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TOBACCO HARM REDUCTION POTENTIAL FOR 'HEAT NOT BURN'

Edward Anselm

CONTENTS

INTRODUCTION

"Heat not burn" is a method of delivering the tobacco experience by heating, rather than igniting it. The potential benefits of this approach involve its ability either to reduce or eliminate completely many of the potentially harmful compounds that form at high temperatures when tobacco is combusted.[1] While not a new technology—R.J. Reynolds Tobacco Co. introduced the Premier brand of "smokeless cigarettes" in 1988[2]—some emerging heat-not-burn (HNB) applications could help reshape the tobacco harm reduction landscape by offering a means to deliver nicotine in ways that more closely reproduce the experience of smoking.

Newer devices that use HNB technology ought to be included in the category of electronic nicotine delivery systems (ENDS), a class that also includes nicotine vaporizers, vape pens, hookah pens, electronic cigarettes and e-pipes. Despite significant evidence that all of these various products are significantly less harmful than traditional combustible cigarettes, the goal of advancing a consistent public-health message urging a harm-reduction approach to tobacco use has been hampered by longstanding biases of the public-health community, evolving understanding of teen exposure and concerns about residual health risks.

Experts agree in principle that moving current smokers to products with lower risk profiles could save millions of lives. E-cigarettes have been quite popular among smokers, especially those who intend to quit. However, most of the 36.5 million remaining U.S. smokers[3] reject e-cigarettes as unsatisfying. HNB technologies could allow a larger fraction of current smokers to practice tobacco harm reduction.

HOW HNB WORKS

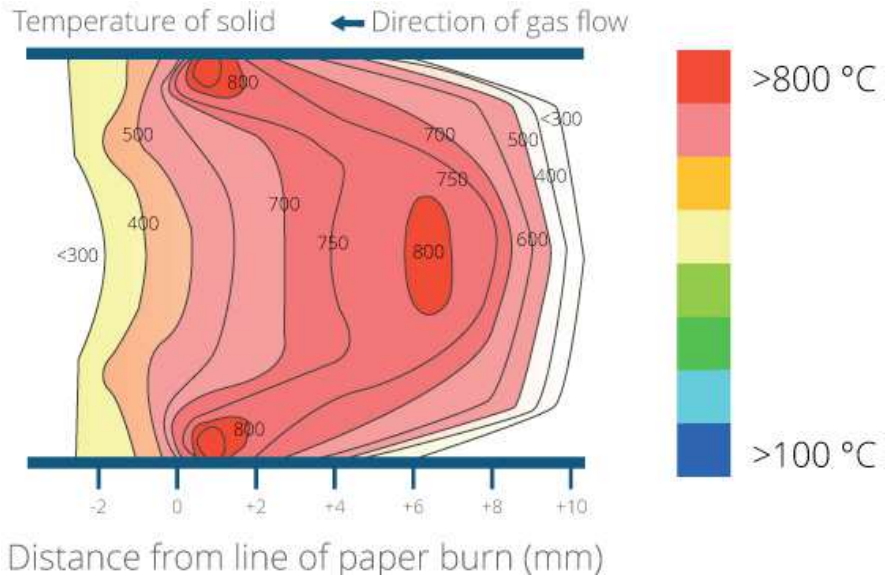
It long has been well-known that the greatest harms from cigarettes are linked to the high temperatures of combustion. Figure 1 illustrates a cross section of the tip of a burning cigarette, which generally exceeds 700 degrees Celsius, or 1300 degrees Fahrenheit. At these higher temperatures, larger and more complex molecules are formed. Many of these chemicals resemble—and may interfere with—human DNA, RNA

1. Phillip Morris International, "Heat-not-burn," PMI Science, Dec. 16, 2014. https://www.pmiscience.com/platform-development/platform-portfolio/heat-not-burn

2. Douglas C. McGill, "'Smokeless' Cigarette's Hapless Start," The New York Times, Nov. 19, 1988. http://www.nytimes.com/1988/11/19/business/smokeless-cigarette-s-hapless-start.html

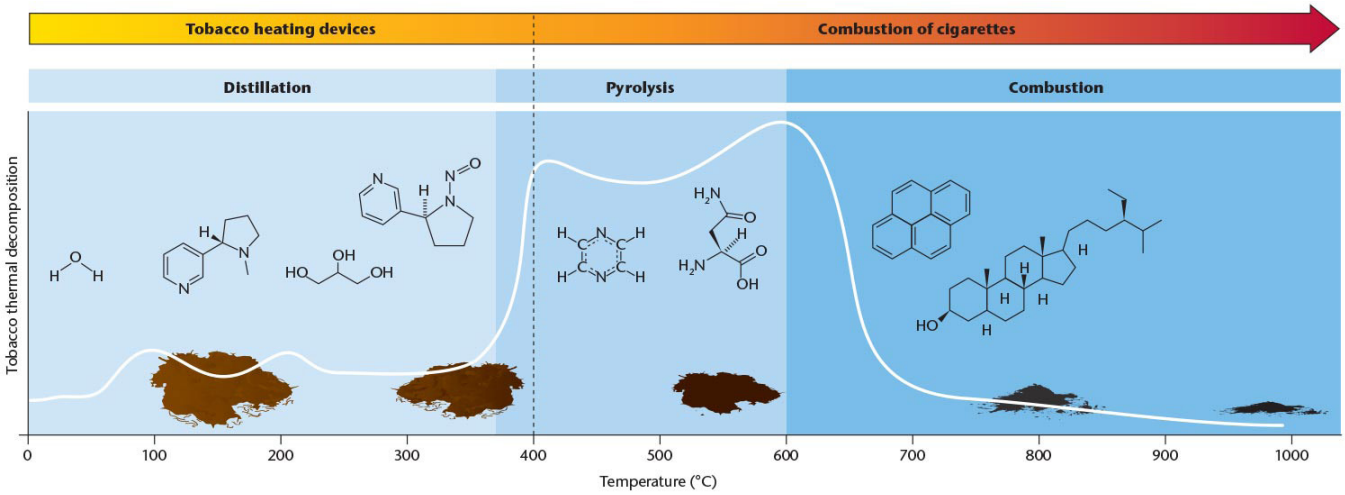
3. Ahmed Jamal, Brian A. King, Linda J. Neff, Jennifer Whitmill, Stephen D. Babb and Corinne M. Graffunder, "Current Cigarette Smoking Among Adults — United States, 2005–2015," *Morbidity and Mortality Weekly Report*, Nov. 11, 2016. https://www.cdc.gov/mmwr/volumes/65/wr/mm6544a2.htm?s_cid=mm6544a2_w#suggestedcitation

FIGURE I: TEMPERATURE AT TIP OF BURNING CIGARETTE



NOTE: Temperature varies considerably depending on the distance from the burning ash.
SOURCE: PMI Science

FIGURE 2: HIGHER TEMPERATURES CREATE MORE TOXIC COMPOUNDS



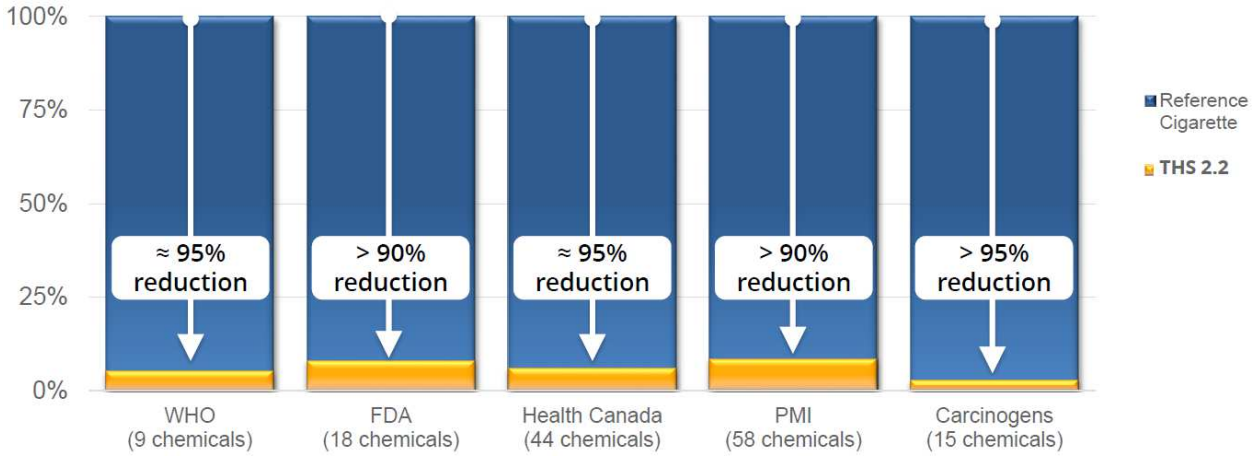
NOTE: Nicotine and tobacco flavors are released from tobacco at lower temperatures. Higher temperatures lead to the formation of more complex compound's known to cause disease.
SOURCE: BAT Science

and other organic molecules important for cellular metabolism. It is therefore these compounds that are responsible for most of the mutagenic and toxic effects of smoke. The threshold temperature to form these complex compounds is about 400 degrees Celsius, or 750 degrees Fahrenheit, as illustrated in Figure 2.

The advance offered by modern HNB products is their ability to regulate temperature and to distill flavor and nicotine from tobacco at much lower temperatures. Tobacco companies have in recent years developed HNB devices—already rolled out in some international markets and local trials—that produce acceptable levels of satisfaction for smokers.

Some current, recent or in-development products include: *IQOS* – Phillip Morris International began sale of its iQOS product in Japan in 2014 and reported sales of 2 million units in 2016. iQOS is a small battery-powered unit into which the user inserts a mini-cigarette. iQOS uses a blade to heat the tobacco to a precise temperature, up to a maximum of 350 degrees Celsius (660 degrees Fahrenheit). The temperature drops off to 300 degrees Celsius (570 degrees Fahrenheit) at 0.2 millimeters, with most of the tobacco heated at 250 degrees Celsius (482 degrees Fahrenheit). The heating process creates a vapor containing nicotine and a variety of tobacco products, which can be inhaled, with no combustion, smoke or ash produced. The preparation of tobacco

FIGURE 3: AVERAGE REDUCTION IN FORMATION OF HPHCS



NOTE: Reductions in harmful and potentially harmful constituents in iQOS THS 2.2 system, when compared to standard cigarettes. There are varying sets of HPHCs defined by different government agencies.
SOURCE: PMI Science

is carefully monitored to produce a consistent vapor and to retain the flavor of the specific tobacco mix. Each mini-cigarette generates 12 to 15 puffs. The device is designed to allow users to preserve the ritual of smoking, including taste, sensory experience and nicotine.[4]

Revo – A relaunch of the product the company previously marketed under the brand Eclipse, Revos were tested by Reynolds American Inc. in the Wisconsin market from February to July 2015. The device heats tobacco with a flow of hot air, which is generated from a hot charcoal at the tip of the device. The user lights the charcoal but the flame does not touch the tobacco. Air drawn through the charcoal is used to heat both the tobacco and a glycerin solvent, which extracts nicotine, tobacco flavors and other chemicals to pass into vapor. There is no combustion of tobacco and no smoke is produced. Revo was withdrawn from the market when sales did not meet expectations.[5]

iFuse – British American Tobacco began test-marketing the "hybrid" HNB device iFuse in Romania in November 2015. Hybrid products combine elements of e-cigarettes with HNB, generally by heating a nicotine liquid into vapor, which picks up flavor as it passes through a bit of tobacco. The iFuse has a target temperature range of between 400 degrees and 575 degrees Fahrenheit, which is enough to vaporize the nicotine and some other volatile compounds into an inhalable aerosol stream, but not enough to burn the tobacco and cause pyrolysis or combustion.[6]

Glo – British American Tobacco also introduced the Glo heat-not-burn product in November 2016. It is currently only marketed in Japan. The device is designed to heat tobacco to about 240 degrees Celsius, or 465 degrees Fahrenheit.[7]
Ploom Tech – Japan Tobacco Inc., which launched the Ploom heat-not-burn product in December 2013 and acquired associated Ploom trademarks and patents from Ploom Inc. in February 2015,[8] launched the hybrid Ploom Tech product in January 2016. As with other hybrid products, the Ploom Tech heats a liquid cartridge to produce vapor, which then passes through a tobacco capsule to pick up flavor. The product is offering in regular tobacco flavor and two menthol flavors. It currently is available only in Japan, where it has significant market share.[9]

In addition to products rolled out by major tobacco companies in select markets, personal vaporizer systems also have been available for some time that use a rechargeable battery, activated by inhaling through a mouthpiece. The devices have adjustable temperature settings in the 300 to 450 degree Fahrenheit range, which allow users to inhale marijuana without burning the leaves. Researcher Christian

4. Jennifer Kaplan, "Philip Morris's Cigarette Alternative Could Hit U.S. in 2017," Bloomberg, Oct. 5, 2016. https://www.bloomberg.com/news/articles/2016-10-05/philip-morris-s-cigarette-alternative-could-reach-u-s-in-2017

5. Richard Craver, "Reynolds' decision to stop marketing of heated cigarette Revo illustrates challenges in selling adult smokers on new products," *Winston-Salem Journal*, Aug. 2, 2015. http://www.journalnow.com/business/business_news/local/reynolds-decision-to-stop-marketing-of-heated-cigarette-revo-illustrates/article_afc1a516-29dc-55a5-8a54-75bd32cddd60.html

6. Stefanie Rossel, "Fun in, harm out," *Tobacco Reporter*, Feb. 1, 2016. http://www.tobaccoreporter.com/2016/02/fun-in-harm-out/

7. Press release, "British American Tobacco launches glo™ – a new-to-world Tobacco Heating Product – in Japan," British American Tobacco, Nov. 8, 2016. http://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAFGKR3

8. Press release, "JTI acquires 'Ploom' Intellectual Property Rights from Ploom, Inc.," Japan Tobacco Inc., Feb. 16, 2015. http://www.jti.com/media/news-releases/jti-acquires-ploom-intellectual-property-rights-ploom-inc/

9. Press release, "Ploom TECH, a new state-of-the-art tobacco vaporizer to be launched online nationally and at certain stores in Fukuoka City, from early March," Japan Tobacco Inc., Jan. 26, 2016.

Lanz and team studied five such commonly marketed systems to document the reduction in combusted products.[10] Through various technical advances, personal vaporizer systems are now available that are portable, lightweight and adaptable for heating tobacco leaf, although none currently are marketed for that purpose.

RELATIVE SAFETY OF HNB

The first consideration when evaluating the health and safety of tobacco products is the presence and relative concentrations of harmful and potentially harmful constituents (HPHCs). There is a direct correlation between the duration and intensity of exposure to these compounds and the various diseases caused by cigarette smoking, including lung cancer, cardiovascular disease and chronic obstructive pulmonary disease

In an effort to provide consumers accurate and useful information, the U.S. Food and Drug Administration's Center for Tobacco Products in January 2011 first published its list of 93 HPHCs known to be present in tobacco products and tobacco smoke.[11] Because of technical challenges in reliably measuring the compounds, the FDA has identified 18 HPHCs that it has deemed essential to evaluate. Other scientific bodies—such as the World Health Organization and Health Canada—have classified the constituents somewhat differently, but with substantial overlap in the literature.[12]

Several major tobacco companies have published papers that compare the concentration of HPHCs from combusted cigarettes with their HNB devices, generally using standardized reference cigarettes to minimize the sources of variation.[13] Given the differences among the devices and the ways in which they are used, it's important that great caution be taken to standardize the volume of vapor measured against the inhalation activity of the user, normalized for nicotine content.[14]

In a 1998 study of 25 compounds in the smoke of reference low-tar cigarettes brands, M.F. Borgerding and colleagues reported a 90 to 95 percent reduction in HPHCs when compared to the Eclipse brand.[15] Scientists from British American Tobacco have demonstrated similar results for their tobacco-heated products, with a reported 98 percent reduction of HPHC compounds.[16] Results from PMI Science, reproduced here as Figure 3, are representative of findings from this large family of studies. The figure demonstrates the reduction of HPHCs present in the aerosol produced by an HNB device when compared to standard reference cigarettes, with each column showing the average reduction for HPHCs as defined by each international classification system. In general, HPHCs—as defined by the FDA—are reduced by more than than 90 to 95 in almost all e-cigarettes and HNB devices that have been studied.[17]

The public-health bodies' formal lists of HPHCs represent just a small fraction of the more than 7,000 chemicals identified in combusted smoke, which individually or in combination may have effects on biological systems. Therefore, a broad range of tests is used to model the early stages of disease processes in vitro. The FDA has published detailed standards for these tests, which are used for all FDA-approved products. The most well-known is the Ames test, a standard measure of bacterial mutagenicity used in the evaluation of drugs and chemicals. Other commonly employed tests include measurements of cytotoxicity (the ability to kill cells) and mammalian genotoxicity (a measure of chromosome changes in the cultures of rat or hamster cells). In Figure 4, the toxicity of combusted smoke is represented as 100 percent, with reductions in the toxicity posed by an HNB product represented graphically. A reduction of more than 90 percent is documented across the three tested toxicity models.[18]

Laboratory models of human disease allow scientists to explore pathological processes in the development of a condition under controlled circumstances. These markers, which can be studied directly in humans, reflect the risk of

10. Christian Lanz, Johan Mattsson, Umut Soydaner and Rudolf Brenneisen, "Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis," *PLOS One*, Jan. 19, 2016. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0147286

11. Center for Tobacco Products, "'Harmful and Potentially Harmful Constituents' in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act (Revised)," Food and Drug Administration, August 2016. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM241352.pdf

12. Konstantinos Farsalinos, I. Gene Gillman, Stephen Hecht, Riccardo Polosa and Jonathan Thornburg, *Analytical Assessment of e-Cigarettes*: 1st Edition, Elsevier, Nov. 14, 2016. https://www.elsevier.com/books/analytical-assessment-of-e-cigarettes/farsalinos/978-0-12-811241-0

13. Ewald Roemer, et al., "Mainstream Smoke Chemistry and In Vitro and In Vivo Toxicity of the Reference Cigarettes 3R4F and 2R4F," *Beiträge zur Tabakforschung International/Contributions to Tobacco Research*, Vol. 25, No. 1, February 2012. https://ctrp.uky.edu/resources/pdf/webdocs/Mainstream%20Smoke%20Chemistry%203R4F,%202R4F.pdf

14. Farsalinos, 2016.

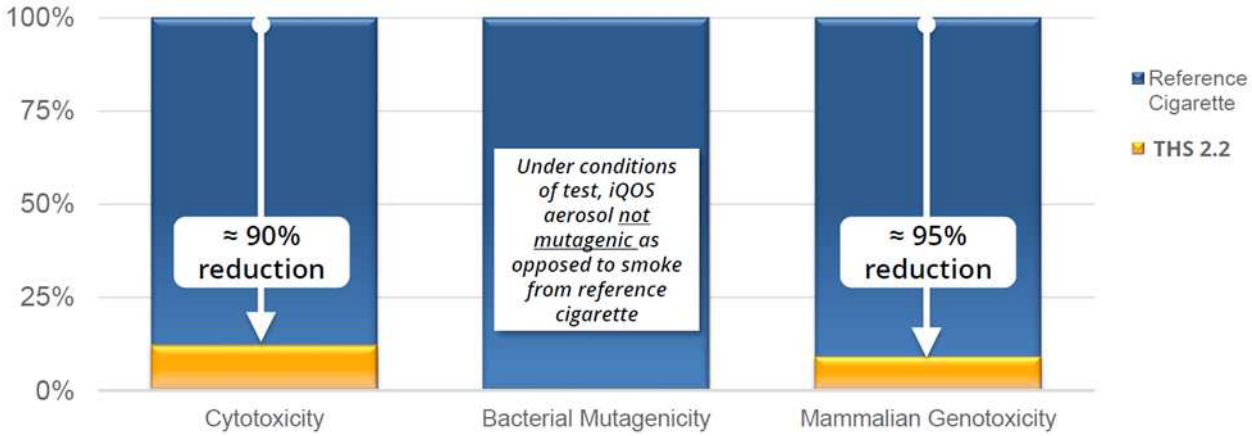
15. M.F. Borgerding, et al., "Chemical and biological studies of a new cigarette that primarily heats tobacco: Part 1," *Food and Chemical Toxicology*, 36(3):169-182, July 1998. https://www.ncbi.nlm.nih.gov/pubmed/9687969

16. Simon Poynton, et al., "Controlled aerosol release to heat tobacco; product operation and aerosol chemistry assessment," SRNT Annual Meeting, March 2-5, 2016. http://www.bat-science.com/groupms/sites/BAT_9GVJXS.nsf/vwPagesWebLive/DOA7MJCN/$FILE/SRNT_SP_2016_(2).pdf?openelement

17. Allison M. Glasser, Lauren Collins, Jennifer L. Pearson, Haneen Abudayyeh, Raymond S. Niaura, David B. Abrams and Andrea C. Villanti, "Overview of Electronic Nicotine Delivery Systems: A Systematic Review," *American Journal of Preventative Medicine*, Vol. 52, Issue 2, pp. e33–e66, February 2017. http://www.ajpmonline.org/article/S0749-3797(16)30573-6/abstract

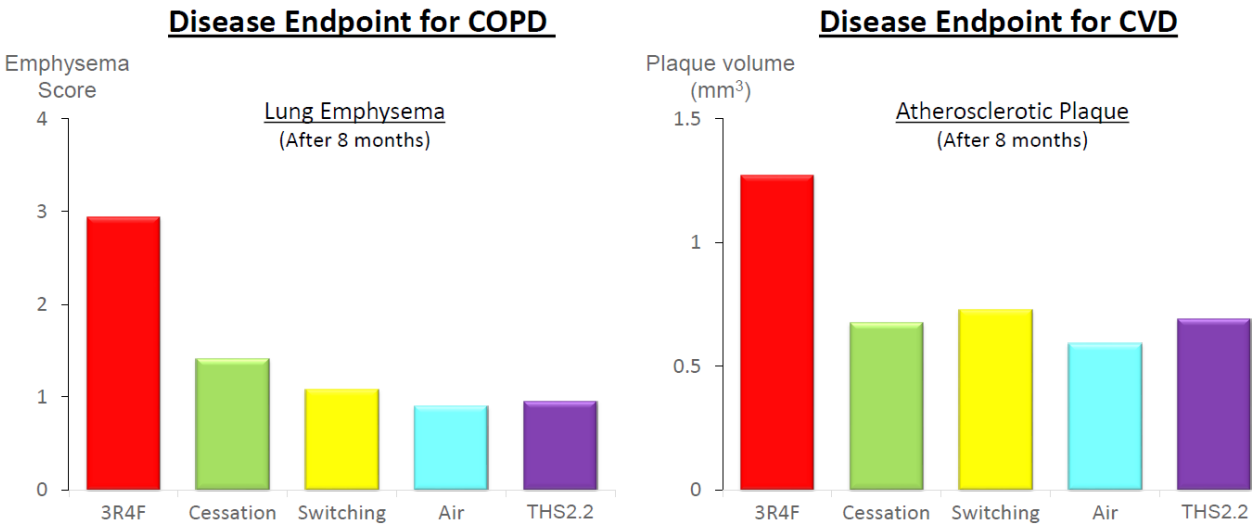
18. Maurice R. Smith, Bruce Clark, Frank Lüdicke, Jean-Pierre Schaller, Patrick Vanscheeuwijck, Julia Hoeng and Manuel C. Peitsch, "Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program," *Regulatory Toxicology and Pharmacology*, Vol. 81, Supp. 2, pp. S17–S26, Nov. 30, 2016. http://www.sciencedirect.com/science/article/pii/S0273230016301891

FIGURE 4: AVERAGE REDUCTION IN TOXICITY COMPARED TO REFERENCE CIGARETTE



NOTE: Smoke from iQOS devices is compared to smoke from standard cigarettes in a variety of biological models that are known to demonstrate the harmful effects of chemicals.
SOURCE: PMI Science

FIGURE 5: IMPACT ON DISEASE ENDPOINTS IN LABORATORY MODEL OF DISEASE



NOTE: The smoke from iQOS devices is compared to smoke from standard cigarettes in a variety of biological models of disease.
SOURCE: PMI Science

disease years before the subject would develop symptoms. J.D. deBethizy's research team first demonstrated in 1990 that users of the original Premier device showed reduced disease markers.[19] J.C. Stewart and colleagues demonstrated the same outcomes for the Eclipse device in 2006.[20]

One common test is to study lung cells for markers that predict emphysema. When bronchial epithelial cultures were exposed to an aerosol from the iQOS device, there were significant reductions in the markers associated with standard cigarette smoke.[21] Another important set of disease markers related to cardiovascular disease is the development of atherosclerotic plaque.[22] In experiments by PMI Science, study samples were examined after eight months of exposure to

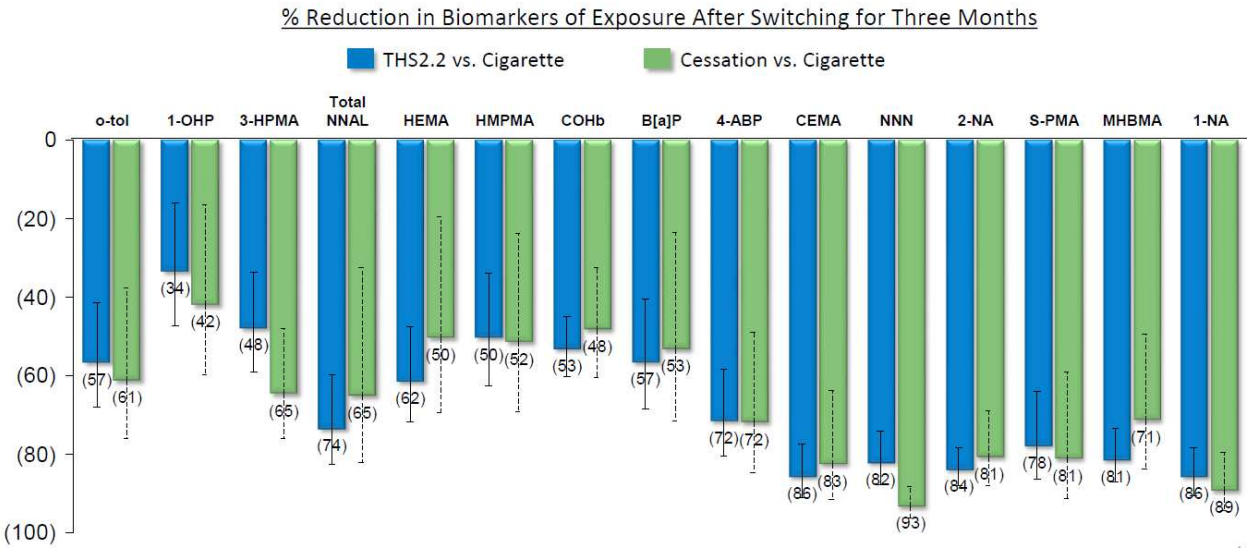
19. J.D. deBethizy, et al., "Chemical and biological studies of a cigarette that heats rather than burns tobacco," *Journal of Clinical Pharmacology*, 30(8):755-763, August 1990. https://www.ncbi.nlm.nih.gov/pubmed/2401755

20. J.C. Stewart, et al., "Changes in markers of epithelial permeability and inflammation in chronic smokers switching to a nonburning tobacco device (Eclipse)," *Nicotine & Tobacco Research*, 8(6):773-783, December 2006. https://www.ncbi.nlm.nih.gov/pubmed/17132525

21. A.R. Iskandar, et al., "A systems toxicology approach for comparative assessment: Biological impact of an aerosol from a candidate modified-risk tobacco product and cigarette smoke on human organotypic bronchial epithelial cultures," *Toxicology in Vitro*, 39:29-51, March 2017. https://www.ncbi.nlm.nih.gov/pubmed/27865774

22. Julie Hoeng, "Animal Model for CVD and inflammation – pMRTP Switching Study," *PMI Science*, July 2, 2013. https://www.pmiscience.com/library/animal-model-cvd-and-inflammation-%E2%80%93-pmrtp-switching-study

FIGURE 6: 90-DAY REDUCED EXPOSURE STUDY – UNITED STATES



NOTE: Biomarkers of exposure are reduced in users of iQOS to the same degree as quitters.
SOURCE: PMI Science

smoke from standard cigarettes, labelled in red in Figure 5. The green bar represents the marker after cessation; yellow shows the effect of switching to the device; and the purple bar represents the effect of HNB aerosol for the entire period. The results suggest HNB use reduces disease-marker activity to the same degree as quitting.

The next level of testing conducted by PMI Science was to measure many of these same markers of exposure and disease processes in humans who use HNB devices. Smokers participating in such studies were kept in controlled environments and randomized to cessation or use of the iQOS device, with 15 biomarkers of exposure tested in the subjects' urine at baseline and 90 days. Testing in Poland showed the disease markers were reduced significantly.[23] In a study in Japan, at 90 days, the percent reduction in exposure biomarkers were roughly equivalent across the iQOS and cessation populations.[24] Figure 6 illustrates the results after a 90-day U.S. study.

The research completed to date by the major tobacco companies generally report that HNB devices produce 90 percent less HPHCs than traditional combustible cigarettes. This reduction in chemical concentration carries through the experimental narrative, from the effects of the compounds in vitro through the measurement of markers of disease in human subjects. In aggregate, the evidence offers a strong case that HNB devices are far safer than smoking combustible cigarettes.

HNB AND THE ENDS MARKET

HNB technologies are geared to capture smokers whose needs are not met by e-cigarettes. A major question for the successful introduction of HNB products is whether they would meet needs that existing ENDS products do not. Smokers who try ENDS devices have a variety of motivations. Some are simply experimenting. Some plan to mix smoking and vaping, or alternate between the two, in what is generally called "dual use." Some seek to replace cigarettes with vaping entirely. And some are looking to cease use of nicotine entirely, possibly by "stepping down" dosage levels.

The number of smokers who have experimented with vaping far exceeds the number of regular ENDS users.[25] For many smokers, the rituals associated with the habit are strongly reinforcing: handling, lighting and oral gratification may be as important as inhaling hot gas. The experience of vaping may be sufficiently different from smoking as to be unsatis-fying to a significant contingent of smokers. HNB products, which use actual tobacco and in some cases call for a heating device to be lit, may more closely mirror smoking rituals in some crucial ways.

23. Christelle Haziza, Guillaume de La Bourdonnaye, Dimitra Skiada, Jacek Ancerewicz, Gizelle Baker, Patrick Picavet and Frank Lüdicke, "Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland," *Regulatory Toxicology and Pharmacology*, Vol. 81, Supp. 2, pp. S139–S150, Nov. 30, 2016. http://www.sciencedirect.com/science/article/pii/S0273230016303312

24. Frank Luedicke, et al., "Reduced exposure to harmful and potentially harmful constituents after 90 days of use of tobacco heating system 2.2 in Japan: A comparison with continued combustible cigarette use or smoking abstinence," *Toxicology Letters*, (258):S89, March 2016. https://www.pmiscience.com/library/reduced-exposure-harmful-and-potentially-harmful-constituents-after-90-days-use-tobacco-1

25. Konstantinos E. Farsalinos, Konstantinos Poulas, Vassilis Voudris and Jacques Le Houezec, "Electronic cigarette use in the European Union: analysis of a representative sample of 27,460 Europeans from 28 countries," *Addiction*, Aug. 21, 2016. http://onlinelibrary.wiley.com/doi/10.1111/add.13506/abstract

While those trying to quit may be more tolerant of a different nicotine-delivery experience, most ENDS users expect a level of nicotine equivalent to what they obtain from cigarettes. As with combusted cigarettes, vapers attempt to maintain a fairly constant level of nicotine throughout the day.[26] The broad range of e-cigarette designs and liquids produce wide variation in generated levels of nicotine.[27]

Some research suggests second and third-generation e-cigarettes are more effective in aiding smoking cessation.[28] Konstantinos Farsalinos, a research fellow at Greece's Onassis Cardiac Surgery Center, has found that second-generation vapor products delivered nicotine more rapidly and efficiently than first-generation products.[29] In another paper, Farsalinos showed that experienced vapers inhale for longer durations to attain their desired nicotine levels, a technique it takes inexperienced vapers some time to learn.[30] There also have been findings that third-generation devices are able to deliver higher levels of nicotine and require fewer puffs to meet a consumer's needs.[31] Thus, it's reasonable to infer the popularity of these third-generation "tank systems" is driven, at least in part, by their greater ability to deliver nicotine.

To make vaping more palatable, particularly with high levels of nicotine, many vapers rely on flavorings. Large-scale surveys of vapers show that some users vary flavors throughout a given day. Farsalinos conducted an Internet-based study of 4,618 ENDS users and found that 63 percent reported vary their flavors on a daily basis.[32] HNB devices are capable of more closely mirroring tobacco flavors than are vaping liquids; they also are capable of producing menthol and other flavors.

ENDS product designs appear to be evolving to meet users' demand for nicotine levels and for a satisfying overall experience. Tobacco companies are closely tracking consumer responses to their HNB products in a number of international markets. Adoption and sales from the Japanese market appear to justify expansion into additional markets, confirming that some consumer needs are met by these products.

FDA REGULATION OF HNB PRODUCTS

Under the Family Smoking Prevention and Tobacco Control Act of 2009 and related regulations, all tobacco products must be registered with the FDA based on their presence in the marketplace as of Feb. 15, 2007.[33] Products established before the predicate date—such as the Eclipse—must submit an application demonstrating that the current product is substantially equivalent to its previously marketed form.

Products introduced subsequent to the predicate date must submit a Premarket Tobacco Application (PMTA). In May 2016, the FDA updated its PMTA draft guidance on how individual ENDS products will be evaluated. This updated framework considers effects not only on users, but also on nonusers, especially young people who might initiate use. For each new tobacco product, detailed sets of reports and analysis will be required, including toxicology, in-vitro, animal testing and human studies. The FDA also requires testing of the devices and the vapor produced in human subjects. Users of these devices and their vapor are to be studied over time to ascertain if biomarkers associated with tobacco-related disease are reduced. In addition, makers of new products will have to report their effects on behavior, including rates of adoption by users of other products, rates of cessation, abuse potential and consumer perceptions.[34]

The FDA also has outlined an additional set of requirements that would allow tobacco products to be marketed as having reduced risk through a Modified Risk Tobacco Product Application (MRTPA).[35] The MRTPA requires product makers to demonstrate that:

> [The] magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial ... [and] the product as

26. Lynne Dawkins, et al., "Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects," *Psychopharmacology*, 233(15-16):2933-41, August 2016. https://www.ncbi.nlm.nih.gov/pubmed/27235016

27. A. El-Hellani, et al., "Nicotine and carbonyl emissions from popular electronic cigarette products: correlation to liquid composition and design characteristics," *Nicotine & Tobacco Research*, ntw280, Oct. 7, 2016. https://www.ncbi.nlm.nih.gov/pubmed/27798087

28. S.C. Hitchman, et al., "Associations between e-cigarette type, frequency of use and quitting smoking: findings from a longitudinal online panel survey in Great Britain," *Nicotine & Tobacco Research*, 17(10):1187-94, October 2015. https://www.ncbi.nlm.nih.gov/pubmed/25896067

29. Konstantinos E. Farsalinos, Alketa Spyrou, Kalliroi Tsimopoulou, Christos Stefopoulos, Giorgio Romagna and Vassilis Voudris, "Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices," *Scientific Reports*, 4:4133, February 2014. http://www.nature.com/articles/srep04133/

30. Konstantinos E. Farsalinos, Alketa Spyrou, Christos Stefopoulos, Kalliroi Tsimopoulou, Panagiota Kourkoveli, Dimitris Tsiapras, Stamatis Kyrzopoulos, Konstantinos Poulas and Vassilis Voudris, "Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naïve users (smokers)," *Scientific Reports*, 5:11269, June 2015. http://www.nature.com/articles/srep11269

31. Theodore Wagener, Evan Floyd, Irina Stepanov, Leslie Driskill, Summer Frank, Ellen Meier, Eleanor Leavens, Alayna Tackett, Neil Molina and Lurdes Queimado, "Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users," *Tobacco Control*, Oct. 11 2016. http://tobaccocontrol.bmj.com/content/early/2016/10/11/tobaccocontrol-2016-053041.abstract

32. Konstantinos E. Farsalinos, et al., "Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins," *Nicotine & Tobacco Research*, 17(2):168-174, February 2015. https://www.ncbi.nlm.nih.gov/pubmed/25180080

33. Food and Drug Administration, "Tobacco Control Act," Feb. 3, 2017. http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm246129.htm

34. Food and Drug Administration, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems," May 2016. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM499352.pdf

35. Food and Drug Administration, "Modified Risk Tobacco Product Applications – Draft Guidance," March 2012. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM297751.pdf

actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users.

CONCLUSION

Major tobacco manufacturers have embarked on comprehensive scientific programs to meet the PMTA and MRTPA requirements for HNB products, with well-funded laboratories and supporting evidence that, for the most part, has been published in peer reviewed journals.

In aggregate, a voluminous literature has established that HPHCs from HNB devices are substantially lower in risk than reference cigarettes; that toxicity and the effect on biomarkers in vitro is reduced; and that the effect on biomarkers in smokers who switch to HNB products is reduced, as well. Numerous additional studies currently are in progress.

While it appears the research programs to support HNB products are well on their way toward meeting the requirements for new and modified risk products, it is not yet clear how stringently the FDA will interpret the guidelines – e.g., whether a 90-day study of human response would be sufficient.

Heating tobacco at lower temperatures than combustible cigarettes allows nicotine to be delivered in ways that retain much of the ritual and experience of smoking. Comprehensive scientific programs have demonstrated these products present significantly reduced risk when compared to traditional cigarettes. Collectively, they represent a new set of tools to reduce the harm of combustible tobacco.

ABOUT THE AUTHOR

Dr. Edward Anselm is medical director of Emblem Health and a senior fellow of the R Street Institute.

Edward is a frequent speaker at population health conferences and has been a strong advocate for reimbursement of smoking-cessation services. Most recently, he implemented the first harm reduction strategy sponsored by a health plan. Building on reim-bursement for smoking cessation and enhanced coverage of FDA-approved smoking-cessation medications, the program seeks to engage patients and their doctors in a dialogue about harm reduc-tion.

He previously served as chief medical officer of Freelancers Health Service Corp./Health Republic Insurance of New York, HIP Health Plan and Fidelis Care of New York. As a health care executive, his focus has been implementation of disease management and case management programs.

Trained in internal medicine at the Rosalind Franklin University of Medicine and Science, Edward for several years ran a primary-care clinic. During his residency at Montefiore Medical Center, initiated a smoking cessation clinic. Since then, he has organized and led a number of clinics at hospitals and in workplace settings.

Edward is a fellow of the New York Academy of Medicine and serves on the board of the New York-metro chapter of Physicians for a National Health Plan. He also teaches courses on tobacco control and other public health topics as an assistant clinical professor of medicine at the Icahn School of Medicine at Mount Sinai.