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TOBACCO HARM REDUCTION: EVIDENCE UPDATE

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INTRODUCTION

Harm reduction policies can work alongside prevention and cessation programs to reduce the health and economic burden associated with combustible tobacco products. A harm reduction approach to smoking is not meant to supersede prevention and cessation measures, but it does recognize that there is no one-size-fits-all, abstinence-only solution that works for everyone. Harm reduction approaches are meant to help mitigate the most severe risks of smoking in the populations that either currently smoke or are most likely to smoke.

While the overall smoking rate in the United States hovers around 15 percent, smoking rates vary widely by education, income and mental health status. Those with a GED, those living at or below the poverty level or people with mental illness are over twice as likely to smoke than the national average, and they tend to smoke more heavily and have a more difficult time quitting.[1] Harm reduction approaches can reduce smoking-related illnesses and death in these populations with disproportionate smoking rates who are either less interested in quitting or find quitting to be more difficult.

As a newer technology, the long-term health effects of e-cigarettes will not be known for several decades. Nevertheless, there is already substantial evidence that they are much less harmful than combustible cigarettes and that switching to e-cigarettes can significantly increase positive health outcomes in those who smoke. For example, in its comprehensive 2016 report, the Royal College of Physicians (RCP) in London concluded that e-cigarettes are unlikely to exceed 5 percent of the risk associated with combustible cigarettes.[2] It also indicated that vaping remains low in adolescent never-smokers (approximately 0.2 percent of younger never-smokers use e-cigarettes) in the United Kingdom and thus recommended an approach based on risk-proportionate regulation that enables smokers to switch to reduced-risk products.[3]

Like the RCP report, the 2018 National Academies of Sciences, Engineering and Medicine (NASEM) report on e-cigarettes found that e-cigarettes are less harmful than combustible ones and concluded that "completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens" and further that, "there is substantial evidence that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems."[4] However, despite the NASEM report's acknowledgment of decreased relative risk of e-cigarettes compared to combustible ones, it also expresses concerns about the limited data on e-cigarettes' potential

1. See, e.g., "Tobacco Use Among Adults with Mental Illness and Substance Use Disorders," Centers for Disease Control and Prevention, accessed July 22, 2019. https://www.cdc.gov/tobacco/disparities/mental-illness-substance-use/index.htm; and "Cigarette Smoking and Tobacco Use Among People of Low Socioeconomic Status," Centers for Disease Control and Prevention, accessed July 22, 2019. https://www.cdc.gov/tobacco/disparities/low-ses/index.htm.

2. "Nicotine without smoke: tobacco harm reduction," Royal College of Physicians Tobacco Advisory Group, 2016, p. 87. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0.

3. See, e.g., "Nicotine without smoke."

4. "The Public Health Consequences of E-cigarettes," National Academies of Science, Engineering and Medicine, January 2018. http://nationalacademies.org/hmd/reports/2018/public-health-consequences-of-e-cigarettes.aspx.

to act as a cessation aid compared to nicotine replacement therapies and about the prospect of youth uptake. As a result, it recommends a cautious approach to regulation of Alternative Nicotine Delivery Systems (ANDS).

However, the primary driver for such differing views is very likely simply the context in which ANDS are examined.[5] For example, when the question is how to protect non-smokers from the risks of ANDS, agencies are biased toward applying a strict definition of the precautionary principle: namely, when conclusive evidence is not available on risks such as toxicity, long-term health consequences or gateway to combustible use, the best practice is to delay action. However, when the focus is shifted to improving the health of smokers (and the immediate versus long-term harms of any nicotine delivery system), employing a harm reduction approach alongside prevention strategies is the obvious course of action.

Put simply, at the present time, while sometimes valid, concerns that aim to protect non-users are often more influential in driving policy changes than evidence that points to a benefit for smokers. And, this will only result in policies that aim to restrict the availability of e-cigarettes, even as it places many current smokers at the considerable risk of continued smoking. It is therefore of the utmost importance that the most recent and robust research and evidence is considered when proposing actions that may have potential to act as a harm reduction tool for both current and future smokers. The fact is that e-cigarettes, heat not burn devices and snus are reduced-risk alternatives that may help smokers quit combustible cigarettes[6] and the associated technology is quickly evolving. In light of this, the present review seeks to provide an updated summary of current evidence that demonstrates the relative toxicity and risks associated with Alternative Nicotine Delivery Systems (ANDS) compared to combustible cigarettes and their potential utility as a cessation device. It then provides a similar update on evidence with respect to youth use and the potential gateway effect.

TYPES OF ALTERNATIVE NICOTINE DELIVERY SYSTEMS

Alternative nicotine delivery systems (ANDS) are becoming a much discussed and popular way for smokers to use nicotine as an alternative to cigarettes. Broadly, the term ANDS encompasses three general categories including electronic cigarettes that do not contain tobacco but deliver tobacco-derived nicotine in a vapor form that is inhaled; heat-not-burn devices[7] that heat tobacco instead of burning to produce an aerosol that is inhaled; and oral products, such as snus, that are lower in both known and potentially hazardous chemicals. In the United States, e-cigarettes are the most widely used of ANDS and while, in general, e-liquid (the term for the liquid that is used to create vapor upon heating) has a similar make up across devices, the devices themselves can vary by size and have open-tank systems that can be personalized to nicotine strength and flavor preference or close-tank systems that use a prefilled cartridge.

Heat-not-burn devices contain tobacco leaf, but use a heating device that heats tobacco to temperatures much lower than those that produce combustion. These devices are most similar in feel to a combustible cigarette and cannot be adapted to user preferences. Currently in the United States, only one heat-not-burn device is approved for sale.[8] And finally, snus is an oral product that originated—and is widely used—in Sweden. Generally speaking, it is a wet, powdered tobacco that is pasteurized to reduce the concentration of harmful chemicals present in the tobacco leaf.

EVIDENCE UPDATE

Harmful Constituents and Health Effects

Toxicant Exposure—When comparing relative toxicity and risk between alternative nicotine delivery systems and combustible cigarettes, most of the focus is and should remain on the harmful constituents present in cigarette smoke, as there are a myriad of chemicals, many of which are known to be dangerous, that are either present in tobacco itself or are released upon combustion that are of great concern. Of these chemicals or constituents, the most dangerous are carbon monoxide (CO), particulate matter (PM), tobacco-specific nitrosamines (TSNA) and volatile organic compounds (VOC).

Carbon monoxide, which is present in any combusted product, deprives tissues from oxygen by displacing the gas from the body's hemoglobin. Testing CO levels in the body is therefore an important indicator of health. CO exposure is not present in ANDS that do not produce combustion, and therefore return-to-normal or "background" levels of CO for ex-smokers is the mechanism by which health improvements are measured. In fact, CO levels that are comparable to non-smokers are often used as biochemical confirmation of sustained switching from combustible to e-cigarettes.

5. Amy Lauren Fairchild et al., "The E-Cigarette Debate: What Counts as Evidence?", *American Journal of Public Health* 109:7 (2019), pp. 1000-06. https://ajph.aphapublications.org/doi/full/10.2105/AJPH.2019.305107?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&

6. Although the NASEM and Public Health England reports focus on e-cigarettes, many of these concerns extend to other alternative nicotine delivery systems (ANDS), including heat-not-burn (HNB) technologies and snus.

7. These are sometimes alternatively referred to as a "tobacco heated product" (THP).

8. The IQOS heat-not-burn device received marketing approval in April 2019. "FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway," U.S. Food and Drug Administration, 2019. https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

Put simply, switching from combustible cigarettes to snus products results in lower levels of carbon monoxide—an 86 percent decrease compared to combustible cigarettes.[9] Moreover, emissions from heat-not-burn (HNB) products showed that CO emissions were approximately 99 percent lower.[10] As a result, the carbon monoxide levels in ANDS users is typically the same as those in non-smoking individuals, which indicates that any residual carbon monoxide exposure is "background" or environmental exposure.

With respect to particulate matter—the mixture of all solid and liquid particles found in air—the composition varies between forms of nicotine delivery systems and the associated health hazards are largely dependent upon the size of particulates and the chemical composition.[11] Of particular concern, is particulate matter less than 10 microns, as it can penetrate deeper into the lung.[12] The dangers of particulate matter are well documented: it impedes lung function by inducing inflammation in lung and cardiac tissue via circulatory processes.[13] A side-by-side comparison of combustible cigarettes and e-cigarettes demonstrates that combustible cigarettes have 18-21 times more fine PM emissions immediately after a puff,[14] and that background particulate matter levels are roughly 100 times lower in environments consistently exposed to e-cigarettes compared to those consistently exposed to combustible ones.[15] Further, an independent analysis of the toxic effects of heat-not-burn products showed that cells exposed to aerosol from heated tobacco had significantly decreased cell death and inflammatory biomarkers, which indicates that particulate matter from HNB aerosols are far less toxic than cigarette smoke. It has also been estimated that use of such products reduces human exposure to particulates by approximately 75 percent.[16]

The two remaining important classes of hazardous constituents, Tobacco Specific Nitrosamines and Volatile Organic Compounds are present in ANDS and in the same form as found in cigarette smoke, but there are important differences when ANDS are compared to combustible cigarettes.

TSNAs are formed from nicotine during the tobacco curing process and are therefore specific to tobacco and nicotine that is extracted from tobacco, which is the nicotine used in e-cigarette manufacturing. VOCs, on the other hand, can be either man-made or naturally occurring, and are not specific to tobacco. Together TSNAs and VOCs may be referred to as 'harmful' and 'potentially harmful' chemicals and are of concern as they are concentrated and directly inhaled and are conclusively linked to long-term health effects such as respiratory cancers, oral cancers and cardiovascular disease associated with smoking.

However, e-cigarette aerosol has between 9 and 450 times lower emissions of many VOCs than combustible cigarettes and these emissions are less complex in their makeup.[17] Tobacco-specific nitrosamines (TSNA) are also up to 1,800 times lower in concentration in e-cigarettes compared to combustible ones.[18] One concern is the production of harmful compounds that occur during the aerosolization of e-liquids, however, this is temperature (and voltage) dependent[19] and is largely the product of power settings that create "dry puffing"[20] conditions.[21] Moreover, the FDA's scientific review of both independent studies and data provided in the recent application for marketing approval of the IQOS heat-not-burn device concludes that harmful and potentially harmful constituents in the aerosols of heat-not-burn were reduced by 54-99.9 percent compared to reference cigarettes.[22]

9. Melissa D. Blank and Thomas Eissenberg, "Evaluating oral noncombustible potential-reduced exposure products for smokers," *Nicotine & Tobacco Research* 12:4 (2010), pp. 336-43. https://www.ncbi.nlm.nih.gov/pubmed/20159791.

10. Kanae Bekki et al., "Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes," *Journal of The University Occupational Environmental Health* 39 (2017) pp. 201-07. https://www.ncbi.nlm.nih.gov/pubmed/28904270.

11. As an oral product, snus does not expose users to particulate matter and is not discussed here.

12. Per Everhard Schwarze et al., "Particulate Matter Properties And Health Effects: Consistency Of Epidemiological And Toxicological Studies," *Human and Experimental Toxicology* 25 (2006) pp. 559-79 http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.913.6073&rep=rep1&type=pdf.

13. Ibid.

14. Roberto Pellegrino et al., "Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM)" *Annali di Igiene* 24:4 (2011) pp. 279-88. https://www.researchgate.net/publication/230721126_Electronic_cigarettes_an_evaluation_of_exposure_to_chemicals_and_fine_particulate_matter_PM.

15. Esteve Fernández et al., "Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study," *Current Environmental Health Reports* 2:4 (2015), pp. 423-29. https://www.ncbi.nlm.nih.gov/pubmed/26452675.

16. Erikas Simonavicius et al., "Heat-not-burn tobacco products: a systematic literature review," *Tobacco Control* (2018), pp. 1-13. https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2019/01/28/tobaccocontrol-2018-054419.full.pdf.

17. Although not an exhaustive list, for example, compared to e-cigarettes, combustible cigarettes have nine times higher levels of formaldehyde, 15 times higher levels of acrolein, 120 times more toulene and 450 times more acetaldehyde. See, e.g., Maciej L Goniewicz et al., "Levels of selected carcinogens and toxicants in vapour from electronic cigarettes," *Tobacco Control* 23 (2014) pp. 133-39; Jennifer Margham et al., "Chemical Composition of Aerosol from an E-Cigarette: A Quantitative Comparison with Cigarette Smoke," *Chemical Research in Toxicology* 29 (2016) pp. 1662-78. https://www.ncbi.nlm.nih.gov/pubmed/27641760.

18. Konstantinos Farsalinos and Riccardo Polosa, "Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review," *Therapeutic Advances in Drug Safety* 5:2 (2014) pp. 67-86. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/pdf/10.1177_2042098614524430.pdf.

19. Mohamad Sleiman et al., "Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals," *Environmental Science and Technology* 50 (2016) pp. 9644-51. https://www.ncbi.nlm.nih.gov/pubmed/27461870.

20. The term "dry puffing" refers to when an atomizer heats up but the canister does not have enough liquid in it to create sufficient vapor.

21. Konstantinos E. Farsalinos et al., "E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions," *Addiction* 110 (2015) pp. 1352-56. https://www.ncbi.nlm.nih.gov/pubmed/25996087.

22. Center for Tobacco Products, "Technical Project Lead Review of PMI IQOS Premarket Tobacco Application," U.S. Food and Drug Administration, 2019. https://www.fda.gov/media/124247/download.

Importantly, levels of major TSNA and volatile organic compound metabolites in e-cigarette users—a measure of actual exposure as opposed to potential exposure—were approximately 3 percent that of cigarette smokers.[23] Further proof of reduced risk in e-cigarette use can also be clearly found through urinalysis, which definitively shows that the decreased toxicant emissions in e-cigarettes also decreases human exposure to Harmful and Potentially Harmful Constituents (HPHCs). Importantly, while HPHC exposure is much lower, total nicotine exposure is similar between the two products, which indicates that e-cigarette users are at a low risk of overcompensation for nicotine intake, which would ultimately mitigate any benefits derived from the reduction of HPHCs.[24] Similar results were found in the IQOS heat-not-burn device application and the FDA supported the conclusion that biomarkers of exposure of 15 harmful or potentially harmful chemicals were significantly reduced.[25] Snus use is also associated with lower levels of at least one TSNA biomarker in those who switch from combustible cigarettes.[26] This indicates that lower concentrations of TSNA in the products result in decreased exposure.

Collectively, these studies show that ANDS use results in decreased toxicant emissions and exposure, and lend support to the theory that at least the products discussed may be considered "reduced risk" and may be used as a harm reduction strategy for smokers. However, while it is easy to predict that such decreases would naturally lead to decreased negative health outcomes when compared to combustible cigarettes and while there is no reason to predict that health outcomes would not be improved in those who switch, it is necessary to acknowledge that an improved toxicant profile is not the only metric by which to consider these products less harmful.

Lung Function and COPD—Acute effects of e-cigarettes on lung function in humans have not been extensively studied, but there is evidence that compared to cigarette smoke, which has significant negative effects on lung function, e-cigarettes have minimal effects on acute lung function following use.[27] Furthermore, we also know that switching from e-cigarettes to combustible cigarettes significantly decreases lung function and increases carbon monoxide levels.[28]

Moreover, a recent examination of patients with Chronic Obstructive Pulmonary Disease (COPD) who switched from combustible to e-cigarettes versus those who did not shows that people who switched had significant and lasting improvements to their health over the three-year study period.[29] Changes were tracked from the baseline period within groups (e-cigarette users or combustible cigarette smokers), comparing the trajectory of symptom progression across time, from baseline to 36 months for those who used e-cigarettes and those who did not.

Overall, patients who switched completely to e-cigarettes had favorable outcomes in COPD scores compared to those who continued to smoke. Specifically, there was improvement in three specific measures of respiratory symptoms and disease progression: an improvement in the COPD Assessment Tool that measures the impact of the disease on patients; a decrease in the number of COPD exacerbations, such as asthma attacks; and increased distance in the six-minute walk test that measures exercise capacity. These improvements were both sustained and significant within the EC group over time (improvements from baseline to 36 months) and also significant between e-cigarette users and the smoking group (those who used EC showed marked improvement compared to the control group). This study also compliments the National Health Interview Survey analysis of COPD patients that reported improved respiratory symptoms after switching,[30] and extends these findings to include specific measures of disease progression and lung function.

Yet another important component of the study is that its contributing authors suggested that studies on health outcomes for smokers who switch that were performed before 2017 should be interpreted with caution, as e-cigarette use and quality was unstable before 2016.[31] It is therefore likely that with improvements in technology, nicotine delivery and the composition of inactive ingredients, switching to

23. Lion Shahab et al., "Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study," *Annals of Internal Medicine* 166 (2017) pp. 390-400. https://www.ncbi.nlm.nih.gov/pubmed/28166548.

24. Ibid.

25. Center for Tobacco Products. https://www.fda.gov/media/124247/download.

26. See, e.g., Jamie Hartmann-Boyce et al., "Nicotine replacement therapy versus control for smoking cessation," *Cochrane Database Systematic Reviews* 5 (2018). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353172.

27. Andreas D. Flouris et al., "Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function," *Inhalation Toxicology* 25:2 (2013), pp. 91-101. https://www.tandfonline.com/doi/abs/10.3109/08958378.2012.758197?journalCode=iiht20.

28. Sandor Barna et al., "First comparative results about the direct effect of traditional cigarette and e-cigarette smoking on lung alveolocapillary membrane using dynamic ventilation scintigraphy," *Nuclear Medicine Communications* 40:2 (2019), pp. 153-58. https://www.ncbi.nlm.nih.gov/pubmed/30531407. It should be noted that unlike most studies that examine lung function in people who switch, this study evaluated changes in lung function in people who switched from e-cigarettes to combustible cigarettes for only one week.

29. Riccardo Polosa et al., "Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up," *International Journal of Chronic Obstructruction Pulmonary Disorder* 13 (2018), pp. 2533-42. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113943.

30. Riccardo Polosa et al., "Evidence for harm reduction in COPD smokers who switch to electronic cigarettes," *Respiratory Research* 17 (2016), p. 166. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5162097.

31. K. Michael Cummings and Riccardo Polosa, "E-Cigarette and COPD: Unreliable Conclusion About Health Risks," *Journal of General Internal Medicine* 33 (2018), pp. 784-85. https://www.ncbi.nlm.nih.gov/pubmed/29564607.

e-cigarettes will result in even more favorable outcomes in later studies.

Put simply, these findings translate to improved health for those who switch, as do others. For example, a 2018 study showed that smokers who switched to heat-not-burn products had improvements in lung function and decreased systemic inflammation, as evidenced by increased forced expiratory volume and decreased white blood cell count—an inflammatory biomarker.[32]

Because snus gained popularity starting in 1960, there is much more robust epidemiological data around their health effects and thus it has been consistently shown that the decrease in exposure to toxicants in those who switch to snus clearly translates to a public health benefit compared to combustible cigarettes. In fact, even conservative estimates indicate that switching to snus can reduce many smoking-related health risks, including oral, pancreatic and colorectal cancers, and heart disease or myocardial infarction (heart attack) by at least 90 percent.[33]

Moreover, a comprehensive review of snus use in Sweden demonstrates that a population-level shift away from combustible cigarette use correlates with a decrease in both oral and lung cancer and incidence of myocardial infarction.[34] There is also no significant association of smokeless tobacco use and incidence of oropharyngeal cancer, as a meta-analysis of oropharyngeal cancer between never-smokers and smokeless tobacco users found that when adjusted for alcohol use, the relative risk and odds ratio is not significant.[35] Further, a review of pancreatic cancer rates in snus users compared to never-users showed that snus had no effect on pancreatic cancer rates after adjusting for smoking.[36] And finally, tobacco-attributable mortality is consistently lowest among men in Sweden compared to other European Union Member States.[37]

Smoking Cessation

The availability of pharmacological interventions to aid smoking cessation is often cited as a reason that innovative, reduced-risk products to help smokers quit, such as e-cigarettes, are unnecessary. However, this argument dismisses evidence that shows that varenicline and nicotine replacement therapies (NRT)—the most traditional forms of quit tool—are not highly effective at helping smokers quit. In fact, in some cases, randomized, controlled trials show no difference between these products and placebo treatments.

As a philosophical point, to many, the use of e-cigarettes, heat-not burn products or snus may not be considered cessation by the strict definition, especially as unlike traditional nicotine replacement therapies, the goal is not complete abstinence from nicotine at a certain point in time. Such an argument may be logical, however, for the purposes of this analysis and as should be broadly applied in public health, cessation refers to switching from the most dangerous form of use to a form that is vastly safer, even if complete abstinence is not the intended result.

And indeed there is precedent for this. When applied to other substances, such as injection drug use, substitution therapy is a commonly accepted method to cease dangerous drug use (especially in injection form) and, if relapse is a threat—as it often is—continued methadone, buprenorphine or naltrexone use is preferable to abstinence, as the risks of relapse likely outweigh the benefits of complete cessation. After all, much like nicotine, the psychoactive ingredient in injection drug use is associated with some risks on its own, but the most significant health risks come from the way the drug is administered and not the drug itself. Accordingly, the following sections outline the most recent evidence with respect to the success of various quitting tools.

Traditional Quit Methods—An extensive 2018 systematic review of randomized controlled trials conducted on a variety of nicotine replacement therapy (NRT) products, including nicotine gum or the nicotine patch, found that smokers who use NRT products are only 10 percent more likely to achieve cessation after at least six months of follow-up than they would be if trying to quit unassisted.[38] The same review suggested that if the rate of successfully quitting in a population without any assistance is 2-3 percent, the rate would only increase by 3-5 percent even if everyone used NRT. In fact, in order to produce only one additional successful cessation from tobacco, 56 people would need to be treated with NRT.

32. See, e.g., Shin-Ichi Hagiwara, "Effects of heat-not-burn tobacco on health are different from conventional cigarette," *European Respiratory Journal* 52:s62 (2018). https://erj.ersjournals.com/content/52/suppl_62/PA1727. It should be noted that while snus use is highest among men in Sweden, it is not predominant in women and this makes a corresponding analysis difficult.

33. Peter N. Lee, "Epidemiological evidence relating snus to health—an updated review based on recent publications," *Harm Reduction Journal* 10:1 (2013), p. 36. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029226/pdf/1477-7517-10-36.pdf.

34. Jonathan Foulds et al., "Effect of smokeless tobacco (snus) on smoking and public health in Sweden," *Tobacco Control* 12 (2003), pp. 349-59. https://www.ncbi.nlm.nih.gov/pubmed/14660766.

35. See, e.g., Peter N. Lee and Jan Hamling, "Systematic review of the relation between smokeless tobacco and cancer in Europe and North America," *BMC Medicine* 7 (2009). https://www.ncbi.nlm.nih.gov/pubmed/19638245.

36. Marzieh Araghi et al., "Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies," *International Journal of Cancer* 141:4 (2017), pp. 687-93. https://www.ncbi.nlm.nih.gov/pubmed/28486772.

37. See, e.g., Lars Ramström and Tom Wikmans, "Mortality attributable to tobacco among men in Sweden and other European countries: an analysis of data in a WHO report," *Tobacco Induced Diseases* 12:14 (2014). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4154048/pdf/1617-9625-12-14.pdf.

38. Hartmann-Boyce et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353172.