



July 10, 2017

Food and Drug Administration
 Division of Dockets Management
 5630 Fishers Lane, Rm. 1061
 Rockville, MD 20852

Re: Comments on Tobacco Product Standard for N-Nitrosornicotine Level in Finished Smokeless Tobacco Products, Docket No. FDA-2016-N-2527

Ladies and Gentlemen:

The undersigned organizations strongly support the FDA’s proposed rule establishing a tobacco product standard for *N*’-Nitrosornicotine (“NNN”) in finished smokeless tobacco products and urge FDA to promulgate a final rule as soon as possible.

The evidence cited by FDA in the proposed rule demonstrates that promulgation of the proposed product standard is appropriate for the protection of the public health under Section 907(a)(3)(A) of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act).¹ This rule is of great importance, not only because of the lifesaving benefits of reducing the toxicity of smokeless tobacco, but also because, as FDA’s first tobacco product standard, it will lay the groundwork for the future use of FDA’s broad authority under Section 907 to change the nature of tobacco products to the benefit of public health.

In brief, the evidence cited by FDA, supported by evidence from other recently published studies, establishes all the following elements:

- NNN is a potent carcinogen;
- Epidemiological evidence establishes that the use of smokeless tobacco products marketed in the United States increases the risk of oral cancer;

¹ 21 U.S.C. §387g(a)(3)(A).

- Reducing the level of NNN in smokeless tobacco products marketed in the United States would reduce the risk of oral cancer for users of such products;
- The presence of smokeless tobacco products currently commercially marketed in the United States that comply with the product standard demonstrates that production of smokeless tobacco products that comply with the product standard is achievable.

I. Smokeless tobacco products used in the United States cause cancer and additional serious health risks.

Smokeless tobacco has been found to cause oral, pancreatic and esophageal cancer, lesions in the mouth and tooth decay, in addition to being addictive. Numerous reviews of the evidence by authoritative organizations support these conclusions. As early as 1986, the Surgeon General concluded that “the oral use of smokeless tobacco presents a significant health risk. It is not a safe substitute for smoking cigarettes. It can cause cancer and a number of non-cancerous oral conditions and can lead to nicotine addiction and dependence.”² Since then, other major health organizations evaluating the evidence, such as the National Cancer Institute (NCI), the National Toxicology Program, and the World Health Organization (WHO) Scientific Advisory Committee on Tobacco Product Regulation have all reached the same conclusions.³ In 2012, after a comprehensive review of the literature on smokeless tobacco, the International Agency for Research on Cancer (IARC) concluded that “there is strong evidence in humans that smokeless tobacco causes cancer of the oral cavity.”⁴ Most recently, in 2014, NCI and the Centers for Disease Control and Prevention (CDC) released a global report, *Smokeless Tobacco and Public Health*, which concluded, “There is sufficient evidence that ST [smokeless tobacco] products cause addiction; precancerous oral lesions; cancer of the oral cavity, esophagus, and pancreas; and adverse reproductive and developmental effects including stillbirth, preterm birth, and low birth weight. Some, but not all, ST products are associated with increased risk of fatal ischemic heart disease, type 2 diabetes, and fatal stroke.”⁵ Furthermore, epidemiological data

² U.S. Department of Health and Human Services (HHS), *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General*, NIH Publication No. 86-2874, April 4, 1986.

³ National Institutes of Health (NIH), National Cancer Institute (NCI), *Smoking and Tobacco Control Monograph No. 2: Smokeless Tobacco or Health: An International Perspective*, September 1992; NCI & U.S. Centers for Disease Control and Prevention (CDC), *Smokeless Tobacco and Public Health: A Global Perspective*, Bethesda, MD: U.S. Department of Health and Human Services, CDC and NIH, NCI, NIH Publication No. 14-7983, 2014; US Department of Health and Human Services (HHS), Public Health Service, National Toxicology Program, *Report on Carcinogens, Eleventh Edition*, January 31, 2005; World Health Organization, Scientific Advisory Committee on Tobacco Product Regulation, *Recommendation on Smokeless Tobacco Products*, 2003.

⁴ IARC Monograph 100E, *A Review of Human Carcinogens: Personal Habits and Indoor Combustions*, 2012 at 295. This conclusion confirmed a nearly identical conclusion reached in the 2007 IARC Monograph (*infra* at note 9), which had surveyed the literature as of 2004.

⁵ NCI & CDC, *Smokeless Tobacco and Public Health: A Global Perspective*, Bethesda, MD: U.S. Department of Health and Human Services, CDC and NIH, NCI, NIH Publication No. 14-7983, 2014, at 14.

show that users of the kinds of smokeless tobacco commonly sold in the United States are far more likely to develop oral cancer than never users.⁶

Even U.S. manufacturers of smokeless tobacco products concede the truth of these statements. One company has stated, “ST products do present health risks...” and “ST products have also been associated with increased risk of oral cancer in some studies...”⁷

The epidemiological evidence demonstrates that use of smokeless tobacco products can cause other types of cancer as well. A study by IARC concluded that smokeless tobacco users have an 80 percent higher risk of developing oral cancer and a 60 percent higher risk of developing pancreatic and esophageal cancer than non-users.⁸ A review of the scientific literature published by IARC concluded that “Smokeless tobacco causes cancers of the oral cavity, oesophagus and pancreas.”⁹

- II. The persistence of high levels of smokeless tobacco use among adolescents supports the necessity for the proposed rule.

The need for the proposed rule is supported by the persistence of high levels of smokeless tobacco use among adolescents. Although cigarette smoking in the U.S. has been on the decline, the latest survey from the Centers for Disease Control and Prevention (CDC) showed that the use of smokeless tobacco among youth has remained troublingly steady since 1999.

Recently released figures from the National Youth Tobacco Survey show that rates of usage of smokeless tobacco among high school adolescents (8.3% among boys and 3.3% among girls in 2016) remains troublingly steady, and an estimated 860,000 adolescents have used smokeless tobacco products during the past thirty days.¹⁰ Moreover, data from the 2014 NYTS found that 43 percent of high school smokeless tobacco users and about 29 percent of middle school smokeless tobacco users used these products frequently (20-30 of the previous 30 days).¹¹

The CDC’s Youth Risk Behavior Survey, another national survey using a different methodology, found that in 2015, 11.9 percent of high school boys and 7.3 percent of all high-school students reported current use of smokeless tobacco products. In at least 19 states, use of

⁶ Boffetta, P, et al., “Smokeless Tobacco and Cancer,” *The Lancet Oncology* 9: 667-75, 2008.

⁷ R.J. Reynolds Citizen Petition, July 28, 2011 (“RJR Citizen Petition”), at 3, 9.

⁸ Boffeta, *supra* note 5, at 668, 669.

⁹ IARC, *supra* note 4, at 309.

¹⁰ U.S. Centers for Disease Control & Prevention (CDC), “Tobacco Use Among Middle and High School Students — United States, 2011–2016,” *Morbidity and Mortality Weekly Report (MMWR)* 66(23), June 16, 2017, at 599.

¹¹ CDC, “Frequency of Tobacco Use Among Middle and High School Students — United States, 2014,” *MMWR* 64(38):1061-1065, October 2, 2015.

smokeless tobacco by high school boys exceeded the national rate.¹² Each year, nearly half a million (480,000) kids ages 12-17 use smokeless tobacco for the first time.¹³

These data establish that the reductions in adolescent smoking rates in recent years have not occurred with respect to adolescent usage of smokeless tobacco products. With large numbers of young people continuing to use smokeless tobacco products, the importance of reducing their disease risk is enhanced.

III. NNN is a potent carcinogen that is present at high levels in many smokeless tobacco products currently marketed in the United States.

Smokeless tobacco use is associated with elevated levels of biomarkers of oral cancer. According to IARC:

multiple features of the carcinogenic process have been observed to occur *in vitro* and *in situ* in the oral cavity of smokeless tobacco chewers and in experimental animals treated with smokeless tobacco. Collectively, the available data on biomarkers provide convincing evidence that carcinogen uptake, activation and binding to cellular macromolecules are higher in smokeless tobacco users than in non-users. Smokeless tobacco is genotoxic in humans and in experimental animals.¹⁴

The epidemiological evidence that cancer is a major health risk from smokeless tobacco use is supported by analysis of the chemistry of smokeless tobacco products. In 1992, NCI identified at least 28 cancer-causing chemicals in smokeless tobacco products.¹⁵ Since then, researchers have documented at least 36 carcinogens¹⁶ on FDA's published list of 93 harmful

¹² CDC, "Youth Risk Behavior Surveillance—United States, 2015," *MMWR* 65(SS-6), June 10, 2016, http://www.cdc.gov/healthyyouth/data/yrbs/pdf/2015/ss6506_updated.pdf.

¹³ Substance Abuse and Mental Health Services Administration (SAMHSA), HHS, *Results from the 2015 National Survey on Drug Use and Health, NSDUH: Detailed Tables*, 2016. <http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf>.

¹⁴ IARC Monograph 89, *Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines*, 2007a, at 362.

¹⁵ NIH, NCI, *Smoking and Tobacco Control Monograph 2: Smokeless Tobacco or Health: An International Perspective*, September 1992, at 97, https://cancercontrol.cancer.gov/brp/tcrb/monographs/2/m2_complete.pdf.

¹⁶ Carcinogens found in smokeless tobacco products include acetaldehyde, aflatoxin B-1, anabasine, arsenic, benz[*a*]anthracene, benzo[*b*]fluoroanthene, benzo[*k*]fluoroanthene, benzo[*a*]pyrene, beryllium, cadmium, chromium, chrysene, crotonaldehyde, dibenz[*a,h*]anthracene, ethyl carbamate (urethane), formaldehyde, indeno[1,2,3-*cd*]pyrene, lead, mercury, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), naphthalene, nickel, nitrate, nitrite, *N*'-nitrosoanabasine, *N*-nitrosodiethanolamine, *N*-nitrosodimethylamine, *N*-nitrosomorpholine, *N*'-nitrosornicotine (NNN), *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, *N*-nitrososarcosine, nornicotine, polonium-210, uranium-235, and uranium-238. Hecht, S, "Recommendations from the Tobacco Product Constituents Subcommittee," Presentation at the August 30 Meeting of the Tobacco Products Scientific Advisory Committee, August 30, 2010, <https://wayback.archive-it.org/7993/20170113150958/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM224807.pdf>.

and potentially harmful constituents,¹⁷ including *N*'-nitrosornicotine (NNN) and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), found in smokeless tobacco products.

NNN is the leading driver of excess oral cancer risk from smokeless tobacco and limiting its levels will save lives and prevent debilitating disease. The carcinogenic agents in smokeless tobacco that have been linked to oral cancer are NNN and NNK. In its monograph on smokeless tobacco, NCI stated, "The evidence that NNK and NNN play a role in human oral cancer induced by snuff is strong. Both compounds are present in significant amounts in snuff and in the saliva of snuff dippers. ... Although there are many questions about the mechanisms by which snuff causes oral tumors in rats and humans, there is no doubt that the presence of NNK and NNN in snuff is an unacceptable risk to people who choose to use these products."¹⁸

The FDA's proposed rule¹⁹ and reports written by Dr. Stephen Hecht, Dr. Dorothy Hatsukami, and Dr. Irina Stepanov in 2014 include additional evidence to support the causal link between NNN and cancer.²⁰ Specifically, FDA stated, in support of its proposed rule, "NNN is a carcinogenic agent found in smokeless tobacco products. ... [O]n the basis of the available scientific evidence, FDA has determined that NNN is the predominant driver of excess oral cancer risk among smokeless tobacco users."²¹

In a review of the science on tobacco-specific nitrosamines (TSNAs) in cigarette smokers, including his own direct research, Dr. Hecht found strong evidence that NNN and NNK are "directly responsible for some cancers observed in cigarette smokers, particularly cancers of the lung and esophagus."²² Drs. Hatsukami and Stepanov also evaluated research studies on TSNAs, concluding, "There is strong evidence to demonstrate that higher levels of some of these carcinogens is associated with greater cancer risk (total NNAL for lung cancer and leukoplakia (pre-cancerous lesions), total NNN for esophageal cancer, PAH for lung cancer) in humans."²³ Dr. Hatsukami's recently published article reiterates her strong support for the proposed standard.²⁴

¹⁷ U.S. Food and Drug Administration (FDA), *Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act: Draft Guidance for Industry*, March 2012, <http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm297752.htm>.

¹⁸ NIH, NCI, *Smoking and Tobacco Control Monograph 2: Smokeless Tobacco or Health: An International Perspective*, September 1992, at 151, https://cancercontrol.cancer.gov/brp/tcrb/monographs/2/m2_complete.pdf.

¹⁹ 82 Fed. Reg. at 8011-8012.

²⁰ Copies of these reports are attached hereto. Drs. Hecht, Hatsukami, and Stepanov are also submitting comments to this docket in support of FDA's proposed rule that endorse making the proposed rule final.

²¹ 82 Fed. Reg. at 8005.

²² Hecht, S, *Proposal for a Standard for Tobacco-Specific Nitrosamines in Cigarette Tobacco and Cigarette Smoke*, 2014, at 12.

²³ Hatsukami, D & Stepanov, I, *Establishing product standards for smokeless tobacco*, February 2014, at 39-40.

²⁴ Berman, M & Hatsukami, D, *Reducing Tobacco-Related Harm: FDA's proposed product standard for smokeless tobacco*. 10.1136/Tobacco Control-2016-053622, published electronically, June 20, 2017.

Leading researchers on smokeless tobacco determined that “TSNA constituent levels, but not nicotine, play an important role in the extent of biomarker exposure, even when taking into account smokeless tobacco pattern of use. Therefore, a product standard for reducing these TSNA, specifically NNK and NNN (the most potent carcinogens), would likely lead to a decrease in exposure.”²⁵ Studies showing lower levels of a biomarker for NNN in participants who switched from US smokeless tobacco products to others with lower NNK levels and those linking higher TSNA exposure to higher risks of cancer demonstrated that not only is it possible to reduce exposure, but doing so can also reduce cancer risks.²⁶

In addition to saving lives lost prematurely to oral cancer, limiting NNN levels in smokeless tobacco can help to reduce the toll of cancer. Reduced suffering, medical visits, and costs associated with treatment will improve Americans’ quality of life.

IV. Epidemiological evidence from Sweden supports the conclusion that implementation of the product standard would significantly decrease the risk of oral cancer for users of smokeless tobacco in the United States.

The conclusion that the proposed product standard would reduce the risk of oral cancer is also supported by epidemiological evidence of oral cancer rates in Sweden, where smokeless tobacco with NNN levels below the levels that would be established by the proposed standard has long been widely used.²⁷

Both Swedish snus as manufactured and marketed in Sweden, and various snus products manufactured by Swedish Match North America and marketed in the United States, have NNN levels below that established by the proposed standard. As FDA recognized when it granted new product marketing orders for the Swedish Match snus products marketed in the United States, the long and widespread experience with these products in Scandinavia and extensive epidemiological studies of the effect of these products on oral cancer rates in Sweden demonstrate that the use of these products raises a far lower risk of oral cancer than all the leading smokeless tobacco brands sold in the United States. As FDA concluded in granting the marketing orders, “ST use in general is associated with elevated risks of oral cancer in the U.S. *but not associated* with oral cancer in Nordic countries where Swedish snus with lower levels of NNN and NNK is used by Swedish snus users.... This suggests that the lower levels of NNN and

²⁵ Hatsukami, D, et al., “Evidence supporting product standards for carcinogens in smokeless tobacco products,” *Cancer Prevention Research* 8(1):20-6, January 2015, at OF5.

²⁶ Hatsukami, D, et al., “Evidence supporting product standards for carcinogens in smokeless tobacco products,” *Cancer Prevention Research* 8(1):20-6, January 2015.

²⁷ Although the Swedish epidemiological evidence supports a significantly lower cancer risk for users of Swedish snus as compared with other smokeless products marketed in the United States, great caution is required in finding the Swedish experience with snus instructive on other issues concerning the population-wide effects of Swedish snus in the U.S., particularly the marketing of Swedish snus as a modified risk product in the U.S.. See Comments of Campaign for Tobacco-Free Kids and Tobacco Control Legal Consortium, Docket No. FDA-2014-N-1051, Modified Risk Tobacco Applications: Applications for 10 Products Submitted by Swedish Match North America, Inc. (November 25, 2014), at 23-33.

NNK in the Swedish snus may reduce the risk of oral cancer in US consumers who use low NNN and NNK-containing snus product as compared to other ST products.”²⁸ (emphasis in original) The data FDA relied on in granting these marketing orders is equally supportive of the proposed product standard.

V. Limits in NNN levels in smokeless tobacco are achievable.

Drs. Hatsukami and Stepanov provided the scientific evidence to support a product standard on TSNA levels for smokeless tobacco and detailed specific ways in the manufacturing process that NNN levels could be lowered. They concluded, “Tobacco product manufacturers currently have the capability to reduce these constituents substantially using well established methods. For example, reducing nitrate content in the soil, using specific types of tobacco leaves, pasteurizing their products, requiring refrigeration of the product are all measures that can be taken to reduce levels of important toxicants and carcinogens.”²⁹

FDA’s proposed rule also detailed the ways that manufacturers and tobacco growers can minimize the risk of NNN formation, through the type of tobacco and fertilizer used, ways the tobacco leaves are cured, processed, and stored, as well as how the final tobacco products are processed and stored.³⁰

At least one manufacturer has successfully demonstrated the feasibility of limiting levels of NNN in smokeless tobacco. Swedish Match recently lowered the threshold for NNN and NNK in its smokeless tobacco products to 0.95 mg/kg,³¹ slightly lower than FDA’s proposed level of 1.0 µg/g. U.S. smokeless tobacco manufacturers have been touting Swedish snus as an example of the success of lower risk tobacco products³²: this is their chance to demonstrate that they can market products with levels of carcinogens comparable to Swedish snus.

FDA’s proposed rule recognizes that manufacturers and tobacco growers will need time to take the steps necessary to implement the rule. By delaying the effective date of the rule for three years, FDA has provided a reasonable interval for such action.

²⁸ TPL Review for PM 0000010-PM 0000017, at 19.

²⁹ Hatsukami, D & Stepanov, I, *Establishing product standards for smokeless tobacco*, February 2014, at 39-40.

³⁰ 82 Fed. Reg. at 8013-8014.

³¹ Swedish Match, “New limit values for GOTHIA TEK®,” Press Release, March 22, 2016, <https://www.swedishmatch.com/Media/Pressreleases-and-news/News/New-limit-values-for-GOTHIA TEK/>.

³² For example, in a filing with FDA in 2012, Altria cited a chart showing sharp reductions in tobacco-related disease for users of Swedish snus to argue that smokeless tobacco product warnings for U.S. products should be modified. [Altria Client Services Inc., *Docket No. FDA-2011-P-0573 – Comments on Citizen Petition filed by R.J. Reynolds Tobacco Company*, February 6, 2012, <http://www.altria.com/About-Altria/Federal-Regulation-of-Tobacco/Regulatory-Filing/FDAFilings/Altria-Comments-on-Citizen-Petition.pdf>.]

Respectfully submitted,

Action on Smoking & Health

American Academy of Family Physicians

American Academy of Oral & Maxillofacial
Pathology

American Academy of Otolaryngology-
Head and Neck Surgery

American Academy of Pediatrics

American Association for Respiratory Care

American Cancer Society Cancer Action
Network

American College of Cardiology

American Heart Association

American Lung Association

American Public Health Association

American School Health Association

American Society of Clinical Oncology

American Thoracic Society

Association of State and Territorial Health
Officials

Campaign for Tobacco-Free Kids

ClearWay Minnesota

Eta Sigma Gamma – National Health
Education Honorary

National Association of Pediatric Nurse
Practitioners

National Center for Health Research

Oncology Nursing Society

Society for Cardiovascular Angiography and
Interventions

Society for Public Health Education

Society for Research on Nicotine & Tobacco

Students Against Destructive Decisions

The Society of State Leaders of Health and
Physical Education

Tobacco Control Legal Consortium

Trust for America's Health

Truth Initiative