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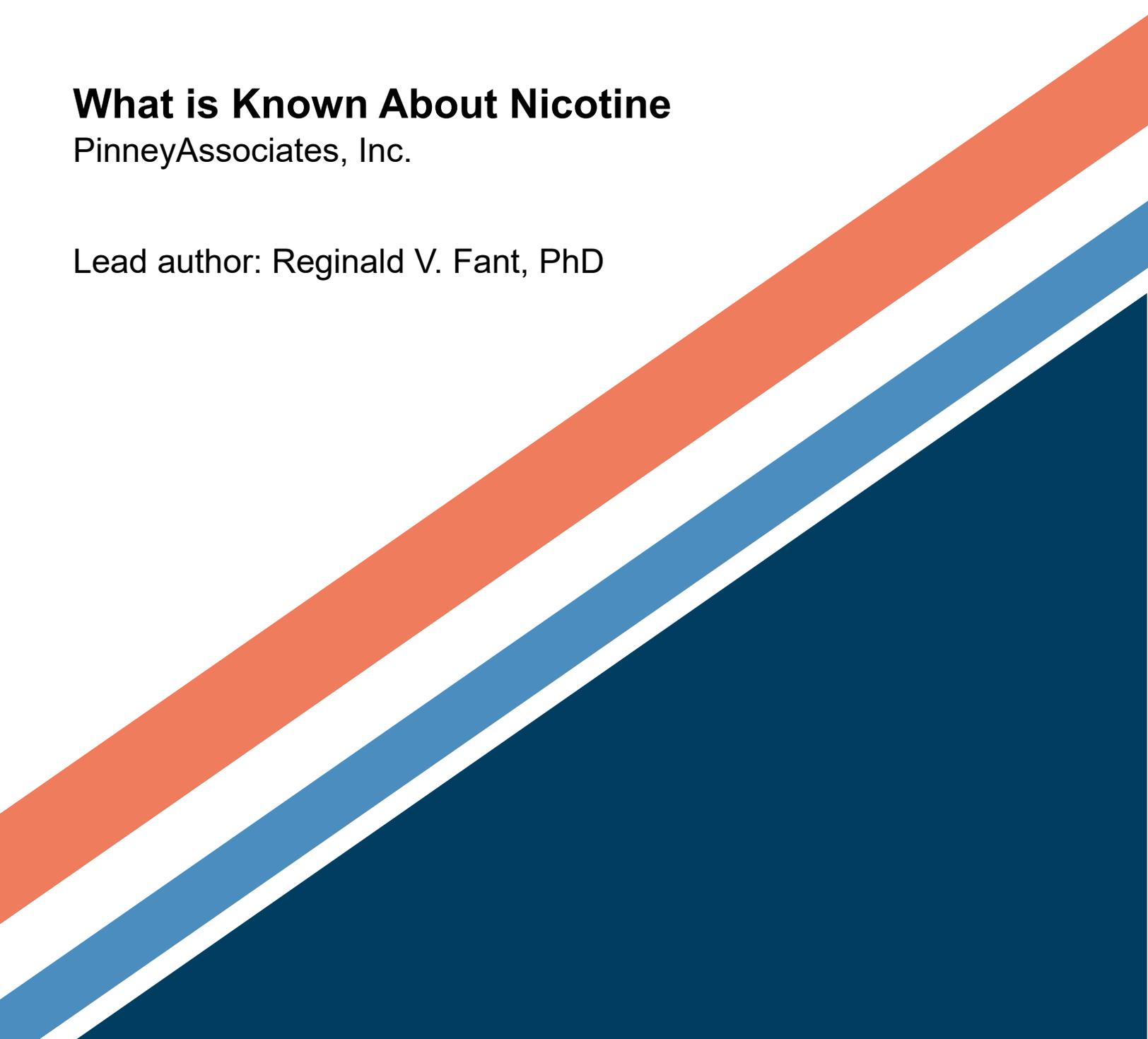
Pinney Associates

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What is Known About Nicotine

PinneyAssociates, Inc.

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1 Executive Summary

This white paper reviews the human health effects of nicotine, when delivered without the by-products of combustion, based on an expert review of the literature. Most of the literature on nicotine is related to its consumption in cigarettes. We know a lot about the harms of smoking, but this does not tell us much about the risk associated with nicotine itself. This is problematic, as we are now seeing a multitude of products on the market that offer users nicotine WITHOUT cigarette smoke. As such, there is a need to understand what we know about the effects of nicotine in the absence of cigarette smoke. Therefore, this paper focuses on what we know about nicotine without smoke, drawing upon research on nicotine replacement therapies (NRT) and smokeless tobacco, especially snus – a low-nitrosamine smokeless tobacco used in Sweden. We use snus data because snus produces exposure to nicotine comparable to combustible cigarettes but has lower levels of many carcinogens, and does not produce carbon monoxide, unlike cigarettes. There is little included on inhalation of nicotine in the form of nicotine vapor products due to the relative paucity of such evidence.

As summarized below, the evidence indicates that while nicotine itself is not entirely benign, the vast majority of the risks associated with smoking come from the inhalation of tobacco smoke. This document briefly reviews the major findings from the evidence regarding the effects of nicotine itself in the absence of smoke including its effect on cancer, respiratory disease, reproduction and fetal development, the developing brain, toxicity, and addiction. This is a summary of the available evidence (rather than a detailed or comprehensive review), drawing heavily on existing authoritative reviews, such as the reports of the U.S. Surgeon General and the Royal College of Physicians.^{1,2,3}

PinneyAssociates, Inc. consults exclusively for JUUL Labs, Inc., to advance relative risk-based regulation of nicotine and tobacco products. For the past 25 years, PinneyAssociates has worked on research and policies to minimize the death and disease associated with smoking combustible cigarettes. Our efforts have included helping smokers gain greater access to nicotine replacement therapies by facilitating over-the-counter availability, as well as advocating for regulations and policies based on the risk continuum for nicotine-containing products.

JUUL Labs, Inc. commissioned PinneyAssociates to write this report, but they had no input into the research or conclusions.

¹ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

² U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

³ Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London, 2016.

1.1 Summary of conclusions

1.1.1 Overall safety and toxicity

Nicotine replacement therapies have been judged safe enough for use without a physician's prescription for over twenty years, and in 2013, the FDA removed the limits on duration of use of NRT when used to prevent relapse.^{4,5} The United Kingdom and other countries in Europe as well as Canada, Australia, New Zealand and other jurisdictions had formed similar opinions and adjusted labeling accordingly. Since that time, no significant safety issues have arisen.

1.1.2 Cardiovascular disease

- Nicotine may contribute to cardiovascular disease, but its impact is much less than in tobacco smoke.
- Human epidemiological studies suggest a minimal contribution of nicotine (in the absence of tobacco smoke) to cardiovascular disease.
- Long-term use of nicotine by smokers in the form of NRT and low nitrosamine smokeless tobacco (snus) has not been associated with increased cardiovascular risk.
- Taken together, research suggests that nicotine poses a low risk to cardiovascular disease.

1.1.3 Cancer

- Nicotine itself is not linked to increased risk of cancer, nor is it listed in authoritative lists of carcinogens.
- There is a biological basis from non-clinical research and animal studies to propose that nicotine could promote (rather than initiate) cancer; however, human epidemiological data do not indicate that nicotine causes or promotes cancer.
- Long-term use of nicotine by smokers in the form of NRT and in snus has not been associated with increased cancer rates.
- Taken together, studies suggest that nicotine poses a low risk to cancer.

1.1.4 Respiratory disease

- Inhaling any substance besides clean air into the lungs should be avoided.
- E-cigarettes have only been widely used for the last decade, so the long-term health effects of e-cigarettes cannot yet be known. There is widespread agreement that smokers who completely switch to e-cigarettes can reduce their risk of smoking-related diseases, including respiratory diseases.
- There are likely to be health consequences associated with the inhalation of vaping-delivered aerosol containing nicotine on respiratory health. The health

⁴ U.S. Food and Drug Administration. Modifications to labeling of nicotine replacement therapy products for over-the-counter human use. Federal Register. 2013:19718-19721.

⁵ Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Chest. 1996;109(2):438–45.

consequences are likely to be of much lower concern than the inhalation of smoke.

- There is no convincing evidence currently of a meaningful impact of nicotine exposure on respiratory health.

1.1.5 Pregnancy and pre-natal exposure

- Nicotine can interfere with the development of a fetus and should be avoided by pregnant women.
- The effects of cigarette smoking on a pregnant woman and her unborn fetus are more severe than those associated with NRT, and there is data to suggest babies born to woman who used NRT compared to smokers were healthier and had fewer developmental concerns.

1.1.6 Nicotine and the developing brain

- Young people should not use nicotine.
- There are no prospective, randomized studies examining the effect of nicotine on the developing brain – such studies would be unethical.
- Animal research suggests nicotine – like other psychoactive substances – can alter brain development. It is unclear how this research translates to humans.
- Nicotine can improve short-term cognitive performance on some tasks.
- For adolescents who smoke chronically, studies suggest a minimal negative effect of smoking on cognitive performance. We would predict that the effect of non-combustible nicotine products would produce even smaller performance decrements than cigarette smoking, if any.

1.1.7 Acute toxicity and poisoning

- Nicotine can be toxic at very high doses but is rarely deadly.
 - Most documented reports of lethal nicotine exposure are in adults due to suicide and thus require intentionally ingesting very large amounts of nicotine at one time.
 - Other reports of lethal nicotine exposure are from accidental exposures among young children consuming nicotine-containing e-liquid.
 - The lethal dose of nicotine requires at least 500 mg ingested nicotine in an adult.

1.1.8 Addiction and physical dependence

- Nicotine is addictive.
- Nicotine's addictive potential depends on how quickly, in what form (e.g., patch, gum, e-cigarette, cigarette), at what dose, and for what duration it is delivered.
- Cigarettes are the most addictive nicotine-containing product currently available, while NRT has been found to have low dependence-potential.
- Available evidence suggests that e-cigarettes have lower dependence-potential than cigarettes, but higher dependence-potential than NRTs.
- It is important that alternatives to cigarettes deliver nicotine effectively and have dependence-potential to help provide a more similar nicotine experience to

smoking than NRTs, which do not have widespread appeal and uptake among smokers at the population level.⁶

2 Background

Cigarette smoking is the dominant mode of tobacco and nicotine use, and the death and disease from tobacco is overwhelmingly caused by cigarettes and other burned tobacco products.⁷ Smoking involves the inhalation of smoke from combustion products, which are primarily responsible for its toxic effects. In the U.S., smoking kills 480,000 people per year.^{8,9}

As discussed in the Royal College of Physicians 2016 report¹⁰, nicotine is not the component of tobacco smoke responsible for most of the morbidity and mortality caused by smoking:

“Nicotine is not, however, in itself, a highly hazardous drug (see Chapters 4 and 5). It increases heart rate and blood pressure, and has a range of local irritant effects, but is not a carcinogen. Of the three main causes of mortality from smoking, lung cancer arises primarily from direct exposure of the lungs to carcinogens in tobacco smoke, COPD from the irritant and proinflammatory effects of smoke, and cardiovascular disease from the effects of smoke on vascular coagulation and blood vessel walls. None is caused primarily by nicotine.” (p.5).

⁶ Abrams DB, Glasser AM, Villanti AC, Pearson JL, Rose S, Niaura RS. Managing nicotine without smoke to save lives now: Evidence for harm minimization. *Prev Med.* 2018 Dec;117:88-97.

⁷ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

⁸ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

⁹ Smoking and Tobacco Use: Fast Facts. Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion. November 15, 2019. Available at : https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm, Accessed March 9, 2020.

¹⁰ Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London, 2016.

The concept that “smokers smoke for nicotine but are killed by tar” has been widely accepted for decades,¹¹ and was reinforced by the 2014 Surgeon General’s Report, which noted the potential for noncombustible nicotine-delivery products to reduce morbidity and mortality.¹² As further stated by the Royal College of Physicians (2016):

“Although the nature and extent of any long-term health hazard from inhaling nicotine remain uncertain, because there is no experience of such use other than from cigarettes, it is inherently unlikely that nicotine inhalation itself contributes significantly to the mortality or morbidity caused by smoking. The main culprit is smoke and, if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all of the harm of smoking could probably be avoided.”¹³ (p.5)

The FDA has established a list of 93 harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke.¹⁴ The list also notes the potential harms from each constituent. Nicotine is included on this list as an addictive product, as well as a reproductive or developmental toxicant. The list does not include nicotine as a carcinogen, respiratory toxicant, or cardiovascular toxicant.

3 Nicotine and its role in smoking-related disease

3.1 Cardiovascular disease

Smoking is a leading cause of cardiovascular disease (CVD), increasing the risk of heart attacks and stroke.¹⁵ CVD includes coronary heart disease (CHD also known as ischemic heart disease), stroke, congestive heart failure, coronary artery disease, and peripheral arterial disease (PAD).¹⁶ The 2014 U.S. Surgeon General’s report concluded that combustion compounds in tobacco smoke, such as oxidizing chemicals, volatile organic chemicals, particulates and carbon monoxide, rather than nicotine, are the primary contributors to increased cardiovascular risk.¹⁶ Carbon monoxide is not a

¹¹ Russell MA. Low-tar medium-nicotine cigarettes: a new approach to safer smoking. *Br Med J*. 1976;1(6023):1430-1433.

¹² U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

¹³ Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London, 2016.

¹⁴ U.S. Food and Drug Administration. Harmful and potentially harmful constituents in tobacco products and tobacco smoke: Established list. April 2012. Available at: <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list>, accessed February 17, 2020.

¹⁵ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

¹⁶ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

constituent of e-cigarettes, and oxidizing chemicals, volatile organic chemicals, and heavy metals are present at much lower levels compared to combustible cigarettes.¹⁷

Nicotine itself may contribute to CVD, but if it does, its impact is substantially lower than combustible tobacco smoke. E-cigarettes and snus contain fewer harmful constituents than combustible cigarettes, which may help users reduce CVD risk when compared to cigarettes.^{18,19}

The potential role of nicotine in atherogenesis (plaque formation in arteries) and in triggering acute coronary events has been discussed extensively in the medical literature.^{20,21} Several effects of nicotine-induced, sympathetic neural stimulation include hemodynamic effects (increased blood pressure, heart rate, cardiac contraction, constriction of blood vessels), arrhythmogenesis, lipid abnormalities, and inflammation.^{22,23}

However, human epidemiological studies suggest a minimal contribution of nicotine (in the absence of combustible tobacco) to CVD. For example, data from the 5-year Lung Health Study, in which participants were actively encouraged to use NRT for several months and many continued to consume NRT for a much longer period, demonstrated no association between sustained NRT use and the occurrence of CVD.^{24,25}

Studies of Swedish snus have also found little contribution of snus use to CVD. One study showed that middle aged snus users had a significantly higher risk of mild hypertension than middle aged non-tobacco users.²⁶ However, two studies comprising a

¹⁷ Benowitz NL. Harms and risks of nicotine? Implications for tobacco harm reduction. Paper presented at the 7th Annual Global Forum on Nicotine. June 17, 2017. Warsaw, Poland.

¹⁸ Murray RP, Connett JE, Zapawa LM. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. *Nicotine Tob Res.* 2009;11:1076–82.

¹⁹ Bolinder GM, Ahlborg BO, Lindell JH. Use of smokeless tobacco: Blood pressure elevation and other health hazards found in a large-scale population survey. *J Int Med.* 1992;232:327-334.

²⁰ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

²¹ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

²² U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

²³ Benowitz NL. Harms and risks of nicotine? Implications for tobacco harm reduction. Paper presented at the 7th Annual Global Forum on Nicotine. June 17, 2017. Warsaw, Poland.

²⁴ Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest.* 1996;109(2):438–45

²⁵ Murray RP, Connett JE, Zapawa LM. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. *Nicotine Tob Res.* 2009;11:1076–82.

²⁶ Bolinder GM, Ahlborg BO, Lindell JH. Use of smokeless tobacco: Blood pressure elevation and other health hazards found in a large-scale population survey. *J Int Med.* 1992;232:327-334.

group of young men and a group of middle-aged firefighters, respectively, failed to note differences between snus users and non-tobacco users with respect to blood pressure.^{27,28}

Several studies have shown no difference between snus users and non-tobacco users on degree of atherosclerosis by measurement of the carotid artery wall thickness,²⁹ or on risk factors for atherosclerosis (blood lipid levels, fibrinogen levels, fibrinolytic activity, insulin resistance).^{30,31,32,33} Three studies have shown no risk of snus use on incidence of myocardial infarction.^{34,35,36}

In conclusion, nicotine may contribute to cardiovascular disease, but its impact is much less than in tobacco smoke.

3.2 Cancer

Nicotine is not a known carcinogen. When smokers inhale cigarette smoke, each puff delivers a mixture of known carcinogens and toxicants as well as thousands of uncharacterized chemicals. Tobacco smoke contains more than 7,000 chemicals, and at least 69 of these can cause cancer.³⁷ These include known potent carcinogens including polycyclic aromatic hydrocarbons (PAHs); tobacco-specific nitrosamines; aromatic amines; and volatile carcinogens such as formaldehyde, acetaldehyde, 1,3-butadiene, and benzene, as well as various heavy metals.

²⁷ Eliasson M, Lundblad D, Hägg E. Cardiovascular risk factors in young snuff-users and cigarette smokers. *J Int Med.* 1991;230:17-22.

²⁸ Bolinder G, Norén A, Wahren J, de Faire U. Long-term use of smokeless tobacco and physical performance in middle-aged men. *Eur J Clin Invest.* 1997a;27:427-433.

²⁹ Bolinder G, Norén A, de Faire U, Wahren J. Smokeless tobacco use and atherosclerosis: An ultrasonic investigation of carotid intima media thickness in healthy middle-aged men. *Atherosclerosis.* 1997b;132:95-103.

³⁰ Bolinder GM, Ahlborg BO, Lindell JH. Use of smokeless tobacco: Blood pressure elevation and other health hazards found in a large-scale population survey. *J Int Med.* 1992;232:327-334.

³¹ Eliasson M, Lundblad D, Hägg E. Cardiovascular risk factors in young snuff-users and cigarette smokers. *J Int Med.* 1991;230:17-22.

³² Bolinder G, Norén A, Wahren J, de Faire U. Long-term use of smokeless tobacco and physical performance in middle-aged men. *Eur J Clin Invest.* 1997a;27:427-433.

³³ Eliasson M, Asplund K, Evrin PE, Lundblad D. Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum-insulin: The northern Sweden MONICA study. *Atherosclerosis.* 1995;113:41-53.

³⁴ Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Tobacco and myocardial-infarction: Is snuff less dangerous than cigarettes?. *Br Med J.* 1992;305:1252-1256.

³⁵ Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. Smokeless tobacco as a possible risk factor for myocardial infarction: A population-based study in middle-aged men. *J Am Coll Cardiol.* 1999;34:1784-1790.

³⁶ Hergens M-P, Ahlbom A, Andersson T, Pershagen G. Swedish moist snuff and myocardial infarction among men. *Epidemiology.* 2005;16:12-16.

³⁷ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

In contrast, authoritative reviews of carcinogens in tobacco and tobacco smoke have not listed nicotine among the carcinogens. This includes reviews of evidence concerning carcinogens in smokeless tobacco by the WHO's International Agency on Research on Cancer and other tobacco products, and the 2010 Surgeon General's Report.^{38,39,40}

For cancer, there is a biological basis from non-clinical research to propose that nicotine could promote cancer. This potential is based on experimental studies that have limitations in replicating human exposure and on mechanistic studies; but human evidence is lacking.⁴¹ In vitro and animal studies have raised concerns about whether nicotine might have cancer-promoting effects.⁴² However, the relevance of these studies to people is uncertain, and human epidemiological data so far do not indicate that nicotine causes or promotes cancer. For example, the Royal College of Physicians concluded that "there is no evidence that this theoretical risk, derived from animal studies, translates into an increase in cancer risk or tumor growth in humans." (p. 1260).⁴³

The Lung Health Study is the only study that provides information about long-term users of NRT.⁴⁴ This study was not designed to directly examine nicotine's potential cancer risk. It was a 5-year randomized trial to assess the effects of smoking cessation and reduction on chronic lung disease and lung function. Among 5,887 persons initially enrolled, the researchers continued to follow them for an additional 7 years (n = 3,220). Study participants were offered NRT without consideration of randomization or study design. Although they were encouraged to use NRT for only 6 months, many continued to use it long term. A total of 75 lung cancers were diagnosed among smokers and quitters of the extended surveillance group, but the use of NRT was not associated with lung cancer (or other cancers).

If nicotine itself caused or promoted cancer, including oral cancer, one would expect snus use to be associated with increased risk of this and other cancers. Two population-

³⁸ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

³⁹ International Agency for Research on Cancer. Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2007;89:1-641.

⁴⁰ International Agency for Research on Cancer. Tobacco Smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012;100E:43-211.

⁴¹ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014

⁴² Grando SA. Connections of nicotine to cancer. *Nat Rev Cancer*. 2014;14(6):419-429.

⁴³ Royal College of Physicians. Harm reduction in nicotine addiction: helping people who can't quit. A report by the Tobacco Advisory Group of the Royal College of Physicians. London, 2007.

⁴⁴ Benowitz NL. Harms and risks of nicotine? Implications for tobacco harm reduction. Paper presented at the 7th Annual Global Forum on Nicotine. June 17, 2017. Warsaw, Poland.

based case-control studies did not show any association between snus use and risk for oral cancer.^{45,46}

One study examined the association between use of tobacco and alcohol and risk for gastric cancer in a population-based study and found no evidence that use of Swedish snus increased the risk of these types of cancer.⁴⁷ Smoking was, however, a risk factor. Another study found that use of Swedish snus is not a risk factor for esophagus and gastric cancer.⁴⁸ A third study examined the relationship between snus and pancreatic cancer in a prospective study and found no association between snus use and pancreatic cancer.⁴⁹ A fourth study found snus use to be unrelated to the incidence of lung cancer.⁵⁰

The long-term data on Swedish snus (low nitrosamine) tobacco and on NRT use in former smokers is reassuring in that these forms of nicotine use do not appear to lead to an incremental risk of cancer. Overall, the epidemiological data show that nicotine itself does not measurably cause or promote cancer in humans. While there is some question regarding nicotine's potential role in promoting tumor growth once cancer has already occurred in nonclinical studies, this hypothesis has not been substantiated in human studies.

3.3 Respiratory disease

Animal data on the respiratory effects of nicotine are mixed. Whereas there are some animal data that indicate a theoretical risk⁵¹, a 90-day inhalation study in rats at a nicotine dose of 6.6 mg/kg/day found several nicotine related responses, but concluded: "Taking into account the overall weight of evidence no adverse effects were observed for propylene glycol/ Vegetable Glycerin/nicotine up to 438/544/6.7 mg/kg/day..." According to the authors, this 6.6 mg/kg/day dose corresponding to a human daily

⁴⁵ Schildt E-B, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int J Cancer*. 1998;77:341-346.

⁴⁶ Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Björklund A, Rutqvist LE. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. A population based case-referent study in Sweden. *Cancer*. 1998;82:1367-1375.

⁴⁷ Ye WM, Ekström AM, Hansson L-E, Bergström R, Nyrén O. Tobacco, alcohol and the risk of gastric cancer by sub-site and histological type. *Int J Cancer*. 1999;83:223-229.

⁴⁸ Lagergren J, Bergström R, Lindgren A, Nyrén O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer*. 2000;85:340-346.

⁴⁹ Araghi M, Rosaria Galanti M, Lundberg M, Lager A, Engström G, Alfredsson L, et al. Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies. *Int J Cancer*. 2017 Aug 15;141(4):687-693.

⁵⁰ Luo J, Ye W, Zendejdel K, Adami J, Adami HO, Boffetta P, Nyrén O. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet*. 2007 Jun 16;369(9578):2015-2020.

⁵¹ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

nicotine dose of 66 mg for a 60-kg adult human (around 3 packs of cigarettes per day).⁵²

Data on the effects of e-cigarette vapor on the airways are limited to studies of short-term exposure. As discussed by the Royal College of Physicians, short-term e-cigarette use has been found to have no effect on spirometric markers of lung function, and another study found no difference in reported adverse events over 12 weeks' use of an e-cigarette with or without nicotine, or conventional NRT.⁵³ However, use of an e-cigarette in healthy individuals for 5 min has been shown to produce negative effects including reduced exhaled nitric oxide (NO) and increase airway resistance, consistent with an irritant effect on the airways resulting in mucosal edema, smooth muscle contraction or increased production of lung secretions in response to the vapor.⁵⁴

Another study reported a reduction in exhaled NO after inhaling vapor from an e-cigarette, with or without nicotine, similar to that produced by conventional cigarette smoke.⁵⁵ Based on the foregoing, it is unclear whether these short-term airway effects will translate into long-term airway damage; however, it does appear that this risk is low relative to smoking combustible cigarettes.

As noted in the 2016 Royal College of Physicians (2016) report:

“As smoking cessation is associated with a reduction in respiratory symptoms in people with respiratory disease, many smokers who switch to an e-cigarette are likely to experience improvements in respiratory symptoms.”⁵⁶

Similarly, a report commissioned by Public Health England concluded:

“There have been some studies with adolescents suggesting respiratory symptoms among e-cigarette experimenters. However, small scale or uncontrolled switching studies from smoking to vaping have demonstrated some respiratory improvements (p. 19).”⁵⁷

This is illustrated in a study that followed a small cohort of patients with asthma, in whom improvements in symptoms and respiratory function were observed after

⁵² Phillips B, Titz B, Kogel U, Sharma D, Leroy P, Xiang Y, et al. Toxicity of the main electronic cigarette components, propylene glycol, glycerin, and nicotine, in Sprague-Dawley rats in a 90-day OECD inhalation study complemented by molecular endpoints. *Food Chem Toxicol.* 2017 Nov;109(Pt 1):315-332.

⁵³ Royal College Physicians. *Nicotine without smoke: Tobacco harm reduction.* London, 2016.

⁵⁴ Vardavas CI, Anagnostopoulos N, Kougias M et al. Short-term pulmonary effects of using an electronic cigarette: Impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 2012;141:1400–6.

⁵⁵ Marini S, Buonanno G, Stabile L, Ficco G. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. *Toxicol Appl Pharmacol* 2014;278:9–15.

⁵⁶ Royal College Physicians. *Nicotine without smoke: Tobacco harm reduction.* London, 2016.

⁵⁷ McNeill A, Brose LS, Calder R, Bauld L & Robson D. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England, 2018.

switching from smoking to vaping.⁵⁸ In that study, the authors reviewed changes in spirometry data, airway hyper-responsiveness (AHR; characteristic feature of asthma consisting of an increased sensitivity of the airways to an inhaled constrictor agonist), asthma exacerbations and subjective asthma control in smoking asthmatics who switched to regular e-cigarette use. Measurements were taken prior to switching (baseline) and at two consecutive visits at 6 and 12 months). Eighteen smoking asthmatics (10 single users, eight dual users) were identified. Overall there were significant improvements in spirometry data, asthma control and AHR. These positive outcomes were noted in single and dual users, presumably due to a reduction in cigarettes. Reduction in exacerbation rates was reported but was not statistically significant.

In 2019, the United States experienced an outbreak of an e-cigarette, or vaping product use associated lung injury (EVALI). The CDC notes that tetrahydrocannabinol (THC) vaping products from informal sources and vitamin E acetate are strongly linked to the outbreak.⁵⁹ Further, a recent study found that “among the case patients for whom laboratory or epidemiologic data were available, 47 of 50 (94%) had detectable tetrahydrocannabinol (THC) or its metabolites in BAL fluid or had reported vaping THC products in the 90 days before the onset of illness”.⁶⁰ Though the CDC notes that other chemicals in THC or non-THC products, cases of EVALI have not been seen outside of the United States and it does not appear that nicotine played a role in the outbreak.

Overall, while more research is needed on the impact of vaping-delivered aerosol containing nicotine on respiratory health, there is little convincing evidence currently of a meaningful impact of nicotine exposure on respiratory health.

3.4 Pregnancy and pre-natal exposure

Smoking is strongly associated with reduced fertility and adverse outcomes of pregnancy. Women who smoke are less likely to conceive, and, if they do, during pregnancy are more likely to deliver prematurely, to have low-birthweight babies who suffer increased perinatal mortality.⁶¹ Although smoking contributes to these risks, some of these effects may be due to nicotine.

⁵⁸ Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, Battaglia E, Russo C. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *Int J Environ Res Public Health*. 2014;11:4965–77.

⁵⁹ Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. (2020, February 25). Retrieved from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

⁶⁰ Blount, B. C., Karwowski, M. P., Shields, P. G., Morel-Espinosa, M., Valentin-Blasini, L., Gardner, M., ... & Corstvet, J. (2020). Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *New England Journal of Medicine*, 382(8), 697-705.

⁶¹ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

According to the US 2014 Surgeon General's report:

“The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth.”⁶²

This conclusion is consistent with that of the Royal College of Physicians: “Questions remain about the safety of nicotine in pregnancy and potential effects on fetal development and mortality.” The report also notes: “Passive maternal smoking during pregnancy increases the risk of stillbirth and developmental anomalies and reduces birth weight.”⁶³

The 2010 Surgeon General's Report discusses the potential role of nicotine on smoking-related harms during pregnancy.⁶⁴ Nicotine may be involved in the development of various congenital anomalies or neurobehavioral problems. Nicotine may also interfere with pregnancy by affecting oviduct function, which may lead to ectopic pregnancy or problems with fertilization and implantation, or by affecting transport of essential nutrients, which could affect fetal growth.

There is clear evidence that smoking causes negative outcomes to the fetus, and that some of the effects caused by smoking may be related to nicotine. However, it should be noted that cigarette smoke contains a number of other chemicals that have been shown to have adverse effects on fetal outcomes.⁶⁵ These include heavy metals (cadmium, mercury, and lead), polycyclic aromatic hydrocarbons, toluene, carbon disulfide, dichlorodiphenyltrichloroethane, styrene, benzene, and vinyl chloride. Carbon monoxide, which is a byproduct of combustion, reduces the blood's ability to carry oxygen to the fetus.

A Cochrane review of the literature on use of pharmacotherapies for smoking cessation during pregnancy included a total of nine trials which enrolled 2210 pregnant smokers: eight trials of NRT and one trial of bupropion as adjuncts to behavioral support/cognitive behavioral therapy. Compared to placebo and non-placebo controls, there was a difference in smoking rates observed in later pregnancy favoring use of NRT. Despite the higher rates of smoking cessation in the NRT groups, there were no differences between NRT and control groups in rates of miscarriage, stillbirth, premature birth,

⁶² U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

⁶³ Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London, 2016.

⁶⁴ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

⁶⁵ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

birthweight, low birthweight, admissions to neonatal intensive care, caesarean section, congenital abnormalities or neonatal death.⁶⁶

Pregnant women should not use nicotine. However, because smoking delivers many substances that could be harmful to the fetus in addition to nicotine, and NRT aids cessation, NRT is a safer source of nicotine, but the benefit-risk ratio must be carefully considered.

3.5 Nicotine exposure during adolescence and the developing brain

According to the 2014 US Surgeon General's Report: "The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development."^{67,68} These consequences may include effects on cognitive ability and/or increases in the rewarding effects of nicotine and other drugs. Some animal model studies show that nicotine exposure in adolescence can induce neuroadaptive changes that persist into the adulthood of the animal. While animal models suggest possible concerns for humans, more research is required to demonstrate if, and at what dosage and duration of exposure, nicotine might have possible adverse effects during adolescent and young adult brain development.

The Report further states:

"Smoking during adolescence has been associated with lasting cognitive and behavioral impairments, including effects on working memory and attention, although causal relationships are difficult to establish in the presence of potential confounding factors. In addition, functional magnetic resonance imaging in humans showed that young adult smokers had reduced prefrontal cortex activation during attentional tasks when compared with nonsmoking controls. Diminished prefrontal cortex activity correlated with duration of smoking, supporting the hypothesis that smoking could have long-lasting effects on cognition" (p. 122).⁶⁹

Similar findings were reported in the 2016 Surgeon General's Report: "Nicotine exposure during adolescence ... can harm the developing adolescent brain." These findings were primarily based on animal research which suggests that "adolescent brains are particularly sensitive to nicotine's effects, such that subsequent self-

⁶⁶ Coleman T, Chamberlain C, Davey M, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. <https://doi.org/10.1002/14651858.CD010078.pub2>

⁶⁷ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

⁶⁸ In the four-level hierarchy for classifying the strength of causal inferences from available evidence, level 2 evidence is suggestive but not sufficient to infer a causal relationship

⁶⁹ U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

administration is more likely, and that same literature indicates that this age group is at risk for a constellation of nicotine-induced neural and behavioral alterations.”⁷⁰

It is unclear why the 2016 report stated more definitively that nicotine “can harm the adolescent brain”, as opposed to “the evidence is suggestive.” The vast majority of the literature cited in the 2016 report to suppose these claims were published prior to 2014, and thus were available for inclusion in the 2014 report. Indeed, the 2016 report notes:

“Limited direct human experimental data exist on the effects of nicotine exposure from e-cigarettes on the developing adolescent brain, but experimental laboratory data have been found to be relevant in animal models to contextualize effects in humans.”⁷¹

These conclusions in the 2016 report were based primarily on animal data of similar quality to those used to develop conclusions for the 2014 report.

Rodent studies have shown that nicotine induces changes in gene expression in the brain to a greater degree with adolescent exposure than during other periods of development.^{72,73} Nicotine exposure during adolescence also appears to cause long-term structural and functional changes in the brain.⁷⁴ Behavioral studies of adolescent rats have also shown negative effects of nicotine exposure.^{75,76}

In the short-term, nicotine enhances some aspects of attention and cognition. For example, a meta-analysis was conducted of 41 studies in which nicotine was administered, and performance was assessed in healthy adult nonsmokers or smokers who were not tobacco-deprived or minimally deprived.⁷⁷ The authors found significant positive effects of nicotine or smoking on six domains: fine motor, alerting attention-accuracy and response time (RT), orienting attention-RT, short-term episodic memory-

⁷⁰ U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: A report of the Surgeon General—Executive summary. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

⁷¹ U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: A report of the Surgeon General—Executive summary. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

⁷² Schochet TL, Kelley AE, Landry CF. Differential expression of arc mRNA and other plasticity-related genes induced by nicotine in adolescent rat forebrain. *Neuroscience*. 2005;135(1):285–97.

⁷³ Poleskaya OO, Fryxell KJ, Merchant AD, Locklear LL, Ker KF, McDonald CG, et al. Nicotine causes age-dependent changes in gene expression in the adolescent female rat brain. *Neurotoxicol Teratol*. 2007;29(1):126–40.

⁷⁴ Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. *Pharmacology and Therapeutics* 2009;122(2):125–39.

⁷⁵ Trauth JA, Seidler FJ, Slotkin TA. An animal model of adolescent nicotine exposure: effects on gene expression and macromolecular constituents in rat brain regions. *Brain Res*. 2000;867(1-2):29–39.

⁷⁶ Counotte DS, Spijker S, Van de Burgwal LH, Hogenboom F, Schoffelmeer AN, De Vries TJ, et al. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. *Neuropsychopharmacology* 2009;34(2):299–306.

⁷⁷ Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl)*. 2010 Jul;210(4):453-69.

accuracy, and working memory-RT. However, longer-term clinical studies that have compared cognitive performance in smokers and nonsmokers have been mixed, and appear to be largely based on whether the smokers were abstinent or non-abstinent.^{78,79,80,81,82,83} In studies that compared non-abstinent smokers to nonsmokers, the differences in cognition appear to be negligible.

Twin studies have shown no effects of smoking on cognition. For example, one study concluded that “Educational achievement did not differ within twin pairs discordant for smoking, in adults and adolescents.”⁷⁹ Similarly, another study concluded: “The (inverse) IQ–smoking association disappeared after adjustments for shared environment and genetics.”⁸⁴

There have also been studies suggesting that adolescent exposure to nicotine could increase the risk of abuse of other drugs, such as cocaine.⁸⁵ As discussed in that review, nicotine exposure during adolescence in mouse models can produce long-term changes in brain structures related to drug abuse that can lead to an increased risk of abuse of other drugs due to the drug having greater reinforcing value.

This “Gateway Hypothesis,” whereby drug usage starts with a legal drug and proceeds to illegal drugs, is controversial in that it is unclear to what extent availability of tobacco and alcohol make it more likely that use of these products precedes use of marijuana, cocaine, and opioids. However, the neural changes seen after nicotine exposure in adolescent mice give credence to the theory that biological changes after nicotine exposure may increase the risk of subsequent illicit drug abuse.

Taken together, these findings suggest a minimal effect of nicotine on cognitive performance.

3.6 Acute toxicity and poisoning

Symptoms of mild acute toxicity include nausea and vomiting, progressing with increased exposure to cholinergic syndrome, which includes diarrhea, increased

⁷⁸ Treur JL, Willemsen G, Bartels M, Geels LM, van Beek JH, Huppertz C, et al. Smoking during adolescence as a risk factor for attention problems. *Biol Psychiatry*. 2015;78(9):656–63.

⁷⁹ Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biol Psychiatry*. 2005;57(1):56–66.

⁸⁰ Musso F, Bettermann F, Vucurevic G, Stoeter P, Konrad A, Winterer G. Smoking impacts on prefrontal attentional network function in young adult brains. *Psychopharmacology (Berl)*. 2007 Mar;191(1):159-69.

⁸¹ Chamberlain SR, Odlaug BL, Schreiber LR, Grant JE. Association between tobacco smoking and cognitive functioning in young adults. *Am J Addict*. 2012 Nov;21 Suppl 1:S14-9.

⁸² Mashhoon Y, Betts J, Farmer SL, Lukas SE. Early onset tobacco cigarette smokers exhibit deficits in response inhibition and sustained attention. *Drug Alcohol Depend*. 2018 Mar 1;184:48-56.

⁸³ Wagner M, Schulze-Rauschenbach S, Petrovsky N, Brinkmeyer J, von der Goltz C, Gründer G, et al. Neurocognitive impairments in non-deprived smokers--results from a population-based multi-center study on smoking-related behavior. *Addict Biol*. 2013 Jul;18(4):752-61.

⁸⁴ Wennerstad KM, Silventoinen K, Tynelius P, Bergman L, Kaprio J, Rasmussen F. Associations between IQ and cigarette smoking among Swedish male twins. *Soc Sci Med*. 2010 Feb;70(4):575-81.

⁸⁵ Kandel D, Kandel E. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. *Acta Paediatr*. 2015 Feb;104(2):130-7.

salivation, increased respiratory secretions, and bradycardia. Severe poisonings can progress further to seizures and respiratory depression.¹ Though there is a risk of acute nicotine toxicity, it is relatively low.

Nicotine is a toxic compound, but the frequent warnings of potential fatalities caused by ingestion of small amounts of tobacco products or diluted nicotine-containing solutions are unjustified. Previous estimates of lethal doses of nicotine for an adult (30-60 mg ingested nicotine) have been deemed inaccurate because they were too low.⁸⁶ The lethal dose of nicotine is at least 10 times higher than previously reported and, at minimum, requires 500 mg ingested nicotine in an adult.⁸⁷

As discussed by the Royal College of Physicians (2016):

“Although nicotine is a toxic compound, overdosing on nicotine products used as directed is almost impossible, given the individual ability to titrate dose and the short half-life of nicotine. However, ingestion of high doses (purposeful or accidental) can be fatal. Historically, the lethal dose of nicotine for a human adult has consistently been stated to be about 60 mg, corresponding to an oral median lethal dose (LD50) of approximately 0.8 mg/kg. However, this figure has recently been disputed in the light of reports of non-fatal suicide attempts or accidents involving nicotine ingestion, leading to an estimate that the lower dose limit for fatal outcomes is likely to be 500–1,000 mg ingested nicotine, equivalent to an oral LD50 of 6.5–13 mg/kg.” (p. 57)⁸⁸

3.7 Addiction and Physical Dependence

Nicotine is addictive. Many factors contribute to the addictiveness of nicotine-containing products. According to 2014 Surgeon General’s Report:

“Nicotine is the major chemical component responsible for addiction in tobacco products. The risk for nicotine addiction depends on the dose of nicotine delivered and the way it is delivered; the potential for addiction increases with the dose delivery rate, the rate of absorption, and the attained concentration of nicotine.” (p.109)⁸⁹

The degree of reinforcing value and dependence potential of nicotine-containing products is related to the formulation. As discussed by the Royal College of Physicians (2016):

⁸⁶ Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Arch Toxicol.* 2014; 88(1): 5–7.

⁸⁷ Kandel D, Kandel E. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. *Acta Paediatr.* 2015 Feb;104(2):130-7.

⁸⁸ Royal College Physicians. *Nicotine without smoke: Tobacco harm reduction.* London, 2016.

⁸⁹ U.S. Department of Health and Human Services. *The health consequences of smoking: 50 years of progress. A report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

The relatively slow delivery of nicotine to the brain achieved by NRT is much less reinforcing, and hence much less likely to generate dependence, than cigarette smoking. However, forms of NRT that deliver nicotine relatively quickly, such as the nasal spray, are thought to be more likely to generate dependence than others. Overall, however, the addictive potential of cigarettes is much higher than that of NRT or other non-inhaled nicotine products. Clinically, very few users of NRT become dependent on it.⁹⁰

The addiction caused by the nicotine in tobacco smoke is critical in the transition of smokers from experimentation to sustained smoking and, subsequently, in the maintenance of smoking for the majority of smokers.^{91,92,93} Substantial longitudinal research has shown that smoking typically begins with experimental use of cigarettes and that the transition to regular smoking can occur relatively quickly, with the smoking of as few as 100 cigarettes.⁹⁴

Longitudinal studies show that there are individual trajectories of smoking as tracked by the index of numbers of cigarettes smoked daily. These trajectories are variable, with some smokers quickly progressing to regular smoking and others doing so more slowly.^{95,96} Research is in progress on the possible role of genetic factors in determining the trajectory of nicotine use.

Different tobacco and nicotine products appear to induce different degrees of dependence, with NRT having very little dependence potential and cigarette smoking

⁹⁰ Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London, 2016.

⁹¹ U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

⁹² Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London, 2016.

⁹³ U.S. Department of Health and Human Services. Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.

⁹⁴ U.S. Department of Health and Human Services. Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.

⁹⁵ U.S. Department of Health and Human Services. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010

⁹⁶ U.S. Food and Drug Administration. Harmful and potentially harmful constituents in tobacco products and tobacco smoke: Established list. April 2012. Available at: <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list>, accessed February 17, 2020.

having the highest potential.^{97,98,99} It is not yet known what degree of dependence might be associated with e-cigarettes, partly because the products are evolving in their ability to deliver nicotine effectively.

However, recent human abuse potential studies of one ENDS product have shown that the abuse liability of that product was significantly lower than the combustible cigarette, but higher than nicotine gum.^{100,101} Some degree of effective nicotine delivery and reinforcement may be necessary if smokers are to switch from smoking cigarettes to using ANDS.

4 Misperceptions about nicotine and the relative risk of vapor products and combustible cigarettes

There are many misperceptions about the absolute and relative harmfulness from electronic nicotine delivery systems (ENDS) products and nicotine, and the evidence suggests that these misperceptions are worsening over time. Some common misperceptions include: ENDS products are as harmful or more harmful than cigarettes^{102,103,104} nicotine is the main cause of smoking related health problems¹⁰⁵, and that

⁹⁷ Fagerström K, Eissenberg T. Dependence on tobacco and nicotine products: A case for product-specific assessment. *Nicotine Tob Res.* 2012;14(11):1382-90.

⁹⁸ Fant RV, Buchhalter AR, Buchman AC, Henningfield JE. Pharmacotherapy for tobacco dependence. *Handb Exp Pharmacol.* 2009;(192):487-510.

⁹⁹ West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl).* 2000;149(3):198-202.

¹⁰⁰ Stiles MF, Campbell LR, Graff DW, Jones BA, Fant RV, Henningfield JE. Pharmacodynamic and pharmacokinetic assessment of electronic cigarettes, combustible cigarettes, and nicotine gum: implications for abuse liability. *Psychopharmacology (Berl).* 2017 Sep;234(17):2643-2655.

¹⁰¹ Stiles MF, Campbell LR, Jin T, Graff DW, Fant RV, Henningfield JE. Assessment of the abuse liability of three menthol Vuse Solo electronic cigarettes relative to combustible cigarettes and nicotine gum. *Psychopharmacology (Berl).* 2018 Jul;235(7):2077-2086.

¹⁰² Nyman AL, Huang J, Weaver SR, Eriksen MP. Perceived Comparative Harm of Cigarettes and Electronic Nicotine Delivery Systems. *JAMA Network Open.* 2019;2(11):e1915680.

¹⁰³ Huang J, Feng B, Weaver SR, Pechacek TF, Slovic P, Eriksen MP. Changing perceptions of harm of e-cigarette vs cigarette use among adults in 2 US national surveys from 2012 to 2017. *JAMA Network Open.* 2019;2(3):e191047.

¹⁰⁴ Kahn C. More Americans say vaping is as dangerous as smoking cigarettes: Reuters poll. 2019 September 24. Retrieved from <https://www.reuters.com/article/us-health-vaping-poll/more-americans-say-vaping-is-as-dangerous-as-smoking-cigarettes-reuters-poll-idUSKBN1W9136>

¹⁰⁵ Yang B, Owusu D, Popova L. Effects of a Nicotine Fact Sheet on Perceived Risk of Nicotine and E-Cigarettes and Intentions to Seek Information About and Use E-Cigarettes. *International Journal of Environmental Research and Public Health.* 2020;17(1):131.

nicotine causes cancer.^{106,107,108} Nicotine misperceptions are widespread and include educated groups such as professors and nurses.^{109,110}

It is important for smokers to have accurate nicotine risk perceptions. Smokers may be discouraged from switching to a less harmful product – including NRTs, which are regulated as safe and effective by the FDA – if they think those products are just as or more harmful than smoking.¹¹¹

As noted above, it is widely accepted in scientific literature that nicotine does not cause cancer. However, the public is still confused and holds this misperception. In a 2016 study conducted by Johnson et al, 80% of participants in the PATH study thought that nicotine caused cancer and 87% of ever tobacco users held this belief, compared to 69% of current tobacco users.¹¹² There is also a lot of uncertainty around the harmfulness of nicotine—a quarter of participants in the study did not know if nicotine caused cancer.¹¹³

O'Brien et al found similar results: researchers found that 49% of study participants incorrectly agreed with the statement “nicotine is the substance that causes most of the cancer caused by smoking” and a further 27% of participants were unsure whether the statement was accurate or not (27%) or correctly disagreed (27%).¹¹⁴

¹⁰⁶ Johnson SE, Coleman B, Tessman GK, Dickinson DM. Unpacking smokers' beliefs about addiction and nicotine: A qualitative study. *Psychology of Addictive Behaviors*. 2017;31(7):744.

¹⁰⁷ Johnson SE. What the public knows and believes about nicotine: Insights from recent quantitative and qualitative evidence. FDA Center for Tobacco Products presentation about PATH survey data. 22nd Annual Meeting of the Society for Research on Nicotine and Tobacco; Chicago, IL: FDA Center for Tobacco Products, 2016.

¹⁰⁸ O'Brien EK, Nguyen AB, Persoskie A, Hoffman AC. US adults' addiction and harm beliefs about nicotine and low nicotine cigarettes. *Preventive Medicine*. 2017;96:94-100.

¹⁰⁹ Patel D, Peiper N, Rodu B. Perceptions of the health risks related to cigarettes and nicotine among university faculty. *Addiction Research & Theory*. 2013;21(2):154-159.

¹¹⁰ Borrelli B, Novak SP. Nurses' knowledge about the risk of light cigarettes and other tobacco “harm reduction” strategies. *Nicotine & Tobacco Research*. 2007;9(6):653-661.

¹¹¹ Persoskie A, O'Brien EK, Poonai K. Perceived relative harm of using e-cigarettes predicts future product switching among US adult cigarette and e-cigarette dual users. *Addiction*. 2019;114(12):2197-2205.

¹¹² Johnson SE. What the public knows and believes about nicotine: Insights from recent quantitative and qualitative evidence. FDA Center for Tobacco Products presentation about PATH survey data. 22nd Annual Meeting of the Society for Research on Nicotine and Tobacco; Chicago, IL: FDA Center for Tobacco Products; 2016.

¹¹³ Johnson SE. What the public knows and believes about nicotine: Insights from recent quantitative and qualitative evidence. FDA Center for Tobacco Products presentation about PATH survey data. 22nd Annual Meeting of the Society for Research on Nicotine and Tobacco; Chicago, IL: FDA Center for Tobacco Products; 2016.

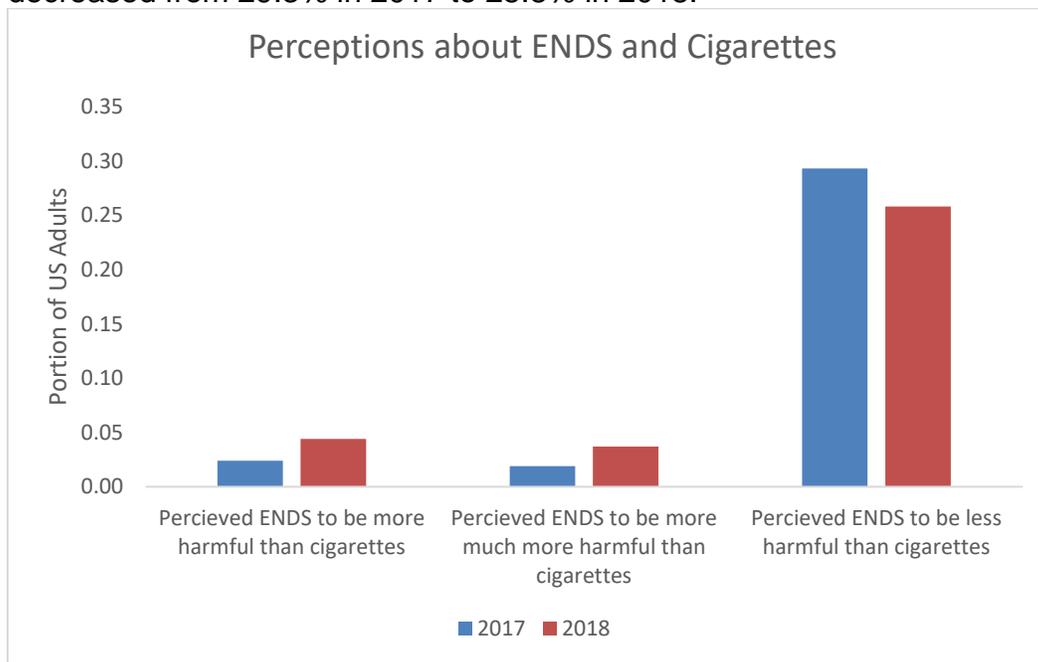
¹¹⁴ O'Brien, E. K., Nguyen, A. B., Persoskie, A., & Hoffman, A. C. (2017). US adults' addiction and harm beliefs about nicotine and low nicotine cigarettes. *Preventive medicine*, 96, 94-100

Healthcare professionals also hold misperceptions. A study conducted by Borrelli et al found that 60% of nurses thought that nicotine caused cancer while 72% believed nicotine patches could cause heart attacks.¹¹⁵

The number of people who consider ENDS products to be more harmful than cigarettes is increasing and is expected to continue to rise. Huang and colleagues note, “the proportion of adults who perceived e-cigarettes as equally harmful as cigarettes more than tripled from 11.5% (95% CI, 10.0%-13.2%) in 2012 to 36.4% (95% CI, 35.1%-37.7%) in 2017.”¹¹⁶

Similarly, Nyman et al found an increase in the number of adults who perceived ENDS to be more harmful than cigarettes:

- Between 2017 and 2018, the perceptions about ENDS being more harmful than combustible cigarettes increased from 2.4% and 4.4%.
- The proportion of adults who found ENDS products to be much more harmful increased from 1.9% in 2017 to 3.7% in 2018.
- The percentage of adults who perceive ENDS products to be less harmful decreased from 29.3% in 2017 to 25.8% in 2018.¹¹⁷



¹¹⁵ Borrelli B, Novak SP. Nurses' knowledge about the risk of light cigarettes and other tobacco “harm reduction” strategies. *Nicotine & Tobacco Research*. 2007;9(6):653-661.

¹¹⁶ Huang, J., Feng, B., Weaver, S. R., Pechacek, T. F., Slovic, P., & Eriksen, M. P. (2019). Changing perceptions of harm of e-cigarette vs cigarette use among adults in 2 US national surveys from 2012 to 2017. *JAMA network open*, 2(3), e191047-e191047.

¹¹⁷ Nyman, A. L., Huang, J., Weaver, S. R., & Eriksen, M. P. (2019). Perceived Comparative Harm of Cigarettes and Electronic Nicotine Delivery Systems. *JAMA network open*, 2(11), e1915680-e1915680.

Smokers also have misperceptions about the relative risks of e-cigarettes compared to cigarettes. Nyman found:

- Between 2017 and 2018, ENDS were increasingly perceived to be much more harmful among current smokers 1.8% in 2017 compared to 4.4% in 2018
- 1% of former smokers believed ENDS were much more harmful in 2017 compared to 3.5% in 2018.
- The percentage of adult smokers perceived ENDS to be equally as harmful as cigarettes increased from 36.4% in 2017 to 43.0% in 2018.
- The percentage of adults uncertain of the comparative harm decreased from 25.3% in 2017 to 19.3% in 2018.¹¹⁸

Misperceptions are especially dangerous in smokers who could benefit in using reduced harm products such as ENDS or NRT. Persoskie et al (2019) analyzed FDA's PATH data and found smokers who perceived e-cigarettes to be equally or more harmful than combustible cigarettes remained dual users and were less likely fully switch to e-cigarettes:

“Based on estimates produced by our weighted analyses, of approximately 10.5 million dual users in 2014–15, nearly 4.3 million did not perceive e-cigarettes as less harmful than cigarettes. Of these 4.3 million, only approximately 115,000 (2.7%) became exclusive e-cigarette users in 2015–16. If these 4.3 million dual users had the same rate of complete switching as those who perceived e-cigarettes as less harmful than cigarettes (7.5%), approximately 205,000 more would have been exclusive e-cigarette users in 2015–16. If their rate of complete switching was the same as those who perceived e-cigarettes as less harmful in both 2014–15 and 2015–16 (11.3%), approximately 370,000 more would have been exclusive e-cigarette users in 2015–16”¹¹⁹

Overall, nicotine misperceptions are widespread pose a risk for smokers who could benefit from switching to a less harmful product. Consumers are confused about the risks associated with ENDS and nicotine products. It important to consider absolute versus relative risk in communicating harms and risks should be communicated on a continuum of harm.

¹¹⁸ Nyman, A. L., Huang, J., Weaver, S. R., & Eriksen, M. P. (2019). Perceived Comparative Harm of Cigarettes and Electronic Nicotine Delivery Systems. *JAMA network open*, 2(11), e1915680-e1915680.

¹¹⁹ Persoskie, A., O'Brien, E. K., & Poonai, K. (2019). Perceived relative harm of using e-cigarettes predicts future product switching among US adult cigarette and e-cigarette dual users. *Addiction*, 114(12), 2197-2205.

5 Summary Conclusions

We conclude the following regarding the potential adverse health effects of nicotine in products that are not combustible tobacco:

Cardiovascular disease

Nicotine does not appear to cause or worsen cardiovascular disease; if it contributes at all, it does so modestly. Its impact is much less than in tobacco smoke. Long-term use of nicotine by smokers in the form of NRT and low nitrosamine smokeless tobacco (snus) has not been associated with increased cardiovascular risk.

Cancer

Nicotine itself is not linked to increased risk of cancer, nor is it listed in authoritative lists of carcinogens. Nicotine does not appear to cause or promote cancer. However, there have been animal studies that suggest a theoretical risk. Long-term use of nicotine by smokers in the form of NRT and in snus has not been associated with increased cancer rates.

Respiratory Health

There is no convincing evidence currently of a meaningful impact of nicotine exposure on respiratory health. However, e-cigarettes have only been widely used for the last decade, so the long-term health effects of e-cigarettes cannot yet be known. There are likely to be health consequences associated with the inhalation of vaping-delivered aerosol containing nicotine on respiratory health. The health consequences are likely to be of much lower concern than the inhalation of smoke.

Reproductive and Pre-Natal Health

Nicotine can interfere with the development of a fetus and should be avoided by pregnant women. Nicotine may cause other reproductive effects (reduced fertility, premature birth, and low birthweight). However, given that other compounds produced by smoking combustible cigarettes (e.g., carbon monoxide) are also responsible for these effects, the risk is likely lower for nicotine without smoke compared to combustible cigarettes. Women who smoke should speak to their health care providers about quitting, including whether use of an NRT is appropriate.

Acute Toxicity and Poisoning

Nicotine can be toxic. Nicotine-containing products should be kept away from children. Acute nicotine poisoning is possible, but this is very rare due to the self-limiting nature of nicotine toxicity. Exposure to nicotine alone is rarely deadly and only toxic at very high doses. Ingestion of nicotine at high doses (whether purposeful or accidental) can be fatal.



Nicotine and the Developing Brain

Young people should not use nicotine. Animal research suggests nicotine – like other psychoactive substances – can alter brain development. It is unclear how this research translates to humans. For adolescents who smoke, studies suggest a minimal effect of smoking on cognitive performance. We would predict that the effect of noncombustible nicotine products would produce even smaller performance decrements, if any, than cigarette smoking.

Addiction and Physical Dependence

Nicotine is the primary ingredient in tobacco that leads to addiction and physical dependence. The abuse and dependence potential of a product are dependent on the dose of nicotine and the rate of delivery. Cigarettes are the most addictive nicotine-containing product, while NRT has been found to have low dependence-potential. Available evidence suggests that e-cigarettes have lower dependence-potential than cigarettes, but much higher dependence-potential than NRTs.

It is important that alternatives to cigarettes deliver nicotine effectively and have dependence-potential to help provide a more similar nicotine experience to smoking than NRTs, which do not have widespread appeal and uptake among smokers at the population level.

Misperceptions

Misperceptions about nicotine may prevent smokers from using NRT – regulated by the FDA as safe and effective – as often as needed and for long enough to prevent relapse to smoking. Confusion about nicotine and its role in smoking-related disease can limit smokers trying and switching completely to reduced risk products that deliver nicotine without combustion.