SRNT

Society for Research on Nicotine & Tobacco • 2424 American Lane • Madison, WI 53704-3102
Tel: 1-608-443-2462 • Fax: 1-608-443-2474 • E-Mail: info@srnt.org • Website: http://www.srnt.org

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments on Food and Drug Administration Docket No. FDA-2016-N-2527, Tobacco Product Standard for N-nitrosonornicotine Level in Finished Smokeless Tobacco Products

Ladies and Gentlemen:

The undersigned submit this comment in the above-designated docket.

The Society for Research on Nicotine & Tobacco ("SRNT") is an international professional association dedicated exclusively to the support of researchers, academics, treatment professionals, government employees, and the many others working across disciplines in the field of nicotine and tobacco research. With members in more than 40 countries, SRNT is truly global in its reach. As a scientific society, SRNT's mission is *to stimulate the generation and dissemination of new knowledge concerning nicotine in all its manifestations.* In support of its mission, SRNT presents an annual scientific conference, where researchers at every career stage present their latest findings, and publishes cutting edge research through our scientific journal, *Nicotine & Tobacco Research*, which is published by the Oxford University Press.

Professors Stephen S. Hecht[1], Dorothy Hatsukami[2], and Irina Stepanov[3], are recognized authorities on the effects of Tobacco-Specific Nitrosamines (TSNAs) in tobacco products and each has published peer-reviewed articles on the subject. In addition, they submitted studies to FDA in 2014 urging FDA to issue a product standard establishing a maximum level of NNN and NNK in tobacco products. Copies of their academic resumes are attached.

The FDA's explanation accompanying the proposed rule provides a comprehensive and compelling argument for the regulation of *N'*-nitrosonornicotine (NNN) in finished smokeless tobacco products, at a level of 1 microgram (µg) per gram tobacco (on a dry weight basis). It correctly notes that several highly respected national and international organizations including the International Agency for Research on Cancer, the U.S. National Cancer Institute, the Centers for Disease Control and Prevention, the U.S.

[1] Wallin Land Grant Professor of Cancer Prevention, Masonic Cancer Center, University of Minnesota.
[2] Forster Family Chair in Cancer Prevention, Masonic Cancer Center, University of Minnesota.
[3] Associate Professor, Division of Environmental Health Science, School of Public Health, University of Minnesota.

Surgeon General, and the Scientific Committee on Emerging and Newly Identified Health Risks all concluded that smokeless tobacco causes oral cavity cancer as well as other cancers including cancer of the esophagus and pancreas. Smokeless tobacco is banned in the European Union, with the exception of Swedish snus which apparently carries a lower risk for oral cancer, most likely due to its low levels of NNN and NNK. The document estimates that in the 20 years following implementation of the proposed standard, 12,700 new oral cancer cases and 2200 oral cancer deaths will be prevented. It notes that the Swedish snus standard of 0.95 µg/g wet weight of NNN + NNK is already in place, and that oral cancer in users of Swedish snus has not been observed. Further, the World Health Organization Study Group on tobacco Product Regulation recommended a regulatory limit for NNN and NNK (combined) of 2 µg/g dry weight of tobacco. Both of these regulatory limits are similar to the proposed FDA limit of 1 µg NNN per gram dry weight of tobacco. The report goes on to document the well-established and potent carcinogenicity of NNN and its well-defined mechanism of action as a genotoxic DNA damaging carcinogen, and correctly states that NNN is the only oral cavity carcinogen occurring in relatively high concentrations in smokeless tobacco products sold in the U.S. It also notes the similarity in rat target tissues for NNN carcinogenicity (oral cavity and esophagus) with the established elevated risks of oral and esophageal cancer in people who use smokeless tobacco products as well as geographical differences where risks for these cancers are higher in countries with high NNN levels in smokeless tobacco. It presents convincing data based on multiple analytical chemistry studies, carried out internationally, that virtually all smokeless tobacco products contain NNN, most often at levels substantially higher than those recommended. Furthermore, it describes epidemiologic studies that have clearly implicated NNN as a cause of esophageal cancer in humans. Collectively, these facts provide clear and undeniable evidence in support of the proposed standard.

We also note that NNN and NNK are considered "carcinogenic to humans" by the International Agency for Research on Cancer (*1*). There is no doubt about the strong carcinogenicity of NNN. It has been tested in multiple species using various different routes of administration and by multiple different laboratories. NNN causes highly significant incidences of tumors at various sites in rats (oral cavity, esophagus, nasal mucosa), hamsters (trachea), mice (lung), and mink (nasal mucosa) (*2*). Of particular relevance to smokeless tobacco use, (*S*)-NNN, the major form in smokeless tobacco, at 14 ppm in the drinking water, caused oral cavity and esophageal tumors in 100% of the tested rats. In the racemic NNN group (28 ppm), a total of 96 oral cavity tumors and 153 esophageal tumors were observed in the 12 rats subjected to necropsy (*3*).

It is remarkable that the amounts of the strong carcinogen NNN in popular smokeless tobacco products sold in the U.S. have for decades remained far higher than those of carcinogenic nitrosamines in any other consumer product designed for oral consumption.

Following the demonstration of the strong carcinogenicity of dimethylnitrosamine by Magee and Barnes in 1956, extensive studies around the world demonstrated the carcinogenicity of approximately 200 structurally varied nitrosamines, which induced tumors at virtually every conceivable site in at least 30 different species (*4*). There is no doubt: virtually all nitrosamines are powerful genotoxic carcinogens, and NNN, a typical nitrosamine that is also a tobacco-specific nitrosamine derived from the tobacco alkaloids nicotine and nornicotine, is no exception. Nitrosamines including NNN cause cancer by mutating critical growth control genes.

The extensive carcinogenicity studies showing that nitrosamines were powerful carcinogens led to concern regarding their occurrence in human food, and beginning in the 1970s, FDA held regular meetings on this subject. Eventually, levels of nitrosamines in processed foods cured with nitrite (bacon, hot dogs, etc) and in beer, decreased to their current amounts which are generally below 5-10 nanograms per gram (5 – 10 parts per billion)(*5*). As summarized in the FDA document, multiple studies including those by the tobacco industry, clearly demonstrate that the levels of NNN in popular smokeless tobacco products sold in the United States are typically in the range of 1 – 10 micrograms per gram dry weight of tobacco, or 1 – 10 parts per million, 100 – 1000 times higher than carcinogenic nitrosamines in any other product designed for oral consumption. There can be no reasonable rationale for permitting this vast difference. Until now, tobacco products have been excluded from basic considerations of safety that are rigorously applied to human food and drinks, with respect to toxicants and carcinogen exposure. The current suggested regulation will be the first attempt to protect the public from the carcinogenic risks of smokeless tobacco products, as has been done for decades with other common products placed in the mouth, although the suggested level of 1 microgram per gram dry weight of tobacco is still approximately 100 times greater than levels of carcinogenic nitrosamines such as *N*-nitrosodimethylamine and *N*-nitrosopyrrolidine present in food or beer.

As outlined by the FDA, tobacco companies have the technology to reduce NNN levels in smokeless tobacco. Evidence for this is the substantially reduced NNN levels in currently-marketed "spitless" smokeless tobacco products including Camel Snus and Marlboro Snus, among others (*6*). It has been known for more than three decades that the type of tobacco chosen; the agricultural, curing and storage processes used; and other manufacturing processes including pasteurization have a large effect on NNN levels (*1*). But these innovations have not been applied to the tobacco industry's most popular products. The FDA document correctly identifies many factors which can be modified to influence the level of NNN in smokeless tobacco products:

- Using a type of tobacco with lower concentrations of NNN
- Using tobacco grown with limited use of nitrogen-rich fertilizer
- Using tobacco processed with different curing methods
- Modification of currently used curing methods
- Using tobacco that had a bacteriostatic, bactericidal, or heated solution applied to leaves during growing, harvesting or curing processes
- Using a non-nitrate reducing bacteria starter culture for fermentation
- Using cleaned and sanitized equipment for processing and manufacturing
- Adding humectants, sodium chloride, or other additives to lower water activity and reduce microbial growth
- Adding bicarbonate and carbonate salt solutions to control pH
- Pasteurization or heat treatment
- Storing products at lower temperature and humidity
- Limiting storage duration

Application of processing modifications such as these, which have been known for many years, is certainly feasible and will produce safer products with considerably lower levels of NNN. Thus, the industry continues to market highly defective smokeless tobacco products which put their addicted

customers at risk for oral cancer. It is hard to justify allowing these products to have higher levels of the powerful carcinogen NNN than are readily achievable with good manufacturing processes.

There are some other carcinogenic compounds in smokeless tobacco: low amounts of some polycyclic aromatic hydrocarbons, some aldehydes such as formaldehyde and acetaldehyde, some other nitrosamines (including NNK), and various metals (*1*) . Future product standards could potentially include some of these other carcinogens, but it is notable that none of these compounds induces oral tumors in laboratory animals. It is also worth noting that the induction of oral cavity tumors in rats, as observed upon NNN treatment, is relatively difficult and rare: In the National Toxicology Program, which tests compounds in F-344 rats at the maximum tolerated dose, only 26 of 574 tested compounds (4.6%) caused oral cavity tumors (*7*).

In summary:

- Smokeless tobacco use is a cause of oral cancer in its users.
- NNN is the most prevalent oral cavity carcinogen present in smokeless tobacco.
- Levels of NNN exposure in smokeless tobacco users are hundreds to thousands times higher than exposure to carcinogenic nitrosamines in food and drink products.
- Reduction of NNN levels in smokeless tobacco products is practical and feasible.
- Smokeless tobacco products with lower levels of NNN will be safer with respect to oral cavity cancer risk.
- More than 40 years have passed since the high levels of NNN in smokeless tobacco were discovered. It is time for action to decrease the risks associated with a highly defective product.

Sincerely,

Dorothy K. Hatsukami, Ph.D.
Forster Family Professor in Cancer Prevention
Professor of Psychiatry
Associate, Director Masonic Cancer Center
University of Minnesota

Stephen S. Hecht, Ph.D.
Wallin Professor of Cancer Prevention
American Cancer Society Professor
American Chemical Society Fellow
Masonic Cancer Center
University of Minnesota

Judith J. Prochaska, PhD, MPH
President, Society for Research on Nicotine & Tobacco
Associate Professor of Medicine, Stanford University

Irina Stepanov, Ph.D.
Associate Professor
Division of Environmental Health Sciences
Masonic Cancer Center

Reference List

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