (2009) compared self-administration of nicotine in rats across a range of infusion durations (3, 30, 60, and 120 s) and found that slow infusions were preferred over fast infusions, and were self-administered at doses as low as 3 µg/kg. Their findings demonstrated that slower self-administration procedure differed pharmacologically from the traditional
procedure, and suggest that administration parameters (i.e. time course of dose delivery) could play a critical role in determining a nicotine reinforcement threshold.

III.b. Acquisition of nicotine dependence

The dose of nicotine necessary for maintenance of smoking may differ from that needed for acquisition of dependence (Hatsukami et al. 2013a). Despite a lack of available data directly addressing the question, Donny et al. (2012) conclude based on cross-study comparison that the threshold for maintenance is likely lower than that for acquisition. This conclusion would be consistent with the observation that pre-exposure to nicotine can increase acquisition of nicotine self-administration (Adriani et al. 2003; Hanson et al. 1979; Shoaib et al. 1997).

Acquisition of dependence among adolescents may present a different case to that of acquisition among adults. As noted previously, adolescent rats and mice appear to be more vulnerable than adults to the reinforcing effects of nicotine (Kota et al. 2008; Kota et al. 2007; Vastola et al. 2002), demonstrating faster acquisition of nicotine self-administration and higher baseline rates compared to adults (Adriani et al. 2002; Chen et al. 2007; Levin et al. 2007; Levin et al. 2003). However, conflicting evidence suggests that adult male rats are more likely than rats in early adolescence to acquire nicotine self-administration at a low dose of nicotine (Shram et al. 2008a; Shram et al. 2008b; Shram et al. 2008c).

Cross-sectional and longitudinal studies indicate that youth who smoke on a less than daily basis report onset of dependence symptoms (Caraballo et al. 2009; DiFranza et al. 2007b; DiFranza et al. 2002; Gervais et al. 2006; Kandel et al. 2007; O'Loughlin et al. 2003) In behavioral studies, adolescent smokers appear to self-administer physiologically active doses of nicotine, despite lower volume puffs relative to adults (Aung et al. 2004; Corrigall et al. 2001; Kassel et al. 2007b; Wood et al. 2004). Expectancies play a significant role in smoking behavior and motivations to smoke among adolescents. Specifically, stronger expectancies about the ability of cigarettes to
reduce negative affect predict smoking escalation, though as expectancies become stronger with increased smoking experience, their effect stabilizes (Heinz et al. 2010; Wahl et al. 2005).

In a study comparing high yield vs. denicotinized cigarettes, smoking resulted in a reduction of negative affect regardless of the nicotine content of the cigarette smoked. This effect was moderated by affect-related expectancies, such that participants who smoked a high-yield cigarette and held strong expectancies for smoking to alleviate negative affect experienced the greatest reductions in negative affect. No change in affect was measured among nonsmoking adolescents (Kassel et al. 2007a).

Importantly, onset of smoking and subsequent exposure to nicotine at adolescence, even at levels below that of daily reinforcement, may serve to lower the threshold for nicotine dependence in adulthood, despite highly attenuated rewarding or reinforcing effects (Breslau and Peterson 1996; Chen et al. 2007; Cui et al. 2006).

**III.c. Reinforcing effects of low nicotine cigarettes**

Evidence from clinical studies demonstrates that denicotinized tobacco can provide a significant degree of subjective satisfaction and immediate craving reduction (Baldinger et al. 1995; Barrett 2010; Buchhalter et al. 2001; Butschky et al. 1995; Donny et al. 2007; Gross et al. 1997; Pickworth et al. 1999; Rose et al. 2000; Westman et al. 1996) although ratings may be reliant on smokers level of dependence (Brauer et al. 2001). Craving suppression appears to be a particularly robust effect that is less sensitive to extinction procedures (Donny et al. 2007). Nicotine-containing and denicotinized smoke suppress craving and ad-libitum smoking equally; by contrast, IV nicotine has only a small effect in suppressing ad libitum smoking (Dallery et al. 2003; Rose et al. 2003).

Low levels of nicotine present in denicotinized cigarettes may be sufficient to maintain smoking behavior. Brain imaging studies show that smoking a single very low nicotine cigarette results in significant (23%) occupancy of α4β2 nicotinic receptors, which are
considered the primary receptor subtype mediating nicotine's reinforcing and other behavioral effects (Brody et al. 2009). The effects of nicotine at low levels may be further reinforced by non-nicotine aspects of tobacco. In a 2010 study, use of denicotinized tobacco was associated with increased feelings of relaxation relative to nicotine, suggesting that non-nicotine factors may be partially or even largely responsible for the calming effects of tobacco smoking (Barrett 2010).

Other processes may exist whereby dependency on cigarettes could be generated even with extremely low intake of nicotine, for example, through receptor desensitization, which can occur with chronic exposure to even very low levels of nicotine (Grady et al. 1994). Desensitization of receptors mediates nicotine's acute reinforcing effects (Lu et al. 1999; Picciotto et al. 2008).

Environment is also likely to play a role in smoker behavior. For example, Donny and Jones (2009) found that denicotinized cigarettes maintained their reinforcing properties throughout a 9-day outpatient assessment period, whereas in a similar inpatient study (Donny et al., 2007), both motivation to smoke and number of denicotinized cigarettes smoked declined somewhat over time. They hypothesized that extinction may proceed more slowly in a naturalistic setting, possibly because of the presence of numerous stimuli associated with smoking (Bouton 2004).

**III.d. Addiction threshold versus reinforcement threshold**

There are no universally accepted definitions of nicotine or tobacco addiction. The World Health Organization defines drug dependence in terms of compulsion, that is, a behavioral pattern in which use of the drug is given priority over other behaviors to an extent that is considered detrimental to the individual or to others (World Health Organization 1992). The 1988 Surgeon General report *The Health Consequences of Smoking: Nicotine Addiction* (USDHHS 1988) adds to the requirement of compulsion that the drug produce psychoactive effects, and that the drug-taking behavior be clearly
reinforced by the effects of the drug. Although these additional criteria are exhibited in most cigarette smokers, they are not universal in all smokers (Benowitz 2008).

Diagnostic criteria widely used for identification of nicotine addiction include the DSM-IV scale, which was developed to assess general drug dependence, and the Fagerström Test of Nicotine Dependence (FTND), used to assess tolerance and severity of dependence. A number of concerns have been raised regarding the validity of these instruments as measures of addiction. The scales correlate poorly with each other, and neither has consistently predicted other indices of smoking behavior or treatment outcomes of smokers (Hendricks et al. 2008; Hughes et al. 2011; Hughes et al. 2004; Moolchan et al. 2002). These scales may also be insensitive to assessing smokers who are in the early stages of nicotine use, having been developed and validated in adult end-stage smokers (Colby et al. 2000; Rose and Dierker 2010).

DiFranza et al. (2010a) argue that diagnostic criteria for addiction should, at the very least, be able to differentiate between individuals who are and are not able to abstain when they decide they want to do so. The authors propose self-assessment of addiction as the gold standard, noting that self-assessed addiction correlates very highly with self-rated difficulty quitting ($r = .89$), and correlates better than the DSM-IV with cigarettes smoked per day and time to the first morning cigarette (Hughes et al. 2004). Self-assessment may also prove more adept at identifying emerging dependence in children than other diagnostic measures. In one study (Rubinstein et al. 2011) adolescent self-assessment of addiction predicted neurophysiological responses to smoking more successfully than the FTND.

Sofuoglu and LeSage (2012) have identified the lack of a consensus on valid methods for assessment of nicotine addiction as a significant challenge to nicotine reduction strategies. The authors propose that the concept of a reinforcement threshold, while at times used interchangeably with addiction threshold, is not synonymous, and may be preferable as a policy basis for establishing a threshold level for nicotine. The
reinforcement threshold would be defined as the lowest nicotine dose that would increase or maintain nicotine self-administration behaviors (i.e. tobacco use).

The authors identify a number of practical advantages. First, the nicotine reinforcement threshold is more clearly defined and easier to measure than an addiction threshold. A drug is considered to be reinforcing if it is self-administered to a greater extent than a vehicle or placebo (Audrain-McGovern et al. 2009). Second, because dependence does not occur if a drug is not reinforcing, the nicotine reinforcement threshold is likely to be lower than the nicotine addiction threshold and may be a more sensitive index for predicting tobacco use below the threshold for addiction (Audrain-McGovern et al. 2009; Glaudier 2004). Third, measures of the reinforcement threshold can be accomplished with short-term studies examining self-administration both in humans and non-humans, and may be easily adapted to assess individual differences (e.g., age, sex, genetic factors) and environmental factors (e.g., stress, peer influence) (Comer et al. 2008).

III.e. Threshold for conditioned stimulus

Given the importance of conditioned stimuli in reinforcing smoking behavior, and the primary role of nicotine in enhancing salience, it may be useful to consider whether a separate nicotine threshold exists for the acquisition of reinforcing properties in non-nicotine stimuli.

Rats trained on a 0.4 mg/kg nicotine dose readily acquire conditioned responding for an unconditioned reward (Besheer et al. 2004; Bevins and Palmatier 2004; Wilkinson et al. 2006) Separate groups assigned to 0.1, 0.2, or 0.4 mg/kg nicotine training dose all show similar acquisition of conditioned responding, though the higher nicotine groups show greater resistance to extinction (Murray and Bevins 2007). The similar acquisition rate across groups might suggest that 0.1 mg/kg nicotine is as salient as the higher nicotine doses. A non-salience explanation involves the rich schedule of sucrose deliveries in nicotine sessions; that is, less nicotine was necessary to prompt conditioned responding
due to the high number of nicotine-sucrose pairings (Besheer et al. 2004; Wilkinson et al. 2006).

Palmatier et al. (2008) compared the effects of a lower (0.03 mg/kg) and higher nicotine dose (0.09 mg/kg), reasoning that the new conditioned properties of an associated stimulus should be based in part on the strength or intensity of the primary reinforcer. They concluded that the conditional reinforcing properties acquired by the stimulus were a direct function of increased dose.

This implies that stimulus control of tobacco seeking behavior will be most potent in subjects exposed to high levels of nicotine, and are likely to be much reduced in the context of very low nicotine. However, the strength of conditional stimuli will also be driven by how frequently the stimuli is paired with nicotine, how correlated with nicotine, and how closely related in time and space. Thus, as suggested in the earlier studies (Murray and Bevins 2007), given enough pairings, even a nicotine dose that would otherwise have been a weaker conditional stimulus could come to be a strong conditioned exciter.

**III.f. Summary of findings on threshold for addiction**

1) Threshold reinforcement studies show strong agreement across both animals and humans. Taken together, these studies provide a preliminary estimate for the reinforcing threshold for nicotine of between 0.1 and 0.5 mg.

2) The threshold for reinforcement is lower when using a self-administration mechanism that more accurately models cigarette nicotine delivery.

3) The threshold for discrimination of nicotine in humans is approximately 0.2 mg, though there is high individual variability.

4) Among adults, the threshold for maintenance appears to be lower than the threshold for acquisition of reinforcing behavior.

5) Acquisition of nicotine use among adolescents may differ from adults. Adolescent smokers have low daily rates of cigarette use, but appear to self-
administer physiologically active doses of nicotine. Expectations of negative affect reduction are a primary motivation for smoking among adolescents.

6) Denicotinized cigarettes (with nicotine yields of 0.05-0.1 mg) can provide a significant degree of subjective satisfaction and immediate craving reduction.

7) Low levels of nicotine present in denicotinized cigarettes may be sufficient to maintain smoking behavior. Alternately, responses to denicotinized cigarettes may reflect conditioned reinforcing effects, or imply that some non-nicotine constituents demonstrate primary effects.

8) The goal of reducing nicotine below the threshold for addiction relies to a significant degree on a reliable measure of addiction. There is no readily accepted measure of addiction applicable to the establishment of a nicotine threshold. Common measures of dependence do not apply to all smokers and may fail to capture adolescent smoking.

9) Among the alternate definitions proposed are self-assessment of addiction (DiFranza) and the reinforcement threshold (Sofuoglu and LeSage).

10) A high nicotine dose provides a stronger conditioned reinforcing effect; however, even a weak nicotine dose may be sufficient for conditioned reinforcement, particularly in the context of many highly correlated pairings (as in the case of long-term smoking).
IV. Feasibility of nicotine reduction

Most studies examining the behavioral effects of nicotine reduction have relied on commercially available low-nicotine products, including so-called denicotinized cigarettes such as Quest. These studies provide valuable insight into the behavioral responses of smokers. However, they do not necessarily reflect the market of commercial products that are likely to be available within the context of mandated nicotine reduction.

Internal tobacco industry documents, although potentially less reliable than published clinical studies, may provide insight into the commercial manipulation of cigarette-delivered nicotine and the range of product approaches that are likely to be employed by tobacco manufacturers (Panzano et al. 2010; Wayne and Carpenter 2009).

IV.a. Cigarette nicotine delivery

Tobacco manufacturers have used brain imaging to determine effective ranges of cigarette nicotine delivery under controlled smoking conditions (Panzano et al. 2010). A study comparing a no nicotine, low nicotine (0.14 mg) and high nicotine (1.34 mg) delivery cigarette observed statistically significant amplitude decreases only in the high nicotine condition (p<0.05) (Gullotta 1981). A similar study compared six styles of cigarettes ranging from .12 mg to 1.1 mg of nicotine. The electrophysiological effect of smoking the 0.12 mg cigarette was indistinguishable from a nicotine-free cigarette, while the cigarettes of 0.21 mg or greater demonstrated measurable effects (Gullotta 1990).

A theoretical best-fit curve relating latency of measured brain response to cigarette-delivered nicotine indicated that latency decrease, as a function of nicotine concentration, was largest up to 0.4 mg per cigarette, and that no further latency shifts occurred beyond approximately 1.4 mg per cigarette. This implies that reductions in smoke nicotine at and below the 0.4 mg level are likely to have the greatest overall
impact on smoker behaviors (Gullotta 1982). Latency effects during controlled versus ad-lib smoking were compared using commercial cigarettes ranging in delivery from 0.11 to 1.04 mg nicotine/cig. Smokers were able to achieve measured CNS effects comparable to that of full flavor cigarettes through compensation even with the lowest (0.11 mg) nicotine delivery (Gullotta 1982).

A study examined whether the effects of a higher nicotine delivery cigarette (0.9 mg) could be replicated by having subjects smoke three lower delivery cigarettes (0.3 mg nicotine). Latency effects were successfully mimicked by the three low delivery cigarettes, whereas the amplitude effects required a single, relatively large intake of nicotine over a short time interval. When three 0.1 mg nicotine cigarettes were compared to a single 0.3 mg cigarette, the latency effects were no longer similar (p<0.05). The authors concluded that the neurophysiological effects of nicotine exhibit “a threshold […] somewhere between 0.1 and 0.3 mg”-- a result consistent with findings described in section III.a (Gullotta 1982).

IV.b. Methods for reducing nicotine in tobacco

Concentration of nicotine in tobacco is a significant correlate to smoke nicotine yield (Connolly et al. 2007), and can be readily altered and controlled by manufacturers (Dunsby and Bero 2004; Hurt and Robertson 1998; Slade et al. 1995; Wayne and Carpenter 2009).

Tobacco types, grades, and stalk positions can produce significant variations in nicotine concentration. Blending of different tobaccos enables manufacturers to balance tobacco characteristics as well as to adjust for natural variations in tobacco nicotine content in order to meet production standards for specific brands and styles (British American Tobacco 1972). Differences of a factor of 10 are possible across tobacco types, and factors of 5 or 6 are common (e.g. 1% nicotine content by weight oriental tobacco, compared with 5% by weight in burley tobaccos) (British American Tobacco 1969). Product differences driven by tobacco selection are not limited to nicotine but
include sugar and ammonia content, aroma and taste characteristics, and relative
harshness and irritation (British American Tobacco 1969; Browne 1990).

Extremely high and low nicotine strains of tobacco were developed for research
purposes with the assistance of public research agencies in both the U.S. and Canada
(Cohen 1971; Gibb 1974; Johnson 1977; Kentucky Tobacco Research Board 1977). In
one example, Brown & Williamson compared 3 strains of burley that contained
approximately 1/20, 1/2, and 9/10 of normal levels of nicotine, demonstrating that
nicotine in the smoke was proportional to nicotine in tobacco (Smith 1972). In other
cases, microbial bacteria were used to actively degrade nicotine while leaving other
components of leaf intact (Geiss 1972; Geiss 1975). Acceptability of tobacco derived
from this process was equal to that of untreated tobacco (Gravely 1973).

The earliest tobacco processing involved steam extraction of burley tobacco and stems
to reduce the irritation commonly associated with their high nicotine content. Later,
ammonia or similar compounds were incorporated into the extraction process (Rickett
1980; York 1977) Treatment of tobacco disassociates the nicotine salts naturally
present in tobacco into free nicotine and the free acid. In the case of heat or steam
treatment, the free nicotine is driven from the tobacco (Ashburn 1961). In other cases
the treatment enables free nicotine to be more easily extracted by means of a solvent
(such as freon), after which the denicotinized extract may or may not be returned.
Extraction processes can support significant reductions in smoke nicotine delivery, while
also demonstrating significant effects on subjective or sensory characteristics of smoke
(Green 1979).

Research conducted by Philip Morris on nicotine reduction prior to development of the
denicotinized brand Next included genetic modification, enzymatic processes, and
nicotine extracted tobacco (Dunsby and Bero 2004). While none completely eliminated
nicotine, reductions were achieved in the range of 80–98%. Quest cigarettes, produced
by Vector Tobacco beginning in 2003, were produced from genetically modified
tobacco.
IV.c. Denicotinized or reduced nicotine cigarettes

Although in principle it should be possible to make tobacco cigarettes that are completely free of nicotine, in most cases the term “denicotinized” indicates tobacco with low nicotine concentration. Generally these cigarettes contain 1 mg nicotine or less, and when smoked on a standard smoking machine, produced nicotine yields (0.05-0.1 mg) equivalent to approximately 5% to 10% of the nicotine yield of standard commercial brands (Benowitz and Henningfield 2013).

The main technical challenge of the denicotinized cigarette is not reducing nicotine but maintaining smoke sensory characteristics and appeal. The earliest nicotine extracted tobaccos, relying on techniques such as solvent or steam extraction, were perceived as “stinging” and “numbing” with extremely low acceptability regardless of tobacco type and despite use of flavorings (Kassman 1986). The differences were not simply due to lack of nicotine, since adding back extracted nicotine in test cigarettes did not restore the cigarettes to the taste of unextracted cigarettes. Analysis identified other tobacco materials that were removed incidentally in the extraction process, including waxes, heavy hydrocarbons, and essential oils, which when added back after extraction improved subjectives. These findings underscored the importance of elements other than nicotine to product acceptance (Kassman 1986; Philip Morris 1995a).

For the brand Next, Philip Morris employed the supercritical extraction technique used to decaffeinate coffee as a means to remove nicotine from tobacco (Dunsby and Bero 2004). Despite ongoing efforts to improve selectivity and limit the underlying effects of extraction, the process altered taste characteristics of the tobacco, leading to exploration of many post-extraction flavoring and casing systems (Houghton 1990). The most successful were menthol-based prototypes that covered much of the unusual taste while also providing some of the impact lost through the removal of nicotine (Ferris Wayne and Connolly 2004; Gullotta 1991).
An extended test of the Next prototype conducted among an internal expert panel found that although extracted cigarettes could be appealing initially, continued smoking through a pack of extracted cigarettes led to increasingly poor acceptability ratings. When nicotine was added back to the extracted cigarette the level of acceptability did not fall over time (Philip Morris 1995b). Alternately, a consumer study conducted among interested smokers found liking ratings for the extracted cigarette improved over time within a cohort of highly motivated smokers, indicating that smokers may be able to adjust expectations under some conditions (Philip Morris 1995a).

IV.d. Free-base nicotine in low delivery cigarettes

Pankow (2001) and others (Ferris Wayne et al. 2006; Henningfield et al. 2004a) have identified the fraction of free-base nicotine in tobacco smoke as critical both to the rate of transfer of nicotine from tobacco to smoke and from smoke to nicotine receptors in the back of the throat and lungs. Standard measures of smoke nicotine delivery do not differentiate between forms of nicotine (Ashley et al. 2009) However, internal industry documents suggest that comparisons of free-base nicotine delivery may provide a more accurate measure of subjective response to products, particularly in low yield brands (Ferris Wayne et al., 2006; Wayne and Carpenter, 2009).

Products which appear to differ significantly by total smoke nicotine can resemble each other in terms of free nicotine delivery. Brown & Williamson compared smoke yields of Marlboro (1.15 mg nicotine) and the high impact, low yield product Merit (0.64 mg) and found essentially the same free nicotine (~0.3 mg) from each brand. The authors concluded that a person smoking both products would have difficulty differentiating between them physiologically (Gregory 1980). Similarly, although Marlboro had less smoke nicotine than Winston, it had a higher level of weaker bases, such as pyrazines. These weaker bases “accounted for the pH being slightly higher” of Marlboro – supporting equivalent levels of volatile or “free” nicotine – despite the fact that nicotine was not as high (Shannon; Dube; Walker; Reynolds 1992)
Limited published measures of free-base nicotine in cigarette smoke suggest that differences in commercial brands differ from those identified by standard smoking protocols (Pankow et al. 2003; Watson et al. 2004). Ranges of free-base nicotine are similar across nicotine delivery categories of full-flavored, light, and ultralight cigarette brands. The degree of filter ventilation increases the proportion of free-base nicotine in mainstream smoke, suggesting that, even without compensatory behavior, a ventilated cigarette will deliver a greater proportion of total nicotine in free-base form (Watson et al. 2004).

**IV.e. Products that support compensatory smoking**

Smokers will adjust their smoking behavior when switched from regular to light (or low-yield) cigarettes so as to maintain their desired nicotine intake (Baldinger et al. 1995; Benowitz et al. 2005; National Cancer Institute 2001). Unlike conventional low-yield cigarettes, reduced nicotine cigarettes do not rely on ventilation for reduced smoke yields, and do not appear to support compensation as easily (Benowitz et al. 2007; Hatsukami et al. 2010a; Rose and Behm 2004a). Rose and Behm (2004a) compared smoking of a cigarette with smoke yields of .2 mg nicotine/14 mg tar to a commercial, highly ventilated low-yield cigarette (.2 mg nicotine/1 mg tar) in a single session ad-lib crossover study, finding substantial compensation for the commercial low-nicotine cigarette but no appreciable compensation with the low-nicotine content cigarette.

Benowitz et al. (2006a) compared smoking behavior versus usual brand for cigarettes with adjusted nicotine content ranging from 1 to 12 mg nicotine. The study found strong compensatory behavior for cigarettes with moderate levels of nicotine, but minimal compensation and significant reduction in nicotine exposure for cigarettes with 1, 2 and 4 mg nicotine (0.1, 0.2, 0.3 mg nicotine yields). The lowest nicotine cigarette had an average nicotine intake of .26 mg, compared to 1.47 mg nicotine for usual brand. A longer term study using the same range of nicotine content (1 to 12 mg), but decreased at monthly intervals over six months found similar results, with a high level of
compensation for the 12 mg cigarette, but only a small degree of compensation at the lowest nicotine content levels (Benowitz et al. 2012).

Hatsukami et al. (2010a) assigned smokers to either 0.3 mg nicotine yield cigarettes, 0.05 mg nicotine yield cigarettes, or 4 mg nicotine lozenges in a six-week switching study. Among those smoking 0.3 mg cigarettes, the number of cigarettes smoked per day increased significantly at each of the first 5 weeks of treatment compared to usual brand, while among those assigned 0.05 mg cigarettes, number of cigarettes smoked per day (relative to baseline) decreased significantly.

These studies suggest that for cigarettes with reduced nicotine content, there may be a threshold below which compensation is less likely to occur. This threshold appears to be in the range of approximately 0.05-0.1 mg smoke nicotine yield. At less extreme levels of reduced nicotine (0.2-0.3 mg), compensatory behaviors are significantly increased.

A similar threshold may exist for commercial, ventilated low yield cigarettes. In a ten week progressive tapering study using commercially available cigarettes, Benowitz et al. (2009) found that forced switching from regular cigarettes to popular low yield cigarettes with machine-determined yields of ≥0.6 mg nicotine resulted in complete or nearly complete compensation, with no reduction in exposure to nicotine or tobacco smoke toxins. When switched to ultralow yield cigarettes in the 0.1 to 0.2 mg nicotine yield range, exposure to nicotine and tobacco smoke toxins were substantially though not entirely decreased (about 40%, versus a 90% reduction in nominal yields).

IV.f. Product formulation and approaches to nicotine reduction

Formulation differences play a key role in product abuse liability and in determination of a threshold for reinforcement. For example, oral smokeless tobacco products appear to support somewhat lower risk of addiction than cigarettes (Hatsukami et al. 2004; Henningfield et al. 1997), and the risk of developing addiction to nicotine replacement
medications appears to be small (Henningfield et al. 2009; USDHHS 1988) even though the absolute nicotine delivery may not differ. Currently, most manufactured cigarettes contain 10–15 mg of nicotine per cigarette, of which approximately 10% is delivered in smoke. This supports a typical systemic intake of 1–2 mg of nicotine per cigarette (Benowitz and Henningfield 2013). A threshold level for nicotine set at the low range of 0.1-0.2 mg per cigarette would on its face require an overall reduction in nicotine intake on the order of 90%.

Various approaches could be considered to achieve such a reduction. A decrease in the nicotine concentration in tobacco could be used to limit total nicotine content per cigarette to a level at or below the intake threshold. This approach would ensure per cigarette nicotine consumption remained below the stated threshold regardless of behavioral changes by the smoker (i.e. increased frequency or volume puffs) or manipulation of the form of nicotine delivery, although it would not prevent an increase in number of cigarettes smoked as a means of obtaining more nicotine. Construction of such a cigarette would pose a likely technical challenge, as it would require a reduction in tobacco nicotine content approximately ten times that found in the commercial denicotinized brands Next and Quest. This reduction would likely result in significant changes in the sensory or taste profiles of the tobacco. No studies have been conducted on the likely behavioral effects of cigarettes constructed at this range of nicotine content.

Alternately, a reduction in nicotine concentration of tobacco could be used to limit nicotine content to a level such that machine measured smoke yields are likely to remain at or below the nicotine threshold. This approach would more closely resemble the commercial products Next and Quest, with smoke nicotine yields of less than 0.1 mg and total nicotine content of tobacco less than 1 mg. The development of saleable brands at this range of nicotine provides strong evidence of the technical feasibility of this approach. The majority of behavioral research on nicotine reduction has been conducted with cigarettes in this range of nicotine.
A third alternative would to meet a threshold for smoke nicotine yields through product parameters other than reduced nicotine concentration, or in combination with reduced nicotine tobacco. This approach could include extreme levels of filter ventilation, high levels of expanded tobacco, and reduced tobacco content. Again, the technical feasibility of this approach has been demonstrated commercially, at the extreme ends of the ultralight category, i.e. those with approximately .1 mg nicotine/1 mg tar yields under machine smoking conditions. Cigarettes following this approach would likely maintain nicotine/tar levels similar to or greater than that of current commercial cigarettes, in contrast to cigarettes with reduced nicotine concentration that would produce smoke with extremely low nicotine/tar ratios. They would potentially support high levels of compensation, through behavioral manipulation such as covering vent holes and altering puffing behavior.

With any of the alternatives outlined above, physical or chemical parameters of cigarette construction could be manipulated to alter the basic formulation of the cigarette. For example, new filters could be employed to alter the form of nicotine (through use of an acid or base) or to change the size distribution of aerosol particles that determine deposition and absorption of nicotine and other constituents (Wayne and Carpenter 2009; Wayne et al. 2004; Wayne et al. 2008). Chemical factors such as tobacco processing, use of additives, or construction parameters including length, width, moisture, and packing density could be used to alter combustion or pyrolysis conditions, to change the balance of smoke composition and sensory characteristics, or introduce new compounds with unique behavioral or sensory effects or that interact with or alter nicotine (Carpenter et al. 2007; Megerdichian et al. 2007; Wayne and Carpenter 2009). Thus, regardless of approach, considerable attention must be paid to product factors other than nicotine delivery.

**IV.g. Summary of findings on feasibility of nicotine reduction**
1) Cigarettes may be pharmacologically active above a certain threshold of smoke nicotine yield, whereas below this threshold (somewhere between 0.1 and 0.3 mg) they are no longer as effective.

2) A single intake of nicotine from a single cigarette over a short time period is more effective than a series of smaller intakes across many cigarettes, particularly at lower levels of nicotine.

3) Reduction of the total nicotine concentration of tobacco is a common practice within the tobacco industry. A wide range of techniques have been employed including tobacco type and leaf selection, genetic selection, microbial or enzymatic treatment, and selective extraction of nicotine.

4) Both selective extraction and genetic modification have proven capable of producing tobaccos with nicotine reduced by 80-95%.

5) Reduced nicotine tobacco has different sensory characteristics to that of unmodified tobacco. This is due in part to the absence of nicotine, but also to loss of incidental compounds such as waxes, hydrocarbons, and essential oils.

6) Total nicotine intake is only one measure of the overall sensory and pharmacological effects of nicotine, and does not differentiate between forms of nicotine. Free-base nicotine is primarily responsible for the sensory impact of nicotine and may be a more accurate measure of subjective or physiological effects, particularly in low or reduced nicotine products.

7) For cigarettes with reduced nicotine content, there may be a threshold below which compensation is less likely to occur. This threshold appears to be in the range of approximately 0.05-0.1 mg nicotine yield. At less extreme levels of reduced nicotine (0.2-0.3 mg), compensatory behaviors are significantly increased.

8) Similar findings are reported for switching studies using denicotinized cigarettes (0.05 mg nicotine), and extremely low nicotine conventional cigarettes (.1-.2 mg nicotine), despite differences in construction and greater available nicotine in rod.

9) Reduction of tobacco nicotine content in cigarettes below the 0.1 mg threshold would require a tenfold reduction beyond that of current denicotinized products. The feasibility and behavioral responses to such a product remain unexplored.
10) The majority of behavioral research has been conducted with cigarettes made with reduced nicotine tobaccos with machine measured smoke yields near the 0.1 mg nicotine threshold.

11) Physical or chemical parameters of cigarette construction can be manipulated to alter the basic formulation of the cigarette such as size distribution of particles, combustion and pyrolysis, and introduction of new compounds. Attention must be paid to product factors other than nicotine delivery.
V. Potential behavioral and population outcomes

Denicotinized cigarettes can reduce smoking of conventional cigarettes by providing a temporary behavioral substitute for conventional cigarettes, and by removing the primary reinforcing effects of nicotine, generating less craving on a continuing basis (Becker et al. 2008). Evidence presented in the previous sections indicates that, while smokers prefer nicotine-containing cigarettes, reduced nicotine cigarettes are capable of providing subjective satisfaction and immediate craving reduction. Some individuals may still continue to smoke following mandated nicotine reduction, whether due to the strong substitution effects reported above, or because the nicotine content in cigarettes remains above their individual threshold for reinforcement (Hatsukami et al. 2010b; Rose 2008).

Behavioral models apply the available evidence on individual level effects of reduced nicotine cigarettes to predict potential population outcomes. However, studies on the acquisition of reduced nicotine cigarette use among non-smoking populations, and on the long-term effects of reduced nicotine cigarette use, remain limited.

V.a. Potential effects on cigarette consumption

Research in behavioral economics has proven its utility in understanding smoker consumption behavior. For example, DeGrandpre et al. (1992) applied demand curve analysis in a meta-analysis of 17 studies examining the effects of nicotine yield on smoking behavior. They found a strong relationship between consumption and nicotine yield suggesting that decreasing the smoker's usual nicotine yield spurred increased smoking behavior.

Within-subjects use of nicotine-containing and denicotinized cigarettes indicates similar elasticities, as increases in unit price cause similar reductions in self-administration. However, when both cigarette types are concurrently available at the same range of unit
prices, the nicotine-containing cigarettes are reliably preferred. This demonstrates that the act of smoking possesses reinforcing value in regular smokers regardless of nicotine content, and that denicotinized cigarettes can serve as an effective behavioral economic substitute for nicotine-containing cigarettes (Shahan et al. 2001; Shahan et al. 1999).

Increasing unit price for nicotine-containing cigarettes, while holding denicotinized cigarette unit price constant, increases consumption of denicotinized cigarettes. The same holds when nicotine gum is used in place of denicotinized cigarettes (Shahan et al. 2000) However, when both alternatives are made available, consumption of nicotine gum diminishes while consumption of denicotinized cigarettes does not (Johnson et al. 2004). Increased price of both denicotinized cigarettes and nicotine cigarettes results in increased gum consumption. These findings suggest that the availability of alternative nicotine-substitutes such as nicotine medications, oral tobaccos, or nicotine-containing electronic cigarettes may have direct effects on self-administration of cigarettes, regardless of cigarette nicotine content.

V.b. Potential effects on topography and smoking behavior

Switching to cigarettes with reduced nicotine content can elicit modest withdrawal symptoms due to decreases in nicotine intake (Benowitz et al. 2009; Benowitz et al. 2007; Hatsukami et al. 2010a; West et al. 1984; Zacny and Stitzer 1988). These findings raise the possibility that withdrawal symptoms might motivate increases in smoking behaviors.

There is little evidence of compensatory smoking behavior for reduced nicotine cigarettes at levels of 0.05-0.1 mg nicotine yield, as indicated earlier (see section IV.e.). Strasser et al. (2007) found an increase in total puff volume in participants smoking reduced nicotine (Quest 3) cigarettes (0.05 mg yield). However, participants in the study were only evaluated in response to their first use of the study cigarettes. Studies over several days or weeks using reduced nicotine cigarettes consistently find no increase in
compensatory smoking. In fact, a decrease in smoking may occur over time, as would be expected during behavioral extinction.

Smoking behaviors measured across a nine-day assessment found initial differences in puff volume, which dissipated as the study progressed, suggesting that puffing behavior may be only temporarily disrupted by the switch to reduced nicotine cigarettes (Donny and Jones 2009). In another 11-day assessment, subjects exposed to reduced nicotine cigarettes showed a reduction in ad lib smoking compared to nicotine-containing condition (Donny et al. 2007). Hatsukami et al. (2010) showed a similar reduction over a six-week treatment period. In a six-month tapering study conducted by Benowitz et al. (2012), cigarette consumption remained unchanged from baseline through week 14, when nicotine content stepped to 4 mg. From this point to the end of the study (week 26), cigarette consumption decreased significantly by 4 cigarettes per day. Nicotine intake compared to usual brand, as measured by plasma cotinine, had declined to 30% of baseline.

In a self-administration study with rats, dose reduction did not elicit withdrawal among the subjects as a group, though it elicited withdrawal among some individuals, and severity of withdrawal was not a determinant of individual differences in compensation (Harris et al. 2011). These findings complement a previous report that a large but partial reduction in brain nicotine levels achieved via administration of nicotine-specific antibodies was not sufficient to elicit withdrawal in rats dependent on a chronic nicotine infusion (Roiko et al. 2009). The data suggest that withdrawal is not a prominent adverse consequence of reductions in nicotine intake for most individuals, and that significant compensatory smoking behavior in the form of greater intensity of smoking or increased number of cigarettes per day is not a likely outcome at very low (0.1 mg) levels of nicotine exposure.

V.c. Potential effects on abstinence and quitting
Studies in both laboratory and outpatient research settings demonstrate that use of reduced nicotine cigarettes over a period of 1–2 weeks weakens the reinforcing effects of smoking (Donny et al. 2007; Rose and Behm 2004a). In clinical trials conducted over periods of six weeks or more (Benowitz et al. 2009; Benowitz et al. 2012; Hatsukami et al. 2010a) smokers consistently report lower levels of dependence following use of reduced nicotine cigarettes.

Reduced nicotine cigarettes may provide a coping mechanism to get through the initial stages of abstinence by replacing some of the conditioned rituals associated with smoking, such as the hand-to-mouth action, the tactile action of puffing on a cigarette and the sensation of smoke in the mouth and throat (Walker et al. 2012). Among smokers seeking to quit, continuous abstinence at week 6 for smokers switched to a 0.3 mg cigarette was 13.5%, and for those assigned a 0.05 mg cigarette was 30.2%. This suggests that a nicotine reduction policy may be more likely to help smokers achieve abstinence when they make an active quit attempt (Hatsukami et al. 2010a).

Reduced nicotine cigarettes may support quitting not only in smokers seeking treatment, but among smokers who have not previously expressed interest in quitting. Benowitz et al. (2007) found that 4 weeks after the end of a 6-week progressive reduction in nicotine content of cigarettes, 25% of enrolled subjects had stopped smoking. A similarly designed study reported 10% of enrolled subjects had quit smoking in the period following progressive reduction again among smokers who had not previously expressed interest in quitting—again among smokers who had not previously expressed interest in quitting (Benowitz et al. 2009). The six month progressive reduction reported a 4% quit rate after completion (Benowitz et al. 2012).

The effects of reduced nicotine cigarettes on quitting may be increased with the additional availability of nicotine-based treatment. When smokers were switched to reduced nicotine cigarettes (0.05-0.09 mg nicotine yield) with and without nicotine patch for a six-week period, the group without patch smoked significantly more cigarettes per day versus those assigned patch, and showed greater withdrawal symptoms, although
craving scores were not different between the two groups. At 36 week follow up, 18% of smokers who had used the reduced nicotine cigarettes alone remained abstinent, compared to 20% of smokers using reduced nicotine/patch combination (Hatsukami et al. 2013b). In another study, those assigned a nicotine patch alongside reduced nicotine cigarettes showed a greater decrease in the number of cigarettes smoked, greater decrease in total volume of cigarette smoke inhaled, and greater withdrawal relief (Donny and Jones 2009).

Walker et al. (2012) conducted a randomized control trial in which use of denicotinized cigarettes was paired to usual Quitline care. An increase in quit rates over usual Quitline care was found, with a positive impact on time to relapse and high participant acceptability. The trial provided strong evidence for the combined use of reduced nicotine cigarettes alongside nicotine replacement therapy (NRT) and behavioral support as an effective smoking cessation strategy.

V.d. Potential effects on acquisition of cigarette use

The available literature provides no quantified estimates of the potential impact of a reduced nicotine policy on smoking initiation. Studies cited in section III.b suggest that expectancies regarding the ability of cigarettes to reduce negative affect play a primary role in acquisition of smoking among adolescents (Heinz et al. 2010; Wahl et al. 2005) and that substitution of denicotinized cigarettes reduces negative affect comparable to that of a nicotine-containing cigarette among adolescent smokers. On the other hand, no change in affect was measured among nonsmoking adolescents with use of reduced nicotine cigarette (Kassel et al. 2007a). This suggests that nonsmoking adolescents are unlikely to proceed to more escalated smoking behavior in the absence of acute nicotine effects. Establishment of a threshold for reduction of negative affect in nonsmoking adolescents would provide further confirmation.

Effects on the likely acquisition of reduced nicotine cigarette use among adult nonsmokers have not been separately explored. Self-administration of a nicotine nasal
Nicotine reduction

Spray has been shown to be similar between dependent and nondependent smokers, and to be greater in both groups than in ex-smokers or nonsmokers. In nonsmokers, self-administration is related directly to pleasurable effects but inversely to aversive effects (Perkins et al. 2001a). Both positive and negative reinforcement expectancies change significantly following initiation of smoking (Doran et al. 2011). Reduced nicotine exposure in adolescence is likely to reduce vulnerability to nicotine dependence in adulthood (section II.b.) More research on the effects of reduced nicotine cigarette use among nonsmokers and non-dependent smokers is needed.

V.e. Potential unintended behavioral consequences

Low level nicotine exposure in adolescents experimenting with reduced nicotine cigarettes could potentially increase risk of addiction to other drugs of abuse (Hatsukami et al. 2010b). In animal studies, very brief exposure to intravenous nicotine doses (only two infusions of 0.03 mg/kg daily for 4 days) in adolescent rats sensitized them to the reinforcing effects of cocaine, suggesting a potential adverse consequence of very limited nicotine exposure in adolescence (McQuown et al. 2007). This daily dose is comparable in humans to the nicotine intake from four standard cigarettes (approximately 4.2 mg), or approximately 40 reduced nicotine cigarettes.

Reduced nicotine cigarettes could potentially serve as starter products for other higher nicotine products, in a manner similar to that previously demonstrated among smokeless tobacco products with low levels of free-base nicotine (Connolly 1995). Dual use of reduced nicotine cigarettes in conjunction with other tobacco products with higher nicotine content, such as oral tobacco or small cigars, could also lead to greater exposure to toxicants (Hatsukami et al. 2010b).

V.f. Potential population differences

As observed in section II.b., non-nicotine smoking factors may be especially important for tobacco dependence in women. Women are less responsive than men to
manipulations of nicotine exposure, and more responsive than men to manipulations of non-nicotine components of cigarette smoking, such as sensory cues (Perkins et al. 2009a; Perkins et al. 1999; Perkins et al. 2006). At least some of this difference precedes the onset of dependence due to chronic nicotine exposure via smoking (Perkins et al. 2009a). Reduced nicotine cigarettes support craving relief among women more than men (Barrett 2010) produce positive subjective effects (satisfaction, relaxation, reduced anxiousness), and reduce smoking intentions among women more than men (Barrett and Darredeau 2012).

These findings suggest that women may be at greater risk to maintain long-term use of reduced nicotine tobacco than men. On the other hand, in a cessation study, tapered use of reduced nicotine cigarettes in combination with nicotine replacement therapy had a greater effect on continuous abstinence at 4 weeks for women than for men (Becker et al. 2008). Walker et al. (2012) observed no difference by gender in the effect of the paired Quitline intervention.

The potential adverse effects of nicotine reduction among those with severe psychiatric disorders remain a concern. A recent study explored the effects of reduced nicotine cigarettes among smokers with schizophrenia (Tidey et al. 2013). Denicotinized cigarettes reduced cigarette craving, nicotine withdrawal symptoms, smoking withdrawal symptoms, and usual-brand smoking, and were well tolerated, with no indication that the reduction in nicotine affected psychiatric symptoms. However, the cigarettes substituted for nicotine containing cigarettes less effectively for smokers with schizophrenia than control smokers, suggesting that long-term use of reduced nicotine cigarettes among those with schizophrenia may be less likely given the presence of nicotine-containing alternatives. Further studies with reduced nicotine among individuals with depression or other serious mental health disorders are warranted.

V.g. Potential health effects
Hatsukami et al. (2010a) reported significant reductions in toxicant exposure following switching to reduced nicotine cigarettes, including tobacco-specific nitrosamines (TSNA), acrolein, and benzene, although no measured reduction was found in exposure to polycyclic aromatic hydrocarbons. The reductions in TSNA were consistent with reduced levels measured in the tobacco, while other toxicant differences were believed to reflect reductions in smoking behavior. These findings support the conclusion that a reduced nicotine policy may support reduced health risks not only among those who quit or fail to acquire tobacco dependence, but potentially among those who continue use of tobacco products despite reduced nicotine (Joel et al. 2012).

The likely reduction in nicotine intake is another potential health benefit to be considered (Joel et al. 2012; Rose and Behm 2004a). Although non-nicotine components of tobacco are the primary causes of tobacco-related disease, nicotine has a number of effects which may be contributors to development of cardiovascular disease, including vasoconstriction, promotion of thrombosis and atherosclerosis, and impairment of insulin sensitivity (Assali et al. 1999; Benowitz 1988). Nicotine may also promote arteriogenesis (Heeschen et al. 2003), which could increase the blood supply to tumors and may inhibit apoptosis (Suzuki et al. 2003), promoting carcinogenesis.

Alternatively, Girdhar et al. (2008) postulate based on in-vivo research that nicotine may moderate the risk of cardiovascular disease caused by non-nicotine smoke components by reducing platelet activation. In this case, reductions in cigarette nicotine content could increase risks for cardiovascular disease. The authors observe that use of pure nicotine as a tobacco substitute has no record of harm, suggesting that the direct health effects of nicotine use are minimal.

No significant difference in adverse health events were identified between those assigned a reduced nicotine cigarette and those assigned NRT only in the Quitline intervention conducted in New Zealand (Walker et al. 2012). The weight of evidence suggests that similar or reduced health risks are the most likely outcome of switching to reduced nicotine cigarettes, but more studies are needed in this area.
V.h. Potential illicit sales of nicotine-containing cigarettes

A number of studies describe the importance of smuggling to cigarette manufacturers as a means of promoting products in low and middle income countries (Lee et al. 2012; Legresley et al. 2008). Most illicit cigarette sales are supply driven, and remain commonplace even where prices and excises remain low (Joossens and Raw 2003). High rates of smuggling are generally on the order of 10-15% (Joossens and Raw 2008; Mecredy et al. 2013; Pavananunt 2011).

No published studies quantify the likelihood of illicit sales of higher nicotine cigarettes within the context of a reduced nicotine market. Givel (2011) describes the outcome of a sales ban enacted in 2004 to end tobacco consumption in Bhutan, with only small quantities of tobacco for personal consumption permitted for import. Smuggling and black market sales increased in the years following the ban, sufficient to support a smoking rate of 10% among Bhutanese men.

In the case of a nicotine reduction policy, both the appeal of reduced nicotine cigarettes, and the availability and appeal of alternative forms of nicotine, are likely to have a significant effect on the extent of illicit tobacco sales (Borland 2013). A recent study in Canada found that contraband cigarettes had less rated appeal among youth compared to leading brands, suggesting that the availability of contraband cigarettes could potentially have a greater impact among addicted smokers versus novice or experimenting users (Czoli and Hammond 2013). Availability of contraband cigarettes have been associated with reduced likelihood of cessation and reduced attempts to quit (Hyland et al. 2005; Hyland et al. 2006; Licht et al. 2011).

V.i. Models of population effects

Tengs et al. (2005) simulated the population effects of a reduced nicotine mandate within the U.S. over a 6-year period. Assuming an 80% decline in smoking prevalence,
Nicotine reduction

A 10% increase in the mortality of current smokers due to compensation, and 10% of smokers assumed to enter the black market annually, their model estimated a cumulative gain of 157 million quality-adjusted life years (QALY) over 50 years. They then varied the model parameters in a number of ways, concluding that as long as smoking cessation increased by 10% or more, smoking relapse and initiation decreased by 10% or more, and compensation increased smoker mortality by no more than 80%, a net gain in QALYs was likely. Significantly, over a range of plausible estimates (0-50% of all smokers), QALYs were uniformly gained rather than lost regardless of the extent of black market entry.

Another simulated model estimated health outcomes assuming that nicotine reduction would reduce the probability of initiating smoking for every age and gender, that the probability of cessation would increase, and that former smokers would have a decreased probability of relapse. Alternately, it considered the possibility that promotion of reduced nicotine cigarettes as “safer” could worsen all three outcomes. Outcome estimates were created for behavior change probability values in increments of 10% from −80% to +80%. The study concluded that a 60% reduction in smoking behaviors (initiation, use, relapse) would offset any plausible increase (50% or less) in harm resulting from compensatory smoking or other unintended health consequences among those who continue to smoke. A modest 20% reduction in initiation, use, and relapse, coupled with a 20% reduction in disease risk among continuing smokers, supported a cumulative gain of 165 million QALY. A significant 80% reduction in initiation, use, and relapse, with no change in disease risk among those continuing to smoke, resulted in an estimated gain of 281 million QALY (Ahmad and Billimek 2005).

A commissioned study modeled the potential effects within Canada of a nicotine reduction policy across tobacco products (IEC; Industrial Economics 2013). The study inputs were based on a literature review as well as interviews with health experts. Consideration was given to outcomes on smoking initiation and cessation, black market increases, substitution of other tobacco products for cigarettes, and potential compensatory behavior. Estimates of the impact on initiation and cessation in the
absence of second-order impacts (black market, substitution, compensation) reduced costs of tobacco-related illness by 19% after 30 years. Assuming an increase in black market share from 15% to 50%, the benefits decreased 40%. Mortality benefits of a nicotine standard were driven primarily by the impact on cessation, while the morbidity benefits were driven primarily by the impact on initiation.

V.j. Summary of findings regarding potential outcomes of nicotine reduction

1) The act of smoking possesses reinforcing value in addicted smokers regardless of nicotine content. Denicotinized cigarettes can serve as an effective behavioral economic substitute for nicotine-containing cigarettes.

2) The availability of alternative nicotine-substitutes such as nicotine medications, oral tobaccos, or nicotine containing electronic cigarettes may have direct effects on self-administration of cigarettes, whether or not the cigarettes themselves contain nicotine.

3) Withdrawal is not a prominent adverse consequence of reductions in nicotine intake for most individuals, and significant compensatory smoking behavior in the form of greater intensity of smoking or increased number of cigarettes per day is not a likely outcome at very low (<.1 mg) levels of nicotine exposure.

4) A nicotine reduction policy may be more likely to help smokers achieve abstinence when they make an active quit attempt. Use of reduce nicotine cigarettes have improved quit rates across a number of studies.

5) Nonsmoking adolescents are unlikely to proceed to more escalated smoking behavior in the absence of acute nicotine effects. Establishment of a threshold for reduction of negative affect in nonsmoking adolescents would provide further confirmation.

6) The use and effects of reduced nicotine cigarettes among nonsmokers and non-dependent smokers are underexplored. In nonsmokers, self-administration of reduced nicotine cigarettes is related directly to pleasurable effects and inversely to aversive effects.
7) Low level nicotine exposure in adolescents could potentially produce risk of addiction to other drugs of abuse. Low level nicotine products could also serve as starter products for other forms of tobacco or other forms of nicotine delivery.

8) Women may be more likely than men to sustain long-term use of reduced nicotine tobacco. Nicotine reduction in schizophrenics had no aversive effects on mental health symptoms; more studies are needed in other at-risk populations.

9) Reduced nicotine may support reduced health risks not only among those who quit or fail to acquire tobacco dependence, but potentially among those who continue use of tobacco products despite reduced nicotine. However, more studies are needed.

10) Illicit tobacco sales may potentially undermine the health goals of a nicotine reduction policy. Although no formal estimates have been attempted, both the appeal of reduced nicotine cigarettes and the availability and appeal of alternative forms of nicotine are likely to have a significant effect on the extent of illicit tobacco sales.

11) Various model estimates have been created to describe the likely effects of a nicotine reduction policy. All indicate a significantly positive effect on health outcomes.
VI. Policy approaches to nicotine reduction

A number of authors propose nicotine reduction of cigarettes in the context of a harm reduction model in which safer products are made more appealing relative to more toxic products (Arnott 2013, Borland 2013, Hatsukami 2013; Britton and McNeil 2013; McNeil et al 2012; Houezec et al., 2011; Hall and West, 2008) This underscores the critical importance of the regulatory framework within which a nicotine reduction policy would take place, as well as the resulting commercial marketplace in which smokers and nonsmokers develop and sustain tobacco or nicotine use behaviors, and the social environment that influences and supports these behaviors.

VI.a. Comprehensive nicotine regulation

The effects of a cigarette nicotine reduction policy would depend to a significant degree on the availability, toxicity, and appeal of alternative nicotine delivery systems, including other forms of (combustible or noncombustible) tobacco, medicinal nicotine, and non-tobacco commercial nicotine products (Hatsukami et al. 2010b). It follows that a successful nicotine reduction policy must take place within the context of comprehensive regulation of all tobacco and nicotine containing products (Gray et al. 2005; Hatsukami et al. 2013a; Le Houezec et al. 2011; McNeill et al. 2012; Zeller et al. 2009).

A single institution with authority over tobacco and nicotine regulation would enable coordination of approaches for different products (Le Houezec et al. 2011). This institution would be responsible for formulating decisions about how tobacco and nicotine products would be regulated, setting performance standards, authorizing health or other product claims, evaluating products in market, and their population effects. Access to a comprehensive surveillance system would be critical in order to be able to respond quickly to any unanticipated changes in nicotine use or health outcomes (Hatsukami et al. 2013a; Le Houezec et al. 2011).
The overarching goals of comprehensive nicotine regulation would be to minimize use of the most toxic nicotine-containing products, to encourage the development of new and improved nicotine delivery systems as alternatives to more toxic products, and to continue to monitor and regulate less toxic products for their health effects (Benowitz and Henningfield 2013; Gray et al. 2005; Le Houezec et al. 2011) Policy approaches could be considered to incentivize smokers to adopt less hazardous forms of tobacco/nicotine use, including restrictions on access, marketing, and use, as well as differential taxation, such that taxes on cigarettes and combusted tobacco are much higher than those on cleaner nicotine delivery products (Benowitz and Henningfield 2013; McNeill et al. 2012; O’Connor 2012).

**VI.b. Performance standards**

Performance standards are necessary to ensure successful implementation of a reduced nicotine policy (Hatsukami 2013; O’Connor 2012). A number of approaches could be considered for determining product nicotine standards: for example, restriction of delivered or inhaled nicotine, or of individual doses of nicotine defined at the level of a single puff. However, focus on the total nicotine available in the unburned cigarette is the most promising approach, given that it is both more easily measured and less subject to behavioral manipulation and individual variability (section IV.f.)

The evidence presented in this report suggests that reduction of nicotine in cigarettes to less than 1 mg nicotine content may be sufficient to reduce dependence in some proportion of the smoking population, with minimal adverse effects. This evidence is drawn from studies using cigarettes constructed with very low nicotine tobacco and design parameters similar to those of standard conventional cigarettes. It is possible and even likely that performance standards which focus exclusively on nicotine content of tobacco would encourage development of cigarettes that contain little tobacco nicotine but which are otherwise quite different in form and function from conventional cigarettes. Examples might include products that release nicotine in a more readily
available (free-base) form, that alter the particle formation or deposition of nicotine, that release the full amount of nicotine within a single dose, that encourage and enable use of multiple cigarettes to maintain dose, or that use nicotine analogs and other pharmacologically active compounds to enhance or replace the effects of nicotine.

Performance standards must be responsive to the changing marketplace (Hatsukami et al. 2013a; Hatsukami et al. 2012; O'Connor 2012; Parascandola 2011). Initial standards should require that products match product parameters of conventional cigarettes across a range of basic physical characteristics including tobacco weight, length, circumference, filter, paper, and ventilation (Wayne and Connolly 2009). New products and technologies must be carefully evaluated and commercial introduction permitted only once products have sufficiently demonstrated reduced risk, addictiveness, and appeal (Carter et al. 2009; Hatsukami et al. 2013a; Hatsukami et al. 2012; Henningfield et al. 2011).

Global standards for addiction and harm should ultimately be set through FCTC processes (McNeill et al. 2012). These global standards could also support further product standards, such as restriction on toxicants (e.g. nitrosamines), physical design parameters that enable or support compensation (e.g. ventilation), flavorants, or other factors that increase product appeal (e.g. menthol). In each case the effects of these standards would need to be carefully evaluated (Hatsukami 2013; Hatsukami et al. 2012; McNeill et al. 2012; O'Connor 2012).

**VI.c. Gradual versus sudden reduction**

In their original proposal, Benowitz and Henningfield (1994) called for a reduction in nicotine levels over a period of 10–15 years, as a means to minimize potential withdrawal among other practical concerns. However, a more gradual reduction in nicotine could have negative health consequences (Hatsukami et al. 2010b). First, it would keep individuals for an extended period at doses of nicotine that maintain smoking behavior. Second, it is possible that a marketwide, gradual shift in nicotine
levels would alter smokers’ relationship to nicotine in unanticipated ways, potentially adjusting the threshold for addiction in the process (Smith et al. 2013). For example, early work on nicotine self-administration found that rats switched to saline extinguished more slowly if they received an intermediate dose reduction prior to saline substitution (Cox et al. 1984).

No studies have yet been conducted that model the effects of a reduction in nicotine over the course of years. However, progressive reduction in nicotine has been considered over a span of weeks or months, demonstrating that gradual declines in nicotine consumption may be administered without significant compensation. Further, once tapering is completed, nicotine intake remains below baseline, suggesting reduced level of nicotine dependence (Benowitz et al. 2009; Benowitz et al. 2012; Benowitz et al. 2007). A strong association exists between magnitude of daily smoking reduction and nicotine dependence, supporting the concept that gradual reductions in intake may reduce nicotine dependence (Mooney et al. 2011). A recent literature review concludes that progressive reduction in the level of nicotine in cigarette tobacco can reduce the level of nicotine dependence in smokers, with minimal compensatory smoking (at levels of smoke nicotine <.1 mg) and without adverse effects (Walker et al. 2009).

Evidence suggests that even immediate reductions in nicotine may be successful in decreasing smoking rates as well as dependence (Donny et al. 2007; Hatsukami et al. 2010a). Smokers switched abruptly from own cigarettes to reduced nicotine content cigarettes for a period of six weeks showed reduced exposure, decreased consumption, and higher rates of cessation (Hatsukami et al. 2010a). Similarly, cigarette consumption declined immediately and motivation to smoke decreased in an 11-day switching study (Donny et al. 2007).

Both gradual and immediate reductions in nicotine at low doses result in similar self-administration behavior in rats, with no compensatory behavior in either group (Smith et al. 2013) A meta-analysis of the effect on quit rates of an intermediate reduction in consumption prior to quitting found no difference between reducing cigarettes smoked
before quit day, and quitting abruptly with no prior reduction (Lindson-Hawley et al. 2012). Taken together, these studies suggest that cigarette nicotine dose reduction may be implemented quickly without significant adverse effects among smokers.

**VI.d. Alternative forms of nicotine**

Some cigarette smokers, when faced with reduced nicotine, are likely to switch to other products seeking more nicotine. The appeal of alternative tobacco products, such as oral and smokeless tobacco, waterpipes, pipes, and cigars, may increase in relation to their ability to substitute for conventional cigarettes more effectively than do the reduced nicotine cigarettes (see section V.a.). Combusted tobacco is significantly more harmful than noncombusted tobacco, which is itself more harmful than clean nicotine products such as nicotine patch or gum (Stratton et al. 2001). Given this continuum of harm, it may be advisable to mandate nicotine reductions not only in cigarettes, but across all combusted tobacco products, minimizing the risk of switching to the most harmful products (O’Connor 2012).

Pharmaceutical products for dispensing nicotine, while much safer than tobacco products, are made unappealing by design in order to avoid abuse liability, and are not intended for long term use (Carter et al. 2009; Henningfield et al. 2011). Although these products may help a smoker through withdrawal more easily, they do not produce sufficient positive reward, particularly in the form of fast and effective nicotine delivery, necessary to provide a reasonable alternative to tobacco products (Rooke et al. 2013).

Electronic cigarettes were designed with the express purpose of replicating the act of smoking, without use of tobacco (Cahn and Siegel 2011; O’Connor 2012). These (or similar) products may present a more viable alternative to cigarettes (Le Houezec and Aubin 2013), and a rapid body of evidence is accumulating on their use and acceptance (Cahn and Siegel 2011; Dawkins and Corcoran 2013; Dawkins et al. 2013a; Dawkins et al. 2013b). Electronic cigarettes produce a vapor of nicotine in combination with other constituents, usually including glycerin or propylene glycol. Currently they are used
primarily for smoking cessation, although for a longer duration than nicotine replacement therapy (Dawkins et al. 2013b). Users believe them to be safer than smoking (Dawkins et al. 2013b).

Electronic cigarettes deliver nicotine more effectively and more rapidly than a nicotine inhaler (Eissenberg 2010) though somewhat less effectively than a conventional cigarette (Cahn and Siegel 2011; Eissenberg 2010). They produce sizeable craving reduction which is attributable at least in part to physical sensory characteristics of the cigarette independent of nicotine delivery (Bullen et al. 2010; Cahn and Siegel 2011). At least some electronic cigarettes demonstrate reliable blood nicotine delivery (mean of 6.77 ng/ml 10 min after 10 puffs, mean maximum of 13.91 ng/ml by the end of the ad lib puffing period). They are capable of reductions in tobacco-related withdrawal symptoms and urge to smoke, provide direct positive effects, and low adverse effects (Dawkins and Corcoran 2013).

VI.e. Cessation and behavioral treatment

As nicotine is reduced to nonaddictive levels, there will likely be a sharp increase in the number of smokers who want to quit (Benowitz and Henningfield 2013; Henningfield et al. 1998). Many will visit physicians seeking nicotine replacement or behavioral therapy to aid cessation or relief from withdrawal symptoms. Effective and affordable treatment offered by health care professionals will be invaluable in ensuring the mandate’s success (Benowitz and Henningfield 2013; O’Connor 2012; Zeller et al. 2009). Coverage by insurance programs is critical, as are individualized services to special populations for whom adverse effects may be heightened, such as those with co-morbid psychiatric disorders (Henningfield et al. 1998). The broad availability of pharmacotherapies and treatment may not only reduce the discomfort associated with reduced nicotine content of cigarettes but may lead to substantial reductions in cigarette smoking and possibly to eventual cessation of all tobacco and nicotine products for some or many current smokers.
VII.f. Surveillance

The public health community has been slow in the past to recognize the potential limitations of regulatory or harm reduction approaches despite early evidence of their ineffectiveness (McNeill et al. 2012; Parascandola 2011). An adequate surveillance system will enable regulators to monitor the impact of tobacco products on prevalence, initiation, and harm, and to address unintended outcomes (Hatsukami et al. 2013a). Mandatory reporting regulations for all nicotine and tobacco products, as adopted in Canada and described in Articles 9 and 10 of the FCTC, are a necessary condition of adequate surveillance, and should include physical design components (tobacco weight, nicotine concentration, filter ventilation), tobacco and added constituents, emissions for combustible products, as well as measures of abuse liability (Carter et al. 2009; Hatsukami et al. 2013a; Hatsukami et al. 2012; McNeill et al. 2012).

Hatsukami et al. (2013a) and others (Stratton et al. 2001) describe a comprehensive approach to tobacco product evaluation that can be effectively applied to ongoing evaluation of reduced nicotine cigarettes. This includes: preclinical tests in animals to assess abuse liability, acquisition of nicotine self-administration in both adolescent and adult animals, and neurophysiological changes that affect function resulting from exposure; human imaging, laboratory, and clinical trial studies that examine the abuse liability, tobacco use behaviors, toxicant exposure, and potential health risks in general and vulnerable populations; and assessment of moderating factors including how the consumer perceives the product and its appeal, and packaging, price, and promotion (Hatsukami et al. 2013a).

Although biomarker testing in large studies of smokers is promising as an evaluation of disease risk, this approach may not be feasible in many countries where resources are unavailable (McNeill et al. 2012). The complexity of tobacco products, and knowledge required to assess toxicology, abuse liability, and outcomes may be an additional barrier. McNeill et al. (2012) identify the need for a global data repository to facilitate implementation of tobacco product regulation and surveillance worldwide. The
repository would ease the burden on regulators by collecting and analyzing data, making global comparisons, and relaying information to national regulators with recommendations in an easily understandable form.

**VI.g. Consumer education and beliefs**

The effects of a reduced nicotine policy will depend in part on how effectively risks are communicated, as well as the relative appeal of reduced nicotine and other tobacco or nicotine products. Beliefs about the increased safety of reduced nicotine products could reduce likelihood of quitting or switching to safer alternatives, and could encourage greater experimentation with cigarettes.

Limited evidence suggests that smokers believe reduced nicotine cigarettes to be less harmful. A 2006 study (Shadel et al. 2006) evaluated beliefs following exposure to a single print advertisement of a nicotine free product (Quest). Smokers made a number of false inferences about the product: that it was lower in tar, healthier, and less likely to cause cancer. The denicotinized Philip Morris brand Next was developed in response to focus group interest in no-nicotine products, based on perceptions that the product would be healthier, as well as facilitate quitting (Dunsby and Bero 2004).

Smokers express doubt about health claims for reduced exposure products, about whether they would actually switch to such a product, and whether they would taste as good as conventional cigarettes (Parascandola et al. 2009). These and other responses are likely to be affected by ongoing marketing and communication efforts by manufacturers, public health communication strategies in support of nicotine reduction, and the relative availability and public knowledge of other tobacco or nicotine products. Education of smokers and nonsmokers about the health risks of tobacco in the absence of nicotine, the relative harm of available products, and opportunities for treatment are critical. Marketing of tobacco and nicotine products will need to be strongly regulated (Hatsukami et al. 2013a; McNeill et al. 2012)
VI.h. Public support for reduced nicotine policy

Recent studies in the U.S. demonstrate strong public support for mandated nicotine reduction. In a survey of 511 nonsmokers and 510 smokers, nearly 2 in 3 (65%) supported reducing nicotine in cigarettes to nonaddictive levels, including 73% of nonsmokers and 58% of smokers. More than 3 in 4 persons (77%), including 81% of nonsmokers and 74% of smokers, supported the reduction of nicotine if it could cause fewer children to become addicted to cigarettes. Nonsmokers were significantly more likely than smokers to support reducing nicotine in cigarettes under both conditions (Connolly et al. 2012). Another survey found that 67% of smokers would support an FDA regulation that made cigarettes less addictive if “nicotine was made easily available in non-cigarette form.” (Fix et al. 2011) A third cross-sectional survey of adults (n=2649), found that nearly half supported nicotine reduction, including 46% of never smokers, 49% of former smokers, and 46% of current smokers. Among smokers, support was highest among those who intended to quit in the next 6 months (Pearson et al. 2013). This survey was the only one to include a neutral response option, and nearly 27% of respondents chose this option, which may explain the higher levels of agreement in the other surveys.

VI.i. Unintended market consequences

Reduced access to nicotine containing cigarettes may increase the demand for contraband cigarettes among addicted smokers (Benowitz and Henningfield 2013). Minimizing the impact of illicit cigarette sales will require effective surveillance strategies (Hatsukami et al. 2013a) as well as policies that limit the scale of the contraband market (Joossens and Raw 2008). Most smuggling worldwide is large-scale and organized, consisting of containers of cigarettes supplied by tobacco manufacturers and exported to countries where they have no legal market (Joossens and Raw 2003; Joossens and Raw 2008) Thus, successful efforts to control smuggling have relied on making manufacturers liable for the safe transport of cigarettes to their legitimate end market.
Chain of custody markings would require manufacturers to print legibly, on all packages of tobacco products, a unique serial number to identify the manufacturer and the date and location of manufacture, and another identifier to show the chain of custody—wholesaler, exporter, distributor, and end market. Other successful anti-smuggling measures include scanners for container detection, prominent fiscal marks on packs, increased punishment, more customs officers, and parliamentary hearings to expose tobacco industry export practices. These approaches have resulted in a reduction in cigarette smuggling from around 15% to 1–2% in Spain and Italy, and significant reductions in the United Kingdom (Joossens and Raw 2008). By contrast, voluntary approaches have had no measurable effect.

Besides large scale, organized smuggling, other types of illegal trade could include bootlegged or counterfeit products. These products could potentially consist of extremely low grade tobaccos with high levels of toxins, or have other unanticipated risks, thus presenting a serious health problem within some subset of smokers. As noted by Benowitz and Henningfield (2013), it is difficult to imagine growth of a bootlegged cigarette industry, operating outside of regulatory control, sufficient in scale to rival the present cigarette market.

Unregulated combustible tobaccos, such as roll-your-own tobacco, could become a substitute for manufactured cigarettes. Other possibilities include significant dual use of reduced nicotine cigarettes in conjunction with nicotine delivery devices, use of pH modification or additives to increase the impact and pharmacology of manufactured products, and significant unanticipated behavioral changes in use of reduced nicotine products as a result of long-term use. Availability of more appealing alternative nicotine products is likely to function as a check on these unintended market outcomes (Benowitz and Henningfield 2013; Hatsukami et al. 2013a).

VI.j. Summary of findings regarding policy approaches to nicotine reduction
1) Comprehensive, coordinated regulation of all tobacco and nicotine containing products is necessary for successful implementation of a nicotine reduction policy.

2) Regulating the total nicotine available in the unburned cigarette is the most promising approach to nicotine reduction, given that it is both more easily measured and less subject to behavioral manipulation and variability.

3) Performance standards which focus exclusively on nicotine content of tobacco would encourage development of cigarettes that contain relatively little tobacco nicotine but which are otherwise quite different in form and function from conventional cigarettes.

4) New products and technologies must be carefully evaluated and commercial introduction permitted only once products have sufficiently demonstrated reduced risk, addictiveness, and appeal.

5) Gradual nicotine reduction over a time course of years may have unintended consequences, which have yet to be studied. Progressive nicotine reduction conducted over a time course of months, as well as immediate nicotine reduction, shows no adverse effects or evidence of compensatory smoking.

6) Smokers are likely to switch to alternative products. The most promising of these are electronic cigarettes or other nicotine devices that provide both nicotine and sensory characteristics like a cigarette, but in the absence of tobacco.

7) Increased availability of behavioral counseling and pharmacotherapies to assist smokers with significant withdrawal symptoms or for those who wish to quit are necessary to support nicotine reduction.

8) An adequate surveillance system is needed to enable regulators to monitor the impact of tobacco and nicotine containing products on prevalence, initiation, harm, and to address unintended outcomes. Efforts may be necessary to assist countries that are unable to support a large-scale surveillance system.

9) Beliefs about the increased safety of reduced nicotine products could reduce likelihood of quitting or switching to safer alternatives. Public health communication strategies and regulation of marketing are critical.
10) Public support for nicotine reduction of cigarettes is high, particularly in the context of making other forms of nicotine available for consumption.

11) Successful efforts to control smuggling have relied on making manufacturers liable for the safe transport of cigarettes to their legitimate end market.

12) Heath threats may be posed by smaller scale contraband cigarettes, unregulated tobacco, dual use, and modifications to reduced nicotine cigarettes intended to increase or replace the effectiveness of nicotine.
VII. Conclusions

Although the science on nicotine reduction and use of reduced nicotine cigarettes remains limited, the level of agreement among available studies is striking. Findings from animal and human studies are broadly comparable, identifying similar thresholds for self-administration, effects of both sensory stimuli and broad classes of tobacco compounds (MAO, alkaloids) on nicotine reinforcement, importance of acquisition of dependence in adolescence versus adulthood, and a relative lack of withdrawal or adverse effects in the context of progressive reduction in nicotine.

Assessing the weight of the evidence presented above, the most likely consequences of mandated nicotine reduction include:

- a reduction in acquisition of smoking and progression to addiction among novice smokers
- a reduction in smoking among some proportion of addicted smokers as a result of behavioral extinction
- an increase in quitting and a reduction in the number of smokers who relapse from quitting
- an increase in use and availability of alternative forms of nicotine, including oral or smokeless tobacco products, nicotine aerosol or vapor products, and medicinal nicotine
- a reduction in health risks for most smokers, reflecting reduced consumption, reduced exposure to tobacco smoke, and reduced toxicants in tobacco (e.g. TSNAs, nicotine).

Possible consequences of mandated nicotine reduction, for which there is currently too little information to make a judgment include:

- an increase among some proportion of smokers in use and availability of black market cigarettes with high nicotine content
- an increase among some proportion of smokers in dual use of nicotine containing products and cigarettes
- changes in the design or construction of reduced nicotine products, whether by manufacturers or by smokers, that alter the delivery characteristics of the product, with unanticipated effects on toxicity, addiction, and appeal
- increased use of nicotine containing products among nonsmokers and those who would not have smoked, due to greater availability, appeal, and lower perceived risk of these products
- greater long-term use of reduced nicotine cigarettes among women than men

Other potential but less likely outcomes of mandated nicotine reduction based on the current evidence include:

- increased smoking behavior (puffing or cigarettes per day) among some proportion of smokers as a compensatory response to lack of nicotine
- increased risk of cardiovascular disease among continuing smokers as a result of exposure to tobacco smoke in the absence of nicotine
- increased use of other drugs of abuse potentiated by exposure to reduced nicotine cigarettes
- a significant black market of high nicotine cigarettes replacing or supplanting the regulated cigarette market
VIII. Recommendations

- A nicotine reduction policy is technically feasible, is supported by smokers and nonsmokers, and is likely to have a significant positive impact on population health.

- Mandated nicotine reduction should take place alongside comprehensive regulation of all nicotine and tobacco containing products. Comprehensive regulation should support the use of products which demonstrate less toxicity, such as medicinal nicotine or nicotine delivery devices, and should reduce availability and appeal of more toxic products.

- There is strong agreement regarding the identification of a threshold for reinforcement of nicotine in cigarettes at around 0.1–0.2 mg of delivered nicotine. This level is at or below the self-administration level of nicotine in human smokers (between 0.1–0.4 mg) and animals (between ~0.2–0.5 mg); at or below the threshold for discrimination of nicotine in both smokers and nonsmokers; and is consistent with internal studies of threshold for latency effects of cigarette nicotine yield conducted by manufacturers (between 0.1–0.3 mg).

- Mandated nicotine reduction over a relatively short time course shows little adverse withdrawal or behavioral effects. A more gradual reduction may have unintended behavioral and health consequences. Availability of effective and affordable treatment and of alternative forms of nicotine will help dependent smokers who experience adverse effects.

- Anticipation of population outcomes is limited in a number of key areas. Research needs include: further establishment of the likely use and effects of reduced nicotine cigarettes in nonsmoking adolescents, nonsmoking adults, and nondependent smokers; further studies among at risk populations such as those with moderate and severe depression; further studies on the comparative health effects of reduced nicotine versus nicotine containing cigarettes; and studies on long-term use of reduced nicotine cigarettes.
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Nicotine reduction


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Figure 3. Examples of marketing claims to use e-cigarettes to “smoke anywhere” and “circumvent smokefree laws” (www.smokingeverywhere.com; www.elitensmoke.com)

Figure 4. Katherine Heigl smoking an e-cigarette on the set of the David Letterman Show, September 2009)
Figure 5. Celebrity Jenny McCarthy in Lorillard’s Blu e-cigarette television commercial (as of October 2013)
Rachel Grana, Stan Glantz, Neal Benowitz
WHO Background Paper on ENDS

DRAFT– v. October 14, 2013

BACKGROUND

E-cigarettes (also known as electronic nicotine delivery systems or ENDS) are a class of products intended to deliver nicotine-filled aerosol (commonly called “vapor”) to a user by aerosolizing a heated solution typically comprised of propylene glycol, glycerol (glycerine), nicotine and flavoring agents (Figure 1). E-cigarettes without nicotine are also available. The first of these devices that started the trend in use we describe in this report was invented by a Chinese pharmacist, Hon Lik, in 2003. The U.S. patent application for the device states that "An electronic atomization cigarette that functions as substitutes for quitting smoking and cigarette substitutes.” (Patent #8,490,628 B2) E-cigarette sales have risen rapidly since they entered the marketplace in 2007. (Cobb, Byron et al. 2010) Products are marketed as healthier alternatives to tobacco smoking, as useful in quitting smoking and reducing cigarette consumption, and useful for circumventing smokefree laws and the ability to "smoke anywhere." (Grana and Ling under review) Part of the exponential rise in sales over the past 3 years (2010-2013) has been due to widespread advertising via television commercials and print advertisements, which often feature celebrities, for the most popular brands, including those owned by tobacco companies. (Felberbaum 2013)

Figure 1. Electronic cigarette
In 2009, the WHO Study Group in Tobacco Product Regulation (TobReg) addressed the emerging regulatory issues pertaining to e-cigarettes. The committee noted that there was very little published scientific evidence on the health effects of e-cigarettes, or their efficacy for smoking cessation (stated in TobReg Report 955) (World Health Organization 2009) and that there was not sufficient evidence to support the cessation and health claims made by companies and those in the public health community who were advocating e-cigarettes for harm reduction. The report states (p.7), "In addition to nicotine dependence, the sensory effects of the product, social and marketing forces and perceptions of harmfulness and potential benefits should be considered in examining the initiation, patterns of use and development of addiction." (World Health Organization 2009) Meanwhile, e-cigarette prevalence has increased dramatically with rapid increase in prevalence in many countries between 2008 and 2012 (Table 1, bottom of document).

Both the 2009 TobReg Report 955 and the 2012 World Health Organization Framework Convention on Tobacco Control (FCTC) Conference of the Parties report on e-cigarettes (November 2012) (FCTC/COP/5/13 2012) articulated concerns about how the products may interfere with implementation of the FCTC, particularly Articles 8, 9, 10, 11, 13, because e-cigarettes mimic tobacco cigarettes, thus interfering with denormalization and limits on the indirect promotion of tobacco use/products. E-cigarettes may hinder protection from exposure to tobacco smoke (Article 8) because, while e-cigarettes emit less air pollution into the environment than conventional cigarettes, they still subject bystanders to “passive vaping.” E-cigarettes are widely advertised and promoted (often inaccurately) as being exempt from clean indoor air laws. In addition, the similar appearance of people using e-cigarettes and those using conventional cigarettes can complicate enforcement of restrictions on smoking conventional cigarettes. In addition, the e-cigarette vapor has not been proven safe for inhalation by bystanders. A main concern with the products was lack of data on the safety of the ingredients in the e-cigarette solution, especially the safety of repeated inhalation of a heated mixture of propylene glycol and other chemicals. In 2009, TobReg recommended that if e-cigarettes were to be considered medicines or tobacco products, they would be subject to the labeling and warnings requirements in Articles 10 and 11. The TobReg report placed great emphasis on the products potential
interference with Article 13, which addresses advertising and sponsorship by industry. Both Articles 8 and 13 address the denormalization of tobacco products and indirect promotion of tobacco products could be undermined in that the appearance of a cigarette-like product that produces a smoke-like vapor.

While the number of published studies on e-cigarettes has increased dramatically, there has been constant innovation in the marketplace of these products and many questions about their safety, efficacy for harm reduction and cessation, and total impact on public health remain unanswered. Both the individual risks and benefits and the total impact of these products occur in the context of the widespread and continuing availability of conventional cigarettes and other tobacco products, with high levels of “dual use” of e-cigarettes and conventional cigarettes at the same time, which raises questions about the suggested harm reduction benefits. It is important to assess e-cigarette toxicant exposure and individual risk as well as health effects of e-cigarettes as they are actually used in order to ensure safety and to develop evidence-based policies and a regulatory scheme that protects the entire population, children and adults, smokers and non-smokers, in the context of how the tobacco industry is marketing and promoting these products.

This report reviews of the literature on e-cigarettes available as of September 2013, as well as an update of tobacco industry involvement in the e-cigarette market, global regulations pertaining to e-cigarettes and potential options for regulation. [NOTE:literature table in progress]

PRODUCTS (TYPES, ENGINEERING)

Electronic nicotine delivery systems (ENDS) have many names, including electronic cigarettes, e-cigarettes and e-hookah. For the purposes of this report all these products will be referred to as e-cigarettes. Product engineering has been evolving since the first e-cigarettes were documented as arriving on the global market in 2007(Pauly, Li et al. 2007). As of late 2013, there was wide variability in product engineering, including varying concentrations of nicotine in the solution that e-cigarettes use to generate the nicotine aerosol (also called e-liquid), varying volumes of solution in the product, different carrier compounds (most commonly propylene glycol with or without glycerol (glycerine), a wide range of additives and flavors, and battery size (which affects how hot the vaporizer gets). Battery size differences results in great
variability in the products' ability to heat and convert the nicotine solution to an aerosol and, consequently, a wide range of levels of actual nicotine delivery as well as the nature of the other chemicals delivered to users and emitted into the surrounding environment. Products come with a variety of nicotine strengths (including some without nicotine), usually expressed in mg/ml of solution or percent concentration. Quality control of the products themselves is highly variable and users can modify many of the projects. In addition, as the types and design of products and their contents continue to evolve rapidly, it is increasingly difficult to determine what an e-cigarette "is," what is may contain, and what it is delivering to the user and the surrounding environment.

The first e-cigarettes were cigarette-shaped, plastic or metal devices comprising three parts: a battery, an atomizer (which attaches to the battery and has a heating element to convert the liquid into a vapor) and a cartridge (which attaches to the atomizer and contains additional heating elements and a wick or fiber where the liquid is placed; Figure 1). In subsequent models a cartridge was created called a cartomizer, which combined the atomizer and the wick/fiber (Figure 2). The cartridge is either refillable or pre-filled with e-liquid. The cigarette-shaped and sized devices are often called “mini” e-cigarettes or "cig-a-likes" by users (who often call themselves “vapers”). There are disposable and rechargeable models (Figure 2). More recent designs are pen-shaped and sized with larger-sized cartomizers (Figure 2) in order to hold more nicotine solution to reduce the amount of times a user needs to refill throughout the day. Some cartridges, called clearomizers, which hold about 1-2ml of e-liquid, are now transparent to allow the user to monitor how much fluid is in the device. The devices with larger cartomizers or clearomizers are sometimes referred to as "tank" systems and hold about 2-3 ml of solution. There are also much larger capacity and technologically sophisticated "tank system" devices (Figure 2) that have various mechanical and, even digital display, features. One such feature is a larger metal casing to hold larger and higher voltage batteries than found in the mini or pen style e-cigarettes. In tank devices the atomizers and batteries can be replaced with more powerful batteries (often called variable voltage devices) or lower electrical resistance atomizers that allow the user to control the heat level provided to the atomizer which aerosolizes the e-liquid. Furthermore, since the first e-cigarette products hit the market, users have been modifying the devices and creating their own; instructions to do so are widely available on the Internet on e-cigarette forum sites and YouTube. A concerning trend that has been occurring at least in the

**Figure 2. Examples of different products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Examples of Brands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disposable e-cigarette</td>
<td>Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing vapor.</td>
<td>NJOY OneJoy, Aer Disposable</td>
</tr>
<tr>
<td>Rechargeable e-cigarette</td>
<td>Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and/or how many puffs may be taken consecutively.</td>
<td>Blu, GreenSmoke, EonSmoke</td>
</tr>
<tr>
<td>Pen-style, medium-sized rechargeable e-cigarette</td>
<td>Larger than a cigarette with a bigger battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs.</td>
<td>Vapor King, Storm, Totally Wicked Tornado</td>
</tr>
<tr>
<td>Tank-style, large-sized rechargeable e-cigarette</td>
<td>Much larger than a cigarette with a bigger battery and typically contains a large capacity refillable cartridge. Often comes with variable voltage batteries and manual switches. Can be easily modified.</td>
<td>Volcano Lavatube</td>
</tr>
</tbody>
</table>

E-liquids are offered in a variety of flavors. A content analysis of 59 e-cigarette websites conducted 2012,(Grana and Ling under review) e-cigarettes and the nicotine solution were found to come in tobacco (95%), menthol (97%), coffee (61%), fruit (73%), candy (71%) and alcohol (10%) flavors, as well as unique flavors such as “cola” and “Belgian waffle.” (Grana and Ling, under review). Flavor is an important product characteristic in determining who is attracted to a product and the ability to get started on a product. The 2012 US Surgeon General’s Report Preventing Tobacco Use among Adolescents and Young Adults found that flavored (conventional) tobacco products are disproportionately used by youth and initiators (U.S.)
Department of Health and Human Services 2012). In recognition of the key role that flavors play in promoting youth tobacco use, cigarettes with these characterizing flavors (with the exception of menthol) have been banned in the U.S. and a flavor ban on nicotine containing products (which includes e-cigarettes) was included in the proposed EU Tobacco Products Directive (TPD) before the vote by EU Parliament on October 2013 which deleted that proposal. (European Parliament 2013) As of September 2013, there were no restrictions on the use of flavors in e-cigarettes anywhere in the world.

PRODUCT SAFETY

There are safety issues with electronic cigarette devices and liquid. Trtchounian and Talbot (2011) examined 6 brands of products for design, content, labeling, quality and product information including warnings. (Trtchounian and Talbot 2011) Most of the e-cigarette starter kits purchased came with some instructions. Most provided information about the battery and how to connect the parts of the devices, but did not come with a list of product ingredients, or health warning messages. Most of the products leaked when handled and cartridges came with fluid leaked on them, creating the potential for dermal nicotine exposure and potential nicotine poisoning. (Trtchounian and Talbot 2011)

Major injuries and illness have resulted from e-cigarette use, which may be related to lack of basic safeguards in the product design and manufacturing process, as well as the contents of the solution. Tobacco product adverse events can be reported to the Food and Drug Administration (FDA), Center for Tobacco Products (CTP). Chen (2012) summarized the 47 adverse event reports filed with the FDA CTP between 2008 and early 2012 regarding e-cigarettes; finding that 8 of these 47 adverse events were serious health issues with examples including hospitalization due to congestive heart failure, hypotension, pneumonia, and chest pain. (Chen 2013) Reporting of an adverse event does not indicate causation, but it does raise questions of biological plausibility that need to be addressed. There was also a reported infant death due to choking on an e-cigarette. Examples of less serious adverse events include nausea, vomiting and sore throat. Moreover, one e-cigarette company also instructs users to draw on the product differently from a cigarette because they might experience adverse reactions, stating: “If
you find yourself smoking your e-cigarette the way you smoke a traditional cigarette, you are doing something wrong. As a matter of fact, if you vape your e-cig as you smoke your cigarette you will find yourself with a sore throat, sore lungs, an incessant cough and irritation in your mouth and throat.” (bold font in original text - http://www.metroecigs.com/content/how-do-you-inhale-an-electronic-cigarette.asp)

An 18-month old girl in the U.S. became seriously ill after drinking e-cigarette liquid in a refill container that was left in the child's reach and did not come with a child-proof cap. (Shawn and Nelson 2013) A child in Israel died of nicotine poisoning from drinking her grandfather’s e-cigarette solution. (Winer May 29, 2013) E-cigarettes have exploded and caught fire, causing serious injury. A man in Florida suffered severe burns and lost half his tongue due to an e-cigarette battery exploding in his face. (CBS NEWS February 16, 2012) A woman in Atlanta escaped serious injury from an e-cigarette that exploded in her home, starting a fire. (Strickland 2013) These problems are common enough that e-cigarette internet forums and some retail websites advise that the lithium batteries may explode or overheat when left to charge for long periods of time or in direct heat exposure or if charged with the wrong charger or a powerful electrical source. The e-cigarette forum e-cigarette-forum.com has a section in which advice is given about the risks of specific battery types: http://www.e-cigarette-forum.com/forum/blogs/baditude/4848-9-battery-basics-mods-imr-protected.html. Because e-cigarettes are not regulated there is no systematic collection of information on these issues. It is also unknown to what extent these problems could be eliminated by stronger regulatory standards on the product itself.

MARKETING

While most attention from the biomedical community has been on the e-cigarette device, the aerosol that it delivers to users (and, to a lesser extent, bystanders), and the potential of e-cigarettes for cessation of conventional cigarettes, much of the public discourse and popular understanding about use of e-cigarettes has been determined by how they have been marketed.
Patterns of tobacco product adoption are driven and reinforced by marketing, so it is important to understand the marketing claims and selling propositions consumers encounter with regard to e-cigarettes. Product marketing designed to attract different segments of the population (such as youth, current smokers, former smokers) will determine use patterns which is one of the main factors contributing to total public health burden from tobacco use. Consumer perceptions of tobacco products (whether cigarettes, smokeless tobacco products, or e-cigarettes) and their risks and benefits are important factors in determining uptake and consequently the total public health burden due to tobacco use. For example, claims that e-cigarettes are less harmful than cigarettes may encourage adoption by non-smokers (potentially children) as well as smokers seeking to quit conventional cigarettes. Promotion of e-cigarettes as a convenient alternative to cigarettes when a smoker cannot light up would blunt the effect of smokefree laws on smoking cessation. The explicit promotion of dual use (as has been done with snus) for places where people cannot smoke cigarettes (Figure 3) has important implications for the ultimate use patterns and health impact of introducing e-cigarettes into the marketplace.

Grana and Ling (under review at AJPM) reviewed a sample of single-brand e-cigarette retail websites (n=59) that were online in 2012 to determine the main marketing messages, type of products sold and unique marketing features on the sites. They found that the most popular claims were that the products are healthier (95%), cheaper (93%) and cleaner (95%) than cigarettes, can be smoked anywhere (88%), can circumvent smokefree policies (71%), do not produce secondhand smoke, and are modern. Health claims were also made through pictorial and video representations of doctors, which was present on 22% of sites. Cessation-related claims (ranging from overt statements that one can use the product to quit smoking to indirect claims such as you’ll never want to smoke tobacco cigarettes again) were found on 64% of sites. Claims about effects on bystanders frequently included statements that e-cigarettes emit "only water vapor" that is harmless to others (76%).

While originally promoted almost exclusively on the internet, marketing expenditures for e-cigarettes have increased dramatically, with the increasing promotion of e-cigarettes on television in some countries (e.g., U.S., U.K.). In the U.S. television advertising is largely by Lorillard, Inc., a multinational tobacco company based in the U.S. and the first of the cigarette
companies to enter the e-cigarette business when it purchased Blu brand e-cigarettes in 2012 (Esterl April 25, 2012) and Sky Cig brand e-cigarettes in 2013. (Esterl October 1, 2013) As of late 2013, Lorillard had the biggest US national TV campaign which includes use of celebrities to glamorize e-cigarettes and shows them inhaling and exhaling what looks like smoke.

The use of celebrities in product marketing has been occurring since at least 2009. (Grana, Glantz et al. 2011) In Poland, a popular ad as of March 2012 featured actor Olaf Lubaszenko with the tagline ‘You can smoke wherever you want.’ In the U.S. Katherine Heigl, a famous U.S. actress went on the David Letterman Show, a popular late night program in the U.S. and spent much of her interview discussing her quit attempt with the e-cigarette and even smoked an e-cigarette on stage with Mr. Letterman (Figure 4). At the time, she had a relationship with the company where a portion of sales of an e-cigarette called the Pitbull were donated to a charity of her choice, Compassion Revolution. The video of the interview with David Letterman was on the site as well as posted on other websites and widely used in many online press releases and advertorials. In the U.K. the commercials range from showing young people out enjoying themselves (SkyCig) to older people who are tired of missing out on major life events due to their smoking (E-Lites), a sentiment more associated with the harm reduction or NRT approach. Jenny McCarthy, a TV host and model, appears in a 2013 Blu advertisement that glamorizes e-cigarette use and emphasizes the romantic opportunity it creates (Figure 5). Moreover, this advertisement is set in a bar which recalls the pairing of cigarettes and alcohol and makes that connection for e-cigarettes, and is likely to appeal to older adolescents and young adults, the population that spends disproportionately more time out in bars trying to develop romantic relationships. Blu also has another actor in its commercials, Stephen Dorff, whose rugged good looks recall the Marlboro Man but in a suit, and e-cigarette brand NJOY uses rebel rockstar Courtney Love.

The fact that a large majority of e-cigarette retail websites encouraged the use of the products anywhere and everywhere (88%), specifically noting places where cigarette smoking would be banned (71%) and places for socializing, has direct implications for regulation of e-cigarettes and implementation of the FCTC. These messages can be used to undermine the idea of smoking restrictions and existing smokefree laws designed to apply to tobacco smoke. It is
important to note that both the e-cigarette companies and the tobacco companies are focusing on creating positive social norms for these products, introducing them into smokefree environments and promoting them as socially acceptable. The totality of the messaging creates familiarity among smokers by emphasizing the similarity to a cigarette and the smoking experience while simultaneously assuring the smokers and their family and friends (and perhaps kids) that it is entirely different than a cigarette. A 2013 commercial for the e-cigarette, FIN, comes with the tagline “Rewrite the Rules,” and a direct quote from the commercial states, “There was a time when no one was offended by it – that time has come again.”

Television and radio have been unavailable to the cigarette and other tobacco companies to market their products in the US (as well as much of the world) since the 1970s. E-cigarette advertising on television and radio is mass marketing of an addictive nicotine product for use in a recreational manner to new generations who have never experienced such marketing. Advertising that emphasizes use anywhere and to get around clean indoor air laws promotes dual use of e-cigarettes and cigarettes.

As of 2013, e-cigarette companies (including cigarette companies who have purchased e-cigarette companies) are marketing e-cigarettes using the same claims, tactics and media channels that were effective at marketing cigarettes to attract young people and deter smokers from quitting before use of these channels to market cigarettes was banned.

PREVALENCE

Adults

U.S. Samples

Using data from U.S.-based ConsumerStyles survey (which is a mail-back survey of a national sample of adults), Regan et al. (2013) found that awareness of e-cigarettes doubled from 2009 to 2010 (16.4% to 32.2%) and ever use of e-cigarettes more than tripled from 0.6% in 2009 to 2.7% in 2010. (Regan, Promoff et al. 2013) Ever use was most common among men, younger
adults and those with lower socioeconomic status. Ever use was higher among smokers than among the general population in 2010 (18.2% v 2.7%, respectively). Current smokers who had tried e-cigarettes did not differ from non-users in intention to quit or past-year quit attempts.

King et al (2013), analyzed data from a companion dataset to the ConsumerStyles, called HealthStyles, collected in 2010 (mail-based and web-based modalities) and 2011 (web-based mode). (King, Alam et al. 2013) They found awareness of e-cigarettes had increased from about 40% to about 58% and ever use had doubled from 3.4% to 6.2% between 2010 and 2011. Ever use was higher in current smokers at both waves (6.8% of the 2010 mail-based sample, 9.8% of the 2010 web-based sample and 21% of the 2011 web-based sample). Ever use among former smokers increased dramatically from 2010 to 2011, from 0.6% and 2.5% in the 2010 samples to 7.4% in the 2011 online sample. Authors note data were weighted to be nationally-representative and the Styles surveys typically yield estimates of smoking prevalence that are almost identical to the nationally-representative National Health Interview Survey. (King, Alam et al. 2013; Regan, Promoff et al. 2013) Moreover, both of these studies reported a similar percentage of U.S. adults who were aware of e-cigarettes in 2010 as the nationally-representative sample in Pearson et al. in 2010 (Pearson, Richardson et al. 2012) (32.2% Regan, (Regan, Promoff et al. 2013) 38.5% and 40.9% in King(King, Alam et al. 2013) vs. 40.3% in Pearson(Pearson, Richardson et al. 2012).

Pearson et al (2012) estimated e-cigarette use prevalence in two studies, the Legacy Longitudinal Study of Smokers (LLSS) and a nationally-representative general population online survey, both conducted in 2010. (Pearson, Richardson et al. 2012) Smokers in the LLSS and the nationally online sample were similar on all demographics except age (those in the LLSS were on average younger) and smoking characteristics and desire to quit with the exception that a greater proportion of smokers in the LLSS had made more than one quit attempt (69% v 31%, respectively). Overall awareness in the online nationally-representative sample (n=2649) was 40.2% and ever use was 3.4%, awareness among smokers was 57% and ever use was 11.4%. Among LLSS cohort (n=3648), awareness was 57.0% and ever use was 6.4%. Moreover in the online sample, almost all current use (past 30-day) of e-cigarettes was among current smokers: 4.1%, compared to 0.5% of former smokers and 0.3% of never smokers. (Current use was not
measured in the LLSS.) In addition, although a low percentage of former smokers (2%) had used e-cigarettes, that rate was over twice the rate among never smokers (0.77%) (Pearson et al., 2012). In the online nationally-representative survey the odds of being an e-cigarette user was associated with intention to quit in the next 6 months (adjusted OR = 1.74; 95% CI: 1.02, 2.98), compared to never expecting to quit; but this was not evident in the LLSS cohort (Pearson et al. 2012).

In a 2010 nationally-representative, mixed-mode survey (telephone-based n=1504, online n=1736; total n=3240), McMillen et al. (2013) assessed the ever use of emerging tobacco products including e-cigarettes among adults in the U.S. Ever use of e-cigarettes among all respondents was 1.8%, with highest rates of use among daily (6.2%), non-daily (8.2%) smokers.(McMillen, Maduka et al. 2012) Past 30-day (current) e-cigarette use did not exceed 1% for any of the “emerging tobacco products, which included e-cigarettes, but 19.7% of ever e-cigarette users reported past 30-day use.

Popova and Ling (2013) found that among a nationally representative panel of current and recent former smokers, 20.1% had ever used e-cigarettes. (Popova and Ling 2013) Ever e-cigarette use was more common in women than men (OR=0.79, 95% CI: 0.63-0.99), persons of Asian ethnicity than white (OR=2.76, 95% CI: 1.03, 7.39), and those aged 18-29 years compared to 60 years or older (OR=2.32, 95% CI: 1.57, 3.42). Among smokers, those with some college education compared to those with a bachelors degree (OR=2.09; 95% CI: 1.13, 3.86) and those with incomes less than $15,000 compared to those with incomes of $60,000 or greater were more likely to be current (past 30-day) e-cigarette users (OR=1.95, 95% CI: 1.17, 3.25). Respondents who had ever tried e-cigarettes were significantly more likely to have tried to quit in the past year and failed than persons who had not tried to quit (OR=1.78, 95% CI: 1.25, 2.53).

U.S. Regional Samples

Choi and Forster (2013) found that among young adults aged 20-28 in the Midwestern US surveyed in 2011, ever use of e-cigarettes was 7.0% and past 30-day use was 1.2%. (Choi and Forster 2013) Among those aware of e-cigarettes, most believe e-cigarettes are less harmful than
conventional cigarettes (52.9%) and 44% believe they can help with quitting smoking. Ever use was more common among 20-24 year olds (25-28 year olds), men, current smokers, and those who believe e-cigarettes are less harmful than conventional cigarettes and can be used for in smoking cessation.

Sutfin and colleagues (2013) found that among college students in North Carolina surveyed in 2009, ever use of e-cigarettes was 4.5% while past 30-day use was 1.5%, with highest use among current smokers. (Sutfin, McCoy et al. 2013) Importantly, they found that 12% of e-cigarette users were never smokers. E-cigarette use was not associated with intention to quit smoking.

**Hawaiian sample of smokers and cessation for e-cigarette use motivation**

A cross-sectional study of Hawaiian daily smokers (n=1567) conducted from 2010-2012, examined e-cigarette use prevalence and associations with quitting attitudes and behaviors. (Pokhrel, Fagan et al. 2013) Thirteen percent of participants reported having ever used e-cigarettes to quit smoking (they did not assess any other reason for using the products). Smokers who had used e-cigarettes to quit were younger, more highly motivated to quit, had greater self-efficacy for quitting, and reported a longer recent quit duration than smokers who had not used e-cigarettes to quit. In the multivariate logistic regression analyses, greater quit motivation (OR = 1.14; 95% CI: 1.08, 1.21), quitting self-efficacy (OR = 1.18; 95% CI: 1.06, 1.36) and having ever used FDA-approved therapies (OR = 3.72; 95% CI: 2.67, 5.19) were significantly associated with greater likelihood of having used e-cigarettes to quit smoking, whereas age (OR=0.98; 95% CI: 0.97, 0.99) and Native Hawaiian ethnicity (OR = 0.68; 95% CI: 0.45, 0.99) were inversely associated with greater likelihood of using e-cigarettes for quitting.

**International Samples**

Adkison and colleagues (2013) estimated rates of e-cigarette use and perceptions of the products in 2010 among current and former smokers in the International Tobacco Control Study conducted in U.K, U.S., Australia and Canada. (Adkison, O'Connor et al. 2013) Likely reflecting the fact that e-cigarettes are freely available in the UK and US and not legal for sale with
nicotine in Australia and Canada, the highest rates of awareness were in the U.K. (54%) and U.S. (73%), while rates were much lower in Australia (40%) and Canada (20%). Prevalence of e-cigarette trial (among those aware) was 20.4% in U.S., 17.7% in the U.K., 10% in Canada and 11% in Australia. Across countries use was higher among those of younger age, higher income, reporting nondaily smoking and who perceive e-cigarettes as less harmful than cigarettes. Despite larges differences in awareness among the countries, current use did not differ among the countries (p=0.114). In current smokers, a marker of dependence (cigarettes per day) was not associated with ever e-cigarette use or past 30-day use (p value not provided).

Dockrell et al (2013) analyzed data from a nationally representative survey of UK adults (2010: n=12597 adults, 2297 smokers; 2010 n=12432, 2093 smokers) finding the prevalence of e-cigarette trial and current use doubled from 2010 to 2012. (Dockrell, Morison et al. 2013) Ever use in 2010 was not measured among former smokers or never smokers, only current non-daily or daily smokers. In 2010, 5.5% of smokers had tried e-cigarettes but no longer used them, which increased to 15.0% in 2012. Current use of e-cigarettes among smokers rose from 2.7% in 2010 to 6.7% in 2012. Ever e-cigarette use among former smokers in 2012 was 2.7% and current use 1.1%; ever use among never smokers in 2012 (only measured in that year) was 0.4% and current use was 0.1%. About 33% of ever e-cigarette users continued to use in 2010 and in 2012. In a multivariate model which included only ex- and current smokers, being an occasional (OR=4.32 95% CI: 2.89, 6.48) or daily smoker (OR=7.33 95% CI: 5.66, 9.48) increased odds of ever e-cigarette use compared to ex-smokers, while older age (age ≥35) decreased odds of ever e-cigarette use compared to 18-34 year olds (OR=0.58 95% CI: 0.43, 0.78). In the model for current e-cigarette use, only being an occasional (OR=6.04 95% CI: 2.92, 12.49) or daily smoker (OR=6.68 95% CI: 4.15, 10.77) increased odds of current e-cigarette use. Authors also analyzed data from a 2010 survey of smokers (n=1308) that included a special battery of e-cigarette questions. A majority of respondents reported that e-cigarettes: “might satisfy the desire to smoke” (60%), “might help cut down on cigarettes” (55%), and “they might help me give up smoking entirely (51%).” Perceived disadvantages included “might be too expensive” (53%), “might not satisfy the desire to smoke enough” (39%), and might be mistaken for cigarettes therefore frowned upon in public” (35%). Among e-cigarette triers (n=494, 37.7% of sample), the most common reason for trying e-cigarettes was “as a substitute for smoking where smoking is
not allowed” (reported by 49% of daily pack a day smokers, 43% of those smoking 10-19 cigarettes per day, and 31% among those smoking 9 or fewer cigarettes per day, p=0.008). Secondary reasons were to cut down (35%) and to quit smoking (31%). The finding that using e-cigarettes to get around smokefree laws is likely reflected in the dominant pattern of dual use in both 2010 and 2012 prevalence data reported in this study.

Single Gender Study

Douptcheva et al (2013) reported data analyses of the Cohort Study on Substance Use Risk Factors (C-SURF), a longitudinal study of Swiss men who are interviewed during enrollment in the army, to examine prevalence and predictors of e-cigarette use.(Douptcheva, Gmel et al. 2013) Among the entire cohort of young men, aged 19-25, 4.9% of participants reported ever trying e-cigarettes. Use differed by smoking status with 9.3% of current smokers reporting trying e-cigarettes, 1.6% of former smokers and 0.4% of never smokers. Excluding 144 occasional e-cigarette users, the conducted an analyses of e-cigarette use among daily smokers (n=1233) that compared daily dual users (25) to daily smokers who never use e-cigarettes (1064); they found no statistically significant differences in cigarettes per day, nicotine dependence or past year quit attempts.

Convenience Samples of Users: Prevalence, User perceptions

There have also been five studies with convenience samples that may provide information about motivations for using e-cigarettes, attitudes and behavior. These studies likely suffer from a bias toward recruitment of persons motivated to quit and enthusiastic about e-cigarettes, limiting the generalizability of the findings.

In an online survey of 81 users of cessation websites and e-cigarette forums conducted in 2009, authors found that most respondents perceived the products as less harmful than cigarettes and used the products to quit smoking or to cut down on conventional cigarette smoking.(Etter 2010) In a subsequent study conducted in 2010, Etter and Bullen (2011) surveyed 3587 adults that were recruited from e-cigarette forums and smoking cessation websites, and employed a
similar questionnaire as Etter 2010. (Etter 2010; Etter and Bullen 2011) They found that top reasons for using the e-cigarette was that users perceive them as less toxic, to ameliorate cravings for and withdrawal from cigarettes, and to help them quit or avoid relapse. (Etter and Bullen 2011)

Siegel et al. (2011) obtained a list purchasers of Blu brand electronic cigarettes from the company and invited them to complete a survey 6 months after making their first purchase (5000 purchasers, 4.5% response rate, sample n=222) in 2010. (Siegel, Tanwar et al. 2011) They found that 31% reported they were not smoking tobacco cigarettes at the 6 month survey timepoint. This study is limited by selection bias (purchasers of one particular product) and very low response rate (4.5%), making these data not generalizeable to e-cigarette users.

In 2011, Dawkins et al., (2012) conducted an online survey of 1347 adults recruited from an electronic cigarette retail website. (Dawkins, Turner et al. 2013) Participants were 70% men, mean aged 43 years, 96% white (72% European), and most (72%) used a "tank" type of e-cigarette with nicotine-filled solution (1% reported using no-nicotine). Seventy-four percent of respondents who had used an e-cigarette reported not smoking for at least a few weeks. Results show that users perceive e-cigarettes as healthier than smoking and pleasant to use. In an analysis of self-reported ex-smokers, "'time to first vape' was significantly longer than 'time to first cigarette' (p<0.001)."

Goniewicz and colleagues (2012) surveyed Polish e-cigarette users recruited from online forums and retail sites in 2010 (n=179) and found that a majority of e-cigarette users were cigarette smokers when they initiated e-cigarette use (86%). (Goniewicz, Lingas et al. 2012) Participants reported using the products as a less harmful alternative to smoking (41%) or to quit smoking (41%) and 66% reported no conventional tobacco cigarette smoking at the time of the survey. Twenty percent of never smokers who tried e-cigarettes stated they initiated tobacco smoking after trying e-cigarettes, suggesting e-cigarette use can be a gateway to smoking and dual use.
In the Czech Republic, Kralikova et al (2012), surveyed 1738 (86% response rate) people they identified as currently smoking or buying conventional cigarettes in 2012. (Cho, Shin et al. 2011; Kralikova, Novak et al. 2013) Forty-six point seven percent had heard of e-cigarettes but never tried them, 23.9% had tried them once, 16.6% had tried them repeatedly, 9.7% reported using them regularly. Of the fifty percent of respondents who had ever tried an e-cigarette, 18.3% reported regular use and 14% reported using them daily. A positive initial experience with e-cigarette use was much higher among those who use e-cigarette regularly compared to those who only tried them once (68.5% v 15.2%, respectively). Of those who tried only once or repeatedly, “not satisfying” was the top reason given by both groups followed by “poor taste.” In depth analyses were conducted for the sample of regular users (n=158). Among regular users, reasons for trying e-cigarettes were to cut down (39%), use where smoking is not allowed (28%) and to quit smoking (27%) (5.3% gave another reason). Regular users who reported that e-cigarettes helped them cut down (n=93) smoked on average 9.7 (SD=6.5) cigarettes per day, while those who did not report that e-cigarettes helped them cut down (N=61) smoked 13.1 (SD=7.0) cigarettes per day (p<.005). Most non-reducers said they used the e-cigarette to circumvent smokefree laws.

Youth

In a survey of Korean adolescent respondents to the 2008 Health Promotion Fund Project survey (n=4,341), 10.2% of students were aware of e-cigarettes. (Cho, Shin et al. 2011) Overall, only 0.5% of students reported having tried an e-cigarette, but there were significant differences in use by gender (0.91% among males, 0.18% among females, p<0.001) and having ever used conventional cigarettes (2.0% among ever cigarette users, 0.15% among never cigarette users, p<0.001)

A subsequent study of adolescent (aged 13-18) respondents to the 2011 Korean Youth Risk Behaviour Survey (n=75,643) found that prevalence of e-cigarette use had greatly increased in just 3 years to 9.4% ever use and 4.7% past 30 day use. (Lee, Grana et al. 2013) Use was also much higher among respondents who used conventional cigarettes: 8.0% ever e-cigarette use among current smokers, 1.4% ever e-cigarette use among non-smokers or former smokers and
3.6% current (past 30-day) use among smokers, 1.1% current use among non-smokers or former smokers).

In the U.S., Pepper et al, 2013 found high levels of awareness of e-cigarettes (67%) but little use among a sample of 228 adolescent males who participated in an online survey in 2011 (less than 1 percent had tried an e-cigarette).(Pepper, Reiter et al. 2013) However, in the multivariate logistic regression only current smoking was strongly associated with increased willingness to try an e-cigarette (OR=10.25, CI: 2.88, 36.46). In the bivariate logistic regression, holding a negative opinion of “the typical smoker” was associated with less willingness to try an e-cigarette (OR=0.58, 95% CI: 0.43, 0.79). These findings demonstrate that adolescent boys who use cigarettes are also susceptible to using e-cigarettes and that negative perceptions of being a smoker may be protective against e-cigarette smoking.

The first national estimates of e-cigarette use among U.S. youth from the National Youth Tobacco Survey document rapid growth of e-cigarette use of e-cigarette use among middle school and high school students in the U.S. from 2011-2012.(Centers for Disease Control and Prevention 2013) Among middle school youth (grades 6-8), prevalence of ever trying an e-cigarette doubled from 1.4% in 2011 to 2.7% in 2012. Similarly, current use (past 30-day use) rose from 0.6% to 1.1%. Among high school youth, ever use doubled from 4.7% in 2011 to 10.0% in 2012, with current use rising from 1.5% in 2011 to 2.8% in 2012. Notably, dual use with cigarette smoking accounts for most of the past 30-day e-cigarette use among middle school youth (61.1%) and high school youth (80.5%). Initiation of nicotine exposure with e-cigarettes is evidenced by the fact that 20% of middle school youth who had tried an e-cigarette and 7.2% of high school youth who had tried an e-cigarette had not tried a conventional tobacco cigarette yet.

Goniewicz studied e-cigarette use among 20,240 students enrolled at 176 high schools and universities in Poland.(Goniewicz and Zielinska-Danch 2012) Surveys were administered September 2010 to June 2011. 23.5% of Polish teens aged 15-19 had ever used e-cigarettes and 8.2% reported past 30-day use. Among 20-24 year olds attending universities, 19.0% had ever used an e-cigarette and 5.9% reported past 30-day use. In the whole sample, 3.2% of never smokers had tried an e-cigarette.
Conclusion

Awareness of and e-cigarette trial has at least doubled in the countries where data are available from 2008 to 2012. In the U.S., awareness is more prevalent among men, but trial is more prevalent among women. All studies of adult use show the highest rate of e-cigarette use among current smokers, followed by former smokers, with little use among non-smokers, although e-cigarette trial and use rose in all of these categories over the past few years (Table 1). E-cigarettes are most commonly being used concurrently with conventional tobacco cigarettes, so-called dual use. The major epidemiologic studies have shown this phenomenon is occurring across countries. In the European studies (UK, Swiss, Czech) the most common reasons given to try e-cigarettes was to use them in places where smoking is restricted and to cut down on smoking, followed by to help with quitting.

The data on e-cigarette use among adolescents is more limited but, like adults, shows rapid increases in awareness and use in 3 countries (U.S., Poland and Korea). As with adults, data suggests that e-cigarette use is most appealing and prevalent among youth who are also experimenting with or current users of tobacco cigarettes. Dual use with conventional cigarettes is the predominant pattern of e-cigarette use - 61% in middle school students and 80% among high school students. Among middle school youth, 20% of those who had tried e-cigarettes had never tried a tobacco cigarette, which suggests that some youth are initiating nicotine addiction with e-cigarettes. Although it is unclear if e-cigarette use among youth leads to cigarette smoking, this possibility should be strongly considered given the widespread availability of cigarettes, and in the U.S., little cigars, cigarillos and smokeless tobacco products. These results indicate rapid market penetration of e-cigarettes among youth, with trial among high school students (10.0%) in 2012 even higher than the 2011 rate for adults, 6.8%.(King, Alam et al. 2013)

These findings are troubling for what they suggest about the trajectory of developing tobacco use. In a longitudinal cohort study of Swedish adolescents that examined trajectories of tobacco use, adolescents who initiated tobacco use with both cigarettes and snus had a significantly elevated risk of progression to current smoking at 18 years old compared to snus
A study of U.S. Air Force recruits sheds light on the trajectory of use with different product initiation. Those who were never smokers when they entered basic training, 5.1% were current users and 2.5% past users of smokeless tobacco. At one-year follow-up the recruits who were current or ever smokeless tobacco users were over 2 times more likely to have started smoking than nonusers. (Haddock, Weg et al. 2001) Post et al. (2010) examined tobacco use and nicotine dependence in Swedish adolescents and found that dual users reported the greatest odds of endorsing the dependence symptoms. (Post, Gilljam et al. 2010) These adolescent dual users also had the highest level of endorsing withdrawal symptoms when trying to quit.

CHEMICAL ANALYSES OF E-CIGARETTES

In 2009, the U.S. Food and Drug Administration (FDA) released a statement that analyses of e-cigarette products revealed the presence of tobacco-specific impurities and one cartridge contained a toxic contaminant used in antifreeze (diethylene glycol). (Food and Drug Administration 2009) In 2011, Trehy et al (2011) published an FDA analysis of 4 e-cigarette products for nicotine and minor tobacco alkaloids in liquids and in aerosol generated from the e-cigarette. (Trehy, Ye et al. 2011) Minor alkaloids refer to alkaloids found in tobacco other than nicotine which are present in much smaller quantities than nicotine. The products that were purchased included NJOY, Smoking Everywhere, CIXI and Johnson Creek e-liquid. (It is not clear in which year the products were purchased.) The puffing procedure was 100 ml puffs taken every 60 seconds for 30 puffs. They found that amount of nicotine measured in the vapor was impacted by the temperature of the solution, with repeated heating of the liquid in short intervals (triggered by short puff intervals) enhancing nicotine release. Thus the amount of nicotine delivered to the user is likely to be dependent on temperature achieved by the heat source and inter-puff interval performed by the user. The analysis of nicotine content of cartridge e-liquid from three of the brands revealed poor concordance of labeled and actual nicotine content, including some labeled as having 0mg nicotine that had nicotine in them. Analysis of the refill solution from the U.S. e-liquid company Johnson Creek showed good agreement (100-110% of advertised content) between labeled and actual content. Liquids tested from one manufacturer contained minor tobacco alkaloids, including myosmine, anatabine, anabasine and in some cases
cotinine and beta nicotyrine. It is likely that these alkaloids were extracted along with nicotine from tobacco as part of the manufacturing process. The analysis of simulated e-cigarette use found that individual puffs contained from 0 µg to 35µg nicotine per puff. Assuming a high nicotine delivery of 30 µg/puff, it would take about 30 puffs to deliver the 1 mg of nicotine typically delivered by smoking a conventional cigarette. A Marlboro cigarette was tested and found to deliver 152-193µg/puff, so 6 or 7 puffs would deliver 1 mg. The levels of minor alkaloids in vapor were below the limit of detection for both e-cigarettes, although levels could be measured from the smoke of a Marlboro. Two products from CIXI labeled as Cialis and Rimonabant flavor contained amino-tadalafil and rimonabant, medicines to treat erectile dysfunction and a cannabinoid (THC) receptor antagonist, respectively. This study demonstrate inconsistency in nicotine amount compared to labeled content of many but not all e-cigarette products. It also shows that the highest nicotine product e-cigarette puff delivers 20% or less nicotine than a puff of a conventional cigarette.

Goniewicz et al. (2012) analyzed 16 brands of e-cigarette products, and 20 samples across brands.(Goniewicz, Kuma et al. 2013) They measured nicotine content in e-liquid and used an adapted smoking machine to measure the nicotine content in 300 puffs of aerosol generated from each product. The amount of nicotine measured in the e-liquid extracted from the cartridges varied from labeled nicotine content by more than 20% in 9 of 20 samples. Similarly, a 20% difference in marked content vs. actual content was found in 3 of 15 e-cigarette refill liquid samples. Across products, nicotine content ranged from 0.5 mg (SD=0.1) to 15.4 mg(SD=2.1).

Cameron et al. (2013) analyzed 7 e-cigarette solutions (e-liquids) to determine concordance between advertised or labeled and actual nicotine content.(Cameron, Howell et al. 2013) Among the 7 samples of e-liquid, 2 were labeled as containing 24mg/ml of nicotine and 5 were not marked with a specific nicotine content, but as "low," "medium," "high" and "super high." For samples with only strength descriptors, expected concentrations were obtained from information on the brands’ websites (low=6-14mg/ml, medium=10-18mg/ml, high and super high=25-36mg/ml). They found that, while all the samples contained nicotine, only 2 were in the expected range and 4 were lower than specified.
Goniewicz et al (2013) analyzed the vapor from 12 brands of e-cigarettes for toxic and carcinogenic compounds, including carbonyls, volatile organic compounds, tobacco-specific nitrosamines. (Goniewicz, Knysak et al. 2013 (online first)) They also compared results from the e-cigarette vapor to the puffs from a medicinal nicotine inhaler. They found varying levels of carbonyls (e.g., formaldehyde, acetaldehyde and acrolein), volatile organic compounds (e.g., toluene) and tobacco-specific nitrosamines present in the e-cigarette vapor. E-cigarette products varied widely in toxicant content per 150 puffs averaged across sampling timepoints (e.g., formaldehyde range: 3.2-56.1 µg; acrolein: 0-41.9 µg, TABLE 2). On one hand, levels of toxicants in the vapor were 9-450 times lower than the same volume cigarette smoke (Table 2). On the other, depending on brand, some toxicants were found at levels higher than the reference product, the nicotine inhaler (e.g., o-methylbenzaldehyde and formaldehyde). Five of the 11 toxicants measured were not detected in the nicotine inhaler at all, including acrolein, toluene, p,m,xylene, NNN, and NNK. They also report the presence trace amounts of three metals (cadmium, nickel, and lead) in the e-cigarette vapor as well as in the nicotine inhaler.

TABLE 2. Levels of toxicants in e-cigarette vapor compared to nicotine inhaler and cigarette smoke (data from Goniewicz et al., 2013)

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Content in Nicotine inhaler mist</th>
<th>Range in content in vapor from 12 e-cigarette samples (per 15 puffs)</th>
<th>Range in content in conventional cigarette micrograms in mainstream smoke from 1 cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>2.0</td>
<td>0.2-5.61</td>
<td>1.6-52</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>1.1</td>
<td>0.11-1.36</td>
<td>52-140</td>
</tr>
<tr>
<td>Acrolein</td>
<td>ND</td>
<td>0.07-4.19</td>
<td>2.4-62</td>
</tr>
<tr>
<td>o-methylbenzaldehyde</td>
<td>0.7</td>
<td>0.13-.71</td>
<td>--</td>
</tr>
<tr>
<td>Toluene</td>
<td>ND</td>
<td>0-0.63</td>
<td>8.3-70</td>
</tr>
<tr>
<td>p,m-xylene</td>
<td>ND</td>
<td>0 - 0.2</td>
<td>--</td>
</tr>
<tr>
<td>NNN</td>
<td>ND</td>
<td>0 - 0.00043</td>
<td>0.0005-0.19</td>
</tr>
<tr>
<td>NNK</td>
<td>ND</td>
<td>0-0.00283</td>
<td>0.012-0.11</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.03</td>
<td>0 - 0.022</td>
<td>--</td>
</tr>
<tr>
<td>Nickel</td>
<td>0.19</td>
<td>0.011-0.029</td>
<td>--</td>
</tr>
<tr>
<td>Lead</td>
<td>0.04</td>
<td>0.003-0.057</td>
<td>--</td>
</tr>
</tbody>
</table>

ND=Not Detected; NOTE: Data were taken from Tables 3 and 4 in Goniewicz et al.
Kim et al. (2012) developed a liquid chromatography-tandem mass spectrometry method for analyzing TSNAs in electronic cigarette replacement fluids (Kim and Shin 2013). They applied their method to 105 refill fluids from 11 different companies in the Korean market. They specifically quantified NNN, NNK, NAT, and NAB, and they present data on total TSNAs in each product. They found nearly a three order of magnitude variation in TSNA concentrations among e-cigarette refill fluids, with total TSNA concentration ranging from 330 µg/ml to 8600 µg/ml. Their data demonstrate significant variability in TSNA composition and quantity among different EC brands and illustrate the importance of screening numerous products to obtain an overview of product variability.

Schripp et al. (2012) analyzed the vapor exhaled by users to determine the presence of toxicants and address the question of secondhand vapor exposure (Schripp, Markewitz et al. 2012). Three studies are described. In the first, a smoker in an 8m³ stainless steel chamber with an air exchange rate of 0.3/hr who puffed 6 puffs from an e-cigarette separated by 60 seconds each time. This puffing regimen in the chamber was repeated with 3 e-liquids (0mg nicotine, apple flavor, 18mg nicotine, apple flavor, 18mg nicotine, tobacco flavor) and one tobacco cigarette. In the second protocol, vapor from three different types of e-cigarettes puffed for 3 seconds each was pumped into a 10 L glass chamber with an air exchange rate of 3/hr. In the third protocol an e-cigarette consumer exhaled one e-cigarette puff into a glass chamber. Three e-cigarette devices were used for these experiments – two that used a “tank” system which is directly filled with e-liquid and one that used a cartridge with a cotton fiber on which to drip the e-liquid. Authors found that vapor from the 8m³ chamber analysis contained low levels of formaldehyde, acetaldehyde, isoprene, acetone, acetic acid, 2-butanodione (MEK), acetone and propional (Table 4 reproduced from article below). Analyses of the vapor in the second protocol (10-L glass chamber) revealed high levels of 1,2-propanediol (propylene glycol), 1,2,3-propanetriol, diacetin (from flavoring), traces of apple oil (3- methylbutyl-3-methylbutanoate), and nicotine. When e-cigarette vapor was directly pumped into a glass chamber, propylene glycol was the predominant element, with lower levels of others. Nicotine release was 0.1 to 0.2 µg/puff.
McAuley et al. (2012) conducted a risk assessment of e-cigarettes funded by the Consumer Advocates for Smoke-free Alternatives Association, CASAA, a pro-e-cigarette advocacy group. (McAuley, Hopke et al. 2012) Key details about the protocol for conducting their "risk assessment" are not described and there are obvious problems with the study that do not warrant its review in this report. In fact, a technical report (below) reviewing the existing data on e-cigarette constituents that was also funded by CASAA excluded this study due to its poor quality, stating:

“Although the quality of reports is highly variable, if one assumes that each report contains some information, this asserts that quite a bit is known about composition of e-cigarette liquids and aerosols. The only report that was excluded from consideration was work of McAuley et al.[23] because of clear evidence of cross-contamination – admitted to by the authors – with cigarette smoke and, possibly, reagents. The results pertaining to non-detection of tobacco-specific nitrosamines (TSNAs) are potentially trustworthy, but those related to PAH are not since it is incredible that cigarette smoke would contain fewer polycyclic aromatic hydrocarbons (PAH; arising in incomplete combustion of organic matter) than aerosol of e-cigarettes that do not burn organic matter [23]. In fairness to the authors of that study, similar problems may have occurred in other studies but were simply not reported, but it is impossible to include a paper in a review once it is known for certain that its quantitative results are not trustworthy.”
Other problems with the analysis and findings include the fact that they did not detect any benzo(a)pyrene in the conventional cigarette smoke despite the fact that it has been established for over 50 years that benzo(a)pyrene is an important carcinogen in cigarette smoke. The most unreliable conclusion in the paper (on page 855, second column, 11 lines from the top) is that “neither vapor from e-liquids or cigarette smoke analytes posed a condition of ‘Significant Risk’ of harm to human health via the inhalation route of exposure.” Given the authors' analysis found that conventional cigarettes did not pose significant risk, there is likely a fatal error in the data, analysis, or both. This paper's conclusions about e-cigarette toxicity does not appear credible as it concludes that cigarettes are not dangerous to inhale.

In a technical report funded by The Consumer Advocates for Smoke-free Alternatives Association (CASAA) Research Fund of the constituents in e-cigarette cartridges and liquid, Burstyn (2013) employs occupational threshold limit values (TLVs) to evaluate the potential risk posed by various toxins at various levels in e-cigarettes. (Burstyn 2013) In reviewing the evidence of risk due to propylene glycol or glycerine exposure the report states that assuming a high level of consumption around 5-25ml of solution a day could produce levels of exposure to propylene glycol and glycerin to justify concern. The author noted that the assessment is limited by "the quality of much of the data that was available for [the] assessment was poor." Based on calculated levels of inhalation, the author concludes that

“…there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (contaminants plus declared ingredients), if it were an emission from industrial process, creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.”

TLVs are an outmoded approach to assessing health effects for occupational chemical exposures that lead to much higher permissible levels of exposure than contemporary agencies use for setting occupational health standards. In addition, occupational exposures are generally much higher (often orders of magnitude higher) than levels considered acceptable for ambient or population-level exposures. (Employing an occupational standard to evaluate risk to the general population is the same approach to risk assessment as those conducted for secondhand smoke by
those affiliated with the tobacco industry, which concluded that secondhand tobacco smoke could not produce any adverse health effects.) Occupational exposures also do not consider exposure to sensitive subgroups, such as people with medical conditions, children and infants, who might be exposed to secondhand e-cigarette emissions.

**Particulate Matter**

Inhaled particle size is an important determinant of where particles will be deposited in the respiratory system and the resulting adverse health effects (U.S. EPA http://www.epa.gov/pm/). All particles less than 10 microns in size reach the respiratory system and potentially cause health problems in the circulatory and respiratory systems. (http://www.epa.gov/pm/health.html). Those whose diameter falls between 2.5 and 10 microns are considered “inhalable coarse particles” and impact the upper airway. Fine particles are defined as particles less than equal to 2.5 micron. Ultrafine particles or nanoparticles, are particles less than or equal to 0.1 micron (0.1 micron = 100 nM). (For reference, conventional cigarette smoke particles have a median size of 200-400 nM.) Both terms ultrafine and nanoparticle are used interchangeably in the scientific community. Fine particles (2.5 micron and smaller) reach the lower lung. The ultrafine particles are mostly inhaled and exhaled, but some do deposit in the lower lung. Ultrafine liquid particles would coalesce with lung fluid to form a film, and constituents would be absorbed after impaction as for larger particles. Solid ultrafine or nano-particles (carbonaceous or metal) can be absorbed directed into cells, and could be toxic. Frequent or high levels of exposure to fine and ultrafine particles can trigger inflammatory processes and heart attacks(Pope, Burnett et al. 2009) and respiratory problems.(Mehta, Shin et al. 2013) Because of these health concerns, the U.S. EPA has standards for particulate exposure by particle size: http://www.epa.gov/air/criteria.html. However, the EPA standards are related to outdoor air pollution particles, which are carbonaceous. It is not clear is the ultrafine particles in e-cigarette vapor will have the same health effects and toxicity as carbonaceous particles to the extent that they are pure liquid particles.

Schripp et al. (2012) observed two peaks in the particle diameter distribution in e-cigarette exhaled aerosol, one at 100 nm and one at 30 nm(Figure reproduced below).(Schripp,
Markewitz et al. 2012) Particle size was observed to decrease as a function of time with specified time intervals, 1, 5, 10 minutes in both the 8m$^3$ chamber and the glass 10 liter chamber, presumably due to evaporation. Exhaled e-cigarette aerosol contained mostly propylene glycol and smaller amounts of related VOCs, apple oil (flavorant) and nicotine. The authors conclude that “'passive vaping’ must be expected from the consumption of e-cigarettes.” Like secondhand cigarette smoke, levels of these chemicals in real environments where e-cigarettes are being used will depend on the density of users and properties of the ventilation system.

Metals in e-cigarette liquid and aerosol were studied by Williams et al (2013) who performed various laboratory analyses on 22 dissected cartomizers (the atomizer and cartridge combined into a single component). (Williams, Villarreal et al. 2013) They examined metal content and quantity in both cartomizer e-liquid and the corresponding vapor using electron microscopy and energy dispersive x-ray spectroscopy. Both the e-liquid and the Poly-fil fibers used to absorb the e-liquid so it can be heated and converted to an aerosol, which comes into contact with heating elements in the cartomizers, contained heavy metals (tin, nickel, copper, lead, chromium). Tin, which appeared to originate from solder joints, was found in the form of both particles and tin whiskers in cartomizer fluid and Poly-fil. E-cigarette fluid containing tin was cytotoxic to human pulmonary fibroblasts. E-cigarette aerosol also contained metals. Levels of nickel were measured that were 2-100 times higher than found in Marlboro cigarette smoke. The nickel and chromium possibly originated from the heating element, which conventional cigarettes would not have. Some nickel, tin and chromium in the aerosol was in the form of nanoparticles (<100 nM). These metal nanoparticles can deposit into alveolar sacs in the lung, potentially causing respiratory problems. This study analyzed e-cigarette models that employ Poly-fil fiber to contain the e-liquid, which is not used in some “tank” systems, where liquid surrounds a heating element or wick. Therefore, it is unknown how the type of e-cigarette device might influence which particles are produced, how many and at what size. There is evidence that some metal nanoparticles may harm human health (from studies of titanium) but the overall health significance is unclear.

Zhang et al. (2103) examined the size of particles and likely deposition in the human body. They examined e-cigarette aerosol produced by a single brand of e-cigarette
(BloogMaxXFusion) using both propylene glycol and vegetable glycerin-based liquids. (Zhang, Sumner et al. 2013) They generated the aerosol by using a smoking machine that was altered to take 25ml aerosol samples for analysis. In order to assess the likely deposition of particles in the human respiratory system, they used two factors: particle size and lung ventilation rates (one for a "reference worker" one for a "heavy worker," 1.2 m³/hr and 1.688 m³/hr, respectively). They found that e-cigarette and tobacco cigarettes produce aerosols with similar particle size, with some particles are in the nanoparticle range (Figure reproduced below). Excerpt: “The e-cig with PG solution generated an immediate peak at 117 nm of 170,000 d N/d log Da (Figure 3), with a VMAD of 250 nm and GSD of 1.6. The VG solution produced an immediate peak at 180 nm of 21,600 d N/d log Da (Figure 4), with a VMAD of 440 nm and GSD of 1.3. The total volume of PG particles was about 30% greater than that of the VG aerosol. The conventional filtered cigarette produced a comparable pattern, with a peak at 215 nm, VMAD of 250 nm, and GSD of 1.4.” The calculated human deposition model predicted that 73-80% of particles are distributed into the exhaled vapor, while 7%–18% of particles would be deposited in alveoli resulting in arterial delivery and 9%–19% would be deposited in the head and airways, resulting in venous delivery. In total, about 20-27% of particles are predicted to be deposited in the circulatory system and into organs from e-cigarette vapor, which is comparable to the 25-35% for conventional cigarette smoke. As expected, the heavy worker model showed more alveolar delivery across puffs compared to the reference worker who would have more head and airway delivery. It is important to note that 25ml would be less aerosol than a user would be expected to inhale (personal communication with Dr. Prue Talbot, UC Riverside).

Ingebrethsen et al. (2012) (all from RJ Reynolds tobacco company) conducted a study of particle size in e-cigarette vapor using three methods (spectral transmission, electric mobility, and gravimetric). (Ingebrethsen, Cole et al. 2012) The spectral method enabled particles in e-cigarette aerosol to be measured without dilution. They found the aerosol particles to average 250–450 nm in size, which is comparable to what has been found with conventional cigarettes. Testing two brand of e-cigarette (one disposable, one rechargeable) and one tobacco cigarette, authors found that the geometric mean particle size ranged from 238 to 387 nm, and was similar for e-cigarette and tobacco cigarettes. (The authors did not describe the composition of the e-liquids, which can potentially affect particle size and concentration.)
Based on the data from all these studies one would expect that e-cigarette vapor could be inhaled into the deep lung, similarly to a tobacco cigarette. The particle concentrations \(10^9/cm^3\) were also similar for e-cigarette and conventional tobacco cigarettes. However, the particles in the Schripp study may be smaller than those that are inhaled because of evaporation prior to measurement, as discussed by Ingebrethsen. (Figure reproduced below)

FIGURE: Example of particle sizes: clockwise from left to right: Schripp et al. 2012; Zhang et al.; Ingebrethsen et al. 2012;

![Aerosol size distribution during consumption of an e-cigarette in an 8-m3 chamber](image)
Cytotoxicity
Bahl et al (2012) screened 41 e-cigarette refill fluids obtained from 4 companies (year of purchase not reported) for cytotoxicity (measured as the ability to kill half of the cells in a culture using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay procedure) to three cell types: human pulmonary fibroblasts, human embryonic stem cells, and mouse neural stem cells. (Bahl, Lin et al. 2012) The latter two cell types were chosen as early prenatal and early postnatal models. A hierarchy of cytotoxicity was determined based on e-cigarette liquid that killed 50% of the cells (IC$_{50}$) for the human embryonic stem cells, which were the most sensitive of the three cell types tested. Results showed that: (1) cytotoxicity varied among products with some being highly toxic and some having low or no cytotoxicity, (2) nicotine did not cause cytotoxicity, (3) all companies has some products that were non-cytotoxic and some that were highly cytotoxic, (4) one company had products that were non-cytotoxic to pulmonary fibroblasts but cytotoxic to both types of stem cells, (5) cytotoxicity was related to the concentration and number of flavorings used. The finding that the stem cells were more sensitive than the differentiated adult pulmonary fibroblasts cells suggests that adult lungs are probably not the most sensitive system to the effects of exposure to e-cigarette aerosol. These findings also raise concerns about pregnant women who use e-cigarettes or are exposed secondhand e-cigarette vapor.

In a study funded by FlavorArt e-cigarette liquid manufacturers, Romagna and colleagues (2013) compared the cytotoxicity of aerosol produced from 21 flavored (12 tobacco flavored and 9 fruit or candied flavored; all contained nicotine) brands of e-cigarette liquid to smoke from a reference conventional tobacco cigarette. (Romagna, Allifranchini et al. 2013) Samples were analyzed for cytotoxicity using an embryonic mouse fibroblast cell line (3T3) via the MTT assay according to UNI ISO 10993-5 standards, which defines cytotoxicity as a 30% decrease in viability of treated cells vs. untreated controls. Only aerosol from coffee-flavored e-liquid produced a cytotoxic effect average of 51% viability at 100% concentration of solution). They concluded that e-cigarette aerosol is much less toxic than cigarette smoke and could be useful products in tobacco harm reduction.
Conclusion

The studies of what is in e-cigarettes are limited by the selection of a handful of products tested (from the hundreds on the market) and by puffing protocol which may or may not reflect actual users puffing behavior. Considering these limitations, the published research demonstrates a lack of standards and quality control for e-cigarettes. (Hadwiger, Trehy et al. 2010; Trehy, Ye et al. 2011; Cameron, Howell et al. 2013; Goniewicz, Kuma et al. 2013) The e-liquid that is aerosolized in e-cigarette devices is not uniform in ingredient content and proportion; some do not even include nicotine. Studies have detected varying levels of nicotine content from labeled amounts, and the presence of volatile organic compounds, tobacco-related carcinogens, metals and chemicals. For the carbonyl compounds (formaldehyde) and the VOCs, the data show lower levels than a cigarette but higher levels than the nicotine inhaler. (Goniewicz, Knysak et al. 2013 (online first)) In addition, the data in Table 2 demonstrate that, depending on brand and sample, an e-cigarette possibly delivers 14 times as much formaldehyde, 7 times as much actaldehyde, 6 times as much o-methylbenzaldehyde as a nicotine inhaler, as well as additional toxicants and carcinogens (acrolein, toulene, p,m-xylene, NNN and NNK), which were not detected at all in the nicotine inhaler (the reference for this study). Some of the chemicals in e-cigarette aerosol are cytotoxic to human cells, particularly embryonic cells. Several chemical that have been found in e-cigarette vapor and e-liquid are on human carcinogens or reproductive toxicants maintained by the California Proposition 65 list, including nicotine, acetaldehyde, formaldehyde, nickel, lead, toluene (http://oehha.ca.gov/prop65/prop65_list/Newlist.html).

Studies that have measured the diameter of the particles comprising e-cigarette vapor have detected small (<10microns in diameter), fine (<2.5microns in diameter) and ultrafine/nanoparticles (<1 micron in diameter). (Schripp, Markewitz et al. 2012; Williams, Villarreal et al. 2013; Zhang, Sumner et al. 2013) The size of particles is important for how they can deposit in the body’s bloodstream, cells and organs. The smaller the particle size, the easier it is for chemicals to enter the bloodstream and cells, potentially effecting damage or changes. Very small particles mostly get inhaled and exhaled. However some fraction of these particles, at least of certain types, may be absorbed directly. Medium sized particles (cig smoke size) are optimal to impact and release their constituents into the airways, and then be absorbed.
At minimum, these studies show that e-cigarette vapor is not merely "water vapor" as is often claimed in the marketing for these products. The thresholds for human toxicity of potential toxicants in e-cigarette vapor are not known, and the possibility of health risks to primary users of the products and those exposed passively to the product emissions must be considered. Based on these studies, the e-cigarettes tested have lower levels of toxicants than conventional cigarettes. However, these studies suggest that switching smokers to a pharmaceutical nicotine inhaler as a harm reduction strategy (long term use among those unable/unwilling to quit) would be a safer approach than using these brands of e-cigarettes, as it delivers fewer toxicants and does not emit fine and ultrafine particulate matter into the environment.

**BIOLOGICAL EFFECTS**

*Nicotine Absorption*

Vansickel et al. (2010) conducted a study with 32 healthy smokers to examine nicotine absorption from e-cigarettes, cardiovascular effects on craving and withdrawal after using an e-cigarette. (Vansickel, Cobb et al. 2010) Participants with no experience of prior e-cigarette use were asked to participate in each of 4 product use protocols (own brand of cigarette, 18mg NJOY “NPRO” e-cigarette, 16mg Crown Seven “Hydro” e-cigarette, and sham-unlit cigarette) separated by 48 hours and after 12 hours of abstinence from tobacco smoking. Flavor of e-cigarette cartridge was matched to the type usually used by the participant. Biological measures were blood plasma nicotine, carbon monoxide (CO), heart rate and subjective effects on craving and withdrawal. They found that 5 minutes after puffing in each condition both e-cigarettes and sham resulted in little or no change from baseline in blood plasma nicotine levels but the expected increased occurred with own brand of tobacco cigarettes (18.8 ng/ml) (Figure reproduced from article below). After 5 minutes of puffing, heart rate increased only for own cigarette brand from 65.7(SD=10.4) to 80.3(SD=10.9) beats per minute. Neither e-cigarette product raised CO, but own cigarette brand smoking raised CO as expected. E-cigarettes decreased some nicotine/tobacco abstinence withdrawal symptoms at lower levels than own conventional cigarette brand at some timepoints in the protocol. This study shows smokers could
experience some modest relief of some withdrawal symptoms and positive subjective effects with e-cigarette use with minimal systemic delivery of nicotine.

In a cross-over trial, (Bullen et al 2011) 40 adult smokers were randomized to the following groups at different times: e-cigarette (Ruyan V8) 16 mg nicotine, 0mg e-cigarette, Nicorette inhalator, or their usual cigarette for four days (with three days in between test rounds). (Bullen, McRobbie et al. 2010) The 16mg e-cigarette resulted in similar serum level of nicotine as the Nicorette inhalator in a similar amount of time (1.3ng/ml at 19.6 min and 2.1ng/ml at 32.0 min, respectively), with the inhaler taking longer. However, both the e-cigarette and the nicotine inhaler achieved much lower peak blood plasma nicotine levels with a longer
time to peak concentration than a tobacco cigarette, which increased blood plasma nicotine to 13.4ng/ml at 14.3 min. The 16 mg e-cigarette and nicotine inhalator reduced desire to smoke over the 60 minute puffing period more than the 0 mg e-cigarette (See Reproduced Figure 2 below). Both 16mg e-cigarette and the nicotine inhalator reduced the desire to smoke and withdrawal symptoms, with no statistically significant differences. Respondents reported a similarly low level of "satisfaction" with both the 16mg e-cigarette and the nicotine inhalator (approximately 3 on a 10 point scale, exact number not reported), but rated the 16mg e-cigarette as more "pleasant to use" than the inhalator by 1.49 units on a 10 point visual analog scale (VAS) scale (p=0.016). The cross-over design is a strength of the study as it tests the methods within the same person at different times. However, authors noted that the 16mg e-cigarettes failed to deliver nicotine to one-third of participants and participants reported failure of the device to function and produce vapor. This study may also be limited by lack of a “practice period” for participants to become familiar with how to use the e-cigarette or nicotine inhalator, as participants had never used them and only 2 participants had ever used the nicotine inhalator. This study was funded by the e-cigarette manufacturer, Ruyan Group Holdings Limited through Health New Zealand Ltd., a company owned by one of the authors, M. Laugesen.

![Figure 2](image)

*Figure 2* Change in desire to smoke from baseline over the first hour after each product use.
Vansickel and Eissenberg (2013) conducted a second study of nicotine delivery and craving suppression, this time in former smokers who were experienced e-cigarette users (at least 3 months of regular use) and brought their own e-cigarette device to use in the protocol (n=8) for use during a 5-hr. session. (Vansickel and Eissenberg 2013) For the first part of the protocol, plasma nicotine, heart rate and subjective effects were assessed at baseline and 5 and 15 minutes after users took 10 puffs (at 30 second intervals) followed by a one-hour ad lib puffing session, where blood was sampled every 15 minutes and during a 2-hour rest (no puffing) session where blood was sampled every 30 minutes. Seven of the eight participants used “tank system” devices with larger batteries than the cigarette-sized products which differed from their previous work with the cigarette-shaped devices. (Vansickel, Cobb et al. 2010) Most of the participants used 18 mg/ml nicotine solution (n=6), 1 used 24mg/ml and one used 9mg/ml. Mean blood plasma nicotine level reached 10.3 ng/ml (SEM = 2 ng/ml) during the 10-puff protocol, which was much higher than previous studies and comparable to that delivered by conventional cigarette smoking. Blood plasma levels reached an even higher mean after one-hour of ad lib puffing (Figure reproduced from the original article below). During ad lib puffing, heart rate increased from an average of 73.2(SD=2.0 beats per minute to 78(SD=1.9) within the first 5 minutes and remained elevated throughout the hour, consistent with the expected effects of nicotine. Nicotine withdrawal symptoms (e.g., restlessness) were relieved over the 75-minute puffing period (Figure reproduced below). Overall, these results show effective nicotine delivery by the users’ own e-cigarettes compared to conventional cigarettes, and subjective effects on withdrawal symptoms suggest the e-cigarette relieves symptoms of nicotine dependence.
Abuse Liability

Vansickel et al 2012 conducted a study of the abuse liability of an 18mg e-cigarette (Vapor King brand) with 20 current, daily smokers. (Vansickel, Weaver et al. 2012) They tested several aspects of abuse liability during a series of four within-subject sessions, 1 of which allowed for product sampling to familiarize users with the device and 3 of which involved the “multiple choice procedure,” (MCP) where participants sample the drug and then make two or more discrete choices between it and another drug/preparation or a series of monetary values.
The first session involved 6, 10-puff bouts of 30 seconds inter-puff interval, each bout separated by 30 minutes. During the MCP sessions, participants chose between 10 e-cigarette puffs and varying amounts of money, 10 e-cigarette puffs and a varying number of own brand conventional cigarette puffs, or 10 conventional cigarette puffs and varying amounts of money. The monetary value at which users chose money over the 10 product puffs was considered the "crossover value," or for e-cigarette and conventional cigarette choice condition crossover value was when participants chose conventional cigarette puffs over the e-cigarette puffs. The crossover values were higher for conventional cigarettes compared to e-cigarettes (average of $1.06 (SD=$0.16) for 10 e-cigarette puffs and average of $1.50 (SD=$0.26) for 10 conventional cigarette puffs (p<0.003). E-cigarettes delivered a similar level of nicotine as a cigarette, but more slowly and require a greater number of puffs than cigarettes to achieve the same nicotine level, and reduced withdrawal symptoms. The authors concluded that e-cigarettes deliver nicotine, can reduce withdrawal symptoms and appear have lower abuse potential compared to conventional cigarettes.

**Conclusion**

The early studies of nicotine absorption found that e-cigarettes delivered a lower level of plasma nicotine than conventional cigarettes (Eissenberg 2010, Vansickel 2011, Bullen 2011), with newer studies demonstrates that when users are experienced and using their own product (mostly tank systems) and engaged in more puff intervals nicotine absorption is similar to that of conventional cigarettes (Vansickel 2013; Vansickel 2012). This difference in nicotine delivery is likely due to the larger voltage batteries in the newer devices which produce more heat and/or atomizers with lower resistance to the heat transfer, resulting in more efficient aerosolizing of the liquid contained in the device. However, despite the greater efficiency at nicotine delivery in the more recent study (Vansicket at al 2013), all of these studies show that e-cigarettes regardless of nicotine delivery can modestly alleviate some symptoms of withdrawal and produce positive subjective appraisal of the e-cigarette as pleasant to use. Moreover, the one study examining abuse liability found that at least one model of cigarette-shaped 18mg e-cigarettes appear to have a lower abuse liability than cigarettes. In the trial comparing nicotine inhalator to e-cigarettes, the nicotine inhalator delivered a similar amount of nicotine as the 16mg e-cigarette, however
authors noted that the e-cigarette malfunctioned and did not deliver any nicotine in a third of participants, which did not occur with the nicotine inhalator. This result highlights the need for product regulation in terms of the device quality and labeling. Only a few brands and models of e-cigarettes were tested in these studies, limiting the generalizability of the findings to other products.

**HEALTH EFFECTS**

Vardavas et al. (2012) conducted a study examining pulmonary function after acute *ad lib* puffing of an e-cigarette (Nobacco, medium, 11mg) in a group of healthy cigarette smokers (n=30). (Vardavas, Anagnostopoulos et al. 2012) All subjects were asked to use the same e-cigarette device (>60% propylene glycol, 11 mg/ml nicotine) as desired for 5 minutes. Subjects refrained from smoking tobacco cigarettes for 4 hr prior to study. On another day, 10 participants selected randomly from the 30 participants were asked to sham-smoke an e-cigarette device with the cartridge removed. Three lung function measures were assessed: spirometry, dynamic lung volumes and resistance and expired nitric oxide (NO). E-cigarette use had no effect on spirometric flows (such as FEV1/FVC) but did significantly increase airway resistance (18%) and decrease expired NO (16%). Sham e-cigarette use had no significant effect, as expected. Acute short term effects suggest that more prolonged e-cigarette use could have greater effects. This study is limited by small sample size, the short period of abstinence before the protocol was executed and the lack of comparison to smoking conventional tobacco cigarettes. Also, because of the short length of exposure, this study cannot lead to any conclusions about the clinical significance of the findings. In addition, smokers in general have high airway resistance with dynamic testing and lower expired NO, likely due to oxidant stress. Despite these limitations, this study suggests that e-cigarette constricts lung peripheral airways, possibly due to the irritant effects of propylene glycol, which could be of concern particularly in people with chronic lung disease such as asthma, emphysema or chronic bronchitis.

Flouris et al assessed the short term effects of active and secondhand e-cigarette and conventional tobacco cigarette use on serum cotinine and pulmonary function in 15 cigarette smokers and 15 never smokers. (Flouris, Chorti et al. 2013) A single brand of e-cigarette made in
Greece and a single e-liquid (> 60% propylene glycol; 11 mg/ml nicotine) was used. The authors attempted to compute how many e-cigarette puffs would deliver the same amount of nicotine as a conventional cigarette using a number of assumptions, some of which are not valid. For example, authors assume that the smoking machine yield of each person’s cigarette indicates amount of nicotine delivered to the smoker, yet there is little to no correlation between yield and actual systemic delivery. The passive exposure study was conducted in a 60m³ chamber. The ventilation (air exchange rate) was not specified. The secondhand cigarette smoke was generated with a target air CO of 23 ppm which is extremely high but which simulates exposure in a very smoky bar. E-cigarette vapor was generated using a pump that operated for the same duration as the cigarette smoking and aerosol was released into the room. The study limitations include using only type of e-cigarette product, studying people who were not regular e-cigarette users, studying a specified puffing (vs ad lib) regimen, using extremely high passive exposure conditions, and studying short term pulmonary effects in healthy people (as opposed to asthmatics, who would be expected to be more sensitive to a lung irritant). The authors found a similar rise in serum cotinine with active tobacco cigarette or e-cigarette use immediately after active use (mean increase about 20 ng/ml). The passive exposure the serum cotinine increase was similar for e-cigarette and tobacco cigarette exposure (averaging 0.8 ng/ml for tobacco cigarette and 0.5 ng/ml for e-cigarette). These results suggest that in cigarette smokers, some e-cigarette devices deliver similar amounts of nicotine as tobacco cigarette smoking. With very heavy passive exposure there is also similar systemic exposure to nicotine from tobacco and e-cigarettes among bystanders. Active cigarette smoking resulted in a significant decrease in expired lung volume (FEV1 / FVC) but not with active e-cigarette or with passive tobacco cigarette or e-cigarette exposure. 

Flouris et al. (2013) studied the effects of passive e-cigarette vapor on white blood cell count. The study is exactly the same as that described by Flouris et al 2013, with a different biomarker outcome. (Flouris, Poulianiti et al. 2012) This study presents the effects of tobacco cigarettes and e-cigarettes, both with active use and passive exposure, on white blood cell count. White cell count is known to be increased acutely and chronically by cigarette smoking, reflecting a chronic inflammatory state, and is associated with future risk of acute cardiovascular events. As expected, active conventional cigarette smoking and exposure to secondhand
conventional cigarette smoke increased the total white blood cell count as well as granulocyte and lymphocyte counts. Active e-cigarette use and passive exposure to e-cigarette vapor did not result in a statistically significant increase in immunological biomarkers over one hour of exposure. This study suggests that the increase in white cell count is mediated more by tobacco combustion products than by nicotine. Although the data are not reported, the figure provided in the paper suggests that the change, if any, is very small, and possibly not of clinical significance. Since the protocol is the same as Flouris et al 2013 (respiratory effects), the same limitations apply.

Hua and colleagues (2013) sought to determine the health impact of electronic cigarettes, using an infodemiological approach. They collected information posted on three electronic cigarette forums: Electronic Cigarette Forum, Vapers Forum and Vapor Talk. Posts were reviewed for reports of both positive and negative health impact. Data were then analyzed with Cytoscape. There were 405 symptoms reported, with the majority negative (326 negative, 78 positive and 1 neutral). These effects encompassed twelve anatomical regions/organ symptoms. The majority of the symptoms affected the mouth and throat, and the respiratory system. Overall, examples of potentially serious negative health effects included: increased blood pressure and asthma attack. Some of the symptoms reported appeared opposite, such as increased and decreased blood pressure, indicating that users of the product may be differently affected.

**Conclusion**

Only a few studies have directly investigated the health effects of exposure to the vapor, and those investigated primary exposure by self-administration (Vardavas et al., 2012; Flouris et al., 2013). One study describes the self-reported health-related events and symptoms reported on e-cigarette fora (Hua 2013). Taken together these studies provide a very limited perspective on the health effects from e-cigarettes. Studies are limited to products have been tested, but some do demonstrate the ability for e-cigarette vapor exposure to result in biological effects. Long-term biological effects are unknown at this time because e-cigarettes have not been in widespread use long enough to assess these effects.
EFFECTS ON CONVENTIONAL CIGARETTE CESSATION

As noted above e-cigarettes are promoted as devices to assist in smoking cessation and most adults who use e-cigarettes are doing so because they believe that they will help them quit smoking conventional cigarettes. The assumption that e-cigarettes will be as effective, or more effective, than pharmaceutical nicotine replacement therapy has also motivated support for e-cigarette use among some public health researchers and policy makers and (as discussed later) formed the basis for public policies on the regulation of e-cigarettes.

Population-based studies

In Adkison et al. (2013) (ITC 4-Country Study noted above) authors presented a longitudinal analysis of data from current and former smokers over 2 timepoints separated by a year. (Adkison, O’Connor et al. 2013) E-cigarette users had a statistically significant greater reduction in cigarettes per day from the first timepoint to the second, one year later (e-cigarette users: 20.1 cig/day to 16.3 cig/day; non-users: 16.9 cig/day to 15.0 cig/day). Although 85% of e-cigarette users reported they were using the product to quit smoking at the initial wave, e-cigarette users were no more likely to have quit one year later than non-users (OR=0.81, 95% CI: 0.43-1.53; p=0.52).

Vickerman et al. (2013) collected data about e-cigarette use among quitline callers from 6 U.S. states assessed at 7-months post enrollment. (Vickerman, Carpenter et al. 2013) 30.9% reported they had ever tried e-cigarettes in their lifetime and the majority of those who have ever tried them used them for less than one month (67.1%) and 9.2% were using them at 7-month survey. Respondents’ main reason for using e-cigarettes was tobacco cessation (51.3%), but it is not known whether the ever use occurred as part of a quit attempt in the past 7 months. Nevertheless, those who reported using e-cigarettes were statistically significantly less likely to quit than those who had not used e-cigarettes (21.7% among callers who used for one month or longer, 16.6% among those who used less than one month and 31.4% among never-users; p<0.001). (Vickerman et al., 2013) The unadjusted odds of quitting were statistically significantly lower for e-cigarette users compared to non-users (OR=0.50, 95% CI: 0.40-0.63).
Grana, Popova and Ling (submitted to NEJM) explored predictors of quitting or relapse among a population of smokers and recent former smokers (n=951) recruited from a nationally representative online panel, who participated in a study in (2011) and one-year later (2012). (Grana, Popova et al. 2013) In a logistic regression model, current e-cigarette use (past 30 days) at baseline did not predict greater likelihood of being quit at one-year follow-up (OR=0.82, 95% CI=0.39, 1.70), controlling only for demographics (age, gender, ethnicity and education). In a second logistic regression model that included baseline cigarettes per day, time to first cigarette and intention to quit in addition to baseline current e-cigarette use, only intention to quit (OR=5.95, 95% CI=2.52, 14.06) and cigarettes per day (OR=0.97, 95% CI=0.94, 0.99) predicted greater likelihood of being quit at one year follow-up and e-cigarettes remained non-significant (OR=0.84, 95% CI=0.39, 1.81). Among recent former smokers at baseline (n=288), neither past 30-day e-cigarette use, nor measure of past history of cigarette dependence, predicted likelihood of relapse at one year follow-up.

Conclusion

There are three population-based longitudinal studies of the effects of e-cigarette use on cessation of conventional cigarettes. Several strengths and limitations should be noted. A strength of the Adkison and Vickerman studies is the assessment of why participants were using e-cigarettes, which is a limitation of the Grana study. In Adkison, 85% of e-cigarette users and in Vickerman 66.5% of e-cigarette users indicated they were using the product to quit or switch “to replace other tobacco,” which limits the possibility that lack of effect on quitting is observed due to a lack of intention to quit by using the device. Although quitline callers represent a small population of smokers motivated to quit, these data present a real-world estimate of the potential effectiveness of using e-cigarettes to quit in a population of motivated to quit. However, this study may be subject to recall bias as e-cigarette use and perceptions was only assessed at 7-month follow-up.

As participants are not randomly assigned to use e-cigarettes in the real world, a strength of the Vickerman and Grana studies are that they provide information on smoking characteristics, including measures of tobacco dependence, which could potentially be a source
of self-selection bias. In the Vickerman study those who tried e-cigarettes did not statistically significantly differ from non-users in cigarettes per day or time to first cigarette, although they were more likely to have tried to quit 2 or more times (Vickerman). In the Grana et al study, e-cigarette users differed in cigarettes per day and time to first cigarette; however, in the multivariate regression predicting quit status that included these dependence factors, e-cigarette use remained non-significant. Therefore, it is unclear to what extent self-selection is occurring and contributes to quit success or failure. More observational, population-based research that assesses e-cigarette use, motivations for use and patterns of use as well as cessation motivation and behavior is needed. In sum, taken together these studies suggest that e-cigarettes are not associated with higher quit rates in the general population of smokers.

**Clinical trials**

Four clinical trials have attempted to examine the efficacy of e-cigarettes for smoking cessation (2 with very small samples). (Polosa, Caponnetto et al. 2011; Bullen, Howe et al. 2013; Caponnetto, Auditore et al. 2013; Caponnetto, Campagna et al. 2013) Three of the four studies did not have a control group who were not using e-cigarettes. (Polosa, Caponnetto et al. 2011; Caponnetto, Auditore et al. 2013) The other study compared e-cigarette efficacy to a standard of care regimen with 21mg nicotine patch (Bullen 2013). None of the trials were conducted with the level of behavioral support that accompanies most pharmaceutical trials for smoking cessation.

Polosa et al. conducted a proof-of-concept study conducted in Italy in 2010 with smokers 18-60 year old not intending to quit in the next 30 days were offered ‘Categoria’ e-cigarettes and instructed to use up to 4 cartridges (7.4mg nicotine content) per day as desired to reduce smoking and to keep a log of cigarettes smoked per day, cartridges used per day and adverse events. (Polosa, Caponnetto et al. 2011) Six-month follow-up was completed with 68% (27/40) of participants. At 6-month follow-up, 13 were using both e-cigarettes and tobacco cigarettes, 5 maintained exclusive tobacco cigarette smoking and 9 stopped using tobacco cigarettes entirely and continued using e-cigarettes (Polosa et al., 2011). Cigarette consumption was reduced by at least 50% in the 13 dual users (25 cigarettes per day (cpd) at baseline to 6 cpd
at 6-months, p<0.001). Most common adverse events reported during the trial were throat irritation, dry cough and mouth irritation, followed closely by headache, nausea and dizziness. Participants reported they would recommend the e-cigarette to a friend yet noted the need for better manufacturing practices as they were frustrated by problems they had operating their devices. This study is limited by use of a non-standard cut-off for considering a smoker abstinent by expired breath carbon monoxide (CO). Also, limitations include use of a product that was noted for poor quality during the trial and lack of a comparison or control group, which could make it difficult to determine if quit rates achieved were not due to chance.

A similar study was conducted by Caponetto et al (2013) with 14 smokers with schizophrenia not intending to quit in the next 30 days.(Caponetto, Auditore et al. 2013) Participants were provided the same “Categoria” e-Cigarette and CO, product use, number of cigarettes smoked, and positive and negative symptoms of schizophrenia were assessed at baseline, week-4, week-8, week-12 week-24 and week 52. Sustained 50% reduction in the number of cigarettes per day smoked at week-52 in 7/14 (50%) participants and median of 30 cig/day decreased to 15 cig/day (p = 0.018). Sustained abstinence from smoking occurred with 2 participants (14.3%) by week 52. Most common side effect was dry cough followed by nausea, throat irritation, and headache. Positive and negative aspects of schizophrenia were not increased after smoking cessation in those who quit. The most common outcome was dual use of e-cigarettes with conventional cigarettes. Study findings are not generalizeable to smokers with mental illness due to very small sample size and lack of a control group.

Caponetto et al. (2013) also conducted a randomized, quasi-controlled trial to examine efficacy of different strength e-cigarettes for smoking cessation and reduction in three study arms: 12 weeks of treatment with the 7.2mg nicotine e-cigarette, a 12-week nicotine tapering regimen (6 weeks of treatment with a 7.2mg e-cigarette and 6 weeks with 5.4mg e-cigarette), and 12 weeks of treatment with a non-nicotine e-cigarette.(Caponetto, Campagna et al. 2013) Reduction occurred in the median value of cigarettes per day at all study visits among all three treatment arms. At one-year follow-up the reduction in median level of cigarettes per day among participants in the 7.2 mg nicotine e-cigarette group was 19 to 12 cpd; the tapered e-cigarette group was 21 to 14 cpd and the non-nicotine e-cigarette group was 22 to 12 cpd. Differences in
reductions between groups were not significant after week 8 assessment. There was no statistically significant difference in 6-month or one year quit rate among the three conditions (one year rates: 4% for placebo e-cigarette users, 9% for low nicotine e-cigarette users and 13% for high nicotine e-cigarette users) (Capponetto 2013). The authors noted that those who initiated quitting in the first few weeks of the study stayed quit, while those who did not remained dual users throughout the study. In addition, 26% of quitters continued to use e-cigarettes at 1 year. Problems with the study include lack of a control group not using e-cigarettes and noted lack of product quality (the authors noted the devices malfunctioned often and new ones had to be sent out frequently over the course of the treatment period). An author on all of these studies, R. Polosa notes that beginning in February 2011, he served as a consultant for the Arbi Group Srl., the manufacturer of the ‘Categoria’ e-cigarette used in the study.

Bullen et al (2013) conducted the first randomized controlled clinical trial of e-cigarettes compared to medicinal nicotine replacement therapy in Auckland, New Zealand. Adult smokers, 18+ who wanted to quit (n=657) were randomised using a 4:4:1 ratio to the 3 study arms (16mg e-cigarettes n=289, 21mg NRT patch n=295, no-nicotine e-cigarette n=73).(Bullen, Howe et al. 2013) Voluntary telephone counseling was offered to all subjects. Subjects were observed at baseline, week 1 (quit day), 12 weeks to 6 months. Fifty-seven percent of participants in the nicotine e-cigarettes group reduced their cigarettes per day by ≥50% by 6 months compared to 41% in the patch group (p=0.002) and 45% in the non-nicotine e-cigarette group (p=0.08). Those randomized to the nicotine patch group were less adherent to the treatment (46%) than the 16mg e-cigarette group (78%) and the no-nicotine e-cigarette group (82%). This may be due to aspects of the study methodology which may have biased the study against success in the nicotine patch group. E-cigarettes were provided by mail for free to participants randomized to either the nicotine or no-nicotine e-cigarette group. Participants in the patch group were provided with usual care for quitline callers in New Zealand, where they are mailed cards redeemable for nicotine patches at a pharmacy at a very reduced rate of about $4 USD for 12 weeks of nicotine patches. In this study they were provided with monetary vouchers to compensate for the $4 that had to be paid for the patches at time of card redemption. There were no statistically significant differences in biochemically-confirmed (breath CO) self-reported continuous abstinence from
quit day to 6 month follow-up between nicotine e-cigarette (7.3%), nicotine patch (5.8%), and non-nicotine e-cigarette (4.1%).

While there are not any longitudinal studies of the effects of e-cigarette use on smoking cessation in youth, there are two cross-sectional studies which suggest that in youth e-cigarettes could be inhibiting cessation of conventional cigarettes.

As discussed above, Lee et al (submitted JAH) assessed the relationship between e-cigarette use and current (past 30 day) smoking, quit attempts, and no longer using cigarettes using the 2011 Korean Youth Risk Behaviour Web-based Survey of 75,643 students aged 13-18 years was analyzed with logistic regression. (Lee, Grana et al. 2013) They found that after adjusting for demographics, current cigarette smokers were much more likely to use e-cigarettes than non-smokers. Among current cigarette smokers, those who smoked more frequently were more likely to be current e-cigarette users. Odds of being an e-cigarette user was 1.58 times (95% CI: 1.39-1.79) higher among students who had made a quit attempt than those who had not. Students no longer using cigarettes were rare among current e-cigarette users (OR 0.10, 95% CI: 0.09-0.12).

Dutra and Glantz (nearly submitted) examined e-cigarette use and conventional cigarette smoking using the 2011 US National Youth Tobacco Survey (NYTS), which was administered to a representative sample of U.S. middle and high school students (n=18,644). Among experimenters with conventional cigarettes (>1 puff, <100 cigarettes), ever e-cigarette use was associated with higher odds of ever smoking (>100 cigarettes; (OR=7.68, 95% CI [5.45-10.83]) and current smoking (OR=7.44, [5.39-10.27]). Current e-cigarette use was associated with an odds of ever smoking of 7.27 [3.99-13.25] and an odds of current smoking of 6.68 [3.82-11.68]. Among experimenters, ever use of e-cigarettes was also associated with lower 30-day (2011: OR=0.22 [0.16-0.30]), 6-month (2011: OR=0.22 [0.16-0.29]), and 1-year (2011: OR=0.22 [0.15-0.32];) abstinence from cigarette smoking. Current e-cigarette use was also associated with lower 30-day (2011: OR=0.15 [0.08-0.28]), 6-month (2011: OR=0.17 [0.07-0.40]), and 1-year (2011: OR=0.15 [0.07-0.34]) abstinence. Among ever smokers of cigarettes (>100 cigarettes), ever e-cigarette use approached significance for the odds of abstaining from smoking in the past 30
days in 2011 (OR=0.55 [0.31-1.01]). Current e-cigarette use was not a significant predictor of smoking abstinence among ever smokers. Thus, e-cigarette use was associated with higher odds of ever or current cigarette smoking and lower odds of abstinence from conventional cigarettes. E-cigarettes appear to be promoting cigarette use among adolescents and discouraging quitting.

**Conclusion**

The quit rates produced in Capponnetto et al 2013 for non-nicotine e-cigarette 4%, tapered nicotine e-cigarette 9% and 7.4mg e-cigarette 13%; 30-day abstinence at one year) were not statistically significantly different. Similarly, in Bullen et al 2013, the quit rates for 16mg e-cigarette, 21mg nicotine patch and 0mg e-cigarette showed no statistically significant differences in continuous abstinence quit rates at 6 months (7.4%, 5.8%, 4.1% respectively). Both of these studies did not show effects of e-cigarette use on quitting, beyond what is seen in unassisted cessation studies with NRT (cite). Both the Capponnetto (2013) and the Bullen et al (2013) randomized trials did not demonstrate a statistically significant difference in quit rates between nicotine e-cigarette and non-nicotine e-cigarettes. In determining the effectiveness of a smoking cessation therapy, active drug is considered efficacious when it outperforms its placebo form, therefore the evidence to date demonstrates that e-cigarettes would not be considered efficacious as nicotine replacement to produce cessation. It is possible that e-cigarettes act as substitutes for the sensory and behavioral effects of conventional cigarettes. Important limitations of the current research include the use of e-cigarettes that deliver relatively low levels of nicotine and provision of minimal behavioral counseling. Studies with more modern products and with more intensive behavioral counseling are ongoing.

Reductions in cigarettes per day were observed in these studies (Polosa, Capponnetto, Caponnetto, Bullen) and in the population-based study (Adkison) among those who did not quit. In the cigarette reduction analyses presented in some of the studies, many participants were still smoking about half a pack cigarettes per day at the end of the study. Light smoking, even 1-4 cigarettes per day, is associated with markedly elevated cardiovascular disease risk. (Bjartveit and Tverdal 2005)
TOBACCO INDUSTRY INVOLVEMENT

In 2012 and 2013 major tobacco companies – Lorillard, Reynolds American Inc, (which is 42% owned by British American Tobacco), Altria (Philip Morris), and British American Tobacco -- purchased or developed e-cigarette products. Lorillard, Reynolds and Altria's products are put forth by subsidiary companies: Lorillard Vapor Corporation, R.J.Reynolds Vapor Company, and Nu Mark, LLC. (owned by Altria). Lorillard acquired e-cigarette companies that produced Blu and SkyCig brands marketed under Lorillard Vapor Corporation. As of 2013, Altria’s Mark Ten e-cigarette is in test market in Indiana, Reynolds’ product, the Vuse, is in test market in Colorado and has planned to roll out national distribution and has created a TV commercial for the launch. BAT markets the Vype in the U.K. In addition, a smaller tobacco company, Swisher, that makes little cigars and cigarillos, also markets an e-cigarette called the e-Swisher.

There is no evidence that the cigarette companies are acquiring or producing e-cigarettes as part of a strategy to phase out regular cigarettes, but some claim to want to participate in "harm reduction." Lorillard CEO Murray Kessler stated in a Sept. 23, 2013 interview with the Wall Street Journal in which he claimed that e-cigarettes will provide smokers an unprecedented chance to reduce their risk from cigarettes. Also, in USA Today he published an op-ed on September 23, 2013 where he stated: “E-cigarettes might be the most significant harm-reduction option ever made available to smokers.” Shortly before this op-ed was published, however, Lorillard gained approval from the US Food and Drug Administration to market a new non-mentholated Newport conventional cigarette, demonstrating the inherent inconsistency in messaging and deeds by expanding their cigarette line while touting their ability to offer a product they claim reduces harm from cigarettes. In this way the cigarette companies get to have it both ways, they offer an alternative to their products while continuing to market their products. In fact as noted in the 2010 Surgeon General’s Report, "How Tobacco Smoke Causes Disease," the tobacco industry has used every iteration of cigarette design to undermine cessation and prevention.
The tobacco companies have e-cigarette issues on their radar as part of their policy agenda. They are still engaging in “smokers rights” activities - where they use seemingly independent groups to interact with consumers directly on political involvement in support of their agenda. Altria has a website called “Citizens for Tobacco Rights” and Reynolds has “Transforming Tobacco.” E-cigarette news and action alerts are featured on the homepages of these websites and include instructions for taking action against bills designed to include e-cigarette use in smokefree laws.

An e-cigarette market analysis report by Goldman-Sachs in 2013 noted that despite currently comprising <1% total industry sales, there is the potential for e-cigarettes to account for 15% of US tobacco market profit by 2020. However, the report noted that “full conversion” from cigarettes to e-cigarettes has not been achieved and most users are dual users with conventional cigarettes. The report noted that products would have a longer lifespan because its users would have a longer lifespan, reflecting the obvious goal of lifelong use of the products and uptake by new users. Importantly, the market analysts remained positive on the long term growth of the tobacco industry with e-cigarettes playing a role, not as a replacement for the tobacco products.

Likewise, after evaluating the cigarette companies’ internal documents and public positions on snus as “harm reduction” in Europe, Gilmore et al. (2013)(Peeters S and Gilmore AB 2013) found that they were entering the market to protect their cigarette business as long as possible. They saw clear lessons for assessing the companies’ involvements in e-cigarettes:

While such evidence must be considered alongside the broader body of evidence around snus and the fact it is significantly less harmful than smoked tobacco, collectively these issues suggest that legalising snus sales in Europe may have considerably less benefit than envisaged and could have a number of harmful consequences. Perhaps of greater concern, however, given that harm reduction using nicotine products is already an established element of tobacco control and recent research suggests scope for benefit via newer nicotine products, are the recent industry investments in pure nicotine products. These raise two concerns. First, one of competition: should such investments continue, competition between cigarettes and clean nicotine products would decrease, limiting the
potential for harm reduction to benefit public health and maintaining the status quo of cigarettes. While a nicotine regulatory authority could ensure that regulation was proportional to harm, it would be powerless to address the issue of competition, so this situation needs close observation. Second, they may enable TTCs [transnational tobacco companies], by presenting themselves as purveyors of nicotine rather than tobacco products, to undermine Article 5.3 of the Framework Convention on Tobacco Control which aims to protect public health policy from commercial and other vested interests of the tobacco industry. Finally, if TTCs are genuinely interested in seeing their cigarette consumers switch to snus (or pure nicotine products), rather than creating new snus/nicotine users and/or dual use opportunities, we would expect to see detailed strategic plans and cigarette sales reduction targets at least for the markets where they intend to introduce these products. However, to this date we have yet to see this.

[citations eliminated] (Peeters S and Gilmore AB 2013)

CURRENT STATE OF GLOBAL REGULATION

Like e-cigarettes themselves, the policy environment related to e-cigarettes is rapidly developing despite the lack of a large base of scientific evidence to support policy development. Most policies are based on the assumptions that e-cigarettes will contribute to reducing the harms of smoking by either promoting smoking cessation or, at least, replacing combusted cigarettes with e-cigarettes. Of increasing concern is the mounting evidence of dual use and youth initiation of e-cigarette use.

European Union Draft Tobacco Product Directive

The draft European Tobacco Product Directive (TPD) as amended on October 8, 2013 creates a new category of “nicotine-containing products” (NCP) for e-cigarettes. (European Parliament 2013) The draft TPD accepts the assumption, contradicted by the scientific evidence presented in this report, that e-cigarettes are effective cessation devices that should be made widely available when it states, “Given the potential of nicotine-containing products to aid
smoking cessation, Member States should ensure that they can be made available as widely as tobacco products.”

The TPD allows marketing of all NCPs with a nicotine level of 30 mg/ml or less without any screening for their quality, safety, or efficacy if they are not presented with medicinal or therapeutic claims. (NCPs that exceed 30mg/ml are prohibited.) The 30 mg/ml threshold protects almost all e-cigarette products currently on the market, as 36 mg/ml is typically the strongest concentration offered in cartridges and e-liquid bottles. There are e-liquid preparations for sale in very large quantities that exceed this concentration (100 mg/ml) (http://wizardlabs.us/index.php?route=product/product&product_id=77), but in a content analysis of e-cigarette retail websites in 2012, no product over 36 mg/ml was found (Grana, Ling under review). The 30mg/ml level is higher than the nicotine content in any of the e-cigarette devices tested in the studies published to date as reviewed in this report.

The draft TPD subjects e-cigarettes to pre-market authorization only if they are “presented as having properties for treating or preventing disease” (i.e., “medicinal products”). This is counter to the assumption made in the TPD that all e-cigarette products should be available because of their potential “… to aid smoking cessation.” This inconsistency within the draft directive is evident when it notes that "Nicotine-containing products - including e-cigarettes - are sold on the Union market. However Member States have taken different regulatory approaches to address health and safety concerns associated with these products. There is a need for harmonized rules, therefore all nicotine-containing products should be regulated under this Directive as a related tobacco product.” To implement this policy, Article 3.7 provides that:

The proposal removes current legislative divergence between Member States and the differential treatment between Nicotine Replacement Therapies and Nicotine Containing Products, increases legal certainty and consolidates the on-going development in Member States. It also encourages research and innovation in smoking cessation with the aim of maximising health gains.
Thus, the draft directive accepts as a premise that NCPs, including e-cigarettes, are "medicinal products" within the meaning of Directive 2001/83/EC because they have properties that are useful "for treating or preventing disease" by aiding smoking cessation. TPD Article 18 seems inconsistent with these provisions, however, since it differentiates between NCPs that are "presented as having properties for treating or preventing disease," which are required to get premarket authorization under Directive 2001/83/EC under paragraph 2 of Article 18, and all other NCPs, which need only follow the notification procedure set out in Article 17.

The TPD prohibits nicotine-containing products with the following types of additives: additives such as vitamins that create the impression of health benefit or reduced risk; caffeine, taurine and other stimulants associated with energy and vitality; and additives having coloring properties for emissions. However, the additives which may impart a characterizing flavor that increase product appeal to children (e.g., chocolate, cherry, strawberry, licorice, menthol) that are explicitly prohibited from tobacco products (conventional cigarettes) are explicitly allowed in e-cigarettes.

E-cigarette manufacturers and importers are nominally required to submit lists of all ingredients contained in and emissions resulting from the use of their products by brand name and type, and including quantities, but the TPD explicitly ensures protection for companies’ trade secrets, creating a loophole while will permit companies to avoid this disclosure requirement by claiming that their ingredient lists are trade secrets, as they have done in response to required submissions to the FDA in the United States.

The TPD requires that “each unit packet and any outside packaging of nicotine-containing products carry the following health warning: ‘This product is intended for use by existing smokers. It contains nicotine which is a highly addictive substance.’” The size and placement of the warning is the same as for tobacco products for smoking other than cigarettes and roll-your-own tobacco: 30%-35% of the external area of the unit pack and any outside packaging, depending of the number of a Member State’s official languages.
The TPD explicitly permits sales of e-cigarettes outside of pharmacies (including any that might be registered as “medicinal products”). E-cigarette sales to buyers under age 18 are prohibited.

The TPD imposes the same “limitations on advertising, sponsorship, audiovisual commercial communication and product placement for tobacco products as set out in Directive 2003/33/EC and Directive 2010/13/EC” to e-cigarettes. It also prohibits co-branding of e-cigarettes and tobacco products: “tobacco trademarks, brand names and symbols are not used on nicotine-containing products.” The ability to co-brand products with a celebrity’s “brand” is unclear.

The TPD is silent on the marketing of e-cigarette devices that do not contain nicotine, so does not create any restrictions on the marketing or sale of these products, particularly to youth. This is an important omission. In contrast to cigarettes or conventional nicotine replacement therapies such as patch, gum, lozenge, there are many different e-cigarette-like products in the current marketplace and many are not sold pre-filled and pre-assembled. (This situation also contrasts with the most similar medicinal product, the nicotine inhaler, which is standardized for use: It has only one cartridge of one nicotine concentration that only fits in one device.) With e-cigarette products, different components of products are sold separately and can be used with several different liquids with varying nicotine content. Indeed, one way that a company could possibly legally evade regulation under the TPD would be to sell nicotine-free e-cigarettes as consumer products then sell the nicotine fluid separately. It is not clear how the nicotine content standards would apply in this context (e.g., bottles of e-liquid, different sized cartridges that can be used on different devices). Moreover, it is not clear how every piece of these devices would be regulated to ensure that they meet safety standards (whether regulated a medicines or consumer products), or even if they would be allowed to be sold separately.

The definition of passive smoking, "'Passive smoking' means the involuntary inhalation of smoke from the combustion of cigarettes or cigars or from the exhalation of one or more smokers," excludes the so-called "vapor" from e-cigarettes, as it only includes the "combustion of cigarettes or cigars." This omission would thus permit the use of e-cigarettes in places that are currently regulated by laws that prohibit "passive smoking."
Perhaps most significantly, the amendments to the TPD adopted on October 8, 2013 eliminated the authority of the European Commission to update the regulations related to e-cigarettes as new information about marketing and use patterns and their direct health effects and effects on cigarette consumption develops in the currently rapidly changing market. Specifically, the requirement that:

The Commission shall be empowered to adopt delegated acts in accordance with Article 22 to adapt the requirements in paragraphs 3 and 4 taking into account scientific and market developments and to adopt and adapt the position, format, layout, design and rotation of the health warnings.

was deleted and replaced with a weak requirement for monitoring and preparation of a report after 5 years that could recommend changes to the TPD (but not make any actual changes).

This change effectively insulates the e-cigarette companies from any science-based regulations for at least 5 years and likely much longer, since it moves the issue back into the political sphere where the tobacco companies are strongest.


NATIONAL POLICIES

FCTC Conference of the Parties Survey Results (2012)

FCTC Conference of the Parties’ report on e-cigarettes, (11/2012, n=33 Parties).(FCTC/COP/5/13 2012) Brazil, Singapore, the Seychelles and Uruguay ban e-cigarettes from being sold or distributed in their countries. Several countries have proposed or enacted regulations. Australia, New Zealand and Switzerland allow e-cigarettes without nicotine to be sold, but residents may purchase e-cigarettes and e-liquid with nicotine over the Internet for personal use (may not sell them in the country). Many with regulations focus on drug delivery
device classification for e-cigarettes with nicotine and that make health claims. For example, Germany's regulation separates e-cigarette products into consumer and medicinal by it nicotine and health claims. If a product contains no nicotine and no health claim it is currently unregulated. However if a product has nicotine in it and is marketed with a health claim, it must go through their drug delivery regulatory scheme to be approved for retail, distribution and advertisement as a medication. Similar regulations exist in Germany, Belgium, Turkey and the U.K. where e-cigarette products require pre-market authorization if they contain nicotine and are marketed with a health claim or if they are intended to be used for smoking cessation. By contrast, in Korea, products without nicotine are regulated as quit aid by the Korean Food and Drug Administration (KFDA) and products with nicotine are treated as tobacco products and regulated by Ministry of Finance.

**United Kingdom**

Policymaking on e-cigarettes in the U.K. is based on two assumptions: (1) harm reduction implemented by shifting cigarette smokers to “cleaner” forms of nicotine delivery is an effective public health policy (cite NICE standards); (2) e-cigarettes are a safe effective form of nicotine replacement; and (3) the widespread introduction of e-cigarettes will increase cigarette cessation and not increase initiation. Specifically, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) has announced they plan to regulate e-cigarettes as medicines because MHRA believes that e-cigarettes function as nicotine replacement for smokers cutting down or quitting:

The consistent evidence from a variety of sources is that most electronic cigarettes use is to support stop smoking attempts or for partial replacement to reduce harm associated with smoking. This is comparable to other nicotine replacement products (e.g., gums, patches, inhalator), which are licensed as medicines. The current evidence is that electronic cigarettes have shown promise in helping smokers quit tobacco but the quality of existing NCPs [nicotine containing products, how MHRA labels e-cigarettes] is such that they cannot be recommended for use.
The MHRA’s regulatory plans focus on ensuring consistency of nicotine delivery and quality control of the e-cigarette devices. Since March 2011 MHRA reviewed evidence regarding safety of the devices and e-liquid and their own analysis of four e-cigarette products, finding that existing products on the market are low quality and not assured for safety (http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con286839.pdf). Their evidence review, like this report, found that products have incongruous nicotine content from labeled values and levels varied for identical products within the same brand and that is just among a selection of brands among the hundreds on the market. The MHRA found diethylene glycol in one product in accordance with the FDA analysis (2009) likely to be from improper processing of propylene glycol. In addition, they found the presence of a toxic contaminant (1,3-bis(3-phenoxyphenooxy) benzene), which they stated has no plausible reason for being in the products. They concluded that the devices cannot be considered safe or effective nicotine delivery devices as the content and delivery of nicotine differs from brand to brand and even within brand. Moreover, their evidence review acknowledges that low levels of known tobacco-specific carcinogens were found in products, likely from low-quality nicotine extraction processes.

Research published after the EU draft directive and MHRA evidence review (http://www.mhra.gov.uk/home/groups/commsic/documents/websiteresources/con286839.pdf) were published provides additional information that should be considered in designing these regulatory approaches. In contrast to the assumption that e-cigarettes would function as a better form of NRT, population-based longitudinal studies which reflect real-world e-cigarette use found that e-cigarette use is not associated with or predict successful quitting (Vickerman, Adkison, Grana Popova and Ling, submitted) and the 1 clinical trial examining the effectiveness of e-cigarettes (both with and without nicotine) compared to the medicinal nicotine patch found that e-cigarettes are no better than nicotine patch and all treatments produced very modest quit rates without counseling. Although more participants liked using the e-cigarette compared to patch and would recommend it to a friend trying to quit.

MHRA noted that their regulation of e-cigarettes as medicines is in accordance with the proposed EU Tobacco Products Directive before it was amended on October 8, 2013,
(http://ec.europa.eu/health/tobacco/docs/com_2012_788_en.pdf) which MHRA assumed will be adopted in 2014 and come into effect by 2016. The MHRA specifies that their program seeks to determine four dimensions to establish medicines licensing for e-cigarettes: “the nature, quality and safety of unlicensed NCPs; the actual use of unlicensed NCPs in the marketplace; the effectiveness of unlicensed NCPs in smoking cessation; and modelling of the potential impact of bringing these products into medicines regulation on public health outcomes.” It is unclear the specific steps to achieve these aims.

As part of what appears to be a broad consensus in the UK that the introduction of e-cigarettes will reduce the harm of smoking, the anti-smoking advocacy group ASH UK has announce that it "does not consider it appropriate to include e-cigarettes under smokefree regulations," (http://www.ash.org.uk/files/documents/ASH_715.pdf), supporting one the e-cigarette companies’ key marketing messages, namely that e-cigarettes can be used everywhere without the restrictions and social stigma of smoking (Grana and Ling, under review; McKee, 2013). It is unclear how the UK plans to address the potential interference with enforcement of existing smokefree laws and potential promotion of smoking as these are mimicking products.

The MHRA does not include any restrictions on e-cigarette marketing. An undated document, “The Regulation of Nicotine Containing Products: Questions and Answers,” attempts to address this issue:

24. **What will be done by the Government to stop manufacturers making their products attractive to young people/children – such as making fruit tasting electronic cigarettes or doing special offers such as two for the price of one?**

Medicines regulation prohibits advertising to children (under 16 years of age). Any licensed medicines would have an age limit – likely to be 18 years of age. One of the reasons for favouring medicines regulation is that it has controls on advertising and promotion and sale and supply. We will look at applications from manufacturers on a case-by-case basis.
If need be, we are able to set particular conditions on the way that products are presented and promoted, especially if they become popular with young people.

At present, we are not aware of any widespread use of e-cigarettes by young people.

These assurances provide little or no protection against aggressive marketing of e-cigarettes to youth; the tobacco companies are long-practiced at developing and implementing effective marketing campaigns directed at youth with similar restrictions for decades all over the world. Evidence published after this agency issued their intended policies has shown rapid e-cigarette uptake among adolescents in the US, (with use doubling from 3.4% to 6.8% among all middle school and high school youth from 2011 to 2012, with rates even higher among older youth in high school 4.7% to 10.0%), mostly among current smokers.

**France**

In contrast to the position ASH UK took in England, the French Health Minister, Marisol Touraine, announced on May 31, 2013 (World No Tobacco Day) that the French government plans to extend existing smoking restrictions to e-cigarettes. These restrictions were undertaken to prevent confusion in enforcement of the national smokefree law and prevent modeling of smoking by a product that mimics cigarette smoking. (http://www.france24.com/en/20130531-french-health-minister-electronic-cigarette-ban-public-places) It will also protect bystanders from being exposed to secondhand e-cigarette vapor.

**Spain**

Although no national action has been taken, regional action has been pursued to treat e-cigarettes the same as tobacco products under their existing state-wide smokefree law. The Catalan Network of Smoke-free Hospitals and the Network of Primary Care issued a statement that there is a lack of evidence of safety and efficacy for e-cigarettes and they act as mimicking products which can create confusion and may interfere with “denormalization.” They stated: “…the Catalan Network of Smoke-free Hospitals and Primary Care recommend that hospitals,
health centers and other healthcare facilities: - Prohibit by internal regulation the use of electronic cigarettes on their premises, both in enclosed places (buildings) and outdoors, similar to that established in the current legislation (Law 42/2010) of sanitary measures to control tobacco snuff products. - Prohibit by regulation for internal system sale, promotion or advertising of these devices in their units, similar to that established in the current Spanish smoke-free legislation (Law 42/2010).”

India

In India e-cigarettes were declared as illegal under Drugs and Cosmetics Act by State Drug Controller in Punjab and the government of India is preparing to ban them. (Per personal communication from Dr. Rakesh Gupta, State Programme Officer, Tobacco Control Cell Punjab)

U.S.

As of October 2013, e-cigarette products remained unregulated by any federal authority, particularly the US Food and Drug Administration (FDA). The Sottera Inc. case ruling that was upheld on appeal in U.S. court, found that e-cigarettes could be regulated as tobacco products unless they are marketed with health and therapeutic claims. (D.C. Circuit U.S. Court of Appeals 2010) The FDA accepted that ruling and issued a letter to stakeholders on April 25, 2011 stating their intent to issue guidance about exercising their deeming authority over e-cigarettes in the future, but, no such deeming authority or guidance had been issued. (FDA 2011)

In the absence of Federal regulations, 23 states have passed bills restricting sales to minors and 3 bills have been passed prohibiting the use of e-cigarettes where smoking is also restricted. There are several bills at the local level restricting many aspects of e-cigarette distribution, sales and use, including minor access restrictions, use indoors and point of sale. The Federal Aviation Administration issued a regulation prohibiting the use of e-cigarettes on domestic flights.

Phillipines
The Philippine Food and Drug Administration recently recommended that e-cigarettes should not be used indoors anywhere that smoking is prohibited.

OVERALL SUMMARY

While most discussion of e-cigarettes among health authorities has concentrated on the product itself, its potential toxicity and use of e-cigarettes to help people quit smoking, the e-cigarette companies have been rapidly expanding using aggressive marketing, including television and radio in many countries using messages that have been long-banned for cigarettes. There appears to be no evidence to the contrary that if existing smokers switched completely from conventional e-cigarettes (with no other changes in use patterns) there would be a lower disease burden caused by nicotine addiction. Evidence available at this time, while limited, however, points to high levels of dual use of e-cigarettes with conventional cigarettes, little benefit for cessation (either on a population basis or compared to available and currently regulated nicotine replacement therapy) and rapidly increasing youth initiation with e-cigarettes. It is unclear what will be the trajectory of the dual use pattern among adults or children, but any uptake in children is very concerning. Nicotine is a highly addictive substance with negative effects on human brain development, which is still ongoing in adolescence.(Dwyer, Brodie and Leslie, 2008; Liao, Chen, Lee, et al. 2012; Lichtensteiger et al, 1988; Navarro et al 1989; Dwyer, McQuown, Leslie, 2009) Evidence from published studies examining dual use of smokeless tobacco, snus and conventional cigarettes among youth and adults points toward a progression to increased cigarette smoking and difficulty with quitting. Also, common reasons respondents give for using the products are to circumvent smokefree laws and to cut down, which reinforce dual use patterns. High rates of dual use which may result in greater total public health burden and possibly increased individual risk if a smoker maintains an even low-level tobacco cigarette addiction for many years instead of quitting.
E-cigarette devices and their components should be evaluated for safety by consumer product safety regulatory authorities and consumers appropriately warned about risks and proper handling. Although the data are limited, the studies to date indicate that e-cigarette vapor would be a source of air pollution and is not "harmless water vapor" as is frequently claimed. Article 13 of the FCTC focuses on smoke-free policies to afford protections for the public and all workers to breathe clean air. When evaluating the risks of exposure to e-cigarette vapor, the standard of comparison should not be whether the vapor is better than the toxic chemical mixture in tobacco cigarette smoke (which is already prohibited), it should be whether the product's emissions introduce toxins into clean air, and their effect on existing public health protections. In contrast to the paucity of research on e-cigarettes, there is an extensive scientific literature showing that smoke-free policies protect nonsmokers from exposure to toxins and encourage smoking cessation (USDHHS, 2006). 100% smoke-free policies have about twice the effect on consumption and smoking prevalence than policies with exceptions (Fichtenberg and Glantz, 2002). Exceptions for e-cigarettes may similarly decrease the effects of smoke-free policies on smoking cessation, and as noted in the CoP report, use of the products in smoke-free environments may also decrease enforcement of Article 13. Introducing e-cigarettes into clean air environments may result in population harm if use of the product reinforces acts of smoking as socially acceptable, and/or if use undermines the effects of smoke-free policies on smoking cessation. Strong smoke-free policies are an integral part of the recognized and proven comprehensive global tobacco control policies (FCTC).

This assessment is based on the assumption that the current policy environment around cigarettes will continue and that there will be little or no effective regulations of e-cigarette marketing and promotion or of how and where e-cigarettes are consumed. This situation could change if the following policies were all implemented:

- Ban conventional cigarettes or regulate nicotine to non-addictive levels.
- Subject and e-cigarette marketing to the same level of restrictions that apply to conventional cigarettes (on the grounds that, while less dangerous than conventional cigarettes, e-cigarettes still deliver the addictive drug nicotine together with other toxic chemicals)
• Tax e-cigarettes at a level comparable to current taxation of conventional cigarettes (and perhaps further increase the tax on conventional cigarettes)
• Prohibit the use of e-cigarettes anywhere that use of conventional cigarettes is prohibited
• E-cigarettes should not be sold to anyone who cannot legally buy cigarettes or sold in any venues where sale of conventional cigarettes is prohibited.
• E-cigarettes should not be co-branded with cigarettes or marketed in a way that promotes dual use.

Should these policies be put in place, it is possible that current conventional smokers who will not quit nicotine would shift to e-cigarettes without major dual use or youth initiation to nicotine addiction with e-cigarettes. Absent this change in the policy environment it is reasonable to assume that the behavior patterns that have been observed for e-cigarettes will persist, which makes it unlikely that they will on balance contribute to reducing the harm of tobacco use and could increase harm by perpetuating the life of conventional cigarettes.

At minimum, these policies should be implemented immediately:
• Regulate e-cigarettes to ensure product quality and safety.
• Prohibit the use of e-cigarettes anywhere where the use of conventional cigarettes is prohibited
• Prohibit claims that e-cigarettes are effective smoking cessation aids until such time as there is convincing scientific evidence that such claims are true for e-cigarettes as they are actually used in the general population.
• Apply the same restrictions on e-cigarette advertising and promotion as apply to conventional cigarettes
• Ban the use of characterizing flavors in e-cigarettes

Because the product, the market, and the associated scientific evidence surrounding the e-cigarette experiment are all evolving rapidly:
• All legislation and regulations related to e-cigarettes should allow for flexibility to adapt regulations expeditiously in response to new science, including evaluation of different models for regulating e-cigarettes, as it accumulates.
• No country or subnational jurisdiction should be compelled to permit the sale of e-cigarettes.
• Legislation and regulations regarding e-cigarettes need to take into account the fact that, unlike conventional cigarettes and other tobacco products and medicinal nicotine replacement therapies, e-cigarettes can be altered by users to change the nicotine delivery and be used to deliver other drugs.
• There should be transparency in the role of the e-cigarette and tobacco companies in advocating for and against legislation and regulation, both directly and through third parties.
• FCTC Article 5.3 should be respected when developing and implementing legislation and regulations related to e-cigarettes.
Table 1. Prevalence of e-cigarette use in various countries as measured by population-based surveys

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country, sample description, n</th>
<th>Ever use among general population (%)</th>
<th>Ever use among smokers (%)</th>
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</thead>
<tbody>
<tr>
<td>Regan et al 2013</td>
<td>U.S., Adults 18+, n=10587 (2009); n= 10328 (2010), ConsumerStyles nationally-representative survey</td>
<td>0.6</td>
<td>2.7</td>
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<td>King et al 2012</td>
<td>U.S., Adults, 18+, HealthStyles survey nationally-representative, mail-back (n=4,184) and online (n=2505) modes n=6689 in 2010, online only n=4050 in 2011</td>
<td>--</td>
<td>2.1 mail, 3.3 online</td>
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<tr>
<td>Pearson et al 2012</td>
<td>U.S., Adults 18+, 2 samples</td>
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<td>Nationally-representative online sample (Knowledge Networks), 2010, n=2649</td>
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<td>3.4</td>
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<tr>
<td>McMullen et al 2013</td>
<td>U.S., Adults 18+, nationally-representative samples recruited via 2 survey modes: telephone-based (n=1504) and online (n=1736), Social Climate on Tobacco Control survey, 2010</td>
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<td>1.8</td>
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<td>Dockrell et al 2013</td>
<td>U.K., Adults 18+, nationally-representative online panel (YouGov), 2010: n=12597 adults; 2010 n=12432</td>
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<td>Adkison et al 2013</td>
<td>ITC 4-country survey, Adults 18+,* July 2010-June 2011*</td>
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<td></td>
<td>U.S. (n=1520)</td>
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<td></td>
<td>Canada (n=1581)</td>
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<td></td>
<td>U.K. (n=1325)</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Year</td>
<td>Age Group</td>
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<td>Australia (n=1513)</td>
<td>U.S., Adults 18+, nationally-representative online sample (Knowledge Networks), current and former smokers, n=1836</td>
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<td>Cho 2011</td>
<td>Korea, Adolescents, middle school and high school, n=4,341, national survey in 2008*</td>
<td>0.5*</td>
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<td>Lee et al 2013 (under review)</td>
<td>Korea, Adolescents, 12-19,</td>
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<td>CDC NYTS 2013</td>
<td>U.S., Adolescents, middle and high school, 2011, 2012 (n’s not reported)</td>
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<td>MS: 1.4</td>
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<td></td>
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<td>HS: 4.7</td>
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