

From: [REDACTED] (SANCO)
Sent: 28 November 2013 13:35
To: [REDACTED]
Cc: [REDACTED] (SANCO); [REDACTED]
Subject: RE: Draft WHO Background Paper on ENDS (comments) and smokeless tobacco
Attachments: 1_Grana_WHO Ecig Report 10-14-13 RACHEL_v2_KB.doc; 4_Smokeless Tob Report for WHO Peer Review 093013_KB.doc

Dear [REDACTED] and all,

Sorry for the late input on 2 of the documents.

- 1) I would like to provide you with some additional comment on the ENDS paper. I agree that this background document is indeed a very good basis for the discussion and would also like to thank [REDACTED] for her very pertinent comments, which I support. I just have a couple of additional remarks which you will find below or (in specific cases) in the document attached:
 - Conclusion chapters sometimes present rather a discussion of the literature instead of clear conclusions: Moreover, they sometimes contain details of studies that would be better placed in the body of the text.
 - As pointed out by [REDACTED], the presentation of results should be more factual and consider the possibility of different interpretations (see specific comment on the interpretation of results of the Bullen et al. paper)
 - Overall, it would facilitate reading if "conclusion" sections could be specified ("conclusion on ...")
 - Please consider checking/updating the paper in light of recent publications (e.g. recent Review by Pepper & Brewer in Tobacco Control)
 - The section on the TPD revision needs a careful revision, in particular as the authors focus to a large extent on certain amendments of the European Parliament to the Commission proposal, thus focussing on the position of only 1 of the European institutions involved in the legislative process. Furthermore, the negotiations by the institutions on the proposal are still ongoing. In that context, I was wondering if it is the purpose of the document to comment on legislative approaches (see also comments in the text)?
- 2) For the document on smokeless tobacco, I introduced a couple of small comments, but didn't have the chance for a thorough reading. It is indeed difficult to shorten the document to 50 pages if you wish that the regional sections should be kept as they are (they alone make up for about 50 pages). However, I noted some duplication between the introduction (which contains "summary and major conclusions") and the key findings chapter. Also, some of the text in the intro chapter already reads a bit like conclusions (see p. 5-8).

Some suggestions for changes:

 - Extract the major conclusions out of the introduction/key findings and make a separate "Executive summary"
 - Possibly concentrate the regional chapters to major findings and put the rest into an Annex (together with all the references).

I will try to take a good look at the other documents before the meeting.

Looking forward to meeting you all next week.

Best regards,

[REDACTED]

PS. I will fly to Brazil already tomorrow (to take advantage of the occasion ☺).

[REDACTED]
Policy Officer, Tobacco Control Team



European Commission
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[REDACTED]

[REDACTED]

[REDACTED]

http://ec.europa.eu/health/tobacco/introduction/index_en.htm

PLEASE NOTE THAT THE CONTENT OF THIS EMAIL INCLUDING ATTACHMENTS IS FOR YOUR PERSONAL USE ONLY

From: [REDACTED] hc-sc.gc.ca]

Sent: Saturday, November 09, 2013 1:23 AM

To: [REDACTED]

Cc: [REDACTED] (SANCO); [REDACTED] (SANCO); [REDACTED]

Subject: Draft WHO Background Paper on ENDS (comments)

Dear [REDACTED],

Sorry for the late input. One of my staff, [REDACTED], has reviewed the ENDS paper. General comments can be found in this e-mail, below, and more specific ones in the attached document.

Regards,

[REDACTED]

GENERAL COMMENTS

Overall, the document is a good start and outlines some important issues.

From a science perspective, I would caution that interpretation of the literature is skewed toward a negative view of ecigarettes, and these conclusions are sometimes, but not always justified. I think the science portion of the paper could be strengthened by objectively presenting pros and cons of ecigs. The account of available literature is thorough, although I would suggest adding new studies as they emerge since this is quite an active field. For example, the cytotoxicity paper by Farsalinos *et al.* (Int J Environ Res Public Health. 2013 Oct 16;10(10):5146-62) merits mention in the discussion on this topic, but was published after this draft was written.

Much of the paper is opinion-based, and does not represent all possible interpretations. I am not sure if this was the original intention of the document? Were the authors perhaps asked to provide their personal opinions and not a thorough issue analysis?

Although not a 'scientific' point, I note that Canada is not mentioned in the summary of global regulation, and it would be beneficial to describe the Canadian situation for completeness. This leads to the point that not all ecigs contain nicotine, and it may be worth factoring this issue into the analysis more prominently.

Lastly, I would suggest a thorough edit of this document, as there are several typos, references 'under review' that will need to be updated, etc.

■

(See attached file: WHO Ecig Report 10-14-13 RACHEL_v2_JM comments.doc)

Rachel Grana, Stan Glantz, Neal Benowitz

WHO Background Paper on ENDS

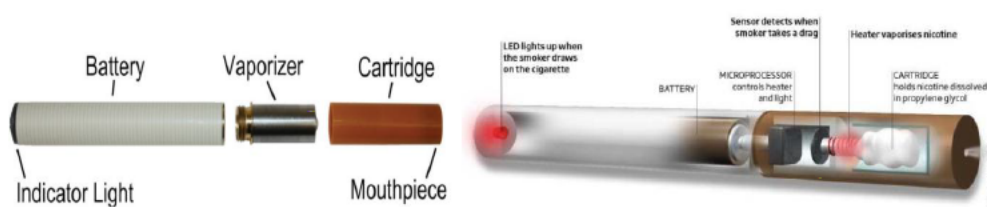
DRAFT– v. October 14, 2013

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)

Comment [KB1]: Do you have any information regarding their market share?

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 it 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

U.S. and is owed largely to the refillable nature of e-cigarettes, is the use of the devices to smoke marijuana in the form of liquid and wax dabs, which is a concentrated form of marijuana, mainly comprising THC. (<http://www.nbcnewyork.com/investigations/ECigarettes-Drugs-Marijuana-Vapor-Pens-Smoking-I-Team-227269001.html> and <http://www.myfoxla.com/story/22305076/its-the-latest-cannabis-craze-a-concerntrated-marijuana-known-as-wax>)

Figure 2. Examples of different products

Product	Description	Examples of Brands
Disposable e-cigarette 	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.	NJOY OneJoy, Aer Disposable
Rechargeable e-cigarette 	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.	Blu, GreenSmoke, EonSmoke
Pen-style, medium-sized rechargeable e-cigarette 	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.	Vapor King Storm, Totally Wicked Tornado
Tank-style, large-sized rechargeable e-cigarette 	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.	Volcano Lavatube

Comment [KB2]: Do you have any information regarding their respective market share?

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)(Grana and Ling under review) systematically 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.

Comment [KB3]: Agree that such advertising should be avoided. However, as not all e-cigarettes even contain nicotine, I would suggest to rephrase the sentence for factual accuracy.

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 large 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 generalizable 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 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 nonsmokers, 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

Comment [KB4]: This whole conclusion chapter is an example for one of my general comments (Conclusion chapters sometimes present rather a discussion of the literature instead of clear conclusions. Moreover, they sometimes contain details of studies that would be better placed in the body of the text).

initiators (OR= 2.54 (95% CI: 1.68-3.91). (Galanti, Rosendahl et al. 2008) (Galanti et al., 2008)

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.

Comment [KB5]: This section presents dual use of cigarettes with a different product (smokeless tobacco). How far can these findings be extrapolated to dual use with e-cigarettes? Consider presenting this information in a "Discussion" chapter

Comment [KB6]: Dual use of which products?

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)

Toxicant	Content in Nicotine inhaler mist	Range in content in vapor from 12 e-cigarette samples (per 15 puffs)	Range in content in conventional cigarette micrograms in mainstream smoke from 1 cigarette
Formaldehyde	2.0	0.2-5.61	1.6-52
Acetaldehyde	1.1	0.11-1.36	52-140
Acrolein	ND	0.07-4.19	2.4-62
o-methylbenzaldehyde	0.7	.13-.71	--
Toluene	ND	0-0.63	8.3-70
p,m-xylene	ND	0 - 0.2	--
NNN	ND	0 - 0.00043	0.0005-0.19
NNK	ND	0-0.00283	0.012-0.11
Cadmium	0.03	0 - 0.022	--
Nickel	0.19	0.011-0.029	--
Lead	0.04	0.003-0.057	--
ND=Not Detected; NOTE: Data were taken from Tables 3 and 4 in Goniewicz et al.			

2013. Lowest and highest values reported in each table were used for each toxicant

Kim et al. (2012) developed a liquid chromatography-tandem mass spectrometry method for analyzing TSNA 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 TSNA 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 propanal (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, diacetyl (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.

Table 4 Concentrations ($\mu\text{g}/\text{m}^3$) of selected compounds during the 8- m^3 emission test chamber measurement of e-cigarette A and conventional cigarette using Tenax TA and DNPH

Compounds	CAS	Participant blank	E-cigarette			Conventional cigarette
			Liquid 1	Liquid 2	Liquid 3	
1,2-Propanediol	57-55-6	<1	<1	<1	<1	112
1-Hydroxy-2-propanone	116-09-6	<1	<1	<1	<1	62
2,3-Butanedione	431-03-8	<1	<1	<1	<1	21
2,5-Dimethylfuran	625-86-5	<1	<1	<1	<1	5
2-Butanone (MEK)	78-93-3	<1	2	2	2	19
2-Furaldehyde	98-01-1	<1	<1	<1	<1	21
2-Methylfuran	534-22-5	<1	<1	<1	<1	19
3-Ethynyl-pyridine ^a	1121-55-7	<1	<1	<1	<1	24
Acetic acid	64-19-7	<1	11	13	14	68
Acetone	67-64-1	<1	17	18	25	64
Benzene	71-43-2	<1	<1	<1	<1	22
Isoprene	78-79-5	8	6	7	10	135
Limonene	5989-27-5	<1	<1	<1	<1	21
m,p-Xylene	1330-20-7	<1	<1	<1	<1	18
Phenol	108-95-2	<1	<1	<1	<1	15
Pyrrole	109-97-7	<1	<1	<1	<1	61
Toluene	108-88-3	<1	<1	<1	<1	44
Formaldehyde ^b	50-00-0	<1	8	11	16	86
Acetaldehyde ^b	75-07-0	<1	2	2	3	119
Propanal ^b	123-38-6	<0.2	<0.2	<0.2	<0.2	12

^aQuantified on the basis of toluene response.^bDNPH method.

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 if 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 8m³ 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

(BloomMaxXFusion) 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 ($10^9/\text{cm}^3$) 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;

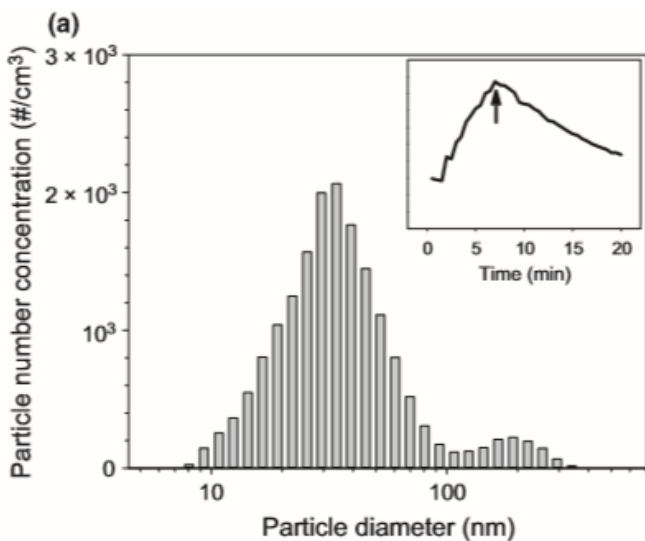


Figure 4a) Aerosol size distribution during consumption of an e-cigarette in an 8-m³ chamber

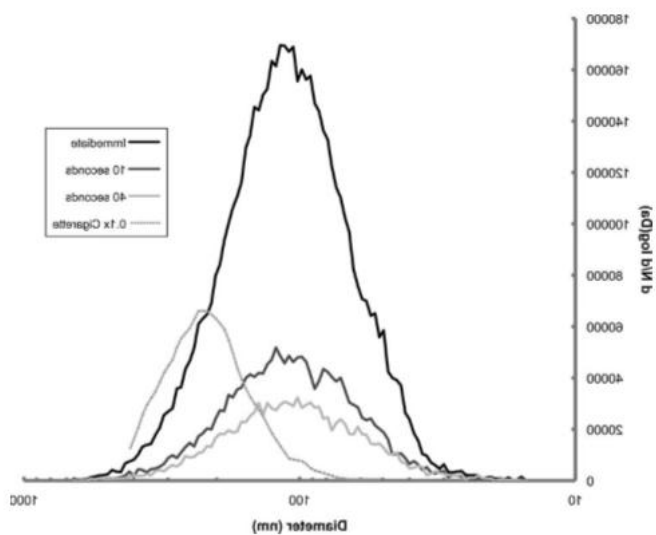


Figure 3. Single puff with propylene glycol-based e-liquid

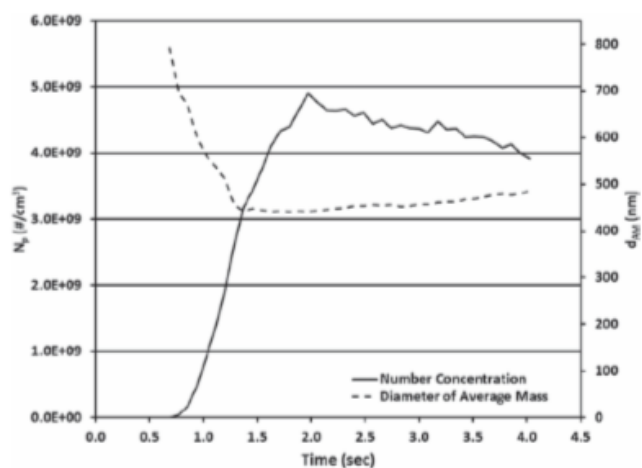


Figure 2. Number concentration and diameter of average mass vs. time for the Brand A e-cigarette produced with a 55 cm³ puff volume over 4 s puff duration.

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 cells 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, Alliffranchini 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 acetaldehyde, 6 times as much o-methylbenzaldehyde as a nicotine inhaler, as well as additional toxicants and carcinogens (acrolein, toluene, 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.

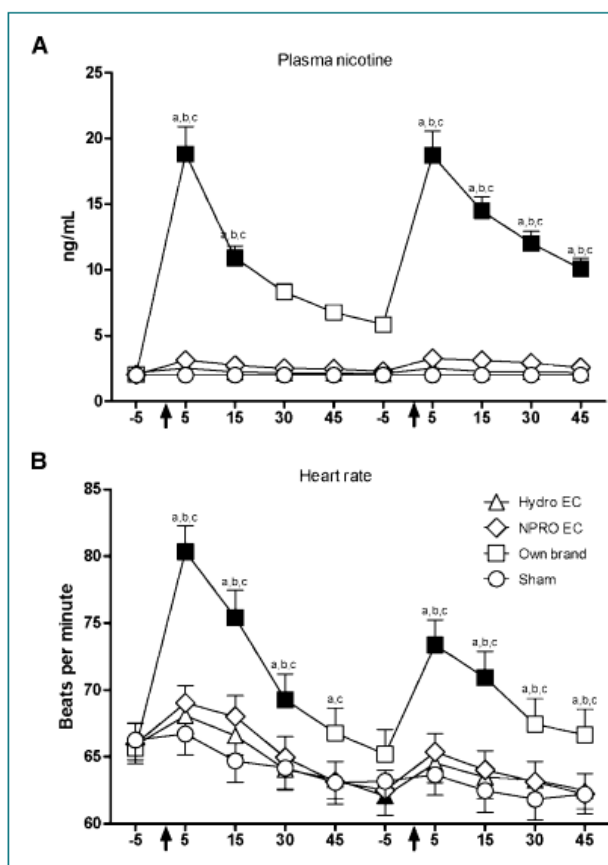
BIOLOGICAL EFFECTS

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 increase 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.

Figure 1. Mean data for nicotine blood plasma (A) and heart rate (B) as a function of condition and time. X-axes, time in minutes relative to product administration; arrows, first and second product administrations. Y-axes, A, nicotine blood plasma concentration (ng/mL); B, heart rate (beats per minute); filled symbols, significant difference from baseline. An "a," "b," or "c" indicates that own brand was significantly different from sham, Hydro EC, or NPRO EC at that time point. A "d" indicates that Hydro EC was significantly different from sham at that time point. An "e" indicates that NPRO EC was significantly different from sham at that time point (Tukey's HSD, $P < 0.05$). Unidirectional error bars, 1 SE.



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.

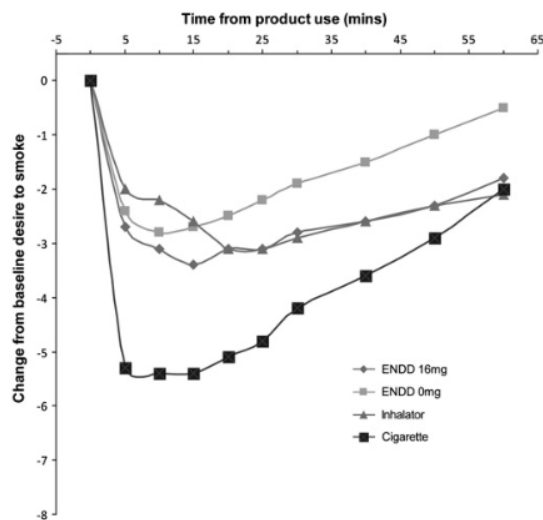


Figure 2 Change in desire to smoke from baseline over the first hour after each product use.

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 = 2ng/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 form the original article below). During ad lib puffing, heart rate increased from an average of 73.2(SD=2.0beats 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.

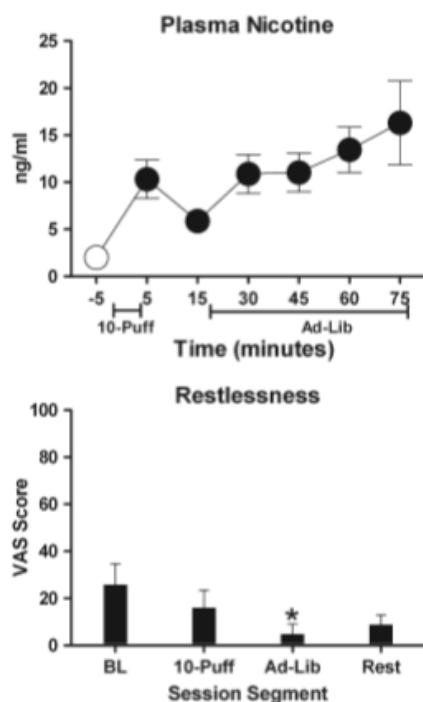


Figure 1. Top panel: $M (\pm 1 SEM)$ plasma nicotine (assay's limit of quantitation = 2 ng/ml; Breland, Kleykamp, & Eissenberg, 2006) levels at baseline (–5) and during the 10-puff and 1-hr ad lib puffing periods. Filled symbols indicate a significant difference from baseline. Bottom panel: $M (\pm 1 SEM)$ response to a visual analogue scale item assessing “restlessness” (0–100 scale) at baseline and the end of the 10-puff, ad lib, and rest periods. An asterisk indicates a significant difference from baseline. Data are from eight electronic cigarettes (EC) using participants who abstained from ECs for at least 12 hr before session. Paired t tests were used to compare means, $p \leq .05$.

Abuse Liability

Vansickle 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 (Vansickel et 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 generalizeability 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. (Hua, Alfi et al. 2013) 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.

Comment [KB7]: Suggest to add a sentence on the weaknesses of such a study (relies on self-reported data, no verification, causal association between symptoms reported and e-cigarette usage unclear)

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 Caponnetto et al (2013) with 14 smokers with schizophrenia not intending to quit in the next 30 days.(Caponnetto, 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.

Caponnetto 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.(Caponnetto, 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 $\geq 50\%$ 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%).

Comment [KB8]: Could you please clarify whether this abstinence is from cigarettes only or from both cigarettes and the replacement (e-cig., patch)? How many switched from cigarettes to e-cigarettes?

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, Capponnetto, 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)

Comment [KB9]: Interpretation of results should be more balanced as it focuses here mostly on the lack of a significant difference of effectiveness between e-cigs with and without nicotine and nicotine patches (where e-cigarettes score better than patches even though the difference is not-significant). However, Bullen et al. conclude that "E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events". Likewise, proponents of e-cigs would most likely focus on the contribution of e-cigs to quitting, as the chance of quitting has been shown to be better than with an established therapy (patches).

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

Comment [KB10]: Please clarify what is meant by “draft TPD”. What is called “draft TPD” in this paragraph seems to represent the amendments proposed by the European Parliament. However, this draft represents the position of only one of the three EU institutions. Moreover, the proposal is still subject to ongoing negotiations. While it is of interest to receive specific recommendations on regulatory approaches and also an overview on the state of regulations in place in the different jurisdictions, I wonder if it is the purpose of this document to present views on ongoing regulatory discussions.

Comment [KB11]: This wording conveys the (wrong) impression that the EU is considering e-cigarette an effective cessation aid, while the wording proposed by the European Parliament only refers to their potential.

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.

Comment [KB12]: This is not an Article of the proposed Directive but a chapter of the Explanatory Memorandum accompanying the legal proposal of the European Commission

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 as medicines or consumer products), or even if they would be allowed to be sold separately.

Comment [KB13]: Please consider that the EU has limited competencies for some of the issues mentioned (e.g. regulation on access to products)

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.

([http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(02\)08275-2/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)08275-2/abstract) and <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000202>)

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 its 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 to 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-phenoxyphenoxy) 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 announced 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 of 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.

<http://www.fda.gov.ph/attachments/article/80233/FA2013-015.pdf>

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.

Comment [KB14]: Could you please clarify what is meant by "disease burden caused by nicotine addiction"

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 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.

Comment [KB15]: Sentence not entirely clear. If conventional cigarettes were banned then (legal) dual use is of course no longer possible but if only their nicotine content was regulated, this conclusion is not so obvious. Furthermore it is not fully clear on what grounds this conclusion is drawn. Why would users switch to e-cigarettes, if they are equally taxed and restrictively marketed as normal cigarettes and if their use in public places was also banned ?

- 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.

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Table 1. Prevalence of e-cigarette use in various countries as measured by population-based surveys

Authors	Country, sample description, n	Ever use among general population (%)					Ever use among smokers (%)			
		2009	2010	2011	2012		2009	2010	2011	2012
Regan et al 2013	U.S., Adults 18+, n=10587 (2009); n= 10328 (2010), ConsumerStyles nationally-representative survey	0.6	2.7	--	--		Not reported	18.2	--	--
King et al 2012	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	--	2.1 mail, 3.3 online	6.2 online	--		--	6.8 mail, 9.8 online	21.2 online	--
Pearson et al 2012	U.S., Adults 18+ , 2 samples									
	Nationally-representative online sample (Knowledge Networks), 2010, n=2649	--	3.4	--	--		--	11.4	--	--
	Legacy Longitudinal Study of Smokers (smokers and former smokers), 2010, n=3648	--	--	--	--		--	6.4	--	--
McMillen et al 2013	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	--	1.8	--	--		--	14.4	--	--
Dockrell et al 2013	U.K., Adults 18+, nationally-representative online panel (YouGov), 2010: n=12597 adults; 2010 n=12432	--	--	--	--		--	2.7	--	6.7
Adkison et al 2013	ITC 4-country survey, Adults 18+,* July 2010-June 2011*									
	U.S. (n=1520)	--	--	--	--			20.4		
	Canada (n=1581)	--	--	--	--			10.0		
	U.K. (n=1325)	--	--	--	--			17.7		

	Australia (n=1513)	--	--	--	--			11.0		
Popova and Ling 2013	U.S., Adults 18+, nationally-representative online sample (Knowledge Networks), current and former smokers, n=1836	--	--	--	--		--	--	20.1	--
Cho 2011	Korea, Adolescents, middle school and high school, n=4,341, national survey of in 2008*	0.5*	--	--	--		--	--	--	--
Lee et al 2013 (under review)	Korea, Adolescents, 12-19,									
CDC NYTS 2013	U.S., Adolescents, middle and high school, 2011, 2012 (n's not reported)	--	--	MS: 1.4 HS: 4.7	MS: 2.7 HS: 10.0		--	--	--	--

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A Summary Report of *Smokeless Tobacco and Public Health:* *A Global Perspective*

**Prepared for the World Health Organization by the National Cancer
Institute**

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Introduction

Smokeless tobacco (ST) products present a complex and widespread challenge to public health that has so far received limited attention from researchers and policymakers. In many regions of the world, such as in India, ST use is the predominant form of tobacco use. Indeed, data from the Global Youth Tobacco Survey show that students aged 13–15 surveyed in 132 countries were more likely to report using non-cigarette tobacco products including ST products (11.2%) than to report smoking cigarettes (8.9%) (CDC 2006). Yet international tobacco control efforts have focused largely on cigarettes, devoting only limited attention to other types of products, including ST.

The Global Challenge

The serious health effects of ST have been documented. A 2004 IARC review found that there is sufficient evidence, based on epidemiologic and laboratory studies, to conclude that ST causes oral cancer, esophageal cancer, and pancreatic cancer in humans (Cogliano et al. 2004; IARC 2004). At least 28 carcinogens have been identified in ST products, including tobacco-specific nitrosamines (TSNAs), which cause tumors affecting the nasal cavity, lung, trachea, pancreas, liver, and esophagus in animal models (NCI 1992). ST use is also a cause of adverse oral health outcomes including oral mucosal lesions, leukoplakia, and periodontal disease (Shulman et al. 2004, Fisher et al. 2005). Additionally, ST products contain nicotine, and users of ST products demonstrate signs of dependence similar to those of cigarette smokers, including tolerance with repeated use and symptoms of withdrawal upon cessation of use (Henningfield et al. 1997).

Although ST use, like tobacco smoking, causes serious health damage, ST use poses substantial challenges for science and public health that are distinct from those presented by tobacco smoking:

1. Wide Range of Products in Use

Understanding the use and impact of ST products is complicated by the diversity of products and related behaviors that exist. A wide range of ST products with different characteristics are in use around the world, including chewing tobacco, snuff, gutka, betel quid with tobacco, snus, toombak, iqmik, tobacco lozenges, and others. Yet limited data are available on the properties of these products, how they are used, and their prevalence within different population groups. This diversity makes it difficult to generalize about these products as a class. Additionally, the ways in

32 which these products are produced, sold, used, and controlled (such as through taxes or
33 marketing restrictions) differ widely across countries and regions.

34 **2. Complex and Limited Data**

35 In addition to the known biologic effects of ST, the overall public health impact of ST use
36 depends on a range of health and environmental factors, including the prevalence and patterns of
37 use of different products in the population, the impact of marketing messages, and the
38 effectiveness of prevention and cessation efforts. While certain groups have been identified as
39 being at increased risk for ST use, limited data are available on why particular populations begin
40 to use ST and what factors are most important in preventing or promoting initiation of ST use.

41 **3. Novel Products and Marketing**

42 Tobacco manufacturers have introduced a new generation of ST products that may have broad
43 consumer appeal due to use of attractive flavorings, such as mint or fruit flavors, and new
44 delivery methods, such as lozenges or small pouches that eliminate the need to spit. Major
45 multinational cigarette companies Philip Morris and R.J. Reynolds have introduced snus
46 products carrying the well-known Marlboro and Camel brand names, thereby putting the
47 marketing expertise of these companies to work in the service of ST products. Tobacco control
48 experts warn that increased marketing of these products may have an adverse impact on
49 population health by appealing to young, new users or by helping current smokers maintain their
50 nicotine dependence (Henningfield et al. 2002). Novel nicotine delivery devices, such as
51 electronic cigarettes, which use heat, rather than combustion, to release a vapor containing
52 nicotine are also being marketed in many countries as an alternative to conventional cigarettes.
53 These products are not addressed in this report, but they may also have an important impact on
54 patterns of tobacco use behavior (WHO 2009).

55 Some tobacco companies have also responded to the tremendous growth in smoke-free indoor air
56 laws by advertising ST products to smokers as a temporary alternative to cigarettes for situations
57 where they cannot smoke, using slogans such as “Enjoy tobacco inside the office? You bet” and
58 “Enjoy tobacco on a 4-hour flight? You bet” (O’Hegarty et al. 2007). In addition to increasing ST
59 use, this marketing strategy may impede smoking cessation efforts by making it easier for
60 smokers to maintain their nicotine addiction between cigarettes. This is an example of how
61 progress made in one area of tobacco control, such as through smoke-free indoor air laws, has

been followed by tobacco manufacturers' efforts to adapt, this time by introducing new products and marketing strategies.

4. Impact on Youth and Development of Ongoing Tobacco Use Behaviors

The potential for increased initiation of ST use among youth also poses a major, ongoing public health challenge. This increased initiation may be caused by increased marketing and the introduction of new flavored products. Indeed, ST use among teens and young adults rose substantially in the United States during the 1970s after the introduction of products that were more accessible to new users (Connolly 1995). These products had lower nicotine content and attractive flavorings, and evidence suggests that users who begin with low-nicotine "starter" products are more likely to subsequently "graduate" to products with higher nicotine content (Tomar et al. 1995). Moreover, a number of studies suggest that ST use is associated with and reinforces use of other tobacco products, including cigarettes. Thus, adolescents who use ST products may also be more likely to move on to cigarette smoking (Hatsukami et al. 2004, Tomar 2003).

5. Limited Treatment Options

Intervention strategies for ST use cessation have had mixed success. Clinical trials have shown that behavioral interventions in particular settings, such as in dental offices, may increase abstinence rates among ST users, although the available evidence is insufficient to support recommendations about the specific intervention components that should be applied (Carr and Ebbert 2006, Severson 2003). In contrast, trials of pharmacotherapies in ST users, including nicotine patch, nicotine gum, and bupropion, have shown no impact on long-term (>6 months) abstinence rates (Ebbert et al. 2004). Some individual study results suggest that pharmacotherapies may help reduce symptoms associated with cessation, such as craving and weight gain, but such symptom reduction has not been shown to have any impact on cessation outcomes (Dale et al. 2007). Moreover, evidence suggests that people who use both cigarettes and ST demonstrate higher nicotine exposure levels and find cessation more difficult to achieve than those who only use ST or those who only smoke (Hatsukami and Severson 1999, Wetter et al. 2002, Spangler et al. 2001).

6. Tobacco “Harm Reduction”

The response to the hazards of ST use is complicated by discussions about the possibility of using ST as a means of harm reduction for cigarette smokers. Some scientists have suggested that ST use may actually reduce harm to smokers by providing an alternative to cigarettes—that is, smokers who switch completely to ST, which does not carry the same risk of lung cancer and respiratory diseases as cigarette smoking, might reduce their overall risk. While smokeless tobacco also causes cancer and other diseases, the overall health risks for a lifetime smokeless tobacco user may be lower than those for a lifetime cigarette smoker.

This inference requires a number of assumptions, however. Given the tremendous diversity of ST products and patterns of use around the world, it is difficult to support broad generalizations about the level of harm associated with ST products as a category. Little is known about the constituents of some ST products or the exposures users receive from them. Will smokers who begin using ST products completely replace their cigarettes, or will they instead become dual product users, which may not yield any health benefit and could potentially increase their risk? Additionally, it is essential to consider the overall population-level impact of increased ST use. For example, will increased promotion of ST products lead to an increase in tobacco use initiation or have an adverse impact on smoking cessation efforts? While the body of evidence on this topic is expanding, definitive studies to answer key questions are lacking. In short, there remain more questions than answers.

Discussions regarding harm reduction have been limited primarily to high-income countries with a long history of tobacco control measures and where cigarette smoking is the predominant form of tobacco use, such as in North America and Western Europe. Because tobacco products, patterns of use, disease profiles, and policy regimes vary so widely across regions, the relevance of these discussions for other regions are limited and are not explored in this report.

Summary and Major Conclusions

The report that follows summarizes current knowledge regarding the properties and characteristics of smokeless tobacco products, followed by a series of regionally-focused chapters that specifically address the context of tobacco use and the existing tobacco control policy and intervention landscape by region. The final section of the report provides some cross-regional observations regarding product characteristics, health effects, industry strategies, and

120 tobacco control measures. This final section also make recommendations regarding information
121 needs and best practices for ST control.

122 Key conclusions from the report are highlighted here:

- 123 • ST is a global problem that is present in at least 70 low-, middle-, and high-income countries
124 and affects more than 300 million people. The greatest burden from ST use is in the South-
125 East Asia Region, which experiences the highest prevalence of ST use (including the
126 majority [89%] of users), carries the highest attributable disease burden, and has the greatest
127 diversity in product types and forms of use. ST use is highly prevalent in India, where it
128 exceeds cigarette smoking among both men and women.
- 129 • The magnitude of disease risks directly associated with ST use appears to differ across
130 countries and regions, likely due in part to differences between ST products and patterns of
131 use. Laboratory analyses have shown widely varying levels of known carcinogens and
132 nicotine in ST products from different regions. And epidemiologic studies of ST users in
133 different regions have reached varying risk estimates for cancer and cardiovascular disease
134 from country to country. Yet data to precisely quantify these differences in disease risk and to
135 identify the factors that drive them are lacking.
- 136 • ST use and marketing present distinct public health challenges in different countries and
137 regions. In particular, there is a divide between some high-income countries (such as in
138 Scandinavia) with high prevalence of low-nitrosamine ST use, reductions in smoking
139 prevalence, and strong tobacco control and regulatory frameworks, and low- or middle-
140 income countries (such as India) where ST products are associated with very high levels of
141 harmful constituents, where marketing of cigarettes is increasing, and a large unorganized
142 business sector makes product control and regulation extremely challenging. Changes in
143 product marketing, patterns of use, and tobacco control programs and interventions may have
144 very different results in these different environments.
- 145 • Changing tobacco industry marketing strategies may influence the future public health
146 impact of ST use. In some high-income countries where restrictions on public smoking have
147 increased and smoking prevalence has decreased, tobacco companies have marketed oral

tobacco products to smokers. However, the impact of this trend on smoking behavior, and possible dual or poly-tobacco use, remains uncertain. At the same time, multinational tobacco companies have an increasing presence among low- and middle-income countries with both smoked and smokeless products.

- In many regions, even those where ST use is highly prevalent, policies and programs aimed at ST use prevention and cessation are generally weaker than those existing for smoked tobacco products: prices are lower, warning labels are weaker, surveillance is less developed, fewer proven interventions are available, and fewer resources are devoted to prevention and control programs.

- Significant challenges exist in monitoring the use and health effects of ST. These challenges include the diversity of ST products and their use, the lack of information to characterize products and manner of use, the informal, unorganized nature of the ST market in some regions, and the limited attention given to tailored educational and intervention programs.

- A wide range of research gaps remain for ST products, including lack of surveillance data, characterization of diverse ST products, health consequences from use of different products, including fetal exposure and reproductive outcomes, better understanding of the economic policies surrounding ST products and their use, and effective region-specific ST education, prevention, and treatment interventions.

- A range of different policies have been proposed or implemented for ST products in some countries, but data are often lacking on their impact or effectiveness. Greater attention is needed to strengthen the use of evidence-based policies for control of ST use, which could include: having tobacco industries disclose the contents of ST products; establishing performance standards for toxicants and maximum pH levels; banning flavorants; establishing effective and relevant health warning labels; increasing taxes on ST products; banning or restricting ST promotions, sponsorship, or marketing; and raising public awareness of the toxicity and health effects of ST products. In sum, prevention and cessation of ST use should form an integral part of any comprehensive tobacco control effort.

- 175 • Capacity for research and public health action around ST is limited in many countries,
176 especially those where the public health burden is greatest. Development of international
177 infrastructure for research and information sharing could enhance the ability of many
178 countries to reduce the consequences of ST use. International collaboration and shared
179 capacity building could include the following: (a) creating regional but globally accessible
180 information clearinghouses for ST; (b) strengthening infrastructure for networking,
181 communication, and collaboration; (c) building collaborations across disciplines and
182 professions (e.g., scientists with policymakers and tobacco control advocates); and (d)
183 developing ways to build research capacity by leveraging existing resources.

184

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238 **Global Smokeless Tobacco Products**

239 **Introduction to Global Smokeless Tobacco Products**

240 Unlike smoked tobacco, which is burned or heated and then inhaled in products such as
241 cigarettes and cigars, or via hookahs, smokeless tobacco (ST) is predominantly used orally
242 (chewed, sucked, dipped, held in the mouth, etc.) or nasally, which results in absorption of
243 nicotine and other chemicals across mucus membranes (Boffetta et al. 2008). Smokeless tobacco
244 products are used in a wide variety of forms with differing ingredients, composition, and toxic
245 emissions (SCENIHR 2008; IARC 2004; IARC 2007).

246 Worldwide, ST products range in complexity from simple cured tobacco to elaborate products
247 with added flavorings and, in some cases, non-tobacco plant material that may affect the
248 attractiveness, addictiveness, and toxicity of the products (SCENIHR 2008; IARC 2007; IARC
249 2004). Preparation, ingredient selection (including non-tobacco plant materials), and mode of use
250 (oral, nasal, etc.) can vary based on geographic locality, ingredient availability, cultural/societal
251 norms, and personal preferences (Boffetta et al. 2008; SCENIHR 2008; IARC 2004; IARC
252 2007).

253 **Product Preparation**

254 ST can be broadly divided into premade and custom-made products (please refer to table on the
255 next page). Premade ST products, which are manufactured for sale and generally consumed as
256 purchased (i.e., “ready-to-use”), can be subdivided into: (1) commercial products (i.e., moist
257 snuff, snus, khaini) that are made in traditional manufacturing settings such as factories or
258 production facilities; and (2) cottage industry products (i.e., toombak, nasway, mainpuri, mawa)
259 that are made on a smaller scale in nontraditional production environments (market stalls, shops,
260 houses, etc.) and often sold in noncommercial packaging (paper or plastic bags; wrapped in
261 paper) (IARC 2004; IARC 2007; SCENIHR 2008).

262 **Characteristics and product examples of premade and custom-made smokeless tobacco products**

Premade		Custom-made
Manufactured	Cottage industry	Vendor/individual
<ul style="list-style-type: none"> • Made in advance for sale • Made in a manufacturing environment • Sealed in labeled commercial packaging 	<ul style="list-style-type: none"> • Made in advance for sale • Usually handmade in nontraditional environments • Often sold in noncommercial packaging 	<ul style="list-style-type: none"> • Made by a vendor or individual according to user preferences, generally for immediate consumption • Involves mixing two or more components (including premade products) together by hand to form a final product
Product examples: <ul style="list-style-type: none"> • Chewing tobacco (plug/twist/loose leaf) • Creamy snuff • Dissolvables • Dry snuff • Gudahku/Gudahka • Khaini • Moist snuff • Kiwam • Rapé • Red toothpowder 	Product examples: <ul style="list-style-type: none"> • Dohra • Gutka • Mainpuri • Nass/Naswar • Nasway • Betel quid (paan) • Rapé • Shammah • Toombak • Tu bur 	Product examples: <ul style="list-style-type: none"> • Gudahku/Gudahka • Iqm k • Nass/Naswar • Nasway • Betel quid (paan) • Rapé • Shammah • Tapkeer • Tobacco leaf • Tombol • Toombak Some premade ingredients are used to make custom-made products: twist, zarda, toombak, gudahku/gudahka, and kiwam.

263 Premade manufactured ST products are available in a wide variety of physical forms, including
 264 but not limited to, twisted tobacco leaves, loose tobacco, ground tobacco, dry tobacco (dry
 265 snuff), tars (chimó), pastes (kiwam), dentifrices (creamy snuff, toothpowder), tobacco-containing
 266 chewing gums, and mixtures of tobacco and other materials (zarda, gutka) (SCENIHR 2008;
 267 IARC 2004; IARC 2007; Swedish Match 2006). Manufactured ST products, such as moist snuff
 268 and snus, are available as loose tobacco or tobacco sealed in porous teabag-like sachets, which
 269 are easily inserted and removed from the mouth. Release of nicotine and presumably other
 270 compounds is greater from loose tobacco than from sachets (Nasr, Reepmeyer and Tang 1998).

271 Increasingly, new varieties of manufactured smokeless products made with the smoker in mind
 272 appear in a discrete, spit-less form that can be used where smoking is prohibited or socially
 273 inappropriate (Carpenter et al. 2009). Since 2001, several tobacco companies, including those
 274 that have traditionally marketed cigarettes, have been introducing dissolvable ST products, which
 275 are made from finely milled tobacco pressed into tablets, sticks, or flat strips that fully dissolve
 276 in the mouth (Connolly et al. 2010; Rainey et al. 2011; Stepanov et al. 2012). Novel products

introduced after about 2010 include tobacco-coated toothpicks, which are sucked on to release nicotine (Seidenberg et al. 2012), and an “energy-enhanced” ST product called Revved Up, made by Southern Smokeless, which is essentially moist snuff augmented with energy drink constituents (Southern Smokeless Tobacco Company 2012). Altria introduced a nicotine disk product called Verve in Virginia in 2012. The chewable disc, which is made of cellulose fibers and a polymer, is impregnated with flavor and nicotine. The disc does not dissolve, but is chewed for about 15 minutes and then discarded (Lawson 2012). Although many novel ST products are not yet widely distributed, they are part of an increasing trend in the development of diverse, new forms of ST products intended to appeal to both smokers and ST users alike.

Premade cottage products can be in the form of pressed cakes (mawa), pellets (nasway), or pulverized tobacco (toombak, shammah), among others. Some premade products are used as the tobacco ingredient in custom-made products; for example, manufactured products (e.g., zarda and kiwam) or cottage products (e.g., mainpuri and toombak) can be used as the tobacco ingredient in betel quid and tombol. The “tobacco ingredient” in products such as mainpuri and toombak may already be mixtures of tobacco with other ingredients such as areca nut, alkaline agents, spices, and silver flakes (IARC 2007; SCENIHR 2008).

Custom-made products, handmade by the user, a relative, or a vendor according to user preferences, are characteristic of smokeless tobacco use in South Asia and Africa, as well as other defined regions with a tradition of smokeless tobacco use, such as Alaska and Brazil. Custom-made products such as tombol and betel quid (also known as paan) are made by combining cured tobacco or a premade tobacco product (e.g., zarda) with one or more ingredients, such as ashes, alkaline agents, areca nut, spices, catechu, or other plant materials (Bhonsle et al. 1990). Spices, for example, can be selected and added to meet the customer’s preferences.

Tobacco Types

Approximately 70 species of tobacco (*Nicotiana*) occur naturally, although few are regularly used for smoked or ST products (Lewis and Nicholson 2007; IARC 2007). The identity of different tobacco species in products can be determined by a chemical analysis of the levels of nicotine and other tobacco alkaloids (Sisson and Severson 1990) and confirmed using infrared analysis (Stanfill et al. 2011). Most commercial tobacco products worldwide contain the species

307 *Nicotiana tabacum* (cultivated tobacco), but *N. rustica* is also frequently grown and used in
308 regions of South America, Africa, and Asia (Lewis and Nicholson 2007; IARC 2007). In India,
309 smoking tobacco tends to be made with *N. tabacum*, but most ST contains *N. rustica*, which has
310 higher concentrations of nicotine and other alkaloids than *N. tabacum* (Bhide et al. 1987, 1989;
311 WHO 2004). Some products, such as khaini and kiwam from South Asia, may contain both *N.*
312 *rustica* and *N. tabacum* (IARC 2007). *N. rustica* is also contained in some forms of naswar,
313 Bangladeshi tobacco leaf, Indian chewing tobacco, maras, zarda, and toombak (Idris et. al 1991;
314 Stanfill et al. 2011; IARC 2007; WHO 2004). Smokeless tobacco products such as toombak may
315 contain *N. glauca* (tree tobacco) (IARC 2007; Steenkamp et al. 2002), which has high levels of
316 the alkaloid anabasine; ingestion of this form of tobacco has been linked to accidental poisoning
317 and fatality in a few cases (Steenkamp et al. 2002; Furer et al. 2011).

318 **Changes in Chemical Composition of Tobacco**

319 ***Alkaloid Formation and Cultivation***

320 As tobacco grows, it absorbs metals, metalloids (Pappas 2011), and nitrate from the soil (Burton
321 et al. 1989a; Burton et al. 1989b) and synthesizes alkaloids, including nicotine and minor
322 alkaloids (e.g., nornicotine, anabasine, and anatabine) in various concentrations, depending on
323 species and variety (Sisson and Severson 1990). Alkaloids are key chemical precursors in the
324 formation of tobacco-specific nitrosamines (TSNAs) (Hecht et al. 1974; Hecht et al. 1978;
325 Spiegelhalder and Fischer 1991), some of which are potent carcinogens (IARC 2007; Hecht
326 1998).

327 Tobacco nitrate content and the presence of certain microorganisms on tobacco leaves contribute
328 to the formation of TSNAs from alkaloids (Fisher et al. 2012). During cultivation,
329 microorganisms (yeast, mold, fungi, and bacteria) and agricultural chemicals can be deposited on
330 tobacco plants. At harvest, tobacco is not generally washed, thus leaves with deposited
331 microorganisms and agricultural chemicals will be processed and the contaminants will be
332 present in the final product. During the subsequent curing step, the tobacco leaves dry, and
333 bacteria, which proliferate to levels 10 to 20 times higher than on the growing leaf (Wiernik et al.
334 1995), begin converting the nitrate (NO_3^-) present in the plant tissue to nitrite (NO_2^-), a process
335 called nitrate reduction. Once nitrite is produced, a chemical process of nitrosation occurs in
336 which nitrite reacts with tobacco alkaloids to generate TSNAs (Djordjevic et al. 1989). Amine

compounds other than tobacco alkaloids can also react with nitrite to form nonvolatile *N*-nitrosamines, volatile nitrosamines, and *N*-nitrosamino acids (SCENIHR 2008; Hoffmann et al. 1995). The International Agency for Research in Cancer (IARC) has classified various nitroso compounds as IARC Group 1 (carcinogenic to humans), 2A (probably carcinogenic to humans), or 2B (possibly carcinogenic) agents (IARC 2012b). The IARC has also classified nitrate and nitrite as Group 2A agents (IARC 2010) because of their potential to form nitroso compounds in the human body after ingestion. There are indications that additional amounts of nitrosamines can be formed in the mouth during ST use (Nair et al. 1987).

Curing

Prior to use in products, tobacco is dried using sun, air, flue, or fire curing. Any given ST product can be produced using various tobacco-curing methods, depending on the manufacturer. The simplest method of tobacco processing is sun curing, the process of drying tobacco leaves in the sun, which is often used in making toombak, gutka, maras, khaini, and nass/naswar; some tobaccos used in betel quid are also sun cured (IARC 2007). Air curing, which involves placing tobacco stalks on wooden staves that are hung in a well-ventilated barn, is usually used in loose leaf and twist chewing tobaccos and moist snuff (Peedin 1999; IARC 2007). Flue curing involves hanging tobacco in an enclosed structure connected to an external heat source without exposing the tobacco directly to smoke (Peedin 1999; Fisher et al. 2012); this method is often used in making chewing tobacco. During fire curing, tobacco is hung in a large enclosed barn and exposed to smoke from hardwood fires that are continuously burning or smoldering, a process directly analogous to producing smoked meat (Miller and Fowlkes 1999). Fire-cured tobacco is used in the production of plug chewing tobacco, moist and dry snuff, and iqmik (Peedin 1999; IARC 2007; Hearn et al. 2013). Fire curing not only causes chemical changes in the tobacco leaf, it also contaminates the tobacco with smoke-related chemicals. As a result, the levels of polycyclic aromatic hydrocarbons (PAHs), phenols, and volatile aldehydes tend to be higher in fire-cured tobacco than air-cured tobacco (Bhide et al. 1987, 1989; Hearn et al. 2013; Leffingwell 1999).

Fermentation/Aging

Fermentation and aging of tobacco are common in the production of tobacco used in cigars (Di Giacomo et al. 2007) and ST (e.g., moist and dry snuff, toombak, taaba) (IARC 2007; Fisher et al. 2012; Tso 1999). During fermentation or aging, the tobacco takes on a more agreeable flavor

368 (Tso 1999). For manufactured products, fermentation can occur in a partially insulated tank
369 (Fisher et al. 2012), which, because of increased microbial activity, can reach high temperatures
370 (up to 65°C) (Di Giacomo et al. 2007). Fermentation of toombak, a cottage industry product,
371 occurs in a closed container at 30 to 45°C for a few weeks, then the tobacco is aged for a year
372 (IARC 2007).

373 Tobacco fermentation involves chemical and biochemical changes (bacteria-mediated reactions)
374 (IARC 2007; Di Giacomo et al. 2007; Fisher et al. 2012). During fermentation, a portion of
375 nitrate in fire-cured tobacco is converted to nitrite, which then reacts with alkaloids to produce
376 TSNA (Di Giacomo et al. 2007; Fisher et al. 2012).

377 During one fermentation study, nitrite levels generated by bacteria resulted in an almost threefold
378 increase in TSNA levels (Di Giacomo et al. 2007). In tobacco or tobacco products, a number of
379 bacteria species have been identified that are capable of converting nitrate to nitrite (nitrate
380 reduction) (Di Giacomo et al. 2007; Sapkota et al. 2010; Ayo-Yusuf et al. 2008; Bao et al. 2013;
381 Winn and Koneman 2006; Cockrell et al. 1989; Fisher et al. 2012). Additionally, several genera
382 of fungi are capable of nitrate reduction (Wahlberg et al. 1999; Pauly and Paszkiewicz 2011; Di
383 Giacomo et al. 2007; Cockrell et al. 1989). Throughout production, the combined capacity of
384 product microorganisms to generate nitrite is a key determinant of the levels of TSNA and other
385 nitrosamines in the final product (IARC 2012a; Brunnemann et al. 1996).

386 Pasteurization, or heat treating, of tobacco is a very effective means of eliminating
387 microorganisms during ST production, and thus preventing the reduction of nitrate to nitrite
388 (Rutqvist et al. 2011). Indeed, Swedish snus, a pasteurized product, generally has lower nitrite
389 and TSNA levels than nonpasteurized products, such as moist snuff and khaini (Stepanov et al.
390 2008; Stepanov et al. 2005). It has also been shown that the additional formation of nitrite and
391 TSNA levels can be prevented by cleaning fermentation equipment before use and “seeding” the
392 fermentation process with non-nitrate-reducing bacteria (Fisher et al. 2012). Together, these
393 observations provide additional support for the idea that the levels of some carcinogenic and
394 toxic agents in tobacco products can be substantially reduced by changing tobacco processing
395 methods.

396 Following fermentation, tobacco may still contain substantial amounts of nitrate, nitrite, and
397 bacteria (such as *Bacillus* spp.) that are active across a wide temperature and pH range
398 (Rubinstein and Pederson 2002; Di Giacomo et al. 2007; Fisher et al. 2012). Moreover, moist
399 snuff products, including South African smokeless tobacco, contain nitrate, nitrite, and viable
400 nitrite-producing bacteria (e.g., *Bacillus* spp.) (Rubinstein and Pederson 2002; Ayo-Yusuf et al.
401 2008; Stepanov et al. 2008). Various strains of bacteria have also been found to directly produce
402 infections, inflammation and periodontal abscesses. (Sapkota et al. 2010; Ayo-Yusuf et al. 2008).
403 Although conditions in ST products are favorable for the presence of bacteria, it is not known
404 which strains of bacteria are most common in ST products.

405 Products from India, such as zarda, mishri, gutka, creamy snuff, and toothpowder, have elevated
406 nitrate levels but lower levels of nitrite. In contrast, Indian khaini contains higher levels of nitrite
407 and TSNA (Stepanov et al. 2005). The high levels of nicotine and other alkaloids in *N. rustica*
408 (Sisson and Severson 1990; Bhide et al. 1987) may contribute to extreme levels of TSNA such
409 as are found in the Sudanese product toombak (Idris et al. 1991; Stanfill et al. 2011).

410 Additives

411 **Flavoring Agents, Spices, Fruit Juices, Sweeteners, Salt, Humectants, Alkaline** 412 **Agents**

413 After curing, aging, and fermentation, further steps for manufacturing smokeless products
414 include cutting the tobacco to the proper width, adding other substances, and adjusting moisture
415 and pH levels (Dube et al. 2008). Manufactured ST products, particularly Western-style forms
416 (e.g., moist snuff, snus) are known to contain flavoring agents, spices, fruit juices, sweeteners,
417 salt, humectants, and alkaline agents (SCENIHR 2008; U.S. House of Representatives 1994;
418 Swedish Match 2012; R.J. Reynolds 2012; U.S. Smokeless Tobacco Company 2012; Phillip
419 Morris 2012). Flavorings used include cocoa, licorice, rum, spice powders, extracts, oleoresins,
420 individual flavor compounds (e.g., menthol, vanillin, etc.), and more than 60 different essential
421 oils (e.g., wintergreen, cinnamon, ginger) (SCENIHR 2008; U.S. House of Representatives
422 1994). The most common flavor chemicals detected in 85 brands of ST, primarily moist snuff,
423 were methyl salicylate, ethyl salicylate, benzaldehyde, citronellol, menthol, nerol, menthone, and
424 caryophyllene (Stanfill 2009). Among many mint and wintergreen moist snuff brands, Chen and
425 colleagues (2010) found high levels of methyl salicylate (18.5–29.7 milligram per gram [mg/g]),

ethyl salicylate (0.17–5.78 mg/g), and menthol (undetectable–5.25 mg/g). Sweeteners added to ST include honey, molasses, saccharin, brown sugar, sugar, and xylitol. Humectants, which are added to maintain product moisture, include agents such as glycerol, glycerin, and propylene glycol (U.S. House of Representatives 1994; SCENIHR 2008; Swedish Match 2012). Dissolvable tobacco products include ingredients such as flavorings, sweeteners, humectants, and alkaline agents, as well as fillers, coatings, binders, colorings, and preservatives (R.J. Reynolds 2012; U.S. Smokeless Tobacco Company 2012; Phillip Morris 2012).

Cottage ST products made in the Eastern Mediterranean region, Africa, and South-East Asia may contain ingredients such as edible oils, metallic silver, potassium nitrate, and soil.

Alkaline modifiers used in manufactured ST products are predominantly chemicals including sodium bicarbonate, ammonium bicarbonate, various metallic carbonates (calcium, sodium, and ammonium), and slaked lime (calcium hydroxide) (SCENIHR 2008; U.S. House of Representatives 1994). Chemical alkaline agents (mostly slaked lime or sodium bicarbonate) are also used in the preparation of cottage products (e.g., toombak, nass, shammah) or custom-made ST (iqmik). In some rural or tribal areas, custom-made or cottage industry ST products are prepared with ashes from the burning of certain woods, plants, or fungi (for example, wood: willow, mamón, paricá; plants: *Aloe vera*, *Amaranthus*, grapevine; fungi: punk fungi [*Phellinus igniarius*]), which significantly increases product pH (IARC 2007; Renner et al. 2005; Blanchette et al. 2002). Unlike rapé products that are mildly acidic, the type of rapé used by the Kaxinawás Indians, who live in eastern Peru and in the States of Amazonas and Acre in Brazil, includes ashes from the paricá tree (*Schizolobium amazonicum*) (Lagrou 1996). Products that contain alkaline ashes, such as iqmik (Hearn et al. 2013) and nass (Brunnemann et al. 1985), have extremely high pH levels (\geq pH 11).

Non-Tobacco Plant Material

In several regions of the world, especially South Asia and the Eastern Mediterranean region, tobacco is commonly combined with substantial amounts of non-tobacco plant material. In those regions, several premade ST products (gutka, mawa, mainpuri, and some zarda products) and custom-made products (betel quid, dohra, tombol) contain areca nut, the seeds of the Areca palm (*Areca catechu*) (IARC 2004; IARC 2007; Stanfill et al. 2011; WHO 2004). Products in South Asia often contain appreciable amounts of spices or other plant materials such as betel leaf

(*Piper betle*) and catechu (*Acacia catechu*) (IARC 2004; IARC 2007; WHO 2004). Alternatively, packets containing non-tobacco condiments, such as supari or pan masala (a mixture of spices, flavorings, and other ingredients), can be purchased separately and combined with tobacco prior to use. In South Asian and Mediterranean countries, custom-made ST products, such as betel quid, dohra, or tombol, are often handmade from tobacco or premade ST (kiwam, zarda, toombak) combined with other ingredients, such as alkaline agents, areca nut, spices, condiments, or other plant material (such as coconut), and rolled in a betel leaf (IARC 2004; IARC 2007; SCENIHR 2008; WHO 2004). Some forms of tombol, such as those used in Yemen, contain khat (*Catha edulis*) (Dr. Ghazi Zaatari, personal communication), a plant that has psychoactive properties (Lee 1995). In South America, rapé and other indigenous forms of nasal ST used in Brazil and Peru contain tobacco mixed with ingredients such as tonka bean (*Dipteryx odorata*), cinnamon powder, clove buds, camphor, sunflower, Peruvian cocoa, and possibly cassava (Wilbert 1987; McKenna 1993; André Oliveira da Silva, personal communication).

Toxic and Carcinogenic Agents in Smokeless Tobacco Products

In general, tobacco contains roughly 4,000 chemical constituents (Rodgman and Perfetti 2009), including nicotine and other toxicants and carcinogens, which are believed to play a crucial role in causing the negative health effects associated with ST use (Khariwala et al. 2012; Yuan et al. 2012; Yuan et al. 2011).

Nicotine and Free Nicotine

Nicotine in tobacco products leads to addiction and persistent use of tobacco products, and thus continuous exposure to numerous toxic and carcinogenic agents, which results in devastating health consequences and premature deaths worldwide (DHHS 2004). Additionally, nicotine is a major precursor of carcinogenic NNK and NNN (IARC 2007). Nicotine has also been associated with fetal toxicity and an increase in cardiovascular risk factors (DHHS 2004).

In an ST product, the entire amount of nicotine present is referred to as total nicotine, which includes both free and bound nicotine. The fraction of nicotine present as free nicotine depends on the pH of the ST product: A higher pH means that a greater proportion of nicotine will be free nicotine, which is the most biologically available form (Tomar and Henningfield 1997; Henningfield et al. 1995; Fant et al. 1999; Djordjevic et al. 1995). Products with similar total

485 nicotine concentrations can contain a wide range of free nicotine concentrations, depending on
486 pH (IARC 2007; Richter et al. 2008).

487 Products with higher free nicotine concentrations generate faster spikes in blood nicotine
488 concentrations and could cause such products to be more addictive (Alpert, Koh and Connolly
489 2008; Henningfield, Fant and Tomar 1997). The addition of alkaline agents and the resulting pH
490 increase in some products may play a decisive role in the targeted delivery of free nicotine. The
491 availability of products spanning a wide pH range may make it easier for ST users to move on to
492 products with increasingly higher nicotine levels (i.e., the graduation strategy) (Alpert, Koh and
493 Connolly 2008; Connolly 1995).

494 The wide ranges of pH, total nicotine, and free nicotine levels among various products have been
495 clearly demonstrated in numerous studies (Brunnemann et al. 1985; Djordjevic et al. 1995;
496 Henningfield et al. 1995; McNeill et al. 2006; Gupta 2004; Richter et al. 2008; IARC 2007;
497 Stanfill et al. 2011; Stepanov et al. 2012; Hearn et al. 2013; Lawler et al. 2013; Zakiullah et al.
498 2012). Combined, these studies include more than 20 product types (e.g., zarda, chimó, gutka)
499 from 12 countries. Products with the lowest pH include chewing tobacco (Brunnemann 1985;
500 IARC 2007; Lawler et al. 2013) and some forms of dry snuff, zarda, and snus (Lawler et al.
501 2013; Stanfill et al. 2011). Toombak, khaini, chimó, naswar, tuiber (tobacco water), and some
502 varieties of African snuff and gutka have values generally between pH 8 to pH 10 (IARC 2007;
503 Gupta 2004; Brunnemann et al. 1985; McNeill 2006; Stanfill et al. 2011; Hearn et al. 2013;
504 Zakiullah et al. 2012); products such as iqmik and nass have the highest known values (pH 11.0
505 to pH 11.8) (Brunnemann et al 1985; Hearn et al. 2013). Products that have both high pH values
506 (due to alkaline agents) and contain the nicotine-enriched *N. rustica* can deliver extremely high
507 levels of free nicotine (Idris 1991; Brunnemann et al. 1985; Stanfill et al. 2011; Hearn et al.
508 2013), such as observed in toombak samples.

509 The wide variation of nicotine levels in various ST products used worldwide depends on the
510 method of tobacco curing (e.g., air cured, fire cured, or flue cured), variety within the type,
511 manufacturing techniques, and tobacco blending approaches used (Borgerding et al.1999; Burton
512 et al. 1992). The content of nicotine and other alkaloids in growing tobacco plants is affected by
513 numerous factors, including genetics, geographic location, climate, fertilization rates, stalk and
514 leaf position, and maturity of the leaf.

Tobacco-Specific Nitrosamines

TSNAs are commonly considered among the most potent carcinogens in all tobacco products (Hecht 1998; IARC 2007). A total of five TSNAs have been identified in ST products: *N*'-nitrosornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), *N*'-nitrosoanatabine (NAT), and *N*'-nitrosoanabasine (NAB). NNN, NNK, and NNAL are among the more common TSNAs and are the most carcinogenic (Hecht 1988; Hecht 1998). The carcinogenicity of NNN and NNK has been reviewed and established by IARC (IARC 2007) as a Group 1 carcinogen and believed to be involved in the induction of oral cancer (Hecht 1998). The pulmonary and pancreatic carcinogenicity of NNAL has been demonstrated in a few animal studies (reviewed in Hecht 1998). NNN, NNK, and NAT generally occur in greater quantities than the other TSNAs (Chamberlain et al. 1988; Hoffmann and Djordjevic 1997; Brunnemann et al. 2002; Österdahl et al. 2004; Stepanov et al. 2005; Stepanov et al. 2008; Richter et al. 2008; Stanfill et al. 2011; Hecht 1998).

Because of NNAL's potential for carcinogenicity, the levels of NNAL present are also important, but these have been reported in smokeless products only occasionally (Prokopczyk 1995; Djordjevic et al. 1993; Richter 2008; Stanfill et al. 2011). However, regardless of the sparse reporting, NNAL carcinogenicity should always be taken into consideration because it is metabolically formed from NNK in ST users. Moreover, NNAL is commonly utilized as a biomarker of exposure to carcinogenic NNK (Hecht 2007).

Worldwide, the use of different tobacco types, processing techniques, and tobacco blending approaches leads to wide variation of TSNA levels in various ST products. Several comparative international reports (Brunnemann et al. 1985; McNeill et al. 2006; Stanfill et al. 2011; IARC 2007) and individual studies on ST products used in different countries (Idris et al. 1991; Österdahl et al. 2004; Stepanov et al. 2005; Richter et al. 2008; Stepanov et al. 2012) provide an informative view of the variations in TSNA levels among countries and product types.

The most current and comprehensive analysis of international samples showed wide variation in TSNA levels in more than 53 products from 9 countries reported in 2011 (Stanfill et al. 2011). The concentration of total TSNAs (that is, the sum of NNK, NNN, NAT, NAB, and NNAL) in the products ranged from 0.084 to 992 µg/g. The highest NNK concentrations were found in

545 Sudanese toombak and dry zarda (Bangladesh) (3.84 µg/g). The highest NNN concentrations
546 were observed also in toombak (Sudan), dry zarda (Bangladesh), khaini (India), and handmade
547 gutka (India). Handmade gutka and mawa from Pakistan had the lowest NNK concentrations.
548 The study found that NNAL levels ranged from 0.004 to 6.77 µg/g, with the highest NNAL
549 concentrations in toombak, dry zarda, and khaini (Stanfill et al. 2011). Extremely high
550 concentrations of TSNA were found in saliva from toombak users (Idris et al. 1991, 1992,
551 1994). Given the high carcinogenic potency of NNN and NNK, it is not surprising that over 50%
552 of oral cancers in Sudanese men are attributed to the use of toombak or other oral products (Idris
553 et al. 1994, 1995; Ahmed et al. 2007; SCENIHR 2008).

554 **Metals and Metalloids**

555 Metals and metalloids are naturally present in tobacco, and amounts of these substances in
556 tobacco are influenced by soil pH, soil composition, and industrial contamination (Adamu et al.
557 1989; Mulchi et al. 1992). Smokeless tobacco products have been reported to contain detectable
558 levels of several metals that are classified as IARC Group 1 carcinogens (i.e., arsenic, beryllium,
559 chromium (VI), cadmium, nickel compounds, polonium-210) or Group 2B carcinogens (i.e.,
560 cobalt, lead) (IARC 2012a). A review of studies of ST products from Ghana, Canada, India, and
561 the United States found detectable concentrations of arsenic (0.1–3.5 µg/g), beryllium (0.01–
562 0.038 µg/g), chromium (0.71–21.9 µg/g), cadmium (0.3–1.88 µg/g), nickel (0.84–13.1 µg/g),
563 lead (0.23–13 µg/g), and cobalt (0.056–1.22 µg/g) (Pappas 2011). A report of metals values in
564 Pakistani naswar showed detectable levels of arsenic (0.15–14.04 µg/g), chromium (0.8–54.05
565 µg/g), cadmium (0.25–9.2 µg/g), nickel (2.2–64.85 µg/g), lead (12.4–111.15 µg/g), and even
566 higher levels of several other metals (Zakiullah et al. 2012).

567 Some ST products also contain mercury, a systemic toxicant, and barium, a dermal irritant (Addo
568 et al. 2008; Shaikh et al. 1992; Dhaware et al. 2009; Pappas 2011) and metals such as aluminum
569 and chromium, which may cause biologic sensitization (Addo et al. 2008; Pappas et al. 2008;
570 Pappas 2011). The potential for exposure to several of the toxic metals listed above (barium,
571 beryllium, cadmium, cobalt, nickel, and lead) was demonstrated by determining how much of
572 these metals transferred from tobacco to artificial saliva (Pappas et al. 2008).

573 The amount of copper in ST products is also of interest. The copper content of areca nuts is
574 higher than that found in other nuts (Trivedy et al. 1997). A study of seven ST product types from

India (zarda, creamy snuff, khaini, etc.) revealed very high levels of copper in four gutka products (237–656 µg/g) compared with other gutka products or other types of ST products (0.012–36.1 µg/g) (Dhaware et al. 2009). Areca nut use has been linked to oral submucous fibrosis (OSF), a condition that affects the mouth, pharynx, and esophagus. It has been suggested that copper upregulates lysyl oxidase, resulting in the excessive cross linking and accumulation of collagen that occurs in OSF (Trivedy et al. 1997).

Among the previously mentioned GothiaTek standards set for the Swedish tobacco industry are guidelines for the allowable levels of metals in Swedish snus: cadmium (1.0 µg/g), lead (2.0 µg/g), arsenic (0.5 µg/g), nickel (4.5 µg/g), and chromium (3.0 µg/g). The average levels of metals in Swedish snus in 2009 were: cadmium (0.6 µg/g), lead (0.3 µg/g), arsenic (0.1 µg/g), nickel (1.3 µg/g), and chromium (0.8 µg/g) (Rutqvist et al. 2011). These low levels of metals in Swedish snus demonstrate that the levels of metals in ST can be monitored and held below certain limits.

Polycyclic Aromatic Hydrocarbons

Compounds such as polycyclic aromatic hydrocarbons (PAHs), phenols, and volatile aldehydes are formed from burning wood and sawdust (Stepanov et al. 2010; Miller and Fowlkes 1999). During fire curing, tobacco is exposed to wood smoke, and these substances can be deposited on the curing leaf. Indeed, levels of PAHs and phenols tend to be higher in tobacco that is fire cured rather than air cured (Bhide et al. 1987, 1989; Hearn et al. 2013; Leffingwell 1999). Products made with fire-cured tobacco (e.g., moist snuff) have higher levels of PAHs, including PAHs that are IARC Group 1 or 2 carcinogens, than products such as snus, which do not contain fire-cured tobacco (Stepanov et al. 2008, 2010).

Ten PAH compounds have been designated as IARC carcinogens or potential carcinogens: in Group 1, benzo[*a*]pyrene (BaP); in Group 2A, dibenz[*a,h*]anthracene; and in Group 2B, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, dibenzo[*a,i*]pyrene, indeno[1,2,3-*cd*]pyrene, 5-methylchrysene, naphthalene, and benz[*a*]anthracene (IARC 2012b). All of these compounds have been found in smokeless tobacco (Stepanov et al. 2010).

Areca Nut

Areca nut, an ingredient in some ST products, is an IARC Group 1 carcinogen (IARC 2012a). Areca nuts are seeds from the Areca palm (*Areca catechu*), which is native to South-East Asia and Eastern Africa. The seed can be used in the ripe or unripe form; can be dried, baked, or roasted; and then cut into slices, crushed, or consumed whole. Betel quid often contains areca nut, among other ingredients such as tobacco, catechu, alkaline agents, and spices, wrapped in a piper betel leaf (IARC 2004).

Areca nut contains compounds such as arecoline and guvacoline that can react with nitrite to form areca-specific nitrosamine compounds (ASNA) (IARC 2004). These ASNAs are also formed in the mouth during use of products containing areca nut (Nair et al. 1987). The areca-derived nitrosoguvacoline (NG) has been shown to induce pancreatic tumors in lab animals, and a mixture of NG and NNK has been shown to induce lung tumors (Rivenson 1988). Another ASNA compound, 3-(*N*-nitrosomethylamino) propionaldehyde, is both highly cytotoxic and genotoxic to human buccal epithelial cells, a finding that is important to understanding tumor induction among users of areca nut-containing products (Sundqvist 1989). Areca nut is a carcinogen and a very harmful substance that should not be included in tobacco products (IARC 2004).

Other Harmful Agents

Flavoring agents are added to ST products worldwide (U.S. House of Representatives 1994; Swedish Match 2012; Dabur India Ltd. 2012):

- Diphenyl ether, a flavor compound with a harsh metallic aroma (Burdock 1995), and camphor have been identified as highly concentrated constituents of some tobacco products and certain spice condiment packs used to make betel quid (Joseph Lisko, personal communication). Diphenyl ether irritates mucus membranes and can cause damage to the liver, kidney, spleen, or thyroid after prolonged exposure (Material Safety Data Sheet 1994; International Programme CS 1997). Camphor can adversely affect the neurological, respiratory, cardiovascular, and gastrointestinal systems. Even small amounts of camphor have caused convulsions followed by depression (International Programme CS 1988). Ingestion of these substances is of note since betel quid can be swallowed during use.

- 631 • Brazilian rapé, a nasal product, contains tobacco mixed with tonka bean, cinnamon powder,
632 or clove buds, but usually lacks alkaline agents. Varieties of rapé produced in the Minas
633 Gerais State of Brazil are known to contain extremely high levels of coumarin, a liver
634 toxicant, which is derived from tonka bean and cinnamon (André Oliveira da Silva, personal
635 communication).
- 636 • Energy-enhanced smokeless products such as Revved Up contain stimulants (caffeine,
637 ginseng), taurine, and vitamins B and C.
- 638 • Some forms of tombol contain khat (*Catha edulis*), a plant that contains cathinone, an
639 alkaloid with amphetamine-like stimulant properties, which purportedly causes euphoria,
640 excitement, and loss of appetite (Lee 1995).

641 **Gaps and Limitations of the Current Evidence Base**

642 Further research is required to better characterize the chemical contents of a wider range of
643 products, including ST products that are used in combination with other non-tobacco plant
644 material. Research is also needed into the role of microorganisms (i.e., bacteria and mold) in
645 altering product chemistry (i.e., generating nitrite and nitrosamines, producing mycotoxins). The
646 effects of bacteria and mold on TSNA levels in products and the conditions that increase TSNA
647 levels are also subjects in need of further study.

648 Because of the complexity of ST products—which can include a variety of tobacco types,
649 chemical additives, non-tobacco plant ingredients, and microorganisms—ST products should not
650 be viewed as a single homogenous product category for assessing composition or health effects.
651 Because of these widely varying characteristics, along with different patterns of use, ST products
652 are likely to differ across regions in their abuse liability, toxicity, carcinogenicity, and impact on
653 health.

654 **Summary/Best Practices**

- 655 • Curing: Air curing is preferred over other methods as TSNA levels are lower in products with air
656 cured-tobacco
- 657 • Pasteurization rather than fermentation is preferred.

- 658 • Storage: Not storing tobacco in warm weather for prolonged periods of time.
- 659 • Additives: Eliminating carcinogenic products such as areca nut and tonka beans.
- 660 • Quick drying tobacco: Many studies have investigated techniques for reducing TSNA
661 levels in tobacco (Anderson et al. 1989; Lewis et al. 2008; Ricket et al. 2008). One study
662 by Wiernik and colleagues proposed a method of quick drying tobacco at 70°C for 24
663 hours to remove excess water and reduce growth of microorganisms, which resulted in
664 decreased nitrite and TSNA levels (Wiernik 1995). Drying tobacco quickly at this stage
665 of curing reduces the microbial activity but lowers tobacco leaf quality

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Smokeless Tobacco in the Region of the Americas

Introduction to the Region of the Americas

The Region of the Americas holds a notable place in the history of tobacco use because the tobacco plant is thought to have originated on the mainland in North, Central, or South America. Cultivation of tobacco in the region dates back at least 5,000 years, and Native Americans were probably the first people to smoke, chew, and inhale tobacco.

Overall national youth prevalence of current ST use ranges from 1.8% in Canada to 9.8% in Barbados, though adequate data was only available for 14 of 35 countries. Smokeless tobacco use was more prevalent among boys than among girls in nearly all countries and localities. The prevalence of ST use among boys ranged from 2.6% in Canada to 11.5% in Barbados, and ST use among girls ranged from 0.8% in Canada to 8.5% in Jamaica. For adults, basic ST prevalence data were available for only nine countries in the region. Among men, the highest prevalence of use among these countries was in the United States (6.9%), while use among women was highest in Haiti (2.5%).

Smokeless Tobacco Products in the Region of the Americas

A diverse range of smokeless tobacco products are in use in the region, including manufactured products such as snuff and chewing tobacco used in the United States and Canada and traditional, locally made products such as chimó used in Venezuela.

Snuff and Chewing Tobacco (North America)

Most of the ST products used in North America are broadly categorized as snuff or chewing tobacco. Three companies account for nearly 90% of the U.S. retail market: U.S. Smokeless Tobacco Company (UST; a subsidiary of Altria), American Snuff Company (a subsidiary of Reynolds American, formerly Conwood Sales Company), and Swedish Match North America (Euromonitor 2011a). Small retailers such as convenience stores and small groceries represented 72% of the ST sales volume in 2010 (Euromonitor 2011a). Nearly all the snuff sold in Canada is U.S.-style moist snuff, and the chewing tobacco products available in Canada are predominantly the same as those sold in the United States.

Two types of snuff are manufactured and used in the United States: moist snuff and dry snuff. Dry snuff is a finely powdered, fire-cured tobacco product (Hoffmann and Djordjevic 1997). It can be used either nasally or orally, although oral use predominates in North America. Moist

975 snuff is by far the most widely consumed type in the United States (Federal Trade Commission
976 2011) and Canada (Euromonitor 2011b). It is typically made from a mixture of fire-cured and
977 air-cured tobacco laminae and stems, which then are shredded (Hoffmann and Djordjevic 1997).
978 Traditional moist snuff is often flavored with wintergreen or various fruit flavors. Loose-leaf
979 chewing tobacco is also used in North America, consisting mainly of air-cured tobacco and
980 generally heavily treated with licorice and sugar (Hoffmann and Djordjevic 1997)

981 TSNA levels in the 39 top-selling brands of United States moist snuff ranged from 4.87
982 micrograms per gram ($\mu\text{g/g}$) (wet weight) for Red Seal Long Cut Wintergreen to 90.0 $\mu\text{g/g}$ (wet
983 weight) for Skoal Key (Richter et al. 2008). All U.S. products had higher TSNA levels than the
984 Swedish product Ettan snus (Swedish Match), which had a TSNA level of 2.8 $\mu\text{g/g}$. Although the
985 technology to reduce TSNA levels exists, U.S. smokeless tobacco manufacturers have not
986 applied it to their most popular products (Hecht et al. 2011). In the top 39 selling brands of U.S.
987 moist snuff, free nicotine in these same moist snuff products ranged from 0.01 to 7.81 mg/g (wet
988 weight), which represents a free nicotine percentage between 0.3% and 79.9%, and pH values
989 between 5.54 and 8.62 (Richter et al. 2008). Loose-leaf chewing tobacco is also used in North
990 America, consisting mainly of air-cured tobacco and generally heavily treated with licorice and
991 sugar (Hoffmann and Djordjevic 1997).

992 Some novel ST products have also been introduced on the U.S. market. Products called
993 “dissolvables” or “dissolvable tobacco products” were introduced starting in about 2001.
994 Dissolvables are made of ground tobacco shaped into compressed pellets, lozenges, strips, or
995 sticks and sometimes packaged to resemble breath-freshening mints or strips. Dissolvables have
996 had a very limited presence in the United States, and some have only appeared in test markets. A
997 recent study on was conducted nicotine and TSNA levels in novel products on the U.S. market
998 (Stepanov et al. 2012). The study looked at 117 regional samples of novel products such as
999 Camel Snus, Marlboro Suns, and Camel Strips, and found that levels of free nicotine in Marlboro
1000 Snus and Camel Snus varied significantly by region. Some regional variations in TSNA levels
1001 were also observed. Overall, Camel Snus had significantly higher TSNA levels than Marlboro
1002 Snus, and Camel Strips had the lowest TSNA levels among all novel products analyzed.

Iqmik (Alaska)

Alaska Native people make an ST mixture known as iqmik by combining tobacco with the ashes from fungus or wood (Renner et al. 2004). Iqmik is prepared either by premastication or by hand mixing, using air- or fire-cured full leaf or twisted leaf tobacco in varying proportions, and different types of ashes based on the user's personal practice (Renner et al. 2005).

Because the alkaline ash used in iqmik has extremely high pH levels (pH of 11-11.8), nearly all nicotine in iqmik is in the free form, which is more rapidly absorbed than bound nicotine (Henningfield et al. 1995). The total nicotine and free nicotine levels in iqmik are much higher than in popular U.S. commercial smokeless products.

Chemical analysis of iqmik samples found pH values between 11 and 11.8. In addition to high levels of free nicotine, iqmik contains other hazardous substances such as TSNA, polycyclic aromatic hydrocarbons (PAHs), and heavy metals (Hearn et al. 2013).

Chimo and Rapé (South America)

In South America, noncommercial ST products are more commonly available than commercial products. The main ST product used in Venezuela is chimó, a mixture of cooked tobacco leaves and flavorings. Use of chimó declined in the second half of the 20th century with the increase in urbanization and the introduction of mass-produced cigarettes. However, in the past 20 years, chimó has re-emerged as a trendy urban youth phenomenon and is perceived among some sectors of Venezuelan society as part of the national identity.

Most chimó production occurs in small family-operated factories scattered across the Andes and the flat lands of Venezuela and Colombia. However, commercially manufactured production of chimó is growing in Venezuela, with increasing sophistication of equipment and methods (Granero and Jarpa 2011). The tobacco leaf is cooked in large metal containers for several days to discharge fiber and starch, and the resulting paste is stored for maturation for up to two years after which sweeteners and flavorings are added according to the manufacturer's proprietary recipe.

In Venezuela, chimó is widely available at local convenience stores across the country. It is produced by either commercial or cottage industries. Sold tax-free, chimó is relatively inexpensive compared with cigarettes,

1032 Chemical analysis of selected samples of commercially manufactured and cottage industry
1033 chimó products found the following upper values: pH = 9.82 and percentage of free nicotine =
1034 95.9%. Therefore, chimó has among the world's highest levels of nicotine content, pH, and
1035 alkalinity in an ST product (Jarpa 2003; Stanfill et al. 2011).

1036 **Region-Specific Observations and Regulation Challenges**

1037 In general, detailed information on ST use is sparse or nonexistent for most countries in the
1038 region. Additionally, little is known about the content of or specific health effects associated with
1039 many of the locally used products such as rapé and iqmik.

1040 Established tobacco control measures, such as increased taxation, graphic warning labels, and
1041 limits on advertising and promotion, are not currently applied consistently across all tobacco
1042 products. Many tobacco control measures applied to cigarettes are not applied to ST products or
1043 are less stringent, such as lower taxes, and lack of pictorial warning labels. In Brazil, no ST
1044 products are licensed for sale, but they are still available in some areas. Controlling and taxing
1045 cottage industry products such as rapé poses a particular challenge. Investments are also needed
1046 to enhance surveillance efforts on ST products, particularly in areas where such products are
1047 available. And there is a general need for epidemiologic studies on the adverse health effects of a
1048 variety of ST products, including traditional products, and of dual use of ST and cigarettes.

1049 Implementation of the World Health Organization (WHO) Framework Convention on Tobacco
1050 Control and proliferation of smoke-free regulations throughout the region can be expected to
1051 accelerate the decline in consumption of cigarettes. The social acceptability of smoking
1052 continues to wane. At the same time, major cigarette manufacturers have taken control of most of
1053 the ST industry in North America and are marketing novel products to nontraditional users,
1054 including cigarette smokers. Dual use of cigarettes and ST is an emerging pattern, especially
1055 among young people, and may be influenced by marketing that encourages dual use. In this
1056 dynamic and shifting landscape, it is increasingly urgent to address ST throughout the region,
1057 while preserving the gains made in reducing smoking consumption.

1058 **Best Practices and Future Needs**

1059 In 2010, Brazil was the world's second largest tobacco producer and the world's largest tobacco
1060 exporter (FAOSTAT 2010). Brazil is among the few countries in the world to establish a public
1061 health-based regulatory structure for tobacco products through its National Health Surveillance

1062 Agency, which was established in 1999 (ANVISA). In Brazil, manufacturers must submit
1063 information about the contents, emissions, packaging, and design of every tobacco product to
1064 ANVISA, the National Health Surveillance Agency. However, because the list of commercially
1065 permitted brands in Brazil does not include ST brands (effectively making ST product sales
1066 illegal), smokeless products marketed and sold illegally in Brazil usually do not contain any
1067 health warnings.

1068 In the United States, the 2009 Family Smoking Prevention and Tobacco Control Act (Tobacco
1069 Control Act) gave the U.S. Food and Drug Administration (FDA) regulatory authority over ST
1070 products. Effective June 22, 2009, the law prohibits sales of cigarettes and ST to individuals less
1071 than 18 years of age, limits modes of sale, prohibits tobacco sponsorship of events, and requires
1072 advertising restrictions including health warning that must take up at least 30 percent of each
1073 principal display panel on the package and at least 20 percent of advertisements, with four
1074 specific rotating messages.

1075 The Tobacco Control Act also gives the FDA authority over standards for manufacturing tobacco
1076 products, requires premarket review of new tobacco products, and requires manufacturers who
1077 wish to market a tobacco product with a claim of reduced harm to obtain a marketing order from
1078 the FDA. While the Act does not currently require pictorial warnings or ban flavorings, the Act
1079 does give the FDA the authority to do so by issuing a regulation. In the United States, taxes are
1080 levied at the federal and state levels. State excise taxes on ST products vary widely in rate and
1081 formula. Some states apply an excise tax rate based on weight and other states set their ST excise
1082 tax rate as a percentage of wholesale price.

1083 In Canada, advertising of ST is subject to the same restrictions as cigarette advertising: These
1084 products can only be advertised to retailers or to adults through direct mail or in adult-only
1085 venues such as bars. Tobacco products cannot be sold to children (that is, anyone under 18). ST
1086 manufacturers must report their products' ingredients and additives to Health Canada. However,
1087 ST products in Canada can still be sweetened with sugar or contain fruit flavorings, even though
1088 such flavorings have been banned in cigarettes and little cigars. Rotating health messages is
1089 required on ST product packaging. ST products are subject to federal and provincial tobacco
1090 laws in Canada, including taxation. Excise taxes on ST products vary by province, but they are
1091 taxed by weight at rates comparable to excise taxes on cigarettes.

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Smokeless Tobacco in the European Region

Introduction to the European Region

Two populations in the European Region have longstanding traditions of smokeless tobacco (ST) use: Scandinavians, particularly in Sweden and Norway, and the large South Asian community that has immigrated to Europe and especially to the United Kingdom. Sweden is exempt from the European Union's tight regulations on the sale of many types of oral and ST products and can therefore manufacture and sell snus legally nationwide (The European Parliament 2001). Within the EU, tobacco products remain widely traded. Globally, the EU is the fourth largest tobacco producer (growing), after Asia, the Americas, and Africa (Bittner and Borsos 2011).

The Global Youth Tobacco Surveys provide national and/or subnational prevalence data for adolescents aged 13–15 years in 12 of 53 countries in the region (CDC 2007–2011). The prevalence of current ST use among adolescents ranges from 1.1% in Montenegro to 6.9% in Estonia. National prevalence data on ST use among adults (people aged 15 years and older) are available in 16 countries in this region. Reported prevalence of current ST use among adults varies from 0.1% in Switzerland to 17% in Sweden. Prevalence was particularly high among males in a few countries, including 17% among Norwegian males, 22.5% among Uzbek males, and 26% among Swedish males.

Smokeless Tobacco Products in the European Region

Europeans use a variety of ST products, including some that are specific to a particular geographic area or population group. Swedish snus is widely used in the Nordic countries of Sweden, Norway, Finland, and Iceland; a range of products are imported from South Asia (India, Pakistan, Bangladesh, and Sri Lanka) and used by communities of South Asian origin in Great Britain; and three national companies produce twisted tobacco for oral use in Denmark, Germany, and the UK (primarily used by the Danes). In Kyrgyzstan and Uzbekistan the predominant form of ST is nasway or nasvay, a multinational product made of locally grown tobacco and an alkaline modifier such as ash or slaked lime (calcium hydroxide).

Snus (Sweden, Norway, Finland, and Iceland)

Although *snus* is the Swedish word for *all* oral or nasal tobacco products, it has become synonymous with the oral moist form of pasteurized ST that is placed under the upper lip, and is

Comment [KB1]: The focus of this chapter is pretty much on snus. How about other smokeless products, e.g. the "Schnupftabak" (nasal snuff) produced and consumed in Bavaria, and recently marketed to young people via student parties

1151 increasingly recognized as such in the international literature. Snus has been manufactured and
1152 marketed in Sweden since the 1820s.

1153 Swedish snus is sold either packed loose or portion-packed in small teabag-like sachets. Both
1154 varieties are sold in round boxes (paper or plastic) or tins. Loose snus is a moist powder which
1155 can be formed into a cylindrical or spherical shape with the fingertips. Longtime users may pinch
1156 the tobacco in place under the upper lip and keep it in the recess between gingiva and lip.
1157 Prepacked portion snus, more widely used, contains smaller uniform portions that can be used
1158 more discreetly. Swedish snus, in both loose and sachet forms, is held under the upper lip for a
1159 period of 30 minutes to a few hours. The nicotine in snus is absorbed through the mucous
1160 membrane of the oral cavity, as are other substances. The juice produced in this process is
1161 usually swallowed and spitting is uncommon.

1162 Snus products differ in packaging, alkalinity, other additives, and flavoring. The largest
1163 manufacturer, Swedish Match, lists over 240 ingredients that are used as flavors in snus,
1164 including herbal extracts (e.g., menthol), spices (e.g., ginger, basil), lime, and alcohol (e.g.,
1165 whiskey) (Swedish Match Company 2011).

1166 Snus manufactured in Sweden is sold in Nordic countries as well as in other countries around the
1167 world. The Nordic market has been fairly stable since the year 2000. There are about a dozen
1168 manufacturers of snus, and Swedish Match is the dominant producer, with about 85% of the
1169 market in Sweden and 70% of the market in Norway (Kesmodel 2011). Smaller domestic
1170 companies market products mostly within the Nordic countries. In the other European Region
1171 countries (non-EU), international tobacco companies such as British American Tobacco, Japan
1172 Tobacco International, Philip Morris, and Imperial Tobacco market snus-type products, but they
1173 differ in their characteristics from Swedish snus. Swedish snus is sold in general stores,
1174 convenience stores, gas stations, tobacco shops, and from vending machines in shops and
1175 restaurants. It is often stored in refrigerators to minimize fermentation and bacterial growth.

1176 Manufacturers of Swedish snus pasteurize their products and most adhere to the GothiaTek
1177 standard, a voluntary standard developed by the industry (Rutqvist et al. 2011). As a
1178 consequence, snus products manufactured in Sweden using this standard show lower measured
1179 levels of some key toxicants, such as nitrosamines, than most products found in other countries.

However, Swedish snus products vary in their levels of nicotine and free nicotine. For example, so-called “starter” brands such as Catch Mint often have a lower pH and less free nicotine, and stronger varieties such as General, the market’s leading brand, have a higher alkalinity so that they deliver more free nicotine.

The GothiaTek standard limits and average content for important toxic constituents in tobacco

Component*	Limit†	Content† (2011) (± 2 SD‡)	Component	Limit†	Content† (2011) (± 2 SD‡)
Nitrite (mg/kg)	3.5	1.0 (<0.5–1.9)	Cadmium (mg/kg)	0.5	0.2 (0.1–1.4)
TSNA (mg/kg)	5	0.7 (0.5–1.1)	Lead (mg/kg)	1.0	0.1 (0.05–0.2)
NDMA (µg/kg)	5	0.4 (<0.3–1.1)	Arsenic (mg/kg)	0.25	<0.05 (<0.05–0.09)
BaP (µg/kg)	10	0.5 (<0.5–0.8)	Nickel (mg/kg)	2.25	0.7 (0.3–1.0)
Agrochemicals	According to Swedish Match Agrochemical Management Program	Below Swedish Match internal limits	Chromium (mg/kg)	1.5	0.3 (0.1–0.6)

Notes: * TSNA = tobacco-specific nitrosamines; NDMA = *N*-nitrosodimethylamine; BaP = benzo(a)pyrene. † Limits and average contents are based on Swedish snus with 50% water content. ‡ SD = standard deviation.

Source: Swedish Match 2012. Available at: <http://www.swedishmatch.com/en/Snus-and-health/GOTHIATEK/GOTHIATEK-standard/>

Zarda, Gutka, and Khaini (United Kingdom)

Zarda, gutka, and khaini are the three major types of ST used by South Asian immigrants in the United Kingdom. Common ingredients in these products are tobacco flakes or powder, with slaked lime (calcium hydroxide) as an alkalinity enhancer. Gutka and zarda contain additional spices and flavorings such as saffron and menthol. Zarda is also mixed with areca nut and other ingredients to produce the homemade product paan/khilli paan. Gutka and khaini are typically sold in small individual sachets, and zarda is sold in larger containers so it can be used in the production of paan by the user at home or by a vendor at a kiosk. (See SEARO section for more on these products)

Within individual boroughs, or neighborhoods, these brands represent between one-quarter and two-thirds of the tobacco products available in the United Kingdom. Outlets serving communities of Indian origin are likely to sell a more homogeneous group of products (gutka and khaini), but those serving the Bangladeshi community are more likely to sell a variety of zarda brands from Bangladesh. These variations reflect differing cultural contexts, with domestically made khilli paan being the predominant form of consumption in Bangladeshi

1203 communities. Zarda is produced commercially, gutka and khaini are often produced by both
1204 commercial and cottage industries.

1205 Marketing of ST in the UK is informal, relying on point-of-sale displays, packaging styles, and
1206 affordability. Most ST products sold in the UK are imported from India and are marketed to
1207 specific ethnic subgroups in the region. Although ST products are required to display warning
1208 labels in the UK, the dominant brands of imported products most often do not comply with this
1209 requirement.

1210 Some of the South Asian ST products used in the UK contain *Nicotiana rustica*, a tobacco with
1211 high alkalinity and a higher concentration of nicotine than the more commonly used tobacco, *N.*
1212 *tabacum*.

1213 One study investigating the toxicity of some of the ST products available in the UK assessed data
1214 on nicotine content and tobacco-specific nitrosamine levels. Nicotine in these products ranged
1215 from 3 milligrams per gram (mg/g) (Manikchard, a gutka products) to 83.5 mg/g (for dried
1216 tobacco leaves). Free nicotine was high in several of the gutka products, ranging from 3.0 mg/g
1217 to 8.0 mg/g, but was much lower in the zarda products (0.1–0.4 mg/g). Tooth-cleaning powder
1218 contained the highest levels of free nicotine, measuring in at 63.2 mg/g. Gutka and tooth-
1219 cleaning powder also had the highest pH levels of the products tested (9.52 and 9.94 for gutka
1220 and the tooth-cleaning powder respectively) (McNeill et al. 2006).

1221 The Niche Tobacco Products Directory (NTPD) (Niche Tobacco Products Directory 2011)
1222 website is managed by the Department of Health and informs the activities of local authorities
1223 and excise enforcement officers with respect to ST regulation and seizure in the UK. This
1224 directory focuses primarily on the tobacco content of a product; it does not report additional
1225 toxicity information. The NTPD data suggest that tobacco content varies considerably,
1226 particularly in Bangladeshi products; the tobacco content of one popular zarda brand was
1227 observed as varying between 5% and 20%. Although zarda alone has a relatively low pH, the
1228 mixture of slaked lime and zarda used in paan/khilli paan varied between pH 12.2 and pH 12.5,
1229 indicating that 99% of the nicotine was available as free nicotine (Croucher 2013).

Nasway (Uzbekistan and Kyrgyzstan)

In Uzbekistan and Kyrgyzstan the most commonly used form of ST is known as nasway or nasvay. As central Asian countries, they are geographically close to Pakistan and Afghanistan (in the WHO Eastern Mediterranean Region) where this product is referred to as nass, naswar, or niswar (SCENIHR 2008; IARC 2007). Nasway contains the same main ingredients as nass, but the published information is insufficient to determine if nass and nasway are exactly the same product.

In Uzbekistan and Kyrgyzstan, nasway is mostly produced as a custom-made or cottage industry product. It is partially manufactured before being sold to consumers. Nasway originating from Pakistan is available for wholesale purchase on the Internet. The core ingredients are locally grown, sun-dried tobacco and an alkalinity modifier such as ash or slaked lime (calcium hydroxide) (SCENIHR 2008; IARC 2007). Other flavorings and spices such as cardamom or menthol may be added according to preference. The product also contains an emulsifying agent such as butter or oil. Water is added during the mixing of ingredients, and the mixture is then rolled into balls. A ball is placed under the tongue on the floor of the mouth and sucked. No marketing data are available for Kyrgyzstan.

Nasway, is made from *N. rustica*, which has a higher concentration of nicotine than common tobacco. Nasway samples have high pH levels and contain more than 70% free nicotine, indicating their high potential for causing dependency (Stanfill et al. 2011).

Region-Specific Observations and Regulation Challenges

The EU is a key player in leading tobacco control efforts within the European Region. Although the sale of moist snuff or snus is restricted in EU countries such as Denmark and Finland, it is allowed in Sweden. The prohibition of snus sales within the EU has been challenged by Swedish Match and by the Swedish Ministry of Trade and Ministry of Health and Social Affairs on numerous occasions. Internet purchases are still possible, but most Internet-based vendors are located in Sweden and they market to other EU citizens (Peeters and Gilmore 2012). Some medical and public health experts have also called for debate on the EU snus ban, responding to suggestions that low-nitrosamine snus products may provide an alternative to cigarette smoking or aid smokers in quitting. (Royal College of Physicians 2007; Medicines and Healthcare

1259 Products Regulatory Authority 2010). However, this view remains controversial and evidence is
1260 lacking to demonstrate that snus is effective in helping smokers to quit.

1261 Although Kyrgyzstan is a signatory to the World Health Organization's Framework Convention
1262 for Tobacco Control (FCTC), Uzbekistan is not. The two countries vary in their commitments to
1263 population protection, cessation promotion, provision of health warnings, and enforcement of
1264 bans on tobacco advertising. Kyrgyzstan has adopted specific national objectives for tobacco
1265 control and a tobacco control budget that funds a national unit for tobacco control, but
1266 Uzbekistan has undertaken neither of these initiatives.

1267 In Uzbekistan, health warnings are required on cigarette packaging only. Tobacco advertising in
1268 the national media and outdoors is banned. Kyrgyzstan is reported to require health warnings on
1269 ST products in addition to cigarettes. Legal mandates also control the percentage of the package
1270 these warnings will cover and specify the number and wording of health warnings as well as the
1271 fines for violations. Kyrgyzstan has a wider range of bans on tobacco advertising, promotion, and
1272 sponsorship than Uzbekistan.

1273 **Best Practices and Future Needs**

1274 Initial tobacco control measures were introduced in the European Region in 1987 (WHO 2002).
1275 The EU is the only regional political and economic entity that has become a full signatory to the
1276 FCTC. When the FCTC negotiations began, the EU had already implemented a public
1277 information campaign and banned TV advertising of tobacco products and sponsorship by
1278 tobacco companies (Faid and Gleicher 2011). The EU tobacco product labeling requirements
1279 predate FCTC Article 11. Since the introduction of the FCTC, the EU has chaired the
1280 Intergovernmental Negotiating Body on Illicit Trade (FCTC Article 15). EU tobacco control
1281 activity is cross-cutting, also affecting taxation, illicit trade, and agricultural policies. As of 2013,
1282 two Nordic countries, Norway and Iceland, follow most of the EU tobacco regulatory framework
1283 although they are not EU members. Point-of-sale advertising is largely unrestricted in Sweden
1284 but banned in Norway, where all tobacco products are stored behind closed shutters marked
1285 "Tobakk" (grey cabinet) or "Snus" (white cabinet). Media advertising of all tobacco products (on
1286 TV, radio, print media, and outdoor billboards) is banned or restricted in Sweden, Norway, and
1287 Iceland. Norway's comprehensive ban on tobacco advertising also bans indirect advertising, such

1288 as advertisements for non-tobacco products that depict tobacco or advertising using colors and
1289 designs that resemble tobacco brands.

1290 The EU Tobacco Products Directive (EU Directive 2001/37/EC) was issued in 2001 and intended
1291 to be a model after which individual states could pattern their own tobacco regulations (The
1292 European Parliament 2001). The Directive establishes warnings on packs, product traceability,
1293 annual reporting of ingredients, and maximum yields of tar, nicotine, and carbon monoxide in
1294 cigarettes, and prohibits use of the terms “mild” and “light.” According to the Directive, text
1295 warnings are mandatory but pictorial warnings are optional. Ten European region countries,
1296 including EU and non-EU member states, have adopted pictorial warnings for cigarettes:
1297 Belgium, Romania, UK, Latvia, Malta, France, Spain, Denmark, Hungary, and Ireland.

1298 In December 2012, the [European Commission](#) adopted a proposal to revise the Tobacco
1299 Products Directive that would place greater restrictions on the manufacture, sale, and
1300 presentation of tobacco products. The proposal maintains a ban on oral tobacco products, except
1301 for Sweden, and proposes major revisions such as a ban on characterizing flavors, prior
1302 notification for retailers intending to sell products across borders (such as Internet retailers) and
1303 for manufacturers intending to sell novel tobacco products, and mandatory pictorial health
1304 warnings for cigarettes but not ST products. The proposal is expected to be adopted by the EU in
1305 2014 and go into effect in 2015–2016.

1306 Tobacco products “for oral use,” namely snus and moist snuff, are prohibited within the EU at
1307 this writing (2013). The UK had previously banned these products following an attempt in the
1308 mid-1980s to introduce a new ST product (Skoal Bandits) that targeted adolescents in the UK
1309 (UK Parliament 1997). Sweden was allowed to retain its use of snus, an oral moist snuff, at its
1310 accession to the EU.

1311 The Directive’s regulations differ for smoked tobacco and ST, most obviously with respect to
1312 requiring that packaging display health warnings. There have been no EU-wide proposals for
1313 pictorial warnings on ST products specifically, although some member states have proposed
1314 adopting pictorial warnings and increasing the size of warnings for cigarettes.

1315 The UK’s 2011 tobacco control plan specifically called upon the National Institute for Health
1316 and Clinical Excellence (NICE) to provide public health guidance to help people of South Asian

1317 origin stop using smokeless tobacco (Department of Health 2011). That resulting 2012 guidance
1318 document proposes a systematic engagement with South Asian communities in the planning and
1319 implementation of smokeless tobacco cessation services. The UK's tobacco control plan also
1320 commits to further developing the Web-based Niche Tobacco Products Directory. The 2009
1321 Health Act for the first time prohibited displays of smokeless tobacco products at the point of
1322 sale in the UK. However, the timetable for implementing the Act has been relaxed, and small
1323 retail outlets, such as those selling ST products, will not be required to comply until 2015.

1324 A variety of innovative tobacco control initiatives have also been proposed or tested and warrant
1325 further development. The London Borough of Brent has classified spitting paan/khilli paan juice
1326 as criminal damage, which is liable to a fixed-penalty enforcement (London Borough of Brent
1327 2010). Novel policies in the country of origin may also impact use of imported tobacco products
1328 in the UK; The number of gutka brands available for purchase in the UK declined following a
1329 2011 Indian Supreme Court order banning the use of plastic as a gutka packaging material
1330 (Venkatesan 2011), thus restricting its export. In Sweden, legislation carries no penalties for
1331 throwing away cigarette butts and snus sachets, and these discarded items outnumber all other
1332 litter on the streets; the environmental impact of this litter awaits appropriate investigation. In the
1333 UK, the 2009 Health Act demonstrates how ST products can be included in legislation along
1334 with smoked tobacco products by simply using the term "tobacco" in place of "cigarettes" or
1335 "smoking". And the Niche Tobacco Products Directory illustrates the potential of a publicly
1336 available Web-based resource.

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Smokeless Tobacco in the Eastern Mediterranean Region

Introduction to the Eastern Mediterranean Region

Tobacco use is prevalent in the Eastern Mediterranean Region, the predominant form being manufactured cigarettes, followed by tobacco used in waterpipes (shisha, nargila). In a few countries, such as Sudan, Yemen, and Pakistan, smokeless tobacco (ST) is traditional and widely consumed. In other countries, such as Egypt, the most populous Arab country, ST use has markedly increased among adults (WHO 2010; CDC no date). As in other regions of the world, the production of ST reflects a combination of cultural practices, local preferences, and the availability of particular tobacco leaves and other ingredients. Products and usage patterns are also influenced by the practices brought by immigrants from their home countries, such as the large population of Asian workers, many from the Indian subcontinent, who have immigrated to some Gulf countries.

Few studies have been published on ST use in the Eastern Mediterranean Region. Data on prevalence rates have been obtained from the Global Youth Tobacco Survey (GYTS), Global Adult Tobacco Survey (GATS), WHO STEPwise Approach to Surveillance (WHO STEPS), and various individual country surveys. Youth (aged 13–15 years) prevalence rates in the region range from 1.6% in Oman to 12.6% in Djibouti (with boys' rates reported at 15.2%), with 14 of 23 countries reporting. Only 5 of 23 countries reported data on prevalence among adults, which range from 1.2% in Libya to 10.7% in Yemen. Some local estimates of ST prevalence rates are quite high, especially in Sudan, where 2011 unpublished estimates presented by the Sudan Toombak and Smoking Research Center report toombak use is as high as 40.7% in the Northern states.

Smokeless Tobacco Products in the Eastern Mediterranean Region

Nass (or naswar) and paan (or betel quid with tobacco) are the most commonly used ST products in Pakistan (Ali 2009; Imam 2007; Khawaja 2006; Merchant 2000; Maher 1994; Shah 1992; Euromonitor 2010) and the UAE (National 2009; Bowman 2008). Shammah is mostly used in Yemen (Ministry of Public Health, Yemen 2003) and Saudi Arabia (Allard 1999; Ibrahim 1986; Salem 1984), and toombak is used in Sudan (Idris et al. 1998).

Nass (Iran and Pakistan)

Nass, also known as naswar or niswar depending on the region in which it is made, is used in many countries, notably Iran (where it is known as nass) and Pakistan (where it is commonly known as naswar). It is made mainly of tobacco, ash, cotton or sesame oil, water, and sometimes gum. Nass is processed by mixing dried tobacco leaves, slaked lime (calcium hydroxide), ash from tree bark, flavoring and coloring agents, and water. Nass users roll this mixture into balls to be placed in the mouth for 10 to 15 minutes and chewed slowly (SCENIHR 2008). Nass is primarily locally-produced on a small scale or custom-made by a vendor (Basharat 2012; Usmanova 2012).

Chemical analysis of nass revealed the following concentrations of the carcinogenic tobacco-specific nitrosamines (TSNAs): 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)—up to 309 nanograms per gram (ng/g) wet tobacco; *N*'-nitrosonornicotine (NNN)—up to 545 ng/g wet tobacco; *N*'-nitrosoanabasine (NAB)—up to 30 ng/g dry tobacco; and *N*'-nitrosoanatabine (NAT)—up to 300 ng/g dry tobacco (IARC 2007).

Naswar contains various toxic/carcinogenic substances, such as heavy metals, in addition to TSNAs. An assessment of the potential toxicity of 30 brands of naswar available in the Pakistani market (Zakiullah 2012) showed that the average values of all toxicants studied were above limits set by model regulatory agencies, including the Agency for Toxic Substances and Disease Registry at the Centers for Disease Control and Prevention (CDC).

Paan and Tombol (Pakistan and Yemen)

In this region, paan, or betel quid, is used mainly in Pakistan. It is produced commercially or by vendors or prepared at home. Slaked lime (calcium hydroxide) and catechu (extract from the acacia tree) are smeared on a betel leaf, which is folded into a funnel shape to which tobacco, areca nut, and other ingredients are added. The tobacco used may be raw, sun dried, or roasted, and it is finely chopped, powdered, and scented. Alternatively, the tobacco may be boiled, made into a paste, and scented with rosewater or perfume. After the betel leaf funnel is filled with the ingredients, the top of the funnel is folded over, resulting in a quid which is placed in the mouth, usually between the gum and cheek, and gently sucked and chewed. Paan is sometimes served in restaurants after meals (WHO 2004).

1463 A national product used in Yemen, tombol, has much the same ingredients, with some variation
1464 in flavorings (National Cancer Institute 2002), but it is not always made with tobacco. Tombol is
1465 made from the tombol leaf (also known as betel leaf), fofal (areca nut), noura, slaked lime
1466 (calcium hydroxide), and catechu. As an ST product, there are three types of tombol: (1) sweet (a
1467 sweetening agent, often coconut, is added to the basic components described above, with or
1468 without tobacco); (2) bitter (additives like clove oil, cardamom, and herbal medicine are used,
1469 with or without tobacco); and (3) tombol with toombak tobacco (a local type of tobacco), which
1470 is available in two varieties: socha, or dry, thin pieces of Yemeni tobacco (similar to Indian
1471 pattiwalla), and zarda, scented tobacco from India (National Cancer Institute 2002). Tombol is
1472 mostly a custom-made product.

1473 Some forms of tombol, such as those used in Yemen, contain khat (*Catha edulis*), a plant that has
1474 psychoactive properties (Baselt 2008). Khat is used in East Africa, Yemen, and Ethiopia. In
1475 Yemen, approximately 80% of males and 30% of females chew khat on a regular basis (Sporkert
1476 2003). Khat contains cathinone, an alkaloid with amphetamine-like stimulant properties, which is
1477 purported to cause euphoria, excitement, increased energy, and loss of appetite (Lee 1995;
1478 Sporkert 2003; Baselt 2008). Cathinone, like amphetamine, is a potent agent that causes
1479 norepinephrine and dopamine to be released in the body (Kalix 1981). Khat is added to tombol
1480 by spreading it in powder form onto a betel leaf to which an alkaline agent (noura) is then added
1481 (Ghazi Zaatari, personal communication, 2013). Tombol containing only khat and tobacco
1482 without noura would contain less free nicotine. Specific chemical and toxicity data are not
1483 available for this product.

1484 **Shammah (Saudi Arabia and Yemen)**

1485 Shammah is made from powdered tobacco, slaked lime (calcium hydroxide), ash, oils, black
1486 pepper, and flavoring agents (Scheifele 2007). The tobacco leaves are sun dried and pulverized
1487 with bombosa (sodium carbonate), and the preparation is usually sold as a dry product. Shammah
1488 is placed in the buccal lower and sometimes upper labial vestibule. Various commercial types of
1489 shammah are available in the market: bajeli, haradi, sharaci, and black shammah), but shammah
1490 is most frequently sold as a cottage or custom product. Black shammah is prepared by mixing
1491 tobacco leaves with a solution of bombosa in water; it is sold as wet shammah. Chemical and
1492 toxicity data is not available for this product.

Toombak (Sudan)

Toombak (IARC 2007), used in Sudan as a traditional national product, is made of sun-dried tobacco (wild *Nicotiana rustica*) mixed with an aqueous solution of sodium bicarbonate called atrun. The mixture is kept in an airtight container for about two hours, after which it is ready for sale. Toombak is rolled into a ball, called saffa, weighing about 10 grams (g). The saffa is dipped into the mouth; men preferentially hold it between the gum and the lip, but women, for aesthetic reasons, hold it between the gum and the cheek or under the tongue on the floor of the mouth. It is sucked slowly for 10 to 15 minutes; a few users may extend this to several hours. Men usually spit periodically, whereas women users typically swallow the saliva generated. Users usually rinse their mouths with water after the saffa is removed (WHO GTCR 2011). Occasionally toombak is also used nasally or postauricular with transdermal effect.

Toombak has the highest levels of free nicotine and nicotine-derived TSNAs ever measured in tobacco products (free nicotine: 5.16–10.6 milligrams per gram [mg/g] wet weight) (TSNAs: NNN, as high as 368,000 ng/g wet weight; and NNK, up to 516,000 ng/g wet weight) (IARC Stanfill 2011).

A 2011 global surveillance report on oral tobacco products (Stanfill 2011) confirmed that, compared to a variety of other global ST products, toombak is among the highest in nicotine concentration, which ranges from 9.56 to 28.2 mg/g in four different samples, and in concentrations of NNK (147,000–516,000 ng/g) and NNN (115,000–368,000 ng/g).

Region-Specific Observations and Regulation Challenges

In the Eastern Mediterranean Region, the production and marketing of ST products, such as nass, paan, shammah, and toombak, are primarily cottage industries that are mainly centered in areas of tobacco farming. The ST industry relies on locally available resources both for producing ST products and for marketing and distributing them to retailers under brand names intended to attract customers in their areas. For example, vendors use names such as Sultan Elkayef (i.e., the one that masters the mind), Wad Amari (a reference to the person who introduced the plant to the area), and Alsanf (which means “the best brand”). Toombak in Sudan is sold in small metal containers called hookahs or in plastic bags called keece.

Some ST products brought in from the Indian subcontinent are marketed to the large immigrant Asian labor force in the Gulf region. In a few countries, such as the United Arab Emirates (UAE)

1523 where there is a ban on ST products, there are reports of health inspectors and police inspecting
1524 and shutting down illegal manufacturing of nass and paan (National 2009; Bowman 2008).

1525 Well-structured regulatory policies are not present in the Eastern Mediterranean Region.

1526 Countries in this region have not made use of taxation as part of a policy of tobacco control.

1527 Taxes on ST products and prices of all types of tobacco products are among the lowest in the

1528 world. Tobacco taxes as a total proportion of government taxes collected are 1%–2% in Syria,

1529 Lebanon, Egypt, and Kuwait; 4% in Tunisia; and up to 5.6% in Algeria (World Bank 2001).

1530 **Best Practices and Future Needs**

1531 Only Bahrain and the UAE have introduced policies banning smokeless tobacco. In 2009 the
1532 government of Bahrain introduced strict anti-smoking regulations and banned the importation of
1533 chewable tobacco products (Time Out Bahrain 2009). Ajman Municipality in the UAE banned
1534 the sale, import, storage, and possession of chewing tobacco and prescribed heavy fines for
1535 violations of the new law (Bowman 2008).

1536 Smokeless tobacco is still an under-investigated topic in the Eastern Mediterranean Region
1537 because most production and marketing are cottage industry activities. A lack of comprehensive
1538 surveillance and the lack of updated data on ST use and its adverse health effects limit the ability
1539 of governments to introduce regulatory policies and design programs to combat ST use in their
1540 countries.

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Smokeless Tobacco in the African Region

Introduction to the African Region

In the African Region, use of smokeless tobacco (ST) products by adults is common in some countries, but prevalence of ST use varies widely across countries and across geographic areas within countries. For instance, although national prevalence data from Nigeria suggest relatively low use rates (3.2% for men and 0.5% for women) (Kishor et al., forthcoming), data from a state in the northeastern geopolitical zone of Nigeria indicated higher rates among people aged 15 years and older (10.8% for men and 4.1% for women) (Desalu 2010). Unfortunately, little information is available on prevalence of use in the region, and the data that are available tend to be dated and/or limited to small areas or subregions. National data that are available on ST prevalence show that current ST use among adults appears highest in Madagascar (22.6% for men, 19.6% for women) and Mauritania (28.3% for men, 9.0% for women) and lowest in Ghana (0.9% for men, 0.2% for women) and Zambia (0.2% for men, 1.2% for women) (Kishor et al., forthcoming; WHO GTCR 2011b). Among youth (13- to 15-year-olds), current ST use ranges from 5.4% in Swaziland to 21.9% in Gambia (Centers for Disease Control and Prevention 2008–2011).

Smokeless Tobacco Products in the African Region

Smokeless tobacco products available in the region include a variety of ST products produced by small cottage industries and custom-made products for personal use or for sale by street vendors. Custom-made or traditional snuff products are sold from plastic buckets in open markets in South Africa and Nigeria and are dispensed in spoon-sized portions that are transferred to plastic bags, as requested by the customer. In Nigeria, it is also possible to request a mixture of local products and imported products. Commercial ST products are also available across the region, although they generally are not as common as cottage and custom-made products. Smokeless tobacco products such as snuff and betel nut with or without tobacco, previously popular only in a limited number of countries, are now being marketed heavily to specific target groups. These groups include women, for use as an alternative to smoking in cultures where smoking by women is not socially acceptable; young people, for whom flavored and milder-tasting “starter” products have been developed; and smokers, for use where smoking is prohibited (Kaduri 2008).

1655 In Algeria, chemma or shammah, the local term for moist snuff, is the most prevalent type of
1656 smokeless tobacco. Dry snuff, called neffa, is taken in through the nose (Euromonitor 2010). In
1657 Uganda and a number of West African countries including northern Nigeria, Cameroon, Senegal,
1658 and Chad, a dry snuff product locally known as taaba is widely consumed orally or by nasal
1659 inhalation. It is prepared from pulverized fermented tobacco and mixed with natron (a mixture of
1660 sodium bicarbonate and sodium chloride). Toombak is an oral snuff that is traditionally made by
1661 small local vendors in Sudan and is fairly common in Chad. Toombak is a custom-made blend of
1662 leaves of the *Nicotiana rustica* variety of tobacco mixed with sodium bicarbonate (baking soda),
1663 and stored for two hours or longer before sale (Idris 1994).

1664 In Tanzania, three types of ST products are used. Kuberi and ugoro (moist oral snuffs) are used
1665 by indigenous people, and tobacco with betel nut (locally called thinso but more widely known
1666 as gutka) is used by migrants of Indian descent. Kuberi is the most popular product, followed by
1667 ugoro, which is wrapped in banana bark when sold. In Ghana, local snuff is prepared by mixing
1668 the dried tobacco leaf indigenous to the forested areas (*N. tabacum*) with chemicals such as
1669 saltpeter (potassium nitrate) and then grinding it into a fine powder. Dried tobacco leaves are also
1670 a form of ST, which is sometimes dipped into the fly ash of wood before use (Addo 2008). The
1671 ash is an alkaline agent added to intensify the delivery of free nicotine; adding alkaline agents for
1672 this purpose is a common practice among ST producers worldwide (Tomar and Henningfield
1673 1997). In South Africa and neighboring countries, including Lesotho, traditional homemade snuff
1674 and a limited range of manufactured products are used. The traditional snuff is prepared by hand-
1675 mixing finely ground sun-dried tobacco leaf and ash (mokgako) from local plants. Mokgako is
1676 used as a condiment or flavor intensifier (Ayo-Yusuf and Swart 2000; Ayo-Yusuf and Peltzer
1677 2006; Ayo-Yusuf and Van Wyk 2005).

1678 With regard to commercially manufactured products, multinational tobacco companies have
1679 introduced various local brand equivalents of Swedish snus in test markets across South Africa
1680 since 2003, albeit with limited sales success to date (Simpson 2005). In South Africa, these snus
1681 products have been promoted with health claims and as convenient to use in situations where
1682 smoking is not permitted. Commercially manufactured ST is also imported into Uganda and
1683 Algeria.

Only limited data are available on the toxicity of ST products used in the region, but product testing suggests considerable variability in the toxicity and nicotine profiles of these products (see the table below). Generally, the commercialized products tend to have lower levels of carcinogenic tobacco-specific nitrosamines (TSNAs) than traditional custom-made products, one exception being traditional products used in Nigeria, which contain notably lower levels of TSNAs than traditional products in Chad, Ghana, and South Africa, and even lower than the levels in the manufactured snus products on the South African market (Stanfill et al. 2011). Toombak has among the highest levels of TSNAs (295,000–992,000ng/g) of any product in the world (Stanfill et al. 2011). Local vendors and small-scale producers and of toombak could reduce the nitrosamine levels by switching from *N. rustica* tobacco species to *N. tabacum*. Traditional snuff products in South Africa and Ghana have been found to contain heavy metals such as chromium, lead, cadmium, or nickel (Addo 2008, Keen 1974).

Toxicity and nicotine profiles of selected smokeless tobacco products used in the African Region*

Country	Products (n)	Heavy metals (ppm)				BaP (ng/g)	TSNAs (ng/g)	pH	Free nicotine (mg/g) (% of total nicotine)
		Cr	Pb	Cd	Ni				
Chad ^a	Toombak† (4)						295,000–992,000	7.38–10.1	5.16 (18.3%)–10.6 (98.6%)
Ghana ^b	Traditional snuff (5)	0.95–1.41		1.06–1.11					
South Africa ^{a,b}	Traditional snuff† (3)	9–84	6–8	1.1–1.5	25–87	4,550	20,500 (n=1)	9.29	5.01 (94.8%)
	Commercial snuff (3)						1,710–4,670	9.15–10.1	1.16 (99.1%)–13.8 (92.9%)
	Commercial snus (2)						1,720–5,850	6.48–7.02	0.47 (2.7%)–1.19 (8.9%)
Nigeria ^a	Traditional† (1)						1,520	9.42	2.39 (96.1%)
	Commercial (1)						2,420	9.02	6.72 (90.7%)

Notes: *Abbreviations: ppm = parts per million. CR = chromium, Pb = lead, Cd = cadmium, Ni = nickel, BaP = benzo(a)pyrene, ng/g = nanograms per gram of tobacco, TSNAs = tobacco-specific nitrosamines, mg/g = milligrams per gram of tobacco.

Notes: †Sudanese toombak data is used for Chad toombak here for comparison.

Sources: (a) For South Africa, Nigeria and Chad, data on pH, nicotine, and TSNA: Stanfill et al. 2011. (b) For Ghana, heavy metals data: Addo 2008. (c) For South Africa, heavy metals and BaP data: Keen 1974.

Region-Specific Observations and Regulation Challenges

The variety of ST products used on the African continent and their modes of production and distribution make establishing policies to control ST use—for example, levying taxes on diverse products from numerous small producers—extremely challenging. There is also a widespread perception that snuff possesses “medicinal” properties (Desalu 2010; Ajani 2001; Ayo-Yusuf, Swart 2000; Peltzer 2001). Medicinal uses that have been reported include relief from physical conditions such as headache, epistaxis, sinus problems, and toothache. In South Africa, some manufactured ST brands are mentholated and tend to attract “health conscious” consumers

1710 (personal communication, Ayo-Yusuf). Previously confidential industry documents also suggest
1711 that manufacturers have used additives or flavorings as part of marketing strategy (1) to mask the
1712 poor quality of some products in Nigeria (Creighton 1985) or (2) to target certain population
1713 groups in South Africa (Wingate-Pearse 1987).

1714 Smokeless tobacco products in the African Region are generally much cheaper than cigarettes
1715 (Desalu 2010; Rantao 2012). In South Africa, excise tax is payable on cigarettes but not on
1716 commercial ST products, therefore ST is much less expensive than cigarettes in South Africa,
1717 and traditional homemade snuff products are even cheaper. Because ST products in the African
1718 Region are usually custom-made or cottage industry product, they are not widely advertised in
1719 the media, and tobacco promotion and advertising beyond the point of sale is banned in some
1720 countries, such as South Africa (Republic of South Africa 1993).

1721 Of the 46 countries in the African Region, 41 had ratified the WHO Framework Convention on
1722 Tobacco Control (WHO FCTC) as of January 2013 (WHO 2013). The five countries that have
1723 not ratified the Convention are Malawi, Zimbabwe, Mozambique, Eritrea, and Ethiopia
1724 (Mozambique and Ethiopia have signed but not ratified). Malawi is one of the leading tobacco
1725 producers in the world; tobacco is grown on about 3% of Malawi's total agricultural land
1726 (Eriksen et al. 2012).

1727 **Best Practices and Future Needs**

1728 Although the majority of countries in the region have ratified the WHO FCTC, many countries
1729 have not implemented regulations targeted at smokeless tobacco. Among countries that have
1730 adopted ST-related regulations (such as an ST sales ban in Tanzania and ST warning labels in
1731 Algeria and South Africa), there is insufficient information available to determine if these
1732 regulations are effective or adequately enforced. In Tanzania, the sale of ST was officially
1733 banned in 2006, although it has been suggested that more stringent monitoring and enforcement
1734 are needed (Kaduri et al. 2008).

1735 While custom-made and cottage industry ST products generally do not carry health warning
1736 labels, some countries have require warning labels on commercial products. In Algeria, ST
1737 containers are subject to the same legislation as the packaging of other tobacco products, which
1738 includes specified health warnings. However, ST product packaging is not subject to the same

1739 warning requirements as cigarette packages, which must have multiple “rotating” health
1740 warnings that are required to cover 15% of the entire package (WHO 2011a). In South Africa,
1741 manufacturers of ST products are required by regulation to place the phrase “Causes cancer” on
1742 every can of snuff (Republic of South Africa 1993).

1743 Considering the region’s limited institutional and financial capacity for tobacco control research
1744 and for tobacco control in general, future efforts to document and monitor use, toxicity, health
1745 effects, and regulation of ST products in the region would benefit from international
1746 collaboration. More research is needed to determine which policy measures would be most
1747 effective at regulating both cottage and commercial ST manufacturers, reducing ST use, and
1748 limiting the populations’ exposure to toxicants in smokeless tobacco.

1749

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1783 [%20Tobacco%20Products%20Control%20Act%20-%20national.pdf](http://www.tobaccocontrollaws.org/files/live/South%20Africa/South%20Africa%20-%20Tobacco%20Products%20Control%20Act%20-%20national.pdf)
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Smokeless Tobacco in the South-East Asia Region

Introduction to the South-East Asia Region

The South-East Asia Region experiences the highest prevalence of smokeless tobacco (ST) use (among both men and women), the greatest diversity of product types and forms of use, and the greatest attributable disease burden of all the WHO regions. Of the 70 countries reporting data on ST prevalence, South-East Asian countries account for 89% of the world's adult ST users (268.6 million of 300+ users) (CDC no date; Kishor et al. forthcoming; WHO 2011d). India alone has more than 220 million ST users and Bangladesh is home to 28 million. Because of their large populations, high prevalence of ST use, and toxicity of the ST products used, the attributable disease burden is very high in countries such as India.

Prevalence of current ST use among men in the South-East Asia Region is high, ranging between 24.9% and 51.4% in five countries, although in Thailand it is less than 2% (WHO 2011d; Kishor et al, forthcoming). Smoking remains more common than ST use in Indonesia, Thailand, Bangladesh, Sri Lanka, and Nepal, but ST use is predominant in India and Myanmar among men. Among women, prevalence of current ST use is particularly high (>15%) in four countries—Bangladesh (27.9%), Bhutan (17.3%), India (18.4%), and Myanmar (16.1%) (WHO 2011d; CDC no date). Prevalence of ST is higher among men than women in most South-East Asian countries, except in Thailand (1.3% for men, 6.3% for women) and Bangladesh (26.4% for men, 27.9% for women) (CDC, no date). Among adolescents aged 13–15 years, ST use is as prevalent as smoking or more prevalent (WHO 2011c), and current ST use ranges from 2.8% in Indonesia to 9.4% in Bhutan (CDC 2007–2009).

Smokeless Tobacco Products in South-East Asia Region

A wide variety of products are used throughout the region, which can be as simple and cheap as unmanufactured tobacco leaves (e.g., sada pata) or as complex as a processed paste made from boiled tobacco and spice flavorings (e.g., kiwam) (WHO 2004, Kyaing 2004, IARC 2004, IARC 2007). Unprocessed ST is sometimes packaged in small pouches like the processed products. Some products, such as mawa or betel quid with tobacco, can be made or assembled by a vendor on demand from users, or users can buy the ingredients from shops and assemble them (as in betel quid and tobacco) or process them (such as by roasting and powdering tobacco flakes to make mishri). Smokeless tobacco products in the region are usually custom-made or produced by

1834 cottage industries, though some products are manufactured by larger local factories or
1835 multinational corporations.

1836 Chewing betel quid with tobacco is a common ST practice in the region, particularly in Nepal,
1837 Indonesia (Lee, Ko et al. 2011), Myanmar (Ministry of Health Myanmar 2009), and Bangladesh
1838 (MHFW Bangladesh 2009). Betel quid is composed of areca nuts, slaked lime paste, and other
1839 minor ingredients such as catechu, all wrapped in a betel leaf. Tobacco is not a necessary
1840 component of betel quid, and many users do not add it. Vendors or users combine the ingredients
1841 to make fresh betel quids for immediate consumption. Although some users believe that betel
1842 quid has beneficial medicinal properties (IARC 1985, Gode 1961), areca nut alone is
1843 carcinogenic (IARC 2004). Users who incorporate tobacco into the betel quid may not consider
1844 tobacco a harmful addition (International Institute for Population Sciences 2010).

1845 Other products that may be used with or without betel quid—such as plain tobacco leaf
1846 (sometimes called sada pata), zarda, and khaini—are seen in Bangladesh, Bhutan, India, and
1847 Nepal. Zarda is processed by boiling broken up tobacco leaves with lime and spices until the
1848 water evaporates. It is then dried, colored with vegetable dyes, and sold in small packets or tins.
1849 Khaini (also known as khoinee, sada, or surti) is usually custom-made by the user by mixing sun-
1850 dried tobacco flakes with slaked lime (calcium hydroxide) in the palm of the hand, but it can also
1851 be commercially manufactured (WHO 2004, IARC 2007). Compared to most other types of ST
1852 in the South-East Asia Region, both zarda and khaini have high levels of tobacco-specific
1853 nitrosamines (TSNAs). A 2011 study by Stanfill and colleagues found that total TSNAs¹ ranged
1854 from 5,490–53,700 nanograms per gram (ng/g) in zarda and from 21,600–23,500 ng/g in khaini.

1855 Mawa, dohra, and Mainpuri tobacco are areca nut-containing custom- and cottage-made products
1856 that are popular in certain districts in India. Mawa is composed of 95% areca nut shavings mixed
1857 with tobacco flakes and slaked lime. It is sold in plastic wrappers. Dohra is a wet mixture of
1858 tobacco, areca nut, catechu, and flavorings. It is sold either as a ready-made mixed tobacco
1859 product or in two packets, one containing tobacco (often zarda or surti), which is mixed with the
1860 contents of the second packet (areca nut, catechu, and other flavorings). Dohra is normally sold

¹ Total TSNAs include: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), *N*'-nitrosoanatabine (NAT) and *N*'-nitrosoanabasine (NAB).

1861 in a plastic bag with a rubber band around it. Mainpuri tobacco is ready-made mixture of
1862 tobacco, slaked lime, areca nut, and flavoring such as camphor and cloves (WHO 2004).

1863 Gutka and pan masala are essentially dried, nearly imperishable versions of betel quid without
1864 the fresh betel leaf; they have become increasingly popular alternatives to traditional betel quid.
1865 Gutka always contains tobacco, but most brands of pan masala do not. These two products are
1866 usually commercially manufactured and are used in India, Bangladesh, Bhutan, Myanmar,
1867 Nepal, and Sri Lanka. Gutka is sold in single-dose, colorful packages that are cheap enough for
1868 children to buy. Gutka and pan masala products frequently carry the same brand names and
1869 similar packaging, allowing manufacturers to circumvent laws banning tobacco advertisements
1870 since they are able to advertise a product that appears identical to tobacco-containing gutka
1871 (WHO 2004).

1872 Some smokeless tobacco products are applied orally as a tooth cleanser. These may be
1873 commercially manufactured, such as red toothpowder (powdered tobacco with herbs and
1874 flavorings), gul (pyrolysed tobacco) and creamy snuff (tobacco paste flavored with mint and
1875 other ingredients); or they may be prepared by the user or a vendor, or in cottage industry (for
1876 example, mishri, which is roasted, powdered tobacco) (IARC, 2004, WHO 2004). These applied
1877 products are mainly used in India, although gul is commonly used in Bangladesh (IARC 2007;
1878 WHO 2004). While people typically use these products to clean teeth, they may become addicted
1879 and increase their rate of use (WHO 2004). Gul has particularly high levels of free nicotine; one
1880 study found that gul had 29.1–31.0 milligrams per gram (mg/g) of free nicotine—higher than any
1881 of the other global ST products tested (Stanfill et al. 2011). Gul also had a high level of total
1882 TSNAs, which ranged from 13,400–17,100 mg/g (Stanfill et al. 2011).

1883 In 1992, an amendment to India's Drugs and Cosmetics Act of 1940 prohibited the manufacture,
1884 sale, and distribution of toothpastes and toothpowders containing tobacco (such as creamy snuff
1885 and red toothpowder), although several studies continue to find nicotine in some brands of dental
1886 care products (Agrawal & Ray 2012; Agrawal & Rajagopal 2009). This is particularly
1887 concerning because the tobacco-containing red toothpowders do not list tobacco as an ingredient.

Region-Specific Observations and Regulation Challenges

Evidence from existing toxicity profiles indicates high levels of TSNAs in products such as khaini and zarda (Stepanov et al. 2005; Stanfill et al. 2011), and areca nut, which is used in many products, contains several harmful constituents. While some studies have assessed toxicant levels in various ST products used in the region, many Asian economies—including the countries where the ST burden is extremely high (India, Bangladesh, and Myanmar)—lack laboratory capacity to test ST products (Health Sciences Authority 2010). The ability to understand and regulate ST in this region are complicated by the wide diversity of traditional products, their production in cottage industries, and the addition of spices, areca nut, sweeteners, and scents.

All member states in the region except Indonesia have ratified the World Health Organization's Framework Convention for Tobacco Control (FCTC). As of 2011, nine of the countries that have ratified the FCTC have adopted comprehensive tobacco control laws. (Timor-Leste has ratified the FCTC and as of December 2012 is in the process of passing national-scale legislation.) Table 1 below summarizes the policies of these countries. However, implementation and enforcement of tobacco control laws is impeded by factors such as high rates of use in large populations, the informal nature of much of the industry, resource limitations, and interference from the organized tobacco industry (WHO 2011a).

Policy measures for controlling smokeless tobacco use in the South-East Asia Region

Countries	Ban on exports	Ban on imports	Ban on advertisement	Ban on sale to minors	Health warning for smokeless tobacco	Ban on sale within 100 yards/meters of a school
Bangladesh						
Bhutan	✓	✓*	✓	✓	Yes†	NA‡
DPR Korea				✓		
India			✓	✓	Yes	✓
Indonesia						
Maldives			✓	✓	Yes§	
Myanmar			✓	✓	Yes§	✓
Nepal			✓	✓	Yes§	✓
Sri Lanka				✓	Yes§	
Thailand		✓	✓	✓	Yes	
Timor Leste						

Notes: ✓ = Ban applied. NA = Not Applicable. * Bhutan allows limited import of tobacco products for personal consumption only, †Health warnings are required on all imported tobacco products (added by the country of origin). ‡Bhutan banned sale of smokeless tobacco products in any location, therefore a specific ban on sale near schools does not apply. §Health warnings are required on tobacco products by the national laws, but there is no specific rule for smokeless tobacco.

Source: Adapted from: World Health Organization. Expert group meeting on smokeless tobacco control and cessation, New Delhi: World Health Organization, Regional Office for South-East Asia; 2011b.

1912 Some of the world's major tobacco producers are South-East Asia countries: India, Indonesia,
1913 Thailand, DPR Korea, and Bangladesh (FAOSTAT 2009). India is one of the world's largest
1914 exporters of tobacco, exporting approximately 50% of its total tobacco production to other
1915 countries (Directorate of Tobacco Development 2006). From 2000–2001 to 2009–2010, legal
1916 exports of chewing tobacco from India increased nearly 450% (Tobacco Board 2011; Tobacco
1917 Board 2004). Indonesia, where tobacco production increased 24.1% between 2000 and 2009,
1918 ranks among the top 10 countries in the world for tobacco leaf production (Erikson et al. 2012).

1919 Reports also suggest that ST products are imported and exported illegally among countries
1920 within the region and those outside (Kabir 2010). Bhutan is reported to have a thriving black
1921 market for tobacco, despite laws prohibiting all tobacco sales, importation, and exportation
1922 (except for importation of limited quantities for personal use) (Magistad 2011; Parameswaran
1923 2012).

1924 Unlike taxes on cigarettes, taxes on ST are low or nonexistent. In the South-East Asia Region,
1925 unmanufactured tobacco sold in loose form is often not taxed. Betel quid with tobacco, which is
1926 sold fresh by street vendors, is not taxed and has no warning labels. In India, the ST industry,
1927 particularly the gutka industry, has grown tremendously in the last three decades. All
1928 manufacturers of tobacco products in India are expected to register with the government and pay
1929 excise taxes, but this is poorly enforced, and it is estimated that only one-fourth of the excise tax
1930 due on the gutka and pan masala industry is actually paid (Rediff News 2007).

1931 While custom- and cottage-made products frequently are not taxed, commercially manufactured
1932 products are taxed in some countries, such as India and Bangladesh. Since the early 1990s, India
1933 has seen a rise in industrial production of chewing tobacco (Panchamukhi 2008). In 2008–2009,
1934 India collected INR 35 billion (US\$632 million) in taxes (Smokeless Tobacco Federation of
1935 India 2011). In 2008–2009, the government of Bangladesh recognized ST (mainly for chewing)
1936 as a manufacturing industry rather than a cottage industry, and has begun to levy taxes on it
1937 (Bangladesh Budget Speech 2008/9). In Bangladesh, ST products were taxed for the first time
1938 under the 2011–2012 budget.

1939 Custom- and cottage- made products, also generally do not display health warnings, even in
1940 countries where commercial cigarettes do contain such warnings. India requires textual and

1941 pictorial health warnings for ST products sold domestically but not for exports; however, the
1942 tobacco industry has challenged this health warning legislation, causing a long delay in
1943 introducing these pictorial warnings (Arora 2010, Oswal 2010). In Thailand, packages of
1944 shredded tobacco meant for roll-your-own cigarettes carry a warning about smoking but no
1945 warning about using tobacco in smokeless form. Nepal passed legislation in 2011 requiring
1946 graphic warnings on all kinds of tobacco products (Framework Convention Alliance News 2011).

1947 Bhutan, India, Maldives, Myanmar, Sri Lanka, and Thailand have prohibited advertisements for
1948 ST, but implementation is sometimes inadequate and more work is needed to improve these
1949 efforts in the region. In India, a ban on direct advertisements is enforced, but indirect
1950 advertisements and surrogate advertisements persist. Direct advertisement continues at points of
1951 sale, and 10.8% of adults have noticed point-of-sale advertisements or promotions of ST
1952 (International Institute for Population Sciences 2010). Bangladesh and DPR Korea have no
1953 restrictions on advertising of smokeless tobacco.

1954 **Best Practices and Future Needs**

1955 Bhutan has introduced the strongest tobacco restrictions of any country in the world. In addition
1956 to banning imports, Bhutan has banned exports, agricultural production, manufacture, and sale of
1957 tobacco and all tobacco products. Bhutan first introduced a ban on tobacco sales in 2004, but
1958 implementation was weak, and a thriving black market for tobacco developed (Givel 2011;
1959 Parameswaran 2012; Bhutan Department of Trade 2004). In 2010, Bhutan passed the Tobacco
1960 Control Act, which imposed harsher penalties and strengthened enforcement (Parameswaran
1961 2012; Parliament of Bhutan 2010). Now individuals may bring in small amounts of ST for
1962 personal use if they declare it and pay a duty. Health warnings are required on tobacco brought in
1963 from another country for personal use.

1964 The Indian Supreme Court has also attempted to ban gutka, one of the most popular ST products
1965 in India, by defining it as a food product. At present, gutka satisfies the legal definition of a food
1966 item and is thus covered, along with “other tobacco-containing food items,” under the Food
1967 Safety and Standards Act of 2006, Regulation 2.3.4 of 2011, which prohibits any harmful
1968 ingredient, including nicotine and tobacco, from being added to food (Singh n.d.; Zolty et al.
1969 2012). This decision essentially bans all gutka products throughout the country, although it was
1970 not widely enforced at first. In April 2012, Madhya Pradesh became the first state to implement

1971 the ban on gutka (Sandhu 2012). As of April 2013, 23 of India's 28 states and 5 of 7 union
1972 territories have banned gutka by invoking Regulation 2.3.4 (Campaign for Tobacco-Free Kids
1973 2013).

1974 India has also enacted and enforced a number of other tobacco regulations in recent years. In
1975 2011, India strengthened their pictorial health warnings on smokeless tobacco packaging by
1976 changing from a picture of a scorpion (first implemented in 2009) to more graphic images of oral
1977 cancer (Tobacco Labeling Resource Centre 2013). India also has among the most comprehensive
1978 restrictions of tobacco advertising, sponsorship, and promotion in the South-East Asia Region.
1979 As of 2012, India is the only country in the region to enact laws restricting tobacco imagery in
1980 movies—for example, they require health warnings to be displayed when tobacco products or
1981 use is displayed on screen (Zolty et al. 2012). While all South-East Asian countries (except
1982 Bangladesh) have comprehensive laws prohibiting the sale of ST to minors, India is among the
1983 few that prohibit selling tobacco within 100 yards of educational institutions. In 2011, India
1984 increased enforcement efforts for this ban with the assistance of some NGOs, local governments,
1985 and courts (Singh 2011).

1986 While both Bhutan and India have made significant steps toward decreasing ST use, additional
1987 surveillance and research are needed to monitor the situation to assess whether these regulations
1988 are adequately enforced, as well as evaluated the impact of these regulations on ST use and
1989 tobacco-related disease. Advocacy campaigns to strengthen and enforce policies restricting ST
1990 and smoking are also needed in most of the region's countries, but these efforts require more
1991 resources, both for the present and the long term. Government action is also needed to curb the
1992 illegal trade in smokeless tobacco both within the South-East Asian Region and between South-
1993 East Asian countries and other regions.

1994

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2126

Smokeless Tobacco in the Western Pacific Region

Introduction to Smokeless Tobacco in the Western Pacific Region

Smoking is the predominant form of tobacco consumption in the Western Pacific Region, which is home to one-third of the world's smokers (Cheng 2009). At present no regional mechanism systematically tracks the prevalence of smokeless tobacco (ST) use, and data on ST use are scarce. The available data indicate that ST use is many orders of magnitude less prevalent than smoking.

Of the few countries that have ST use data, rates vary from 22.4% among men aged 25–64 years in Micronesia, to 0.7% among males older than 15 years in China and Cambodia. Among women, prevalence of ST use ranges from 12.7% in Cambodia to essentially 0% in China. In some countries (e.g., Cambodia, Malaysia, and Vietnam), the rates of ST use are higher in females than males (WHO GTCR 2011; CDC no date). Among adolescents in the four countries where data are available (Cook Islands, Macau, Malaysia, and South Korea), prevalence of current ST use ranges from 2.1% in Macau to 8.7% in Cook Island (CDC 2008–2011). Rates among boys and girls are similar.

Smokeless Tobacco Products in the Western Pacific Region

Chewing Tobacco With Areca Nut

The literature on ST use in the Western Pacific focuses primarily on chewing tobacco mixed with areca nut/betel quid. The areca nut is the seed of *Areca catechu* fruit, which is an important agricultural product in the Western Pacific Region and other parts of the world (IARC 2004). The areca nut is chewed by itself, or in combination with the leaf or fruit of a pepper plant (*Piper betle*) and lime powder, the mixture being popularly known as “betel quid.” Fresh nuts are consumed in both the fully ripe and unripe stages (WHO 2012; IARC 2004). The fine white lime powder (calcium oxide, or quicklime) used in the betel quid is usually the end-product of burning coral rock, sea coral, or shells (IARC 2004), and it must be kept in sealed containers to stay dry. As an alternative, water may be added to produce slaked lime (calcium hydroxide). Tobacco (either loose tobacco or as a portion from a cigarette) and other flavorings (spices such as cardamom and even garlic) may be added to the betel quid to enhance the flavor and heighten the physiologic effects (WHO 2012).

2156 Use of areca nut/betel quid does not involve tobacco use in all cultures. For instance, areca nut
2157 chewers in island countries within Melanesia (Fiji, Papua New Guinea, Solomon Islands,
2158 Vanuatu) as well as in Taiwan and Hunan province, China, are unlikely to add tobacco to their
2159 quid (WHO 2012; IARC 2004). Tobacco is added to the areca nut/betel quid in certain areas,
2160 especially in the Pacific Islands, Cambodia, Vietnam, and the Philippines. Where areca nut/betel
2161 quid is consumed with tobacco, national and subnational published studies indicate that
2162 prevalence and patterns of consumption vary both across and within countries. Key informant
2163 interviews conducted in 2005 by the Secretariat for the Pacific Community (SPC) in several
2164 Pacific island countries highlighted the rising prevalence of areca nut/betel quid consumption
2165 among younger people and the increasing practice of adding tobacco to the quid (WHO 2012).

2166 The growing popularity of chewing areca nut/betel quid with tobacco has spurred the emergence
2167 of local sales of areca nut and prepackaged betel quid as a cottage industry in several Asia–
2168 Pacific countries. For example, in Palau it is possible to purchase premade quids from local
2169 vendors, and the ingredients for a quid are increasingly becoming available at convenience stores
2170 and neighborhood shops throughout Micronesia (personal communication, C. Otto 2011). In
2171 Guam, a community-based participatory research project on tobacco points of sale revealed that
2172 over 50% of manufactured tobacco retail outlets also sold fresh betel nut, *P. betle* leaf, and lime,
2173 which were usually displayed beside or close to cigarettes, cigarette lighters, or candy (David
2174 2011).

2175 Areca nut is considered an IARC Group 1 carcinogen (IARC 2004). Arecoline, a major areca nut
2176 alkaloid, is considered the most important carcinogen in the areca nut. Areca nut extract (ANE)
2177 is highly cytotoxic and genotoxic to cultured human oral mucosal epithelial cells and fibroblasts
2178 (connective tissue cells). Researchers from Taiwan have published studies on the toxicologic
2179 profile and toxic effects of betel quid without tobacco (Chen 2008), but toxicity information on
2180 the combination of areca nut/betel quid with tobacco, as used in the Western Pacific, represents a
2181 data gap for the region.

2182 ***Other Types of Smokeless Tobacco***

2183 It is likely that other types of ST are used in the region, but data are not readily available. In
2184 addition to chewing tobacco, snuff may be used in Guam and the Northern Mariana Islands
2185 (CNMI). In Japan in 2003, the Swedish company Swedish Match initiated consumer testing for a

2186 brand of tobacco gum called “Firebreak,” which was launched in Sweden in 2006 (Swedish
2187 Match 2006); however, specific data on the prevalence of use of this product could not be found.
2188 In Kiribati, young people are using a novel form of ST, a mixture of tobacco from cigarettes with
2189 immature green coconuts (personal communication with Kireata Ruteru, 2011).

2190 **Region-Specific Observations and Challenges**

2191 Existing measures to control ST use in the Western Pacific involve both supply- and demand-
2192 reduction strategies. Compared to policies and interventions to reduce smoking, actions to
2193 control ST use in the Western Pacific are rudimentary and often fail to consider the sociocultural
2194 context of the region as it relates to other forms of tobacco use. In part, policy inconsistencies
2195 stem from ambivalence regarding areca nut/betel quid use in contrast to tobacco use. This
2196 ambivalence arises partly from the long-held popular notion that chewing areca nut/betel quid is
2197 symbolic of cultural identity, and partly from a general lack of awareness of the negative effects
2198 of areca nut/betel quid chewing. Efforts to educate policymakers and the public should focus not
2199 only on smokeless tobacco but also on areca nut/betel quid, because use of areca nut/betel quid is
2200 closely linked with ST use.

2201 Current policies and interventions vary across countries in this region. Some countries have
2202 instituted bans on ST (Australia, New Zealand), bans on ST manufacturing (Taiwan), or bans on
2203 ST importation (Japan, Hong Kong, Singapore, Taiwan). However, the ST importation bans in
2204 Hong Kong, Japan, Singapore, and Taiwan have had no impact on the consumption of areca
2205 nut/betel quid with tobacco because the tobacco used is often taken from cigarettes and other
2206 sources.

2207 Western Pacific countries are highly impacted by forces of economic globalization, and the high
2208 priority placed on international trade in the region presents both benefits and obstacles to
2209 effective tobacco control. For example, economic rather than public health goals may make
2210 governments reluctant to impose trade restrictions on tobacco products, and this position could
2211 undermine tax policies and other measures to raise tobacco prices. Under the ASEAN Free Trade
2212 Agreement (AFTA), tobacco products made in ASEAN countries with at least 40% of the raw
2213 materials from the ASEAN subregion are subject to a tariff-reduction scheme mandated in the
2214 agreement, thus encouraging use of these products (ASEAN Secretariat 1992). Furthermore, the
2215 sale and distribution of areca nut also contribute to government revenue sources, and therefore

2216 exports of these products have increased to meet the demands of migrants. Internet sales are
2217 likewise increasing (Van McCrary 1998).

2218 Because cultivation, sales, and distribution of areca nut/betel quid with tobacco most often occur
2219 as part of the informal economy, regulation through taxation (other than taxing cigarettes) is
2220 challenging. In Taiwan, areca growing and the sale of betel quid are rapidly growing businesses
2221 that appear to parallel the expansion of the cigarette market. Although international tobacco
2222 companies have not begun marketing the product, Taiwanese betel quid producers have set up
2223 neon-lit roadside kiosks around the country, where scantily clad young women, known as “Betel
2224 Quid Barbies,” sell betel quid and cigarettes to motorists (Wen 2005). Since areca nut and betel
2225 quid use are culturally ingrained in many Asia–Pacific societies, there is little need for extensive
2226 marketing outside of local channels. On the other hand, anecdotal reports indicate that
2227 commercial ST products produced by national and multinational tobacco companies are
2228 becoming more visible and that advertising for these products is increasing. Hong Kong,
2229 Singapore, and Taiwan prohibit advertising and promotion of ST products.

2230 **Best Practices and Future Needs**

2231 Existing data on ST use, toxicity, and health effects are scarce and fail to provide an accurate and
2232 comprehensive picture of the magnitude of the problem and its attendant health, economic, and
2233 social consequences. Without an effective surveillance system, there is no reasonable way to
2234 gauge changes in prevalence over time within countries and across the region, or to measure the
2235 effectiveness of policy and program interventions. Although we know that areca nut contains
2236 carcinogenic compounds, detailed toxicologic data are incomplete, with most of the studies
2237 conducted on areca nut and betel quid without tobacco. Addressing the multiple data gaps should
2238 be the first step toward developing an effective and coordinated response to controlling ST use in
2239 this region.

2240 The Western Pacific Region is the first and, to date, the only WHO Region to achieve a 100%
2241 ratification rate for the WHO FCTC. Globalization is facilitating the diffusion of ideas and
2242 examples of successful national tobacco control strategies across the Western Pacific countries
2243 and areas and is mobilizing support for implementation of the FCTC (da Costa 2009).

2244 Despite the challenges for implementing ST use restriction policies in this region, there are many
2245 success stories. For example, in 1986, the government of the Australian state of South Australia
2246 became the first government in the world to ban ST; the ban became national in 1991 (Chapman
2247 2001). New Zealand has also banned ST (WHO 1997). In March 2010, the Marshall Islands
2248 became the first Pacific island country to ban importation, distribution, and sales of areca
2249 nut/betel quid, with violations punishable by a fine of up to US\$100 and 30 days in jail
2250 (Secretariat of the Pacific Community 2010). While some of these bans contain loopholes such
2251 as allowing importation of ST products or areca nut for personal consumption (Australian
2252 Competition and Consumer Commission 2012; Marshall Island Journal 2011), they still
2253 represent significant strides toward reducing the burden of tobacco-related health, economic, and
2254 social consequences.

2255 In addition to banning ST, Singapore has also taken steps to keep pace with industry
2256 developments and preempt the entry and spread of new products in local markets. In July 2010,
2257 the government of Singapore passed an amendment that expanded the scope of the 1993 Tobacco
2258 (Control of Advertisements and Sale) Act. Novel and emerging forms of tobacco products, such
2259 as tobacco derivatives (dissolvable tobacco) and nicotine-based products, are now subject to the
2260 same regulatory control as existing ST products, and the Minister for Health is empowered to
2261 ban a wider array of products, including more types of smokeless tobacco.

2262

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Key Findings and Recommendations

Key Findings

1) Smokeless Tobacco Use Is a Complex Global Problem

Smokeless tobacco (ST) use is a global problem affecting an estimated 300 million people across about 70 low-, middle-, and high-income countries. All six WHO regions contain a significant population of ST users, and almost all countries for which data are available report some level of ST use. In countries with the highest prevalence, most current users report daily use of ST. ST use poses an extremely complex public health challenge, as product characteristics, patterns of use, health effects, marketing and production practices, and public health and policy responses vary widely between countries and regions.

ST has a disproportionate impact in some countries and subpopulations. The majority of adult ST users (89%, or approximately 268 million) live in low- and middle-income countries in South-East Asia. There are an estimated 220 million adult ST users in India alone, where overall adult prevalence is 26% (exceeding the prevalence of cigarette smoking), followed by Bangladesh with 28 million ST users (27%), and Myanmar with 11 million ST users (30%). The figures presented here represent only those countries for which data are available; data are lacking for some key regions, including some countries in South-East Asia where substantial ST use might be expected.

In most countries ST use is more prevalent among men than women. However, several countries reported high use of ST among both men and women. In several countries in the African, South-East Asian and Western Pacific Regions, prevalence of ST use among women significantly exceeded that of men. Some studies have found that women report initiating ST use during pregnancy because they believe it will alleviate symptoms of morning sickness (Senn et al. 2009, Singh et al. 2009), and ST use during pregnancy has been associated with adverse reproductive outcomes. More research is needed to understand the factors that lead to high prevalence of ST use among women in these countries.

ST use is also prevalent among youth in many countries. Of the 57 countries for which sufficient national data were available to be included in this report (using GYTS surveys of students aged 13–15 years), all reported some ST use among youth, and 33 reported overall use greater than

2347 5% among youth. As with adults, ST use is generally higher among males than females. In many
2348 regions, ST products are marketed and sold in ways that may appeal to youth, such as in
2349 publications with a high youth readership or next to candies and snacks in street stalls and
2350 kiosks.

2351 A high prevalence of ST use is also seen among some population subgroups even within
2352 countries where overall prevalence is low compared with cigarette smoking, particularly among
2353 native populations and recent immigrants. For example, while prevalence of ST use among
2354 Alaskan non-Native adults is similar to the U.S. average, prevalence among Alaska Native adults
2355 is three times greater. Similarly, in Brazil the use of rapé is rare among urban populations but
2356 more common among rural native populations. Immigrants from regions where ST use is
2357 prevalent may bring their practices with them. For example, the use of gutka or betel quid with
2358 tobacco has been found to be very common among first-generation immigrants from Bangladesh
2359 and India living in New York and London. And reports suggest that some youth, such as those in
2360 Venezuela and Micronesia, may view ST products as a means to express national identity or
2361 traditional culture.

2362 **2) Smokeless Tobacco is Not Safe**

2363 There is substantial evidence that ST products cause addiction, precancerous oral lesions, cancer
2364 of the oral cavity, esophageal and pancreatic cancer, and adverse reproductive outcomes,
2365 including stillbirth, preterm birth, and low birth weight. Data from some countries have
2366 demonstrated a link between ST and increased risk of fatal myocardial infarction or stroke. All
2367 ST products contain chemicals known to cause harm, such as tobacco-specific nitrosamines
2368 (TSNAs) and polycyclic aromatic hydrocarbons (PAHs). In fact, a well-developed model
2369 describes the mechanistic pathway by which the TSNAs *N*'-nitrosonornicotine (NNN) and 4-
2370 (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are metabolically activated and induce
2371 primary DNA lesions that may ultimately lead to cancer. Thus, all ST products are hazardous to
2372 use.

2373 **3) Health Impact May Vary Across Countries**

2374 The total public health impact of ST use is related to the disease risks associated with particular
2375 products, their prevalence, the manner of use, and the underlying burden of disease (which may
2376 also be influenced by other risk factors). Currently available data are insufficient to support an

estimate of the total global disease or mortality burden of ST use. Additionally, because smokeless tobacco use is limited or more recent in many countries, particularly in higher income countries, research and data collection have lagged. However, estimates of attributable risk for countries where adequate data are available show wide variation in the attributable disease burden. For example, most studies from Sweden have not shown an association between ST use and oral cancer, but studies in India have shown very high relative risks (from 2 to 14) for oral cancer. These differences may be due in part to differing levels of harmful constituents in the products. For example, reported levels of TSNA in ST product samples from a variety of countries, and within the same country, vary by many orders of magnitude. One laboratory study comparing samples of products from India found that total TSNA content varied from 0.1 to 127.9 µg/g. Likewise, an analysis of U.S. moist snuff products showed a 70-fold difference in NNAL content across leading brand, whereas products in Sweden show less variation in TSNA levels because they adhere to specific standards for TSNA levels.

In general, the greatest disease burden from ST use occurs in low- and middle-income countries where the highest relative risks have been recorded and the greatest numbers of users live. Those countries face a multi-pronged challenge: They are home to the most diverse array of products, some of which are extraordinarily high in toxicants, but their ability to regulate ST products and implement effective tobacco control measures is hampered by limited resources and the local, unorganized nature of the tobacco manufacturing and retailing. For example, India experiences high oral cancer rates (Ferlay et al. 2008), and it is estimated that more than 50% of oral cancers in India (and Sudan) can be attributed to ST use (Boffetta et al. 2008).

4) Smokeless Tobacco Products Are Diverse

The term “smokeless tobacco” covers a large and extremely diverse group of products. They differ in color, appearance, consistency, packaging, and manner of use. They also vary in their mode of manufacture or preparation (premade vs. custom-made), in the scale of production (large-scale manufacturing, cottage industry, or individual vendor preparation), and in their ingredients (type of tobacco leaf, alkaline agents, flavorants, and other non-tobacco content, such as areca nut or tonka bean). The best estimates indicate that, by volume, 91.3% (648.2 billion tons) of ST worldwide (710.2 billion tons) is sold in traditional cottage industry markets (Euromonitor International 2010).

2407 ST products also vary greatly in their chemical composition, with some products containing
2408 extremely high levels of carcinogens, nicotine, and free nicotine (the most rapidly absorbed
2409 form). For example, levels of TSNA in ST products vary by as much as 400-fold (Stanfill et al.
2410 2011). A 2008 survey of 39 top-selling brands of U.S. moist snuff showed a more than 500-fold
2411 range in free nicotine (Richter 2008). Levels of toxicity, carcinogens, and free nicotine are
2412 influenced by a wide range of factors, including species of tobacco plant used, characteristics of
2413 the soil in which the tobacco was grown (e.g., the concentration of nitrite and certain metals),
2414 curing methods (air-cured vs. fire-cured), processing methods (pasteurized vs. fermented),
2415 addition of certain ingredients (tonka bean, areca nut, alkaline agents), and conditions under
2416 which the final products were stored. Based on research to date, steps could be taken to reduce
2417 the presence of carcinogens or other toxicants in ST products, including reduction or elimination
2418 of the use of fire-cured tobacco, improved prevention of microbial contamination, changes in
2419 fermentation, elimination of ingredients such as areca nut and tonka bean, and improvements in
2420 storage conditions.

2421 Despite this enormous product diversity, some important common cross-product observations
2422 can be made. The practice of adding alkaline agents to boost nicotine delivery is commonly
2423 found in a number of traditional and manufactured ST products around the world (such as punk
2424 ash added to iqmik in Alaska, slaked lime added to khaini in India, or sodium bicarbonate added
2425 to toombak in Sudan). Adding flavorings (e.g., menthol, cocoa, licorice, rum, aniseed, cinnamon,
2426 clove) and sweeteners (e.g., molasses, honey, dextrose, sorbitol, fruit juices) is also a common
2427 practice and may make the product more appealing to youth and new users (Henningfield et al.
2428 2011). Additionally, there appears to be a growing emphasis on increased convenience and ease
2429 of use in the marketing of ST products in countries at different income levels. Gutka, a dried,
2430 prepackaged version of the fresh betel quid traditionally mixed to order by a vendor or user, has
2431 become increasingly popular in India and is now a large-scale industry. At the same time, in
2432 high-income countries such as the United States, tobacco product manufacturers have packaged
2433 moist snuff in pouches that do not require spitting, marketing them to smokers as a discreet and
2434 convenient alternative for settings where they cannot smoke.

5) Marketing Strategies Are Made to Appeal to Youth

Tobacco industry marketing strategies also show some common trends. Across high-, middle-, and low-income countries, tobacco product manufacturers utilize colorful packaging, suggestive names and slogans, cross-branding with non-tobacco products, price discounts, health or medicinal associations, and lifestyle marketing appeals to sell their products.

In middle and low-income countries, marketing strategies may pose a particular challenge for tobacco control efforts by circumventing existing tobacco control measures, using brand names for their nontobacco products, and use of packaging that appeals to youth. For example, manufacturers in India use the same brand names for their non-tobacco products as for tobacco-containing products in an effort to circumvent India's ban on tobacco product advertisements on television. Use of small single-use packaging makes products inexpensive and more easily available to youth and may dilute the impact of tobacco taxes. In addition, large-scale marketing campaigns are generally absent for traditional cottage industry products, but large multinational companies have entered markets in some low- and middle-income countries and have begun to produce some traditionally cottage industry products on a larger, commercial scale.

5) Smokeless Tobacco Products are Evolving to Capture More Users

In high-income countries such as the United States, a number of manufacturers have introduced novel ST products, using new product formulations (e.g., reduced nitrosamines, dissolvable formulations, spit-free pouches, new flavorings) and marketing practices (e.g., targeting current smokers and devising innovative packaging). These products and practices may appeal to new groups of users. For example, novel snus products have been marketed to smokers for use in settings where they cannot or do not want to smoke, using imagery that emphasizes trendiness, urbanity, freedom, and sophistication for both men and women. And U.S. cigarette manufacturers have introduced ST products with popular cigarette brand names such as Marlboro and Camel. These new marketing strategies raise concern because they may increase initiation, deter people from quitting smoking or other tobacco use, or result in dual use or use of multiple tobacco products.

6) Interventions and Knowledge about Health Effects Are Limited

In all regions, evidence-based interventions tailored to the prevention and cessation of ST use are limited. In some regions, knowledge about the health effects of ST use is limited even among

2465 health professionals. The existing evidence for treatment programs comes largely from high-
2466 income countries, and data on smokeless tobacco quit rates are not available for most countries.
2467 Thus, there is a particular need to develop and test interventions targeted at low-income
2468 populations or countries where the burden of ST use is greatest.

2469 **7) Smokeless Tobacco Policies Are Varied and Often Weaker than for Smoking**

2470 A diverse range of programs and policies have been implemented in different countries and
2471 municipalities to address ST use; however, limited data are available to evaluate the impact of
2472 these interventions. Some countries and municipalities have banned entire classes of tobacco
2473 products, such as the ban on gutka sales imposed by some states and subregions in India. In
2474 many countries, a lower standard has been applied to ST products compared with cigarettes. For
2475 example, in many regions, even those where ST use is highly prevalent, policies and programs
2476 aimed at ST use prevention and cessation are generally weaker than those for smoked tobacco
2477 products: prices are lower, warning labels are weaker or nonexistent, surveillance is weaker,
2478 fewer resources are devoted to prevention and control programs, and fewer proven interventions
2479 are available. While restrictions on smoking in public places, even outdoors, have been
2480 vigorously pursued in many countries around the world to both smoked and nonsmoked tobacco
2481 products, few efforts have been made to apply these rules to all tobacco products.

2482 **Overall Challenges**

2483 **1) Not Focusing on the Smokeless Tobacco Problem**

2484 The public health challenge of ST warrants far greater attention and action than it has so far
2485 received, considering the magnitude and complexity of the problem, industry marketing, trends
2486 in patterns of use, and a lack of effective interventions. According to Euromonitor International,
2487 the global market for both modern and traditional snuff products is projected to increase by 24
2488 percentage points between 2011 and 2016, compared to only a projected 7 percentage point
2489 increase in the market for cigarettes (Euromonitor dataset). Moreover, while the WHO
2490 Framework Convention on Tobacco Control (FCTC) applies to all tobacco products, many of the
2491 strategies developed under the Conference of Parties to date are focused on cigarettes, and no
2492 specific guidance has been developed regarding ST products.

2) Limited Data to Inform Decisions

The prevalence of ST use is particularly high in some low- and middle-income countries and among low- income populations. The major challenge that faces these countries is the limited data to help craft policies and programs. For example, data on pricing, tax structures, and sale of ST products and marketing strategies are very limited, especially in those countries where ST use is most prevalent. Cottage industry production makes collection of taxes more challenging and probably less effective. Additionally, information on the cost of health care to treat ST-related diseases is nonexistent. This is a particularly significant gap in the data needed to inform the control of ST use.

3) Emerging New Products in High Income Countries

While the public health burden falls disproportionately on low- and middle-income countries, the findings and gaps identified in this report have substantial public health importance for high-income countries as well. The United States, with 9 million ST users, is among the countries with the largest populations of ST users. Between 2005 and 2010, sales of moist snuff grew by US\$2.04 billion following increased marketing of these products (Euromonitor 2011). National surveys also suggest that between 2000 and 2010 ST use in the United States rose among youth, particularly high school males (CDC 2012; Johnston et al. 2011; SAMHSA 2009). The major challenges faced by the U.S. and potentially other high income countries include the number of many different types of tobacco products that are emerging in the market. As noted previously, novel snus-type products using familiar cigarette brand names (Camel and Marlboro snus) are being marketed to smokers for use in settings where they cannot smoke (Timberlake et al. 2011; Mejia and Ling 2010). This trend may adversely impact smoking cessation efforts by encouraging dual use as an alternative to tobacco use cessation. Additionally, dual use of ST and cigarette smoking could have greater health risks than smoking alone (USDHHS 2010, Teo 2006), and although cigarette smokers who permanently switched to ST exclusively decreased their risk of some diseases specific to smoke exposure, those who quit tobacco use altogether lowered their mortality rates from lung cancer, coronary heart disease, and stroke more than those who switched to ST use, as evidenced from a single study that examined this effect (Henley 2007).

4) Harm Reduction Debate

Another challenge revolves around the smokeless tobacco harm reduction debate. Some have suggested that ST products, particularly those low in nitrosamines, could act as harm reduction agents for cigarette smokers, especially in high-income countries with lower disease burdens related to ST use. However, as this report suggests, the assessment of risks and benefits in such a strategy, particularly on a population level, is complex and uncertain. In almost all countries, ST products have widely varying levels of addictive potential and toxicity. Furthermore, available data do not allow for identifying specific levels of product constituents with quantifiable risk reductions. Additionally, no rigorous studies have demonstrated the effectiveness of a ST product for smoking cessation or as a complete substitution for cigarettes..

Comment [KB2]: Could there be a chapter on the role of smokeless tobacco for initiation and cessation?

Research Needs

This summary offers guidance to researchers, public health practitioners, and policymakers on addressing the public health impact of ST use around the globe.

1) Surveillance and Monitoring

Comprehensive surveillance is needed to assess the scope of ST use and changes in patterns of use, and to evaluate the impact of policies, interventions and other steps that could be taken to address ST use. Surveillance and monitoring of trends in ST use should include information on populations and subpopulations that use ST, types of products used, patterns and intensity of use, combined use of other tobacco products, and attitudes, beliefs, and perceptions about tobacco products. For example, the existing CDC-led Global Tobacco Surveillance System and WHO STEP surveys could be expanded to provide greater coverage of ST. Smaller, targeted surveys are needed in order to assess the impact of novel products or rapid changes in use and to understand patterns among specific subgroups. Standardized measures of ST use and exposure, including quantity and frequency of use, are also needed. The WHO's Tobacco Questions for Surveys (CDC, WHO 2011) provides a subset of basic questions that can be added to existing surveys, and this resource could be further expanded and tailored to specific products and regions.

2) Products

Given the diversity of products and modes of manufacture around the world, a more comprehensive characterization of the properties of different products, their constituents, and methods of manufacture is needed. Where resources are available, biomarker studies to examine

2553 actual human uptake (absorption and excretion) of nicotine and toxicants as a result of active and
2554 secondhand (e.g., fetal) exposure to ST would be valuable. Additionally, attention should be
2555 given to non-tobacco products that are frequently used in conjunction with tobacco, such as areca
2556 nut. Further research is needed to develop standardized testing methods for diverse products. The
2557 laboratory standards being developed by the WHO Tobacco Laboratory Network for testing
2558 cigarettes could be expanded and adapted for ST products.

2559 **3) Health Effects**

2560 While there is a significant body of research on particular health effects of ST use in a few
2561 countries, the diversity of products, practices, and patterns of use precludes broad generalizations
2562 about health effects. Most studies of health effects have been conducted in Scandinavian
2563 countries, the United States, and India. Because of the diversity in toxicant and nicotine levels
2564 across ST products, applying results from one country to another country is problematic. Even
2565 within a country, ST products can vary tremendously. Also, mixed results in some studies (such
2566 as in cardiovascular disease effects) and small numbers suggest the need for further
2567 investigation. The effects of ST use on birth outcomes need further characterization, especially
2568 considering the high prevalence of ST use among some subgroups of women of reproductive
2569 age. In order to link specific types of products with particular health effects, studies are needed
2570 that link the constituent profile and biomarkers of exposure and biomarkers of effect to specific
2571 ST products with health consequences; establishing these links may be extremely challenging for
2572 custom-made and cottage industry products with little or no standardization. Studies should also
2573 investigate the health effects of other ingredients and combinations of ingredients frequently
2574 used in ST products, such as areca nut or tonka bean.

2575 **4) Economics and Marketing**

2576 Very little information is currently available on pricing and sales volume of ST products in many
2577 countries. While many studies have been conducted on the price elasticity of cigarettes, for
2578 example, comparable data for ST are very limited. Given the high prevalence of ST use in some
2579 low- and middle-income countries and among poor and rural populations, pricing information
2580 may be especially important for understanding patterns of use and developing effective public
2581 health interventions. Information on price, taxes, affordability, and trade should be collected
2582 routinely. Additionally, locally relevant data are needed to demonstrate the economic benefits of
2583 tobacco control measures because some countries with active tobacco industries may seek to

2584 delay or defeat actions to reduce ST use out of concern for the potential impacts on national
2585 economies. Lastly, ongoing surveillance of tobacco industry marketing strategies is important,
2586 particularly following the implementation of new policies or regulations, or the entrance of new
2587 multinational tobacco companies into the market..

2588 **Building Capacity**

2589 Enhancing surveillance, pursuing a research agenda, and implementing new policies and
2590 interventions to address ST use will require increased scientific and public health capacity in
2591 low- and middle-income countries, particularly those that are confronted with high burdens of ST
2592 use. Increased in-country capacity to conduct tobacco control research is critical to the
2593 development and implementation of effective interventions, as these interventions must be
2594 responsive to local populations and contexts. In addition, robust local capacity enhances the
2595 sustainability of evidence-based policies and programs, as local researchers and institutions are
2596 well positioned to respond to changes in the tobacco control environment over time by
2597 generating new relevant knowledge to inform modifications or new approaches. At the same
2598 time, greater capacity for communication and collaboration across countries is increasingly
2599 important. As tobacco use trends change, innovative policies and interventions are introduced in
2600 different countries, and the tobacco industry adopts new marketing strategies, an enormous
2601 “natural experiment” is under way that provides unique opportunities for research and
2602 evaluation. Making use of these opportunities will require coordinated surveillance, information
2603 sharing, and research efforts. With this in mind, the following recommendations are made to
2604 enhance collaboration and infrastructure (some of which have been described in Article 20 of the
2605 FCTC):

2606 **1) Regional Clearinghouses**

2607 Create regional information clearinghouses for ST that can be readily accessed electronically by
2608 people from all parts of the world. These clearinghouses can inform stakeholders within and
2609 outside a region about ST product characteristics, patterns of use, policies and interventions that
2610 have been implemented, and the results of any research or evaluation conducted.

2611 **2) Infrastructure for Networking, Communication, and Collaboration.**

2612 One mechanism for facilitating this goal would be to develop a Web portal to serve as a
2613 repository and index to information on ST product characteristics, constituents and ingredients,

2614 manufacturing and promotion methods, product price, and packaging and marketing materials.
2615 This Web portal could also bring together the regional clearinghouses described above and
2616 provide a forum for discussion about research design, research results, and policies.

2617 **3) Build Collaborations among Scientists, Tobacco Control Advocates, and**
2618 **Policymakers.**

2619 These collaborations are critical for translating research into policy and ensuring that policy
2620 needs inform research studies. Collaborations across countries and regions are especially
2621 important to making comparisons between different products, environments, and interventions.
2622 Countries with more mature tobacco control programs can provide expertise and assistance to
2623 countries that are newly implementing programs and policies.

2624 **4) Build Research Capacity**

2625 Develop ways to build research capacity by better leveraging existing resources such as the
2626 Tobacco Laboratory Network, the Global Adult Survey and Global Youth Tobacco Survey, and
2627 the Tobacco Harm Reduction Network. Research capacity can also be enhanced by attracting
2628 and training new researchers—especially those in middle- and low-income countries—and
2629 encouraging collaborations between new and experienced researchers.

2630 **Intervention and Policy Needs**

2631 Tobacco control policies, programs, and interventions applied to cigarettes and smoked tobacco
2632 products should be applied, enforced, and monitored with equal strength to ST products,
2633 particularly in regions where the burden of ST use is high. Prevention and cessation of ST use
2634 should form an integral part of every comprehensive tobacco control effort. At the same time, ST
2635 products pose some distinct challenges compared with smoked products, and specific policy
2636 needs may vary across countries, depending on products, patterns of use, industry marketing, and
2637 the tobacco control environment. The following in particular should be addressed for the control
2638 of ST products:

2639 **1) Apply FCTC requirements to Smokeless Tobacco Products**

2640 Specific guidelines are needed to ensure that the FCTC requirements are applied to ST products
2641 as well as cigarettes. For example, the FCTC binds parties to ban or restrict sponsorship and
2642 marketing of tobacco products, prohibit sale to minors, and track and monitor illicit trade.

2643 Additional guidance can help ensure that the FCTC requirements are fully applied to a diverse
2644 array of ST products as well.

2645 **2) Educate the Public about Harms of Smokeless Tobacco**

2646 In all regions, greater awareness is needed about ST use and its health effects, including
2647 education of health professionals, consumers (with particular attention to youth and women of
2648 childbearing age), policymakers, and community leaders. Dissemination of information about the
2649 toxicity of tobacco products may be particularly important in geographic areas where tobacco
2650 products are premade through cottage industries, or custom-made at home or at the point of sale.
2651 Greater awareness is also needed among policymakers, health professionals, and the public
2652 regarding the public health impact of ST use and changing patterns in industry marketing and
2653 consumer use.

2654 **3) Develop Product Standards for Smokeless Tobacco Products**

2655 Product standards for ST products need to be developed, implemented, and evaluated. Levels of
2656 known toxicants in ST products vary widely, as does the impact of storage and processing
2657 practices on toxicant levels. Feasible measures for reducing levels of toxicants in the product
2658 include reducing the use of *Nicotiana rustica*, limiting bacterial contamination that can promote
2659 nitrosation and carcinogen formation, and requiring tobacco to be air-cured, pasteurized, and
2660 refrigerated. The WHO Study Group on Tobacco Product Regulation has recommended
2661 mandating upper limits on ST toxicants; this would include setting the upper limit of NNN plus
2662 NNK at 2 micrograms per gram of dry weight tobacco, and the upper limit for benzo[a]pyrene at
2663 5 nanograms per gram of dry weight tobacco.

2664 Research is needed that can form the basis for establishing maximum levels of pH in ST
2665 products. Additives that increase pH in tobacco products boost the amount of free nicotine
2666 available for absorption, and products with higher free nicotine levels are more addictive.

2667 **4) Consider Ban on Flavorants**

2668 Some countries, such as the United States and Canada, have banned flavorings in cigarettes
2669 (except menthol), but they have placed no such limits on the use of flavorants in ST products. A
2670 variety of flavors and other additives are used to enhance the appeal of tobacco products and
2671 facilitate uptake (Henningfield et al. 2011, Tobacco Products Scientific Advisory Committee
2672 2011). A recent U.S. study showed that more ST users (who were seeking an intervention) had

2673 initiated with or switched to a mint-flavored ST product than non-flavored products (Oliver et al.
2674 2012). Banning or limiting certain additives and flavorants may serve as an effective tool for
2675 reducing the attractiveness of ST.

2676 **5) Stronger Public Health Warnings**

2677 Many countries require health warning labels on ST packaging, but most of these labels contain
2678 only textual warnings and lack the graphic images that have been implemented for cigarette
2679 labels. For cigarettes, FCTC Article 11 of the FCTC recommends pictorial warning labels and
2680 mandates that health warnings cover at least 50% of the cigarette packet. These standards have
2681 not been uniformly used with ST products.

2682 **6) Increase Taxes**

2683 Taxes on ST products could be increased (Article 6 of the FCTC). WHO expert panel
2684 recommended that ST be taxed at “a level sufficient to act as a disincentive, and at least at the
2685 level at which cigarettes are taxed” (WHO 1988, p. 64). The same guidelines the WHO FCTC
2686 gives for taxing cigarettes can be applied to ST and all other tobacco products. These
2687 recommendations include an excise tax that makes up at least 70% of the retail price, with the
2688 use of specific excise tax being favored over *ad valorem*. Having a more uniform tax structure
2689 across tobacco products would curtail the practice of substituting other tobacco products, which
2690 would be of particular concern in countries that have very toxic ST products. Due to challenges
2691 inherent in tax collection in traditional markets, taxation of tobacco leaves or a presumptive tax
2692 (compounded levy per manufacturing machine) may be considered. Earmarking a portion of ST
2693 tax revenues to fund ST interventions, other tobacco control efforts, or public health in general
2694 would increase their overall benefit as well.

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Description of Representative Products From the Four Broad Categories of the Smokeless Tobacco Products Used Globally

Product category (other names)	Region/country of use *	Mode of use †	Production ‡	Form/type of tobacco	Added ingredients
Category 1. Tobacco with little or no alkaline agents (generally <pH7) (with or without flavorants)					
Loose leaf	AMR: United States	C, S, H	Commercial	Tobacco leaves (air-cured)	Sugar and/or licorice and other sweeteners
Mishri (masheri, misri)	SEAR: India	A, D, S	Cottage; Custom	Tobacco (powdered)	
Nicotine chewing gum	WPR: Guam, Japan	C	Commercial	Tobacco (finely ground)	Chewing gum base, xylitol
Plug	AMR: United States	C, S, H	Commercial	Tobacco leaves	Licorice, sweeteners
Tobacco leaf	SEAR: India, Bangladesh, Myanmar, Bhutan	C, IN	Custom	Tobacco leaves	
Twist	AMR: United States	C, H	Commercial	Tobacco (dark and air-cured leaf)	Tobacco leaf extracts and sometimes sweeter or flavorings
Red toothpowder (laldant manjan)	SEAR: India	A, D	Commercial	Tobacco (powdered)	Herbs, flavorings. Additional plant-related ingredients such as ginger, pepper, and camphor, among others, may be used. Flavorings may be added.
Tapkeer (bajjar, dry snuff)	SEAR: India	A, H, N	Custom	Tobacco (fermented fire-cured)	
Watery tobacco	SEAR: Myanmar	G	Cottage	Tobacco	Water
Kiwam (qiwam, kimam)	EMR: Pakistan SEAR: Nepal, India, Bangladesh	C, H, IN	Commercial	Tobacco	Spices (cardamom, saffron, and/or aniseed), additives such as musk, and may contain silver flecks
Tombol (bitter tombol)	EMR: Middle East	C, H	Custom	Tobacco	Areca nut (fotal), slaked lime, noura, betel leaf (tombol leaf), catechu, and flavorings such as clove oil, cardamom, or herbal medicine
Hogesoppu (leaf tobacco)	SEAR: India	C, IN	Cottage	Unprocessed tobacco bundled in long strands	
Kaddipudi	SEAR: India	C, IN	Cottage	Powdered sticks of raw tobacco stalks and petioles	Sometimes molasses and water
Gundi (kadapan)	SEAR: India	C, IN	Cottage	Tobacco (coarsely powdered)	Coriander seeds, other spices and aromatic, resinous oils
Pattiwalla without lime	SEAR: India	C, IN	Cottage	Tobacco (Sun-dried flaked)	
Snus	EUR: Sweden, Norway, Finland, Denmark, Iceland AMR: United States, Canada, Brazil AFR: South Africa	H	Commercial	Tobacco (heat-treated, pasteurized)	Sodium carbonate, moisturizers, salt (sodium chloride), sweeteners, flavorings, water
Category 2. Tobacco with appreciable amounts of alkaline agents (>pH 7)					
Iqmik	AMR: United States (Alaska)	C	Custom	Tobacco	Tree fungus ash (also known as punk, araq, or buluq ash) or other ash derived from burning drift wood or willow bushes

Product category (other names)	Region/country of use *	Mode of use †	Production ‡	Form/type of tobacco	Added ingredients
Nass (naswar)	EMR: Pakistan, Iran, Afghanistan, United Arab Emirates AFR: South Africa EUR: Turkmenistan	C, S, H	Cottage; Custom	Tobacco	Nass: ash, cotton or sesame oil, water, and sometimes lime or gum Naswar: slaked lime, ash, indigo (or other coloring agent), oil, water, and sometimes flavorings such as cardamom and menthol
Chimó	AMR: Venezuela, Columbia	H, S	Commercial; Cottage	Tobacco leaf	Baking soda (sodium bicarbonate), brown sugar, ashes from the Mamón tree (<i>Melicocca bijuga</i>), and vanilla and anisette flavoring. Ingredients vary by region.
Shammah	EMR: Saudi Arabia, Yemen AFR: Algeria	H, S	Cottage; Custom	Tobacco	Slaked lime, ash, black pepper, oil, flavorings, and bombosa (sodium carbonate)
Nasway (nasvay)	EUR: Uzbekistan, Kyrgyzstan	H, S	Cottage; Custom	Tobacco leaves (sun- and heat-dried)	Tobacco leaves, slaked lime, water, and sometimes ash from tree bark, butter or oil, flavorings, or coloring agents
Toombak	EMR: Sudan	H, N, S	Cottage; Custom	Tobacco (fermented, sun-dried)	Atrun (sodium bicarbonate)
Creamy snuff	SEAR: India	A	Commercial	Tobacco	Clove oil, glycerin, spearmint, menthol, camphor, water
Gudakhu/Gudakha	SEAR: India	A, H	Commercial; Custom	Tobacco (powdered)	Molasses, red soil, slaked lime
Gul	SEAR: India, Bangladesh	A, D	Commercial	Pyrolysed tobacco leaves	Sugar or molasses, alkaline modifiers, and other unknown ingredients
Dry snuff	AMR: Canada, United States AFR: South Africa, Nigeria EUR: Germany	H, S, N	Commercial	Tobacco (fermented fire-cured)	Flavorings
Ghana traditional snuff (tawa)	EUR: Ghana	H, N	Cottage; Custom	Tobacco leaves (dry)	Salt peter (potassium nitrate), ashes
Neffa	EMR: Libya, Tunisia AFR: Algeria	N	Cottage; Custom	Tobacco (dry)	
Tumbaco	AFR: Congo	N	Cottage	Tobacco (dry)	
Nigerian traditional snuff (taaba)	AFR: Nigeria, Cameroon, Senegal, Chad, Uganda	H, S, N	Cottage; Custom	Tobacco (dry fermented)	Natron (a mixture of sodium bicarbonate and sodium chloride)
Traditional South African snuff (snuif)	AFRO: South Africa, Lesotho, Swaziland	S, N	Cottage; Custom	Tobacco leaf (sun dried)	Ash from local plants (e.g., amaranthus, aloe vera leaves)
Dissolvables	AMR: United States	DI, S, H	Commercial	Tobacco pressed into tablet, strip or sticks	Alkaline agents, humectants, preservatives, flavorings
Tobacco water (tuiber)	SEAR: India	G, H	Cottage; Custom	Tobacco smoke	Water, alkaline agents
Moist snuff	AMR: United States, Canada, Mexico AFRO: South Africa	H, S	Commercial	Tobacco (fermented air- or fire-cured)	Flavorings (spices, essential oils, extracts), sweeteners, inorganic salts, humectants, preservatives
Khaini	SEAR: India, Bangladesh, Nepal, Bhutan	S, C, H	Commercial; Custom	Tobacco	Slaked lime paste and sometimes areca nut
Zarda	SEAR: India, Bangladesh, Myanmar, Nepal, Bhutan EMR: Yemen	C, IN	Commercial	Tobacco	Slaked lime or other alkaline agents, spices, vegetable dyes, and sometimes areca nut and/or silver flecks

Product category (other names)	Region/country of use *	Mode of use †	Production ‡	Form/type of tobacco	Added ingredients
Category 3. Tobacco with various alkaline modifiers and areca nut					
Dohra	SEAR: India	C	Custom	Tobacco	Areca nut, slaked lime or other alkaline agents, and other ingredients such as catechu, peppermint, cardamom
Gutka	SEAR: India, Bangladesh, Nepal, Myanmar, Sri Lanka EMR: Pakistan	C, H	Commercial; Cottage	Tobacco	Areca nut, slaked lime or other alkaline agents, catechu, sweeteners, and flavorings
Mainpuri (kapoori)	SEAR: India	C, H, IN	Cottage; Custom	Tobacco	Slaked lime or other alkaline agents, areca nut, camphor, and other spices
Mawa	SEAR: India	C	Cottage; Custom	Tobacco	Slaked lime, areca nut
Betel quid (paan)	SEAR: India, Sri Lanka, Bangladesh, Myanmar, Thailand, Indonesia, Nepal, Maldives EMR: Pakistan, United Arab Emirates WPR: Lao Democratic People's Republic, Palau, Cambodia, Malaysia, Vietnam, Federal States of Micronesia	C, H	Cottage; Custom	Tobacco; Other smokeless tobacco products may be used such as kiwam and zarda	Areca nut, slaked lime, betel leaf, and often catechu Other ingredients vary regionally: cardamom, saffron, cloves, aniseed, turmeric, mustard, sweeteners
Tombol (sweet tombol)	EMR: Yemen	C, H	Custom	Tobacco	Areca nut (fotal), slaked lime, noura, betel leaf (tombol leaf), catechu, and sweeteners such as coconut
Category 4. Tobacco with other plant material (tonka bean, cinnamon, clove, etc.) containing toxicants (coumarin, camphor, eugenol), stimulants (khat, caffeine), etc.					
Rapé and NuNu	AMR: Brazil	N	Cottage	Tobacco leaf (dried)	One or more ingredients: tonka bean, clove, cinnamon powder, camphor, Peruvian cocoa, cassava, ashes from select trees
Tombol with khat	EMR: Yemen	C, I	Custom	Tobacco	Areca nut (fotal), slaked lime, noura, betel leaf (tombol leaf), catechu, and khat
Caffeinated moist snuff	AMR: United States	H	Commercial	Tobacco (fermented air- or fire-cured)	Caffeine, flavorings (spices, essential oils, extracts), sweeteners, inorganic salts, humectants, preservatives, ginseng, B and C vitamins

Notes: Categories are based on product constituents (labels, known ingredients) and available pH data.

* World Health Organization Regions:

AFR: African Region

AMR: Region of the Americas

EMR: Eastern Mediterranean Region

EUR: European Region

SEAR: South-East Asia Region

WPR: Western Pacific Region

† Mode of Use Categories:

A=Applied to the teeth or gums

C=Chewed

D=Dentifrice (teeth cleaning)

DI=Dissolves in the mouth

H=Held in mouth

S=Sucked

G=Gargled

N=Nasal Use

I=Ingredient in betel quid or other custom-made product

‡ Production Category Definitions:

Custom: Product is prepared by a vendor or at the home.

Commercial: Product is commercially manufactured (large-scale, branded).

Cottage: Product is manufactured by local, small-scale industry (sometimes family run business, not branded).