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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]

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.

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.

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

A separate review of long-term NRT use combined with psychotherapy had only slightly better results.[39] Long-term NRT use showed a 14 percent abstinence rate at one year after quitting and high-dose, long-term treatment with psychotherapy had between a 19 and 20 percent abstinence rate. Nevertheless, such low rates of long-term cessation (between 5-20 percent of NRT users) suggests that NRTs cannot be considered a highly effective cessation aid.

And, although it has been suggested that varenicline is a sufficient tool for aiding cessation, the fact is that it only works for a minority of tobacco users. For example, a randomized, controlled trial of the efficacy of nicotine patches, varenicline and combination NRT found no difference between the cessation rate at 26 weeks follow-up for any type of NRT, with abstinence rates hovering around 14 to 16 percent for all three treatments.[40] Varenicline did, however, result in more reported adverse reactions than use of the nicotine patch.[41]

While traditional quit methods, such as NRTs and varenicline are FDA-approved for smoking cessation, it is clear that neither are terribly effective for their intended purpose. In recognition of this, the FDA has recently modified recommendations that people use these products for a maximum of 12 months to encourage them to use as long as necessary to achieve full cessation.[42] However, even under supervision and the best circumstances, successful quit rates do not exceed 20 percent.

E-cigarettes—In the United Kingdom, e-cigarettes have outpaced traditional quit methods (varenicline, nicotine replacement therapies or counseling).[43] They are also gaining popularity in the United States,[44] and with a higher degree of success.[45]

For example, a randomized trial comparing NRT with e-cigarettes showed a higher abstinence rate among participants in the e-cigarette group compared with the group that received NRT: at one year, it was 18 percent in the e-cigarette group and only 10 percent in the NRT group. Interestingly, among participants who were abstinent at one year, compliance was eight-fold higher among those who used e-cigarettes.[46]

Similar results were demonstrated using United States Census Bureau data. Of current smokers and recent quitters, e-cigarette users were more likely than non-users to attempt to quit smoking, 65 and 40 percent respectively, and they also had a greater chance of success at 8.2 and 4.8 percent respectively.[47] A separate analysis lends support to the hypothesis that long-term e-cigarette users enjoy an even higher rate of successful quitting.[48] Further, it should be noted that these data are collected from 2016 and before, which as previously discussed, means there is a strong likelihood that newer-generation devices have since increased quitting success rates.

Currently, "dual use" is defined as any combination of combustible use and e-cigarette use. While dual use may be thought of as a transition to complete abstinence, studies that examine it do show that dual users can maintain long-term significant reductions (>50 percent) in the number of cigarettes smoked per day. Both the aforementioned study and emerging evidence suggest that there is a harm reduction application then for e-cigarettes even when not exclusively used. Moreover, even while officially deemed "dual users," those who used e-cigarettes dramatically decreased their use of combustible cigarettes—from 21.9 cigarettes per day at the first evaluation point to 1.5 cigarettes per day at the final evaluation point 36 months later.[49] This decrease was only observed among the e-cigarette users while the average cigarette consumption per day among the control group (combustible cigarette smokers) remained stable at 20 cigarettes per day, throughout the 36-month observation period.

39. Matthew J. Carpenter et al., "Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature," *Drugs* 73 (2013), pp. 407-26. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3662024.

40. Timothy B. Baker et al., "Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial," *Journal of the American Medical Association* 315 (2016), pp. 371-79. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4824537.

41. Ibid.

42. "The Food and Drug Administration's Approach To Evaluating Nicotine Replacement Therapies; Public Hearing; Request for Comments" U.S. Food and Drug Administration, 2017. https://www.federalregister.gov/documents/2017/11/30/2017-25671/the-food-and-drug-administrations-approach-to-evaluating-nicotine-replacement-therapies-public.

43. See, e.g., Ann McNeill et al., "Evidence review of e-cigarettes and heated tobacco products 2018," Public Health England, 2018. https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review/evidence-review-of-e-cigarettes-and-heated-tobacco-products-2018-executive-summary; S. Jackson et al., "Moderators of real-world effectiveness of smoking cessation aids: a population study," *Journal of Addiction* (May 2019). https://www.ncbi.nlm.nih.gov/pubmed/31117151.

44. See, e.g., Farhad Riahi et al., "Tobacco smoking and nicotine delivery alternatives: patterns of product use and perceptions in 13 countries," *F1000 Research* (2019). https://f1000research.com/articles/8-80.

45. See, e.g., Peter Hajek et al., "A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy," The New England Journal of Medicine 380 (2019), pp. 629-37. https://www.nejm.org/doi/full/10.1056/NEJMoa1808779; Shu-Hong Zhu et al., "E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys," *British Medical Journal* 358 (2017), p. j3262. https://www.bmj.com/content/358/bmj.j3262.

46. Hajek et al., pp. 629-37. https://www.nejm.org/doi/full/10.1056/NEJMoa1808779.

47. Zhu et al., p. j3262. https://www.bmj.com/content/358/bmj.j3262.

48. Yue-Lin Zhuang et al., "Long-term e-cigarette use and smoking cessation: a longitudinal study with US population," *Tobacco Control* 25 (2016), pp. supp i90-i95. https://tobaccocontrol.bmj.com/content/25/Suppl_1/i90.

49. "Health effects in COPD smokers who switch to electronic cigarettes," pp. 2533-42. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113943.

Finally, another study that evaluated the transitions between e-cigarette use and combustible cigarette use among adults provides some indications of factors that contribute to dual users becoming exclusive e-cigarette users.[50] For example, daily e-cigarette users at the time of initial measurement were more likely to be abstinent from combustible cigarette use at the time of the second measurement than non-daily e-cigarette users. The study also found that dual users who reported smoking greater than fifteen cigarettes per day, began smoking before the age of 16 or consuming their first cigarette within thirty minutes of waking were less likely to have abstained from smoking later in the study. This study is supported by others with similar findings.[51]

The use of e-cigarettes as a quit tool remains controversial, however, studies consistently indicate that among those who use e-cigarettes to quit smoking, nearly twice as many are successful compared to those who choose NRT. While dual use is a concern, including the possibility that the combined use of cigarettes and e-cigarettes might strengthen one's dependence on nicotine, in the studies discussed, people who are dual users while attempting to quit dramatically reduce their use of combustible cigarettes. And, with improvements in the technology, nicotine delivery and proper regulations surrounding nicotine strength, it is likely that these already-positive outcomes could be improved dramatically.

Heat-not-burn—Heat-not-burn technology has contributed to a dramatic decline in cigarette consumption in Japan, where cigarette volumes have fallen by 33 percent in three years, from 43.6 billion sticks in Jan-March 2016 to 29.1 billion sticks in Jan-March 2019.[52] Analysts at Citi Group attribute this disruption of the cigarette market to heated tobacco products.[53]

To date, few studies have evaluated heat-not-burn products as a means of cessation, however, one study explored awareness, ever-use and current use of these products among a sample of adult, never, former and current smokers in the United States.[54] Despite small sample sizes for some categories, it found that a 2016 sample of current smokers with intentions to quit in the next month or next six months had significantly higher odds of being aware of heat-not-burn products compared to smokers that did not intend to quit. This suggests that people seeking to quit are made aware of such products as a potential quitting tool. Also, the odds of currently using a heat-not-burn product were significantly higher among people reporting intentions to quit smoking in the next six months than people reporting never intending to. Although not statistically significant, the 2017 sample followed the same patterns as the 2016 sample. These results may indicate that smokers intending to quit in the near future will use heat-not-burn products as a method to assist in their attempt.

Snus—Thanks in large part to the use of snus, smoking prevalence is very low in Sweden compared to the rest of the European Union (5 versus 26 percent),[55] where their use is banned.[56] Further, a 2011 review of seven cross-sectional studies evaluated the association between snus use and smoking cessation in Norway.[57] Evidence from these demonstrates that daily snus use is associated with being a former smoker. These findings provide evidence that snus can—and do—contribute to smoking cessation. Additionally, the study noted that former smokers make up the largest proportion of snus users, followed by occasional smokers, then daily smokers. This suggests that snus may also help users to decrease cigarette consumption. And, finally, the study concluded that never-smokers make up the smallest proportion of snus users. This suggests that snus is unlikely to attract people who have not used nicotine, and almost certainly does not attract enough never-smokers to offset the public health benefits of snus to smokers and former smokers.

Further, an updated analysis from Sweden's *Your Country Your Life* population survey shows that snus users who are never-smokers are much less likely to take up smoking than those who initiated on tobacco using a different product. Furthermore snus users who initiated *after* they had started smoking were more likely to quit smoking completely.[58]

50. Blair Coleman et al., "Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013-2015)," Tobacco Control 28 (2019), pp. 50-59. https://tobaccocontrol.bmj.com/content/28/1/50.

51. See, e.g., Sara Kalkhoran et al., "Electronic Cigarette Use and Cigarette Abstinence Over Two Years among U.S. Smokers in the Population Assessment of Tobacco and Health Study," *Nicotine and Tobacco Research* (2019). https://www.ncbi.nlm.nih.gov/pubmed/31298296; Seung-Hwa Lee et al., "Effect of Electronic Cigarettes on Smoking Reduction and Cessation in Korean Male Smokers: A Randomized Controlled Study," *Journal of the American Board of Family Medicine* 32:4 (2019), pp. 567-74. https://www.jabfm.org/content/32/4/567.long.

52. "Japanese Domestic Cigarette Sales Results, Monthly reports 2016-19," *Japan Tobacco*, June 2019. https://www.jt.com/media/news.

53. Adam Spielman, "The new world of tobacco," Citi Group, April 18, 2018, p. 20. https://thefly.com/landingPageNews.php?id=2691422&headline=PM;BTI-Citi-upgrades-Philip-Morris-downgrades-BTI-in-new-world-of-Tobacco.

54. Amy L. Nyman et al., "Awareness and use of heated tobacco products among US adults, 2016-2017," *Tobacco Control* 27 (2018) pp. s55-s61. https://tobaccocontrol.bmj.com/content/27/Suppl_1/s55.

55. "Attitudes of Europeans towards tobacco and electronic cigarettes," *Eurobarometer* 458 (ay 2017). http://data.europa.eu/euodp/en/data/dataset/S2146_87_1_458_ENG.

56. Ibid.

57. Karl E. Lund et al., "The association between use of snus and quit rates for smoking: results from seven Norwegian cross-sectional studies," *Addiction* 106 (2011), pp. 162-67. https://www.ncbi.nlm.nih.gov/pubmed/20883459.

58. L. Ramström et al., "Patterns of Smoking and Snus Use in Sweden: Implications for Public Health," *International Journal of Environmental Research and Public Health* 13:11 (2016), p. 1110. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5129320.

Together these studies indicate that, while traditional cessation aids do increase the likelihood of successful quitting, they are very far from being the ultimate solution. For the many smokers who will not successfully quit using pharmacological cessation tools, an alternative to combustible cigarettes (like e-cigarettes, heat-not-burn or snus products) is vital to improving quality of life and health.

Youth Use and Gateway

Prevention of youth uptake of smoking or other tobacco use is the most effective way to decrease smoking rates in the long-term. As of 2012, nearly two-thirds of current adult smokers started before age 18, and nearly 95 percent started before age 26.[59] Currently, many existing regulations, such as bans of advertising or use of cartoons as logos or "spokespeople," or geographic restrictions around where tobacco can be used or sold, specifically target appeal and access in the adolescent age group. These restrictions have proven to be effective in contributing to the dramatic decrease in youth smoking from 1996 to date. However, the emergence of e-cigarettes has proven to be controversial in the context of youth use. While some public health advocates may view e-cigarettes as a way to displace smoking in adolescents who would otherwise smoke, public health agencies in the United States and across the globe view e-cigarette use in and of itself to be extremely problematic. Of particular interest is the significant increase in use rates from 2017-2018.[60]

Youth Uptake—Although looking at the percentages of youth who use e-cigarettes on a population level may suggest cause for concern, data cited by the FDA indicates that the situation is not as dire as has been publicized. For example, the 2018 National Youth Tobacco Survey (NYTS) shows that 20.8 percent of high school students surveyed had used an e-cigarette during the past 30 days.[61] However, this subpopulation represents a wide spectrum of use patterns, from trying one puff to habitual use. But, with regard to habitual use, the Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report* (MMWR) references the NYTS data and states that 27.7 percent of high school students that reported using *any* e-cigarettes in the past 30 days could be considered regular users—for at least 20 of the past 30 days.[62] Accordingly, it appears that only 5.7 percent of high school students are habitual e-cigarette users.

Although youth e-cigarette use has attracted the most attention, trends in combustible cigarette use are equally important to consider for comparison. From 1996 to 2017, rates of combustible cigarette use continued to decline among youth.[63] In 2018, two of the largest surveys of youth tobacco use arrived at different conclusions regarding rates of combustible cigarette use during the past 30 days. The Monitoring the Future (MTF) survey reported 8 percent of youth had used combustible cigarettes during the past 30 days, a two percent decrease from 2017.[64] However, 2018 NYTS results indicated a slight increase in combustible cigarette usage compared to 2017 (from 7.6 percent in 2017 to 8.1 percent in 2018).[65] Despite the decreases in combustible cigarette use, the all-tobacco use rate remained relatively steady from 2009 to 2017. Then, 2018 saw a 5.6 percent increase in any tobacco product use among high school students compared to 2017 rates.[66] Taken together, this indicates that a product or products other than combustible cigarettes are likely the driving force behind the stagnation of tobacco product use among adolescents.

Of course, there is more to these the statistics. Most population-level, surveillance reports reference past-30-day use of combustible cigarettes, e-cigarettes or other tobacco products because this statistic is valuable to capture the combined prevalence of experimentation and habitual use. However, using just one measure to represent the extent of youth use fails to capture the differences in patterns and frequency of use between individuals. For example, a person who tries an e-cigarette once is different from a person who vapes only at social gatherings, and both are very different from a person who uses an e-cigarette daily. As noted previously, 5.7 percent of high school students use e-cigarettes 20 or more days per month. This is as opposed to the more frequently cited statistic that 20.8 percent of high school students have used

59. Office of Smoking and Health, "2014 Surgeon General's Report: The Health Consequences of Smoking—50 Years of Progress," U.S. Dept. of Health and Human Services, January 2014, p. 708. https://www.ncbi.nlm.nih.gov/books/NBK179276/pdf/Bookshelf_NBK179276.pdf.

60. Center for Tobacco Products, "2018 NYTS Data: A Startling Rise in Youth E-cigarette Use," U.S. Food and Drug Administration, February 2019. https://www.fda.gov/tobacco-products/youth-and-tobacco/2018-nyts-data-startling-rise-youth-e-cigarette-use.

61. Ibid.

62. Karen A. Cullen et al., "Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students—United States, 2011–2018," *Morbidity and Mortality Weekly Report* 67 (2018), pp. 1276–77. https://www.cdc.gov/mmwr/volumes/67/wr/mm6745a5.htm.

63. Andrea S. Gentzke et al., "Vital Signs: Tobacco Product Use Among Middle and High School Students—United States, 2011–2018," *Morbidity and Mortality Weekly Report* 68 (2019), pp. 157-64. https://www.cdc.gov/mmwr/volumes/68/wr/mm6806e1.htm?s_cid=osh-vs-mmwr-full-001.

64. See Richard A. Miech et al., "Monitoring the Future National Survey Results on Drug Use, 1975-2017: Volume I Secondary school students," University of Michigan Institute for Social Research, 2018. http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2017.pdf; and Richard A. Miech et al., "Monitoring the Future National Survey Results on Drug Use, 1975-2018: Volume I Secondary school students," University of Michigan Institute for Social Research, 2019. http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2018.pdf.

65. See, e.g., Teresa W. Wang et al., "Tobacco Product Use Among Middle and High School Students—United States, 2011–2017," *Morbidity and Mortality Weekly Report* 67 (2018), pp. 629-33. https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a3.htm; Gentzke et al., pp. 157-64. https://www.cdc.gov/mmwr/volumes/68/wr/mm6806e1.htm#F2_down.

66. "Overall Tobacco Trends," American Lung Association, June 10, 2019. https://www.lung.org/our-initiatives/research/monitoring-trends-in-lung-disease/tobacco-trend-brief/overall-tobacco-trends.html.

an e-cigarette during the past 30 days—which could mean that they merely tried one once.[67]

Moreover, further analysis indicates that tobacco use does not exist in a vacuum and that the current deep focus on e-cigarettes may be misplaced. When cigarette, cigar or smokeless tobacco use is taken into account, merely 0.6 percent of regular e-cigarette users have never tried another tobacco product.[68] These differences demonstrate the need to consider more than just one measure of prevalence when evaluating youth e-cigarette use.

Although any tobacco product use among young people is of concern, it is important to maintain perspective on the magnitude of the problem. And, on this account, an often-overlooked consideration is that youth e-cigarette use may, in fact, be displacing combustible use. This means that in a thus-far unquantified number of cases, youth who may have otherwise started using combustible cigarettes may instead be using e-cigarettes exclusively. Diverting youth from beginning combustible cigarette use by establishing e-cigarette use instead may be providing a health benefit, assuming these young people remain exclusive e-cigarette users.

Gateway Use—In terms of concerns about whether e-cigarettes act as a gateway, the report from the National Academies of Sciences, Engineering and Medicine adds fodder to the debate by considering the hypothesis that the strong positive association between vaping and cigarette use is due to common risk factors for both behaviors. However, these conclusions are derived mainly from short-term studies that track individual behavior, which might be very different than a trend of behavior on a population-level. Indeed, the report's findings indicate that on a population level, as e-cigarette use increased, smoking prevalence has decreased.[69] Accordingly, to establish the validity of the "gateway hypothesis"[70] is very difficult and would require the analysis of large, longitudinal studies that adequately control for known confounders. However, the NASEM report's use of a single data source and lack of consideration for past trends in smoking does not rely on such data and thus the validity of the associations it presents is questionable.[71] And, in fact, studies have shown that while there are significant reciprocal associations between e-cigarette and cigarette use on an individual level, trajectory analysis indicates a stronger association from cigarette to e-cigarette use than the other way around.[72]

Furthermore, the existence of e-cigarettes has coincided with a more rapid decline in smoking rates than was seen in previous years. For example, using a time-series model of smoking prevalence that accounts for the years where vaping was not prevalent (prior to 2014), a 2018 study found that across five datasets and 22 measures, the rate of decline in experimentation and established use of cigarettes increased after 2013, which coincided with vaping becoming more popular among young people.[73] After 2014, in all measures, the trend in smoking prevalence moved downward. This suggests not that e-cigarettes are acting as a gateway to youth combustible smoking, but rather that they are actually decreasing combustible cigarette use in young people. Similar results have occurred in the United Kingdom, as an analysis of national survey data found no significant change in smoking rates following the emergence of e-cigarettes from 2010 on, and that social acceptance of smoking among youth is still declining, which strongly suggests that e-cigarettes are not responsible for the renormalization of smoking.[74]

CONCLUSION

The importance of ANDS in contributing to the improved health of smokers cannot be overstated. This does not mean that such products are without risk, but how their use is viewed and applied has important implications for current and future smokers.

It has been conclusively shown that the profile of dangerous constituents, including particulate matter, lack of carbon monoxide and HPHCs is much more favorable in the ANDS discussed than that of cigarettes. Not surprisingly, the decrease in exposure to these constituents leads to positive health outcomes for smokers who switch. While concerns about poor cessation outcomes for those who switch from combustibles to ANDS and e-cigarettes acting as a gateway to combustible use for those who otherwise would not smoke

67. "Youth Tobacco Use: Results from the National Youth Tobacco Survey," U.S. Food and Drug Administration, May 29, 2019. https://www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey.

68. Brad Rodu, "The 2018 American Teen Vaping Epidemic, Recalculated," May 16, 2019. https://rodutobaccotruth.blogspot.com/2019/05/the-2018-american-teen-vaping-epidemic.html.

69. See, e.g., "The Public Health Consequences of E-cigarettes." http://nationalacademies.org/hmd/reports/2018/public-health-consequences-of-e-cigarettes.aspx.

70. The gateway hypothesis refers to a pattern where less risky behavior precedes progressively riskier behavior. See, e.g., Michael L. Miller et al., "Testing the Gateway Hypothesis," *Neuropsychopharmacology* 42:5 (2017), pp., 985-86. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5506797.

71. See, e.g., David T. Levy et al., "Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check," *Tobacco Control* (2018). https://www.ncbi.nlm.nih.gov/pubmed/30459182.

72. See, e.g., Krysten W. Bold et al., "Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth," *Pediatrics* 141 (2018). https://pediatrics.aappublications.org/content/141/1/e20171832; Michael S. Dunbar et al., "Disentangling Within- and Between-Person Effects of Shared Risk Factors on E-cigarette and Cigarette Use Trajectories From Late Adolescence to Young Adulthood," *Nicotine and Tobacco Research* (2018). https://www.ncbi.nlm.nih.gov/pubmed/30277535.

73. Levy et al. https://www.ncbi.nlm.nih.gov/pubmed/30459182.

74. Britt Hallingberg et al., "Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross sectional survey data in England, Scotland and Wales," *Tobacco Control* 0 (2019), pp 1-10. https://tobaccocontrol.bmj.com/content/early/2019/03/08/tobaccocontrol-2018-054584.

are valid, they are unfounded. The most recent and robust trials indicate that ANDS users are twice as successful in achieving abstinence and that e-cigarettes have not renormalized combustible cigarettes.

A narrow view of ANDS products might convince public health advocates and researchers to be skeptical, but placed in a broader context of comparative risk, ANDS are likely to gain much more support—to the benefit of those trying to quit combustible cigarettes, and perhaps even to those who might have otherwise gone on to smoke.

The differences between the two outlooks among public health agencies in the United Kingdom and the United States have important ramifications in both attitudes and regulatory approaches to ANDS. For example, recent analysis shows that in the United Kingdom, 57 percent of smokers surveyed perceived e-cigarettes to be less harmful than cigarettes.[75] This compares to only 33 percent with the same understanding in the United States.[76] Furthermore, as the FDA and other regulatory bodies in the United States (and other countries) continue to put the majority of focus on prevention and abstinence-only approaches, harm reduction approaches fall by the wayside—to the great detriment of the many people who could benefit from them. The assumptions and potential consequences of current and proposed regulatory strategies aimed at ANDS therefore warrant not only further—but more robust—analysis.

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75. Samara Wilson et al., "Harm perceptions of e-cigarettes and other nicotine products in a UK sample," Addiction 114:5 (2019), pp. 879-88. https://onlinelibrary.wiley.com/doi/full/10.1111/add.14502.

76. See, e.g., Jidong Huang et al., "Changing Perceptions of Harm of e-Cigarette vs Cigarette Use Among Adults in 2 US National Surveys From 2012 to 2017," Journal of the American Medical Association 2:3 (2019). https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2729471.