Literature Review

Quantitative Study to Develop VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users

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LIST OF ABBREVIATIONS

Abbreviation	Definition
3R4F	3R4F cigarettes (Kentucky University)
ACSH	American Council on Science and Health
ALI	Air–Liquid Interface
AOR	Adjusted odds ratio
ASH	Action on Smoking and Health) in the U.K.
BoBE	Biomarkers of Biological Effect
CCs	Conventional Cigarettes
CFA	Confirmatory Factor Analysis
CI	Confidence Interval
C-NRT	Combination nicotine replacement
CSE	Cigarette Smoke Extract
CS	Control smokers/ no Axis I disorder
CV	Cardiovascular
CVD	Cardiovascular disease
DCs	Dendritic Cells
DT	Deceleration Time
ECIG	Electronic cigarette users
GS	Global Strain
HCC	HepatoCellular Carcinoma
HPHCs	Harmful and Potentially Harmful Constituents
Iqmik	Homemade smokeless tobacco prepared with dried tobacco leaves mixed with alkaline ash
IVRT	Isovolumetric Relaxation Time
IVRTc	Corrected-to-heart rate IVRT
kDM	Known Diabetes
LN-SLT	Low-Nitrosamine smokeless tobacco
LV	Left Ventricular
MPI	Myocardial Performance Index
MRTPs	Modified Risk Tobacco Products
NIC	transdermal nicotine replacement
NNAL	4-(methylnitrsoamino)-4-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N'-nitrosonornicotine
NRT	Nicotine replacement therapy
NTC	Non-consumers of tobacco
PAH	Polycyclic Aromatic Hydrocarbons
PGT	Pathological Glucose Tolerance
PLA	Placebo
PREP	Presumed Reduced Exposure Product cigarette
RR	Relative risk
SES	Socioeconomic status
SM	Heavy Smokers
SMK	Cigarette Smokers
SNUS	Moist smokeless tobacco
SS	Schizophrenia
ST	Smokeless Tobacco
STC	Smokeless Tobacco Consumers
tcpO2	Transcutaneous partial oxygen tension
THS 2.2	Tobacco Heating System 2.2
TSNA	Tobacco-Specific Nitrosamines
VLNC	Very low nicotine content

1 KEY ROLES

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2 CONSUMER PERCEPTIONS LITERATURE SUMMARY

2.1 LITERATURE SUMMARIZING CONSUMER PERCEPTIONS OF THE HEALTH RISKS OF TRADITIONAL TOBACCO PRODUCTS

This section summarizes published scientific literature related to consumers' perceptions of the health risks of using different tobacco products, including cigarettes, e-cigarettes, nicotine replacement therapy (NRT), snus, and moist snuff. This information addresses the following aspects of the 2012 Food and Drug Administration Draft Guidance for Modified Risk Tobacco Product Applications (MRTPAs) and the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (the Deeming Rule):

- Consumers' beliefs about the health risks of using the cigarette relative to other tobacco products, including those within the same class of products;
- Consumer beliefs about the risks of using the cigarette relative to quitting all tobacco use;
- Consumer beliefs about the health risks of using the cigarette relative to cessation aids.

A comprehensive literature search was conducted to identify published information relevant to consumer perceptions of health risk associated with cigarettes and other tobacco products. A comprehensive and in-depth critical review of publications was carried out. These publications were further reviewed to assess which specific category(ies) in the Draft Guidance each article addressed. Studies of consumer perceptions of tobacco (cigarette) products are summarized.

2.2 CHARACTERISTICS OF CONSUMER PERCEPTION STUDIES PUBLISHED IN THE SCIENTIFIC LITERATURE

The most common research methods used for understanding consumers' perceptions of tobacco products are surveys and focus groups. Some studies reviewed in this section have the primary objective of assessing consumers' perceptions of various tobacco products. Other studies have different primary objectives but also collect some perception information to complement the study's primary findings. Consumer perception studies span a wide range of participant characteristics. These include adolescents, tobacco control professionals, health care providers, and members of the general public. In addition, studies have evaluated perceptions among Current Smokers, Former Users, and Never Users as well as addressed perception of health risk and other risks of exposure to different types of tobacco products, including: e-cigarettes, moist snuff, chewing tobacco, snus, NRTs, and cigarettes.

2.3 THE ABILITY OF CONSUMERS TO UNDERSTAND THE MODIFIED RISK CLAIMS AND THE SIGNIFICANCE OF THE INFORMATION IN THE CONTEXT OF ONE'S HEALTH

None of the published scientific literature did address the consumer perception and comprehension of specific modified claims that are proposed by the Modified Risk Tobacco Application (MRTP). However, as a general principle, providing clear and concise information about the relative risks of tobacco products to consumers may increase the accuracy of smokers' knowledge about the products, as well as their interest in trying the products.

Tobacco products' claim, message and warning statements have been controversial in the past few years. Two major tobacco companies have petitioned the FDA to change the wording of a warning label on their smokeless tobacco products ("This product is not a safe alternative to cigarettes") to read, "No tobacco product is safe but this product presents substantially lower risks to health than cigarettes." During an April 2015 review, the Tobacco Products Scientific Advisory Committee (TPSAC) to the FDA voted against the warning change, with members noting, among various concerns, inadequate research on the statement's development and consumers' perceptions and understanding of it (U.S. Food and Drug Administration, 2015a).

Regulation of tobacco product marketing is needed, particularly the marketing of emerging products for which Current Smokers are forming beliefs and attitudes based on the messages on the package. In one study, Wackowski, Olivia A et al., 2016, showed that e-cigarettes are believed to be safer than cigarettes; there was general understanding among participants that two versions of reduced-risk statements conveyed that e-cigarettes are not necessarily safe but are safer than regular cigarettes. Most participants also appeared to agree that the phrase "substantially lower risks" meant that e-cigarettes are safer, and some specifically noted that it meant e-cigarettes present "a lot less" risks to health than regular cigarettes. Two e-cigarette users quantified "substantially lower" as meaning "more than half" and two other e-cigarette users thought it suggested that "you might not get cancer" from using e-cigarettes, and that the risks are "obviously" lower.

Participants across all groups also agreed that the statements would make e-cigarettes seem appealing compared to cigarettes, particularly to smokers, and would likely encourage their use. Several e-cigarette users agreed that the reduced-risk messages were "true" and "accurate," which in turn changes the perceptions about health risk of smoking particular tobacco products such as e-cigarettes.

In a study conducted by Kaufman, Annette R et al., 2016, perceptions of addiction were driven strongly by advertisements, whereas harm perceptions were not. Understanding consumer perceptions of tobacco products is crucial to effectively address addiction and health risk reduction.

More research is needed to identify the framing, wording and placement (e.g., within or in addition to a warning) that could potentially increase population-level benefits and minimize harms. Adkison, Sarah E et al., 2015, suggest assessments of MRTPs for regulatory purposes should include measurement of social norms, which would allow messages of reduced risk to be compared to general tobacco perceptions. Furthermore, surveillance efforts that track use of new MRTPs should include measures of social norms to determine how norms change with prevalence of use. According to Phillips, Carl V et al., 2005, reduced harm messages are clearly false and likely harmful, representing violations of ethical standards.

Surveys indicated that the public generally did not view smokeless tobacco as harmless, but they did report smokeless as being less harmful than cigarettes despite expert interpretations to the contrary. Subsequent research has shown that the “not a safe alternative” message is misinterpreted by consumers to indicate that smokeless is “not safer” than cigarettes, which was not established and has been disconfirmed by subsequent assessments of that question (Lynn T. Kozlowski, 2018)

Regarding exposure to toxins and harmful chemicals, most of the studies claimed e-cigarettes, snus, and smokeless tobacco are less toxic compared to cigarettes, but they are not completely safe, and asserted more research is required to evaluate individual risk (Murphy et al., 2017) (Farsalinos, Konstantinos E et al., 2014). Data from Azzopardi, David et al., 2016, confirms ePen aerosol induced 97%, 94%, and 70% less cytotoxicity than 3R4F cigarette smoke based on matched EC50 values at different dilutions (1:5 vs. 1:153 vol:vol), mass (52.1 vs. 3.1 µg/cm2), and nicotine (0.89 vs. 0.27 µg/cm2), respectively. Test doses where cigarette smoke and e-cigarette aerosol cytotoxicity were observed are comparable with calculated daily doses in consumers.

Contradictory to the above “less toxic” claims, Vassallo, Robert et al., 2015, claimed that presumed reduced harm PREP cigarettes induce equivalent or greater antigen presenting cell dysfunction relative to 3R4F cigarettes and illustrated the importance of independent validation and testing of similar products claimed to be associated with reduced toxicity relative to other cigarettes.

In a comparative study of salivary cotinine concentrations from Honarmand, Marieh et al., 2018, salivary levels of cotinine were not significantly different in smokeless tobacco users and cigarette smokers. In addition, increases in the number of cigarettes smoked and in packs of smokeless tobacco used were associated with increased salivary levels of cotinine. The increase was higher in smokeless tobacco consumers.

When exposure to nicotine and carcinogens among Southwestern Alaskan Native cigarette smokers and smokeless tobacco users was studied, nicotine concentrations were highest in cigarette tobacco and TSNAs highest in commercial smokeless tobacco products. The participants smoked on average 7.8 cigarettes per day. Nicotine exposure, assessed by several biomarker measures, was highest in ST (iqmik) users, and similar in cigarette users. TSNA exposure was highest in smokeless tobacco users, and polycyclic aromatic hydrocarbon exposure was highest in cigarette smokers (Benowitz, Neal L et al., 2012).

Study methods, participant characteristics, study findings and strengths and limitations of these studies are presented in Table 1.0 and Table 2.0.

2.4 THE ABILITY OF CONSUMERS TO UNDERSTAND THE HEALTH RISKS OF USING THE CIGARETTE RELATIVE TO OTHER TOBACCO PRODUCTS

When the health risk of cigarettes is compared with others forms of tobacco as a cause of cancer, cardiovascular diseases (CVD), and respiratory diseases, cigarettes are perceived to be more harmful compared with other forms of tobacco products. Very few studies claim tobacco products are safe; more research data is required to judge potential long-term effects.

According to Levy D. et al., 2004, experts perceive cigarettes to be 90% more hazardous compared with smokeless tobacco products such as Iqmik, which scored mean ratings of only 9% and 5% of the risk associated with smoking for those ages 35 to 49 and 50+ respectively. Median mortality risks were estimated to be only 2% to 3% for lung cancer, 10% for heart disease, and 15% to 30% for oral cancer relative to cigarette smoking.

The findings from Lee P.N., 2013, consistently demonstrate that continuous smokers have clearly higher risk of CVD and cancer compared with switching from cigarettes to snus. Moreover, risk in switchers is no different from that in smokers who quit smoking.

Results from Hassan, Manal M. et al., 2008, showed sex differences were observed in the relationship between hepatocellular carcinoma (HCC) and cigarette smoking and alcohol consumption. Controlling for smoking exposure might be a prudent approach to the prevention of HCC, especially in patients with chronic viral hepatitis infections. However, in non-cigarette smokers, use of smokeless tobacco (chewing tobacco and snuff), cigars, pipes and passive smoking exposure was not related to HCC.

The comparison between healthy heavy smokers and e-cigarette users made by Farsalinos, Konstantinos E et al., 2014, showed prolonged isovolumetric relaxation time and corrected to heart rate isovolumetric relaxation time; decreased early diastolic (EM) and early diastolic (SRe); and elevated doppler flow and tissue doppler in heavy smokers. No such differences, however, were observed in e-cigarette smokers.

Marano, Kristin M et al., 2015, showed that CVD risk is increased in cigarette smokers and in comparison with smokeless tobacco consumers. That is, although no tobacco product has been shown to be safe and without risks, the health risks associated with cigarettes are significantly greater than those associated with the use of smoke-free tobacco and nicotine products.

According to Eliasson M et al., 2004, smoking and ex-smoking are distinctively risk factors for type 2 diabetes, but the use of snus does not seem to carry the same increased risk. Estimates for snus users are slightly but insignificantly elevated with wide confidence intervals and compatible, at the most, with an excess risk that is much smaller than that of smokers.

Study methods, participant characteristics, study findings and strengths and limitations of these studies are presented in Table 1.0 and Table 1.1.

2.5 CONSUMER BELIEFS ABOUT THE RISKS OF USING THE CIGARETTE RELATIVE TO QUITTING ALL TOBACCO USE

It is reasonable to assume that, to the extent consumers believe use of cigarette causes health risks, they would believe quitting all tobacco use would reduce or eliminate such risks. This section relies on consumers' perceptions of the health risks of using cigarettes relative to quitting all tobacco use. In general, most consumers recognize that cigarette use is associated with health risks. From almost all literature studies, the majority believe that cigarettes are associated with either general or specific health risk (Levy D., et al., 2004; Lee P.N., 2013; Hassan, Manal M et al., 2008; Farsalinos, Konstantinos E et al., 2014; Marano, Kristin M et al., 2015; Eliasson M et al., 2004) and also believe cigarettes are toxic (Benowitz, Neal L et al., 2012; Honarmand, Marieh et al., 2018; Azzopardi, David et al., 2016; Murphy et al., 2017; Farsalinos, Konstantinos E et al., 2014). Quitting cigarettes substantially decreases risk in the long run (Pan, An et al., 2015) and increases years of life expectancy (Doll, Richard et al., 2004; Taylor, Donald H et al., 2002)

Study methods, participant characteristics, study findings, and strengths and limitations of these studies are presented in Table 7.5.7-1-1, Table 7.5.7-1-2 and Table 7.5.7-1-3.

2.6 CONSUMER BELIEFS ABOUT THE HEALTH RISKS OF USING THE CIGARETTE RELATIVE TO CESSATION AIDS

Only a small number of studies were found in our literature search that made direct comparisons of consumers' perceptions of health risks between cigarettes and smoking cessation aids. According to Tidey, Jennifer W et al., 2012, reducing the nicotine content of cigarettes to non-addictive levels may be a promising approach for reducing nicotine dependence among people with schizophrenia in comparison with transdermal nicotine replacement.

According to Haustein KO et al., 2002, abrupt cessation of smoking and temporary administration of nicotine medications improved microcirculatory parameters (during weeks 4-12 vs. baseline) – such as plasma fibrinogen level, reactive capillary flow (t–pmax), tcpO2, haematocrit, and WBC count – to the same extent as that observed during the subsequent smoke and nicotine-free period (weeks 12-26). Nicotine has no significant effects on the blood supply to the myocardium or the risk factors for coronary heart disease and NRT can thus have beneficial effects after only a few days of substitution for a proportion of normal daily cigarette consumption.

However, there are many studies that proved advantages of cessation aids over cigarettes and showed cessation aids helped smokers to quit or reduce smoking (Kralikova, Eva et al., 2009; Apelberg, Benjamin J et al., 2010; Baker, Timothy B et al., 2016).

Study methods, participant characteristics, study findings, and strengths and limitations of these studies are presented in Table 7.5.7-1-4.

2.7 SUMMARY AND CONCLUSIONS

This literature review addresses the following aspects of the FDA Draft Guidance for cigarettes:

- Consumers' beliefs about the health risks of using the cigarette relative to other tobacco products;
- The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health.

There is widespread confusion and misperceptions among consumers about the relative health risks of cigarettes and other tobacco products as well as cessation aids. In summary, research suggests that most consumers believe that cigarettes are more harmful than other tobacco products.

Research indicates that messages designed to discourage smokers from smoking cigarettes may indirectly influence consumers' behavior to switch to other tobacco products such as e-cigarettes, which are perceived to pose lower risk of addiction and exposure than cigarettes.

Quitting tobacco altogether is associated with low health risk and mortality. Smoking any tobacco product is associated with some level of health risk, exposure and addiction.

3 TABULATED INDEX – STUDY SUMMARIES

TABLE 1. THE ABILITY OF CONSUMERS TO UNDERSTAND THE RISK CLAIMS AND THE SIGNIFICANCE OF THE INFORMATION IN THE CONTEXT OF ONE'S HEALTH

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Zee Ying Lim, et al., 2015	The Impact of Cigarette Type on Consumers' Perception of Health Risks of Smoking	**Objectives**: To review the perception of health risks of different types of cigarettes across smoking status, age-group and gender, and to determine if smokers perceive differences in health risks based on the taste of cigarettes alone. Totally 240 smokers and 250 non-smokers were selected based on inclusion criteria. Both smokers and non-smokers were recruited according to gender and age groups of 18 to 29 years old, 30 to 49 years old, and 50 years old and older. Under each age group, 40 male and 40 female smokers and non-smokers were recruited respectively. Cigarette packs used in this study were NEXT with three different types, namely regular, lights and menthol cigarettes. After signing written consent form, participants were presented with cigarette boxes, a pair at a time, followed by questioner. Participants were required to select one of the two packages in response to each question, for a total of 3 pairs of cigarette packages.	In this Study following data was analysed • Which packet would expect to deliver the most tar if were to smoke it? • Which packet would expect to have the smoothest taste? and • If were to choose between these two types, which one would participant buy if they were trying to reduce the risks to your health?	A repeated measures ANOVA conducted to compare between the three types of cigarettes in the presence of tar showed a significant difference between the ratings given to the three types of cigarettes, $F(1.911, 454.810) = 71.775$, $p < .001$, partial $\eta 2 = 0.232$. Pairwise comparisons showed significant differences between all three types of cigarettes, $p < .001$. Regular cigarettes were rated to be highest in presence of tar, followed by menthol, then 'lights'. Similarly comparison between the three types of cigarettes regarding the smoothness of taste showed a significant difference between the ratings given to the three types of cigarettes, $F(1.886, 450.826) = 4.992$, $p = .007$, partial $\eta 2 = 0.020$. Pairwise comparisons showed significant differences between menthol and the other two types of cigarettes, $p < .01$, but not between regular and 'lights' cigarettes, $p > .05$. For the three types of cigarettes regarding health risk. Results showed a significant difference between the ratings given to the three types of cigarettes, $F(1.843, 440.479) = 36.476$, $p < .001$, partial $\eta 2 = 0.132$. Pairwise comparisons showed significant differences between regular and the other two types of cigarettes, $p < .001$, but not between 'lights' and menthol cigarettes, $p > .05$. Regular was rated as higher in health risk. A non-smoker is a significant predictor of selecting 'lights' over regular cigarettes as being able to reduce health risks. Specifically, being a non-smoker increases one's odds 1.953 times compared to smokers. Interestingly, although both smokers and non-smokers tend to perceive 'lights' cigarettes as being able to reduce health risks over regular ones, non-smokers were more susceptible to perceive 'lights' cigarettes as a 'healthier' choice. As smokers were found to rely on differences in taste to gauge health risks of different types of cigarettes. Hence, the ban on deceptive descriptors on cigarette packaging may not eliminate differences in perception of health risks.	Limitations: Participants were not recruited using random sampling, hence the findings here might not be generalizable to the entire Singaporean population. The sample here has included a heterogeneous group of smokers and non-smokers of different gender and age-group. Another limitation might be the 'forced choice' nature of types of cigarettes presented for participants' selection. This might result in a higher level of endorsement of the type of cigarettes which might not have been chosen otherwise. Furthermore, there was no option for participants to indicate 'no difference'. However, previous studies which provided this option typically found only less than 5% of participants selected this option

TABLE 1., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Phillips, Carl V et al., 2005	You might as well smoke; the misleading and harmful public message about smokeless tobacco	**Objective**: To examine the extent overstatement "Compared to smoking cigarettes, use of Western smokeless tobacco (ST) products is associated with a very small risk of life-threatening disease (with estimates in the range of a few percent of the risk from smoking, or even less)" a systematic review of websites containing information about ST and health risks was conducted A Google search for [tobacco AND cancer AND (smokeless OR snuff OR dip OR spit OR chew OR chewing)], the latter disjunction covering most of the synonyms for "smokeless". Search was conducted on 3 May 2003 and stored the results offline so they would not change when re-accessed.. Search reported 763 results (after Google's algorithms eliminated many, but not all, multiple similar hits), which was used as dataset.	In this study following information was collected from website • Very little accurate comparative risk information • Misleading comparative risk information • Explicit claims of equal risk • Relative popularity • Explicit claims of equal risk • Implicit claims that ST is worse than cigarettes	Very few websites provided accurate information. Two organizations, ASH (Action on Smoking and Health) in the U.K. and the American Council on Science and Health (ACSH) in the U.S. were the most prominent sources of accurate comparative risk information. Only three other sites mentioned that ST use is not as bad as cigarettes. Astonishingly, any other statements about the much lower risk of ST compared to smoking was found. 237 of the remaining 309 websites were discussing the risks of smoking and ST in proximity to each other. Most of the other 72 sites either contained very little substance (often just a passing mention that ST poses health risks), appeared very low in our results, or both, so these numbers tends to understate how common the juxtaposition of health claims about cigarettes and ST is. 108 websites that claimed that the risks from ST are as bad as or worse than those from smoking were identified. Most often this took the form of an explicit statement that ST is not safer than smoking. It is worth noting that this is equivalent to saying that you are better off, or at least no worse off, deciding to smoke rather than use ST.Of the 108 websites making claims that ST is as bad or worse than cigarettes, 26 suggested that ST is worse than smoking by likening the risks and then identifying differences that exclusively favour smoking. 100 websites made statements that directly imply that risks from ST are comparable to those of smoking, while another 29 simply juxtaposed the two risks without suggesting there are differences. (Most of those that made explicit claims also included some of these implicit claims.) Of 44 website populated with respective to Relative popularity, 13 claim ST is as bad or worse than cigarettes and 19 others that use one of the rhetorical devices to imply the risks are similar.	**Limitations:** While websites do not contain all popularly available information, many people searching for information on this topic would start with a web search and most organizations that have a stated position on the topic, particularly those actively trying to influence popular opinion through other media, have a web page that reflects their claims. Thus, the information in web pages is likely to be representative of all information reaching the average consumer.

TABLE 1., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Haziza et al., 2016a	Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement	**Objective**: The study aimed to demonstrate exposure reduction to a selected set of HPHCs when switching from CCs to THS 2.2, as compared to continued CC use and smoking abstinence (SA) for 5 days. This study was a controlled, randomized, 3 arm parallel, single-center study in confinement. 166 participants were enrolled based on screening fulfilment. Of 166 participants, were randomized, with 80, 40, and 40 participants in the THS 2.2, CC, and SA groups, respectively. 158 participants completed the study with 2 participants in the SA group who voluntarily withdrew from the study	In this study following data was analysed. • Biomarkers of exposure to selected HPHCs • Exposure to nicotine • Cytochrome 1A2 activity • Human puffing topography • Urge-to-smoke symptoms • Safety	The study demonstrated that switching from CC smoking to THS 2.2 use resulted in substantial reductions in exposure to 15 selected HPHCs. The kinetics and the magnitude of decrease of biomarkers of exposure levels observed in the THS group were approaching the levels observed in the SA group for the majority of the biomarkers of exposure. Nicotine uptake was similar between the THS and CC groups at the end of the 5 day exposure period after users had started to adapt to a new product, and with a transitional period of changing puffing behaviour, were able to achieve their desired nicotine level. The combination of the results of nicotine exposure and subjective effect measures indicated that THS 2.2 offered comparable satisfaction with regards to taste and sensorial experience, to that which was observed in CC smokers. No SAEs or severe AEs were reported during this study, with the total number of AEs being very low and evenly balanced across study groups	**Limitations:** The study should be taken with the limitations inherent to the design. The study was too short to fully assess the reduction in exposure to NNK with THS 2.2 use as total NNAL has an apparent half-life of 10–18 day. **Strength**: A strength of the study was that all urinary biomarkers of exposure were measured in 24-h urine collection using validated methods. Compared to partial urine or spot urine, 24-h urine collection is considered the most accurate approach to measure excretion of the metabolites generated from exposure to HPHCs
Azzopardi, David et al., 2016	Electronic cigarette aerosol induces significantly less cytotoxicity than tobacco smoke	**Objective**: This study describes a robust in vitro method for assessing the cytotoxic response of e-cigarette aerosols that can be effectively compared with conventional cigarette smoke. An exposure system, comprising a smoking machine, traditionally used for in vitro tobacco smoke exposure assessments, was adapted for use with e-cigarettes to expose human lung epithelial cells at the air–liquid interface (ALI). Dosimetric analysis methods using real-time quartz crystal microbalances for mass, and post-exposure chemical analysis for nicotine, were employed to detect/distinguish aerosol dilutions from a reference Kentucky 3R4F cigarette and two commercially available e-cigarettes (Vype eStick and ePen).	In this study following data was analysed. Quantification of deposited aerosol and nicotine mass at the exposure interface Cell exposure to tobacco smoke and e-cigarette aerosols and Cell viability assessment	ePen aerosol induced 97%, 94% and 70% less cytotoxicity than 3R4F cigarette smoke based on matched EC50 values at different dilutions (1:5 vs. 1:153 vol:vol), mass (52.1 vs. 3.1 µg/cm2) and nicotine (0.89 vs. 0.27 µg/cm2), respectively. Test doses where cigarette smoke and e-cigarette aerosol cytotoxicity were observed are comparable with calculated daily doses in consumers.	**Strength**: This experiments could form the basis of a larger package of work including chemical analyses, IN VITRO toxicology tests and clinical studies, to help assess the safety of current and next generation nicotine and tobacco products.

TABLE 1., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Vassallo, Robert et al., 2015	Extracts from presumed "reduced harm" cigarettes induce equivalent or greater toxicity in antigen-presenting cells	**Objective:** This study was designed to compare the relative antigen presenting cellular toxicity of Eclipse, a presumed reduced exposure product (PREP) cigarette, when compared with the reference research 3R4F cigarettes (Kentucky University). A murine macrophage cell line, murine bone marrow derived dendritic cells (DCs) and human monocyte-derived DCs were incubated with extracts generated from PREP and Kentucky reference 3R4F cigarettes, to determine the relative toxic effects of the different cigarette smoke extracts on cellular viability, oxidative stress, T-helper-1 (Th-1) polarizing cytokine production and general gene expression.	In this study following data was analysed Relative cellular toxicity of Eclipse CSE (cigarette smoke extract) compared to 3R4F CSE Suppression of interleukin-12 (IL-12) production by Eclipse and 3R4F CSE Determination of cellular heme-oxygenase 1 (HO-1) levels Relative toxicity of Eclipse and 3R4F CSE on global gene expression by bone marrow derived murine DCs	PREP cigarette and 3R4F cigarette smoke extracts induced equivalent oxidatively-mediated cellular heme oxygenase-1 (HO-1) protein levels in macrophages and DCs. Cellular viability determination demonstrated greater induction of cell death by apoptosis and necrosis by PREP extracts in DCs. The production of the key Th-1 polarizing cytokine interleukin-12 (IL-12) by activated DCs or macrophages was suppressed to an equivalent or greater extent by PREP extracts. Microarray studies performed on bone marrow derived murine DCs incubated with PREP or 3R4F cigarette extracts showed identical genotoxic profiles.	**Limitation:** The use of an IN VITRO strategy as proposed herein may be considered a significant limitation. Further validation of IN VITRO findings by well-designed IN VIVO studies are indeed important to study toxicity profiles that assess the potential risks associated with whole animal exposure to the tobacco product. **Strength:** in vitro studies have the advantage of relative simplicity in design and reproducibility, rendering such assays useful bioassays for toxicity screening.
Foulds, J et al., 2003	Effect of smokeless tobacco (snus) on smoking and public health in Sweden.	**Objective:** To review the evidence on the effects of moist smokeless tobacco (snus) on smoking and ill health in Sweden. Narrative review of published papers and other data sources (for example, conference abstracts and internet based information) on snus use, use of other tobacco products, and changes in health status in Sweden were reviewed.	In this study following information was collected Delivery of harmful substances Nicotine delivery Snus harmful to health and is it less Harmful to an individual user than Cigarettes? Pattern of nicotine use in Sweden over the past century The net effects of snus on Public health in Sweden	Snus is manufactured and stored in a manner that causes it to deliver lower concentrations of some harmful chemicals than other tobacco products, although it can deliver high doses of nicotine. It is dependence forming but does not appear to cause cancer or respiratory diseases. It may cause a slight increase in cardiovascular risks and is likely to be harmful to the unborn fetus, although these risks are lower than those caused by smoking. There has been a larger drop in male daily smoking (from 40% in 1976 to 15% in 2002) than female daily smoking (34% in 1976 to 20% in 2002) in Sweden, with a substantial proportion (around 30%) of male ex-smokers using snus when quitting smoking. Over the same time period, rates of lung cancer and myocardial infarction have dropped significantly faster among Swedish men than women and remain at low levels as compared with other developed countries with a long history of tobacco use.	**Limitations:** Use of a specific type of smokeless tobacco (snus) in Sweden has been cited as an example where this may have had an overall positive effect on health, but there is considerable debate over the role of alternative non-smoked tobacco products in reducing the harm to health caused by tobacco.

TABLE 1., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Lynn T. Kozlowski., 2018	Origins in the USA in the 1980s of the warning that smokeless tobacco is not a safe alternative to cigarettes: a historical, documents-based assessment with implications for comparative warnings on less harmful tobacco/nicotine products.	**Objective:** This paper explores the history of the establishment of warnings with emphasis on the 'not a safe alternative' warning and the bases for claiming that smokeless was 'not safe' (absolute harm) versus 'not safer than cigarettes' (relative harm). Results of searches of Truth Tobacco Industry Document archives and transcripts of legislative hearings were analysed. Critical assessments were made of the evidence-base.	In this study information on following topics were covered. Can Smokeless tobacco cause cancer The public health community responds that smokeless is 'not a safe alternative to cigarettes'	New evidence of oral cancer causation emerged along with a much-publicized case of a teenager dying of oral cancer. To avoid an addiction warning, the industry accepted a compromise 'not a safe alternative' warning, which had not been initially proposed and which the cigarette industry may have sought in order to constrain the smokeless tobacco industry. The evidence presented supported smokeless only as 'not safe' and not 'as harmful as cigarette smoking.' Surveys indicated that the public generally did not view smokeless tobacco as harmless, but they did generally report smokeless as less harmful than cigarettes despite expert interpretations to the contrary. Subsequent research has shown that the 'not a safe alternative' message is misinterpreted by consumers to indicate that smokeless is 'not safer' than cigarettes-which was not established and has been disconfirmed by subsequent assessments of that question.	**Limitations:** The tobacco industry documents cannot be assumed to represent all discussions and perspectives that may have been at issue surrounding the warning labels. Alternative interpretations of the documents, media reports, and hearing testimony may be possible. For complex historical issues, any one person's account of the explanations for events, even from a witness or participant may not be an accurate rendering of the matter.
Honarmand, Marieh et al., 2018	Comparison of Salivary Cotinine Concentrations in Male Smokers and Smokeless Tobacco Users	**Objective:** This study compared the salivary level of cotinine in male smokeless tobacco users and smokers. This is a cross-sectional (descriptive-analytical) study, stimulated saliva samples from 30 male smokers and 30 male smokeless tobacco consumers were collected and their cotinine contents were measured using the competitive ELISA method according the standard curve.	In this study following data was analysed Compare salivary cotinine levels between the two groups. Determine the relationship between salivary cotinine levels and tobacco consumption. $P<0.05$ was considered significant.	Among the 60 subjects with the mean age of 21.27±2.6 years, the average level of cotinine in smokers (12.32±7.5 ng/ml) had no significant difference with that of smokeless tobacco consumers (11.23±4.4 ng/ml) ($p=0.49$).	**Limitation:** This study was the potential lack of generality to other populations and was conducted in one city.
Murphy et al., 2017	Assessing modified risk tobacco and nicotine products: Description of the scientific framework and assessment of a closed modular electronic cigarette	**Objective:** The main objective is to propose a framework comprising pre-clinical, clinical, and population studies to assess the risk profile of novel tobacco products. The utility of this framework is assessed through the pre-clinical and part of the clinical comparison of a commercial e-cigarette (Vype ePen) with a scientific reference cigarette (3R4F).	In this study data was collected from Preclinical studies Clinical studies Population studies	The most comprehensive dataset on a single e-cigarette to date and when considered in their totality are in line with the findings of Public Health England, that ePen has the potential to be a reduced risk product in comparison to cigarettes. However, longer term clinical studies will be required to fully determine this potential and to demonstrate individual risk reduction. Furthermore, a range of pre- and post-market studies are required to substantiate them as products that can reduce risk on a population level.	**Limitations:** The nature of tobacco products, their use and subsequent impact on health is complex, so a multi-disciplinary framework is required for the comprehensive evaluation of novel nicotine and tobacco products and the substantiation of health related claims. Some of the challenges of this approach will be the harmonisation of approaches, agreement of methodologies and standardisation across the various studies.

TABLE 1., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Adkison, Sarah E et al., 2015	Validation of a Measure of Normative Beliefs About Smokeless Tobacco Use	**Objective:** The primary goals for the current research were to (1) develop a measure for normative beliefs about smokeless tobacco (ST) and establish the underlying factor structure, (2) evaluate the structure with confirmatory factor analysis (CFA) utilizing an independent sample, and (3) establish the measure's predictive validity by assessing the scales' ability to discriminate between those who do and do not use ST products and express an interest in low-nitrosamine snus among a sample of adolescents. Respondents (smokers and nonsmokers aged 15–65; N = 2991) completed a web-based survey that included demographic characteristics, tobacco use history and dependence, and a measure of attitudes about ST adapted from the Normative Beliefs about Smoking scale. A second sample of youth (aged 14–17; N = 305) completed a similar questionnaire.	In this study following Parameters were considered for evaluation: Demographic Characteristics for Each Sample Normative beliefs about ST Perceived prevalence of ST use Internal Consistency and Test-Retest Reliability Confirmatory Factor Analysis Concurrent Validity	Respondents from first administration (N = 2991; Adults: 1999, Youth: 992) who completed a re-administration 3 months later, 42% (N = 1251; Adults: 52.8%, Youth: 19.1%) had complete data at both administrations. Chi-square tests of independence showed that respondents who completed the second administration were more likely to be older adults ($X2$ (3, N = 2991) = 318.72, P < .001), male ($X2$ (1, N = 2991) = 25.58, P < .001), those who reported ever smoking ($X2$ (1, N = 2991) = 88.67, P < .001), and those who reported ever use of ST ($X2$ (1, N = 2991) = 12.04, P < .001). The 11-item normative beliefs about ST questions submitted to exploratory factor analysis with principal axis factoring and promax rotation, to allow for correlated factors produced the anticipated three-factor solution and accounted for nearly three-quarters of the variance at each administration reflecting: (1) perceived prevalence of ST use, (2) popularity of ST among successful/elite, and (3) approval of ST use by parents/peers. The scale for the perceived prevalence of ST had a high internal consistency (T1: $\alpha = 0.935$, T2: $\alpha = 0.939$) and demonstrated good test-retest reliability (ICC: 0.718). The scales for popularity of ST among successful/elite elements of society (T1: $\alpha = 0.882$, T2: $\alpha = 0.890$) and approval of using ST by parents/peers (T1: $\alpha=0.914$, T2: $\alpha=0.898$) had a high internal consistency, though test re-test reliability was moderate (ICC: 0.572 and 0.523, respectively). At the item level, for the prevalence scale, items had ICCs > 0.6 reflecting good test-retest reliability; the successful/elite scale and parents/peers had ICCs > 0.4 reflecting moderate test-retest reliability. Confirmatory factor analysis with data from the youth sample demonstrated good model fit. Logistic regression demonstrated that the scales effectively discriminate between ST users and nonusers and are associated with interest in trying snus.	**Limitations:** This study utilized a web-based panel which limits the generalizability of findings to the broader population. Only able to evaluate interest in trying snus with a single question targeting interest generally but not actual intention to use the product in some defined time frame. Do not have long-term prospective data on the actual uptake of ST/snus, so were unable to examine the predictive validity of future uptake of ST as predicted by responses to the perceived norms scales. The independent sample used to confirm the structure of the data included only adolescents, so were unable to affirm that this measure would be effective for understanding normative beliefs about ST products for adult respondents.

TABLE 1., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Kaufman, Annette R et al., 2016	Perceptions of harm and addiction of snus: An exploratory study.	**Objective:** The objective of study is to utilizes a combination of eye-tracking methodology to examine advertisement viewing patterns, survey, and semistructured interviews to measure perceptions (i.e., harm and addiction), related to snus print advertisements among a sample of young-adult male smokers. Participants were 22 male smokers ages 19–29 (M = 26.64, SD = 2.92). Five snus advertisements were each displayed for 20 s and eye movements were tracked. Participants responded to questions about harm and addiction after each advertisement and interviews were conducted after seeing all advertisements. For each advertisement, descriptive statistics were calculated and regression analyses predicted harm and addiction perceptions from eye tracking areas of interest (e.g., warning label).	Parameters considered in tis study were Eye Tracking Harm Perceptions Addiction Perceptions Qualitative Themes Behavioral Intentions	The quantitative findings from study show that addiction perceptions were driven strongly by components of the advertisements, whereas harm perceptions were not. Our qualitative findings suggest that half of the participants, unprompted, viewed snus as a smoking cessation aid. There is no evidence that snus is associated with cessation among U.S. smokers and manufacturers have not submitted snus to the FDA for consideration as a cessation aid. Findings also suggest that individuals may not look at warning labels on some advertisements in real life viewing situations. The amount of time it takes a viewer to see a warning label may depend on features of the advertisement.	**Limitations:** This is a small, exploratory study, due to the small convenience sample and laboratory setting, the findings have limited generalizability. Strength: Studies examining snus have focused mainly on non-Hispanic White samples but in this study a more diverse sample of predominately African American male smokers were utilized. The role of race and socioeconomic status (SES) in the advent of emerging tobacco products is important and future research may consider studying more diverse samples.
Wackowski, Olivia A et al., 2016	Smokers' and e-cigarette users' perceptions of modified risk warnings for e-cigarettes	**Objective:** To qualitatively examining perceptions of potential modified-risk warnings for e-cigarettes. In this study six focus groups between 2014 and 2015 with 27 adult e-cigarette users and cigarette-only smokers who provided comments on two versions of a modified risk warning for e-cigarettes: 1) "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes" (as proposed by two companies for their smokeless tobacco products) and 2) "WARNING: This product may be harmful to health, but is substantially less harmful than cigarettes" (an alternative developed by our team) was conducted.	In this study data was collected on Overall perceptions of reduced risk statements and Comparison between messages	Most believed that e-cigarettes are safer than cigarettes and some thought the messages were true and accurate, many were skeptical and uncomfortable with the warnings because they did not "seem like a warning" and because use of the phrase "substantially lower risks" could be misleading and difficult to understand. Several thought the second warning was stronger (e.g., more active, more specific). Modified risk messages about e-cigarettes may impact perceptions and use of the product.	**Limitations:** A small local convenience sample which did not include non-smokers or youth, whom such messages have potential to attract. Also, participants viewed these reduced-risk statements after other more traditional proposed e-cigarette warnings, which may have biased them to be more skeptical of such messages then if they were presented first or were the main focus of the study.

TABLE 2. THE ABILITY OF CONSUMERS TO UNDERSTAND ABOUT THE HEALTH RISKS OF CIGARETTE RELATIVE TO OTHER TOBACCO PRODUCTS

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Benowitz, Neal L et al., 2012	Exposure to nicotine and carcinogens among Southwestern Alaskan Native cigarette smokers and smokeless tobacco users.	Objective: To investigate possible mechanisms of increased cancer risk, levels of nicotine and tobacco-specific nitrosamines (TSNA) in tobacco products and biomarkers of tobacco toxicant exposure in Southwestern AN people were studied. Participants included 163 cigarette smokers, 76 commercial smokeless tobacco, 20 homemade smokeless tobacco prepared with dried tobacco leaves mixed with alkaline ash (iqmik), 31 dual cigarette smokers and smokeless tobacco, and 110 nontobacco users. Tobacco use history, samples of tobacco products used, and blood and urine samples were collected.	In this study following data was analysed Chemical constituents of tobacco products Subjects and tobacco use behaviour Exposure to nicotine, 4-(methylnitrsoamino)-4-(3-pyridyl)-1-butanol (NNAL), N′-nitrosonornicotine (NNN), and polycyclic aromatic hydrocarbons (PAH) metabolites Correlations among biomarkers and tobacco consumption measures	The nicotine concentration was highest in cigarette tobacco. Concentrations of NNK, NNN, and other TSNAs in commercial smokeless tobacco products were substantially higher than in cigarettes. Levels of NNK and other TSNAs in iqmik were considerably lower than that of cigarettes or commercial smokeless tobacco. The Fagerstrom test of nicotine dependence score averaged 2.6, SD 2.1; 1.9, SD 1.9 for smokers and dual users, respectively. The smokeless tobacco users used on average 1.6 tins per week; iqmik users used 1.2 tins per week; and dual users used on average either 1.3 tins of smokeless tobacco or 0.5 tins of iqmik per week. The Severson smokeless tobacco dependence score averaged 4.0, SD 3.3; 5.5, SD 3.3; and 3.0, SD 4.1 for smokeless, iqmik, and dual users, respectively. Non smokers reported that 97.3% had a smoking ban in their homes and 96.4% had no second hand smoke exposure at home or in steam baths. All nicotine intake measures were twice as high in iqmik users than in cigarette smokers. Nicotine intake was also greater on average in commercial spit tobacco users than in smokers and greater in iqmik users than in spit tobacco users. The average plasma cotinine concentration in tobacco nonusers was 0.3 ng/mL. The highest levels of NNAL were seen in commercial smokeless tobacco users followed by dual users and then cigarette smokers. NNAL levels in iqmik users were on average much lower than levels in commercial smokeless tobacco users but not significantly different from those in cigarette smokers. Urine NNN levels were not significantly different comparing the various tobacco user groups, but were significantly lower in nonusers. PAH metabolite concentrations were highest on average in cigarette smokers. Average PAH levels were similar across all groups, except levels of 1-hydroxypyrene in nonusers were significantly lower than cigarette smokers. Among cigarette smokers there were significant correlations between urine nicotine equivalents and plasma cotinine ($r = 0.73$), urine NNAL ($r = 0.73$), urine NNN ($r = 0.58$), urine 2-napthol ($r = 0.70$), urine 1-hydroxypyrene ($r = 0.53$), and cigarettes per day ($r = 0.49$), with all $P < 0.0001$. Among commercial smokeless tobacco users there were significant correlations between urine nicotine	**Limitations:** Only AN people in one region, the Bristol Bay region of southwest Alaska, who volunteered to participate were studied. Participants were primarily Yupik. The AN people in other areas of Alaska have different ethnic backgrounds and different cultural influences which could influence smoking behavior and exposure to tobacco toxicants. **Strength:** Although, the number of subjects using iqmik only was relatively small, this article provides new data on exposure to carcinogens among users of this tobacco product and indicate the potential increased addiction risk among this population. There are no other published data on human exposure to nicotine and carcinogens among iqmik users, so these data are unique.

				equivalents and plasma cotinine (r = 0.72), urine NNAL (r = 0.87) and urine NNN (r = 0.66), all P < 0.001; urine 2-napthol (r = 0.33, P < 0.01) and tins/wk (r = 0.26, P < 0.05). There was no significant correlation with 1-hydroxypyrene. For iqmik users there was a significant correlation between urine nicotine equivalents and plasma cotinine (r =0.78, P <0.001) and urine NNN (r =0.48, P <0.05); but not with urine NNAL or PAH metabolites or with tins/wk. Urine NNAL and urine NNN were significantly correlated in smokers (r = 0.59) and spit tobacco users (r = 0.67), both P < 0.0001.	

TABLE 2., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Hassan, Manal M et al., 2008	Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study.	Objective: The main aim of this study is to assess the associations between the risk of hepatocellular carcinoma (HCC) and passive smoking and the use of noncigarette tobacco products, by taking into consideration the confounding effect of cigarette smoking and other significant risk factors for HCC. A case-control study at The University of Texas M. D. Anderson Cancer Center was conducted, where 319 HCC patients and 1,061 healthy control subjects were personally interviewed for several HCC risk factors.	Following data was gathered from the study Risk factors for HCC Risk modification of cigarette smoking by other risk factors	In case of use of Non-cigarette tobacco products there was not significantly associated with an elevated risk of HCC development. However, heavy use of pipes and cigars conferred approximately 2.6- and 1.7-fold increases, respectively, in risk of HCC after controlling for demographic characteristics and other significant risk factors for HCC; but the association observed among cigarette smokers was not statistically significant ($p = 0.07$ and 0.09, respectively). With respective to passive smoking: During cigarette smoking, a significant difference in passive smoke exposure was observed between non smokers cases ($n = 52$, 59.1%) and controls ($n = 351$, 74.5%); $p = 0.002$. Such difference is related to the significantly higher exposure of control subjects, compared to case patients, to passive smoke during childhood (37 cases [42%] and 273 controls [58%], $p = 0.0003$). For adulthood exposure, however, there were no significant differences between case patients (45.5%) and control subjects (53.3%), $p = 0.3$. In case of smokeless tobacco (chewing tobacco and snuff) among non smokers, the exposure time of passive smoking was similar for exposed case patients and control subjects (mean ± SE, 24.2 ± 2.5 years for case patients; 26.5 ± 0.7 years for control subjects) ($p = 0.5$). Moreover, no significant relationship between the development of HCC and years of exposure during childhood, adulthood (at home and at work) or total lifetime. Furthermore, subjects who were exposed to passive smoking had no increased risk of HCC that could be correlated with the age at first exposure or age at cancer diagnosis. The estimated AORs were 0.5 (95% CI, 0.1–1.9) and 0.6 (95% CI, 0.3–1.1) for patients who were ≤50 and >50 years old, respectively, at HCC diagnosis. Regular cigarette smoking was associated with HCC in men: adjusted odds ratio (AOR), 1.9 (95% CI, 1.1–3.1). Heavy alcohol consumption was associated with HCC in women: AOR, 7.7 (95% CI, 2.3–25.1). Cigarette smoking interacted synergistically with chronic infection of hepatitis C virus in men: AOR, 136.3 (95% CI, 43.2–429.6) and with heavy alcohol consumption in women: AOR, 13.7 (95% CI, 3.2–57.9).	**Strength:** It is generally accepted that accurately assessing the relationship between noncigarette tobacco use and cancer risk is difficult. Obstacles include the lack of standard measurements for cigar size and tobacco type, variations in the behavior of people using these types of products (inhalation versus chewing), the low prevalence of noncigarette tobacco exposure in the general population (compared to the marked prevalence of cigarette smoking) and the potential confounding effect of high socioeconomic status among cigar and pipe users. All of these factors may bias measurements of the cumulative intake of noncigarette tobacco products. But in this study, assessment was done for several smoking types with proper adjustment for confounding factors. Both HCC patients and control subjects were personally interviewed using a structured and validated questionnaire for several sources of smoke exposure.

TABLE 2., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Lee., 2013	The effect on health of switching from cigarettes to snus –A review	**Objective:** The main objective of this study is to evaluate the health effects of switching from cigarettes to snus Six epidemiological cohort or case-control studies were identified through literature search, all from Sweden, and comparison of cancer or cardiovascular disease risk in current snus users who formerly smoked ("switchers") with that of never snus users who continued to smoke ("continuers") or of never snus users who quit smoking ("quitters") were evaluated.	Data on following parameters were gathered. Covariate-adjusted relative risks (RRs) or odds ratios (ORs) with 95% confidence limits (CIs)	The six studies reported results for between one and four endpoints, giving a total of 13 data sets. Based on 13 sets of comparisons, one for oral cancer, one for stomach cancer and 11 for various cardiovascular disease endpoints, switchers were consistently found to have a lower risk than continuers, with relative risks varying from 0.35 to 0.61, and a similar risk to quitters. Based on estimates from four studies for ischaemic/coronary heart disease or acute myocardial infarction, meta-analyses gave combined relative risk estimates of 0.55 (95% confidence interval 0.45–0.68) for switchers vs. continuers and 1.02 (95% confidence interval 0.83–1.26) for switchers vs. quitters.	**Limitations:** The number of studies providing relevant data is low. None of the studies provide any information on how risk varies by time of switch to snus. While there are plenty of other data on the time course of the decline in risk following quitting smoking. Definition of switching, though the best there is from the available data, does not separate those who switched immediately from smoking to snus, those who took up snus some time after quitting smoking, or those who ended up as snus only users after a period of dual use. **Strength:** Despite these potential limitations, the consistency of the findings is remarkable. All 13 of the RR or OR estimates comparing switchers and continuers are in the range 0.35–0.61, while all of the estimates comparing switchers and quitters are 0.76 or over and did not significantly ($p < 0.05$) differ from 1.0.

TABLE 2., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Levy D., et al., 2004	The Relative Risks of a Low-Nitrosamine Smokeless Tobacco Product Compared with Smoking Cigarettes: Estimates of a Panel of Experts	Objective: How harmful is daily use of snus compared to daily use of cigarettes? A nine-membered panel of experts were asked to determine expert opinions of mortality risks associated with use of low-nitrosamine smokeless tobacco (LN-SLT) marketed for oral use. A modified Delphi approach was employed.	Parameters evaluated in this study were Median relative risks for individual users of LN-SLT Median mortality risks relative to smoking	For total mortality, the estimated median relative risks for individual users of LN-SLT were 9% and 5% of the risk associated with smoking for those ages 35 to 49 and ≥50 years, respectively. Median mortality risks relative to smoking were estimated to be 2% to 3% for lung cancer, 10% for heart disease, and 15% to 30% for oral cancer. Although individual estimates often varied between 0% and 50%, most panel members were confident or very confident of their estimates by the last round of consultation. In comparison with smoking, experts perceive at least a 90% reduction in the relative risk of LN-SLT use.	**Limitations:** The construction of the questionnaire may have created differences in panel members' interpretation and responses. A relatively small number of panel members participated compared with prior Delphi analyses
Eliasson M et al., 2004	Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study	**Objective:** To explore the effect of smoking and smokeless tobacco, 'snus', on the risk of type 2 diabetes. This study used data from the northern Sweden component of the World Health Organisation Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study. Briefly, information was collected during four population-based surveys in 1986, 1990, 1994 and 1999 . In addition, follow-up information on about 70% of participants from the first three surveys was collected in 1999, with duration of follow-up of 5, 9 and 13 years (1994, 1990 and 1986 cohorts, respectively)	In this study data was collected on Prevalence of known diabetes (kDM) and pathological glucose tolerance (PGT) according to tobacco use Incidence of kDM and PGT according to tobacco use	Compared with never users, the age-adjusted risk of prevalent clinically diagnosed diabetes for ever smokers was 1.88 (CI 1.17-3.0) and for smokers 1.74 (0.94-3.2). Corresponding odds ratios for snus users were 1.34 (0.65-2.7) and 1.18 (0.48-2.9). We found no increased risk of prevalent PGT in snus users or smokers. Former smokers and snus users had an insignificantly increased risk for PGT. Compared with nonusers, the age-adjusted risk of developing clinically diagnosed diabetes during follow-up was 4.63 (1.37-16) in consistent exclusive smokers, 3.20 (1.16-8.8) in ex-smokers and no cases in consistent snus users. The risk of PGT during follow-up was not increased in consistent tobacco users but evident, although not statistically significant, in those who quit snus during the follow-up period, 1.85 (0.60-5.7). Adjustment for physical activity and alcohol consumption did not change the major findings.	**Limitations:** This report is the first population-based, cross-sectional and longitudinal study of the influence of smokeless tobacco use, in the form of snus, on the occurrence of diabetes. Although over 3000 subjects were included, the number of diabetes cases is small, which is the major limitation of study results, leaving with wide confidence intervals and risk of type II errors.

TABLE 2., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Marano, Kristin M et al., 2015	Study of cardiovascular disease biomarkers among tobacco consumers. Part 3: evaluation and comparison with the US National Health and Nutrition Examination Survey	**Objective**: To evaluate Cardiovascular disease (CVD) biomarkers of biological effect (BoBE), including hematologic biomarkers, serum lipid-related biomarkers, other serum BoBE, and one physiological biomarker, in adult cigarette smokers (SMK), smokeless tobacco consumers (STC), and non-consumers of tobacco (NTC) Data from adult males and females in the US National Health and Nutrition Examination Survey and a single site, cross-sectional study of healthy US males were analyzed and compared.	In this study data was on following biomarkers were collected in all 3 data sets Hematologic biomarkers Serum lipid-related biomarkers Serum BoBE A physiological biomarker	Within normal clinical reference ranges, statistically significant differences were observed consistently for fibrinogen, C-reactive protein (CRP), hematocrit, mean cell volume, mean cell hemoglobin, hemoglobin, white blood cells, monocytes, lymphocytes, and neutrophils in comparisons between SMK and NTC; for CRP, white blood cells, monocytes, and lymphocytes in comparisons between SMK and STC; and for folate in comparisons with STC and NTC.	**Strength:** Comparison of data from a single site cross-sectional study with data from NHANES (Data sets 1 and 2) is a strength of this evaluation. NHANES is a well-established biomonitoring program in the US. NHANES data provide a large sample, which is designed to be representative of the US population, and individual level data are available to account for potential confounders such as age, race/ethnicity, and BMI.
Farsalinos, Konstantinos E et al., 2014	Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes.	Objective: The purpose of this study was to examine the immediate effects of electronic cigarette use on left ventricular (LV) function, compared to the well-documented acute adverse effects of smoking. Echocardiographic examinations were performed in 36 healthy heavy smokers (SM, age 36 ± 5 years) before and after smoking 1 cigarette and in 40 electronic cigarette users (ECIG, age 35 ± 5 years) before and after using the device with "medium-strength" nicotine concentration (11 mg/ml) for 7 minutes.	Following parameters were evaluated: Mitral flow diastolic velocities (E, A) their ratio (E/A), deceleration time (DT), isovolumetric relaxation time (IVRT), corrected-to-heart rate IVRT (IVRTc), Mitral annulus systolic (Sm), and diastolic (Em, Am) velocities, Myocardial performance index was calculated from Doppler flow (MPI) tissue Doppler (MPIt), Longitudinal deformation measurements of global strain (GS), systolic (SRs) and diastolic (SRe, SRa) strain rate	Baseline measurements were similar in both groups. In SM, IVRT and IVRTc were prolonged, Em and SRe were decreased, and both MPI and MPIt were elevated after smoking. In ECIG, no differences were observed after device use. Comparing after-use measurements, ECIG had higher Em ($P = 0.032$) and SRe ($P = 0.022$), and lower IVRTc ($P = 0.011$), MPI ($P = 0.001$) and MPIt ($P = 0.019$). The observed differences were significant even after adjusting for changes in heart rate and blood pressure.	**Limitations:** A small sample size was studied, and examination focused only on immediate effects. The results do not indicate that electronic cigarettes are absolutely safe for the cardiovascular system. Other parameters known to be adversely affected by acute smoking, such as coronary microvascular and endothelial function or vascular distensibility, were not examined.

TABLE 2., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Pan, An et al. 2015	Relation of active, passive, and quitting smoking with incident diabetes: a meta-analysis and systematic review.	**Objective:** A meta-analysis of prospective studies was conducted to investigate the associations between various smoking behaviours and diabetes risk. 88 eligible prospective studies with 5 898 795 participants and 295 446 incident cases of type 2 diabetes were identified by systematically searched MEDLINE (up to May 3, 2015) and Embase (up to April 16, 2014) for reports of prospective studies, using search terms related to smoking, diabetes mellitus, and studies with a prospective design.	In this study data was collected on following parameters: Active smoking and risk of incident type 2 diabetes Passive smoking and risk of incident type 2 diabetes Smoking cessation and risk of incident type 2 diabetes Absolute risk difference and population attributable fraction	Compared with never smoking, the pooled Relative risk (RR) (95% CI) of type 2 diabetes was 1·37 (1·33-1·42) for current smoking (84 studies), 1·14 (1·10-1·18) for former smoking (47 studies), and 1·22 (1·10-1·35) for passive smoking (7 studies). The associations persisted in all subgroups, and a dose-response relation was found for current smoking and diabetes risk: the RRs (95% CIs) were 1·21 (1·10-1·33), 1·34 (1·27-1·41) and 1·57 (1·47-1·66) for light, moderate, and heavy smokers, respectively, compared with never smokers. We estimated that 10·3% in men and 2·2% in women of type 2 diabetes cases (approximately 25 million) were attributable to cigarette smoking worldwide if smoking is causally related to diabetes. Compared to never smokers, the pooled RR (95% CI) from 10 studies was 1·54 (1·36-1·74) in new quitters (<5 years), and 1·11 (1·02-1·20) in long-term quitters (≥10 years).	**Limitations**: A significant heterogeneity across studies for the association between active smoking and diabetes risk, which may result from very large number of included studies, differences in study populations, study quality, analysis strategies, and participant's characteristics. Residual confounding is still possible given that smoking is commonly related to other unhealthy lifestyle factors (e.g., poor diet, excessive alcohol use, and physical inactivity) and comorbidities. Misclassifications existed in the assessment of exposure (self-reported smoking status only at baseline in most studies) and outcome (self-reported or linkage-identified incident diabetes in many studies).

TABLE 3. CONSUMER BELIEFS ABOUT THE HEALTH RISKS OF USING THE CIGARETTE RELATIVE TO QUITTING ALL TOBACCO USE

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Doll, Richard et al., 2004	Mortality in relation to smoking: 50 years' observations on male British doctors.	**Objective:** To compare the hazards of cigarette smoking in men who formed their habits at different periods, and the extent of the reduction in risk when cigarette smoking is stopped at different ages. Prospective study from 1951 to 2001 was conducted. 34 439 male British doctors. Information about their smoking habits was obtained in 1951, and periodically thereafter; cause specific mortality was monitored for 50 years.	Parameters used for assignment were: Mortality by smoking habit and cause of death Effects on overall mortality Hazards among cigarette Smokers born 1900-1930 Mortality on stopping smoking Mortality by age stopped Smoking Lung cancer mortality	The excess mortality associated with smoking chiefly involved vascular, neoplastic, and respiratory diseases that can be caused by smoking. Men born in 1900-1930 who smoked only cigarettes and continued smoking died on average about 10 years younger than lifelong non-smokers. Cessation at age 60, 50, 40, or 30 years gained, respectively, about 3, 6, 9, or 10 years of life expectancy. The excess mortality associated with cigarette smoking was less for men born in the 19th century and was greatest for men born in the 1920s. The cigarette smoker versus non-smoker probabilities of dying in middle age (35-69) were 42% nu 24% (a twofold death rate ratio) for those born in 1900-1909, but were 43% nu 15% (a threefold death rate ratio) for those born in the 1920s. At older ages, the cigarette smoker versus non-smoker probabilities of surviving from age 70 to 90 were 10% nu 12% at the death rates of the 1950s (that is, among men born around the 1870s) but were 7% nu 33% (again a threefold death rate ratio) at the death rates of the 1990s (that is, among men born around the 1910s).	-NA-

TABLE 3., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Taylor, Do nald H et al., 2002	Benefits of Smoking Cessation for Longevity	Objective: This study determined the life extension obtained from stopping smoking at various ages. Estimated the relation between smoking and mortality among 877 243 respondents to the Cancer Prevention Study II. These estimates were applied to the 1990 US census population to examine the longevity benefits of smoking cessation.	Parameters considered for evaluation: Misclassification Bias Due to Change in Smoking Status Benefits of Smoking Cessation	Life expectancy among smokers who quit at age 35 exceeded that of continuing smokers by 6.9 to 8.5 years for men and 6.1 to 7.7 years for women. Smokers who quit at younger ages realized greater life extensions. However, even those who quit much later in life gained some benefits: among smokers who quit at age 65 years, men gained 1.4 to 2.0 years of life, and women gained 2.7 to 3.7 years.	Limitations: only mortality is considered as an endpoint. analyses did not directly control for duration of smoking or age at quitting, even though controlled for age directly.

TABLE 4. CONSUMER BELIEFS ABOUT THE HEALTH RISKS OF USING THE CIGARETTE RELATIVE TO CESSATION AIDS

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Tidey, Jennifer W et al., 2012	Separate and Combined Effects of Very Low Nicotine Cigarettes and Nicotine Replacement in Smokers with Schizophrenia and Controls	**Objective:** This study investigated the separate and combined effects of acute nicotine replacement and sensorimotor smoking replacement, in the form of Very low nicotine content (VLNC) cigarettes, on cigarette craving, withdrawal symptoms, and usual-brand smoking in schizophrenia (SS) and control smokers (CS). This study used a within-subjects design to investigate the separate and combined effects of sensorimotor replacement for smoking very low nicotine content [VLNC] cigarettes vs. no cigarettes and transdermal nicotine replacement (42 mg nicotine [NIC] vs. placebo [PLA] patches) in smokers with schizophrenia (SS; n = 30) and control smokers without psychiatric illness (CS; n = 26)	Parameters measured were: Smoking During the 5-hr Controlled Administration Periods Subjective Effects of Sensorimotor and Nicotine Replacement Effects of Sensorimotor and Nicotine Replacement on Usual-Brand Smoking VLNC Tolerability and Acceptability	This study indicate that smoking VLNC cigarettes during the controlled administration periods reduced cigarette craving, nicotine withdrawal symptoms, smoking habit withdrawal symptoms, and usual-brand smoking in both SS and CS. Furthermore, VLNC cigarettes were well tolerated overall, and there was no indication that acute VLNC smoking affected psychiatric symptoms in SS. Transdermal nicotine substituted less effectively than sensorimotor replacement for usual-brand cigarettes under these study conditions, in that it reduced cigarette craving but to a lesser extent than did VLNC cigarettes, and had no effect on usual-brand smoking during the 90-min ad libitum smoking periods.	**Limitations:** The potential problem with this approach is that switching from normal nicotine content to VLNC cigarettes could increase carcinogen exposure if smokers compensate for the reduction in nicotine yield by smoking more intensely

TABLE 4., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Haustein KO et al. 2002	Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorheology.	**Objective:** The objective of this study was to test whether stopping smoking but continuing to administer nicotine in the form of NRT, would result in decreased plasma viscosity and fibrinogen levels. This is Open, parallel-group trial (intervention group and control smokers), where One hundred and sixty-four subjects were instructed to stop smoking and received NRT for 12 weeks and 33 acted as controls. After 12 weeks, NRT was discontinued, and all subjects were followed-up at 26 weeks.	Parameters investigated were: Normalization of RBC deformability, reactive capillary blood flow and transcutaneous partial oxygen tension (tcpO2), and changes in established cardiovascular (CV) risk factors (haematocrit, haemoglobin, WBC count).	Plasma viscosity, fibrinogen, erythrocyte deformability, reactive capillary blood flow, transcutaneous partial oxygen tension (tcpO2) and haematocrit, assessed at 4, 8, 12, and 26 weeks. Results. After 6 months, plasma fibrinogen (9.95 vs. 8.24 micromol x L(-1) at baseline; $P < 0.003$), reactive capillary flow (t-pmax: 9.3 vs. 11.2 s at baseline; $P < 0.005$), and tcpO2 (50.4 vs. 34.9 mmHg at baseline; $P < 0.0001$) were significantly improved in abstainers, but changes in plasma viscosity and erythrocyte deformability were inconclusive. Other CV risk factors, such as haematocrit and white blood cell count, decreased to a greater extent in abstainers than in relapsers. Expired carbon monoxide concentrations reflected the changes in smoking and decreased in abstainers from 30.4 ppm at baseline to 4.2 ppm; $P < 0.0001$)	-NA-

TABLE 4., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Kralikova, Eva et al., 2009	Smoking cessation or reduction with nicotine replacement therapy: a placebo-controlled double blind trial with nicotine gum and inhaler	Objective: The present study investigated the efficacy of nicotine replacement therapy (NRT) to facilitate either smoking cessation or a reduction in smoking by 50% or more during a 6-month treatment period, with follow-up at 9 and 12 months. The safety of NRT use, while smoking, was also investigated. This multi-center, double-blind placebo-controlled study helping smokers (N = 314) to reduce or quit smoking.	Parameters evaluated Treatment choice and compliance Efficacy Prognostic factors Intention to quit Plasma cotinine levels Expired carbon monoxide Adverse events	Significantly more smokers managed to quit in the Active group than in the Placebo group. Sustained abstinence rates at 4 months were 42/209 (20.1%) subjects in the Active group and 9/105 (8.6%) subjects in the Placebo group (p = 0.009). Sustained abstinence rates at 12 months were 39/209 (18.7%) and 9/105 (8.6%), respectively (p = 0.019). Smoking reduction did not differ between the groups, either at short-term or long-term. Twelve-month reduction results were 17.2% vs. 18.1%, respectively. No serious adverse events were reported.	Advantage: This study differed from previous trials because smokers could choose one of two NRT products, gum or inhaler, and were given the opportunity to quit or reduce.

TABLE 4., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Apelberg, Benjamin J et al., 2010	Estimating the Risks and Benefits of Nicotine Replacement Therapy for Smoking Cessation in the United States	**Objective:** To compare potential population-wide benefits and risks, this study examined the potential impact of increased nicotine replacement therapy (NRT) use for smoking cessation on future US mortality. A simulation model incorporating a Monte Carlo uncertainty analysis, with data from the 2005 National Health Interview Survey and Cancer Prevention Study II was developed.	Data was gathered on following: Relationship to Overall Tobacco-Related Mortality Burden Safety of Nicotine Replacement Therapy Use	From this study a gradual increase in the proportion of NRT-aided quit attempts to 100% by 2025 would lead to 40 000 (95% credible interval = 31 000, 50 000) premature deaths avoided over a 20-year period. Most avoided deaths would be attributable to lung cancer and cardiovascular disease. After we incorporated assumptions about potential risk from long-term NRT, the estimate of avoided premature deaths from all causes declined to 32 000.	**Limitations**: any attempt to predict future mortality patterns will, of necessity, require many assumptions to bridge evidence gaps and will come with related uncertainties. It was also assumed that mortality rates among never-smokers remained constant into the future. However, numerous factors may result in changing rates over time, including improvements in detection and treatment and trends in the prevalence of risk factors over time

TABLE 4., CONTINUED

Author	Report Title	Study Methods	Primary Study Measurements and Endpoints	Author's Findings Regarding Perception of Health Risk	Comments
Baker, Timothy B et al., 2016	Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial.	Objective: To compare the efficacies of varenicline, combination nicotine replacement therapy (C-NRT), and the nicotine patch for 26-week quit rates. This study is Three open-label smoking cessation pharmacotherapies for 12 weeks: 1) nicotine patch only (n=241); 2) varenicline only (including 1 pre-quit week; n=424); and 3) C-NRT (nicotine patch + nicotine lozenge; n=421). 6 counselling sessions were offered.	Parameters measured were: The primary outcome was carbon monoxide-confirmed self-reported 7-day point-prevalence abstinence at 26 weeks. Secondary outcomes were carbon monoxide-confirmed self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at weeks 4, 12, and 52.	Among 1086 smokers randomized (52% women; 67% white; mean age, 48 years; mean of 17 cigarettes smoked per day), 917 (84%) provided 12-month follow-up data. Treatments did not differ on any abstinence outcome measure at 26 or 52 weeks, including point-prevalence abstinence at 26 weeks (nicotine patch, 22.8% [55/241]; varenicline, 23.6% [100/424]; and C-NRT, 26.8% [113/421]) or at 52 weeks (nicotine patch, 20.8% [50/241]; varenicline, 19.1% [81/424]; and C-NRT, 20.2% [85/421]). At 26 weeks, the risk differences for abstinence were, for patch vs varenicline, -0.76% (95% CI, -7.4% to 5.9%); for patch vs C-NRT, -4.0% (95% CI, -10.8% to 2.8%); and for varenicline vs C-NRT, -3.3% (95% CI, -9.1% to 2.6%). All medications were well tolerated, but varenicline produced more frequent adverse events than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion.	Limitations: This was an open-label study means that the outcome measures may have been influenced by expectations or biases of the participants or staff. Availability of 6 counselling sessions and the fairly good attendance at such sessions may have diluted the effects of the pharmacotherapies.

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