FDA's Proposed N-nitrosonornicotine (NNN) Standard: Epidemiological Evidence

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Abstract

The US Food and Drug Administration (FDA) has advanced a proposed product standard of 1µg/g dry weight N-nitrosonornicotine (NNN) content in finished smokeless tobacco (ST) products, citing selected findings from epidemiology to support the proposed limit. The purpose of this work was to evaluate FDA's application of epidemiological literature. An independent review was undertaken, and identified a number of inaccuracies. First, FDA combines oral cancer relative risk (RR) estimates for men and women, which is inappropriate given the RR between the sexes is widely different. Furthermore, men are the predominant users of ST. Second, FDA relied upon Swedish epidemiology to indicate current (low) levels of NNN in modern Swedish ST products are not associated with increased risk of oral cancer; however, NNN levels in Swedish ST in use during the time of the epidemiology studies were higher than levels in current products. Third, FDA relied on studies of international ST products (e.g., Asia and Africa), yet the composition and production practices associated with ST products unique to Asia and Africa differ markedly from those of US products, and are not applicable to US ST products and users. Fourth, NNN concentrations in products used by study participants in the available epidemiology studies cannot be estimated precisely, and there is substantial heterogeneity in the concentration of NNN and other toxicants across and within ST product types. Finally, FDA's conclusion that NNN is the predominant driver of excess oral cancer risk among ST users is inconsistent with existing scientific data, as urinary levels of NNN are generally higher among ST users compared with smokers, yet smokers incur a substantially higher risk for oral cancer than ST users. Thus, considered objectively, the available epidemiology data do not support the proposed NNN standard.

Introduction

The Tobacco Control Act allows FDA to establish a tobacco product standard if such a standard is appropriate for the protection of the public health, taking into consideration the scientific evidence. Here, a review of the epidemiological data demonstrates FDA has misinterpreted the evidence, and it is thus unclear that the proposed NNN standard is in fact appropriate for the protection of public health. FDA asserts that the proposed standard will prevent approximately 12,700 new cases of oral cancer and approximately 2,200 oral cancer deaths over the next 20 years. FDA's assertion, however, rests on a series of improper analyses and interpretations of epidemiological data.

Methods

- A comprehensive review of literature relied upon by FDA in the proposed standard was conducted to assess the validity and appropriateness of studies to inform the proposed rule with regard to timeframe, location, methodology, and outcomes.
- An independent comprehensive, critical review of additional pertinent epidemiological evidence was undertaken.

Results

FDA overstates the evidence pertinent to oral cancer risk among US ST users, as follows:

- When estimating RR, data were combined for men and women (RR=2.16), overstating risk.
- Ignored the fact that men have lower oral cancer risks than women (RR=~1 vs. ~6, respectively; Rodu & Cole 2002);
- Ignored the fact that men are much more likely than women to use ST.

Results (Continued)

- When estimating RR, FDA relied upon studies that failed to control for positive confounding of ST use and oral cancer risk by cigarette smoking and alcohol consumption, the primary drivers of oral cancer risk.
- Relied on studies of ST users in Africa and Asia that are not relevant for estimating cancer risks among US ST or Scandinavian ST users, due to substantial differences in product composition, ingredients, and production practices.

The circumstantial evidence suggesting an association between NNN and oral cancer risk is weak:

- Data from epidemiological studies demonstrate that Swedish snus users do not show meaningful increases in oral cancer risk (data not shown) even though NNN levels in products used by participants on-study (i.e., historic levels) were higher than current snus product NNN levels (Table 1).
- Urinary NNN is higher among ST users compared to smokers (Stepanov & Hecht, 2005), yet oral cancer is risk is higher among smokers than ST users (Henley et al. 2005; Thun et al. 2000).
- US moist snuff and chewing tobacco products, containing a wide range of NNN levels, present similarly low oropharyngeal cancer risks. Five US studies of oropharyngeal cancer reporting risk estimates separately for chew, snuff, and non-specified ST within the same population cohort, showed two studies with higher risks attributed to moist snuff and three studies with higher risks attributed to chewing tobacco (Figure 1).

Table 1. NNN Levels in Swedish Smokeless Tobacco Over Time

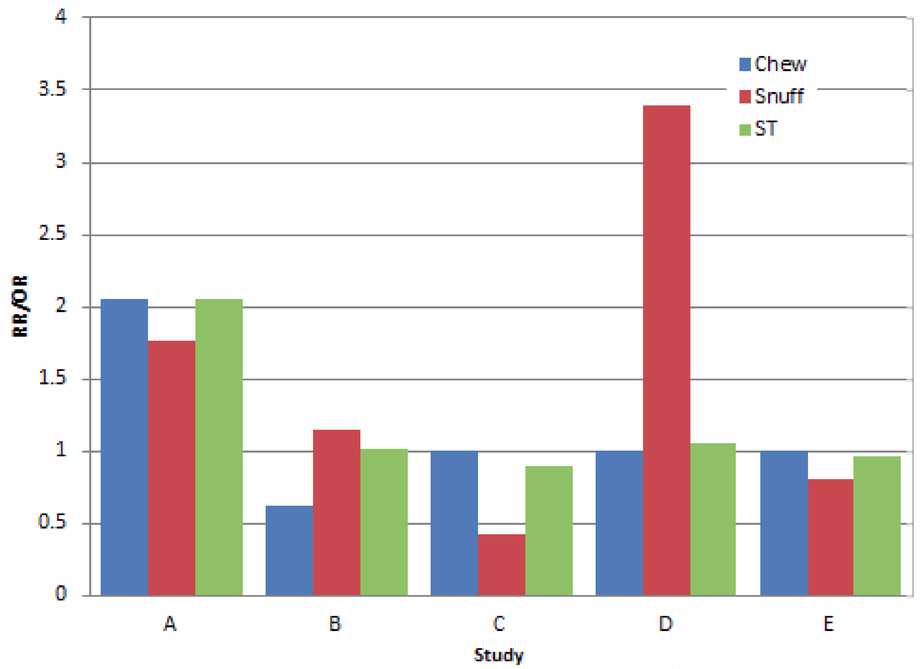
Date	NNN Levels (µg/g dry weight)	Source
1980	3.53-77.1	Hoffmann & Adams 1981, Djordjevic et al. 1993
1982	4.00-6.10	Djordjevic et al. 1993
1984-1985	3.05-4.14	Brunnemann et al. 1985
1984-1993	5.0->10.0	Rutqvist et al. 2011
1989-1990	5.24-5.67	Hoffmann et al. 1991, Djordjevic et al. 1993
1994-2000	2.0-5.0	Rutqvist et al. 2011

Table 2. NNN Levels in US Smokeless Tobacco Over Time

Date	NNN Levels (µg/g dry weight)		Source
	Chew	Snuff	
1980	--	3.5-39	Hoffmann & Adams 1981, Djordjevic et al. 1993
1981	--	19.0-33.0	Djordjevic et al. 1993
1984	--	0.8-89.0	Hoffmann et al. 1984
1984-1985	0.67-28.0	5.8-64.0	Hoffmann et al. 1986, Brunnemann et al. 1985
1984-1987	--	1.34-64.0	Hoffmann et al. 1988
1985	0.65-6.5	2.2-17.75	Chamberlain et al. 1988
1986	--	5.8-123.1	Brunnemann et al. 1987, Hoffmann et al. 1986, Djordjevic et al. 1993
1987-1988	--	1.5-81.3	Djordjevic et al. 1989
1988	--	8.5-13.8	Djordjevic et al. 1993
1989-1990	--	4.14-57.1	Hoffmann et al. 1991
1990	--	9.6-10.4	Djordjevic et al. 1993
1992	--	5.7-6.4	Djordjevic et al. 1993
1994	--	3.04-17.2	Hoffmann et al. 1995
2000	--	3.1-15.4	Brunneman & Hoffmann 2002
2006-2007	0.66-5.05	0.67-14.4	Borgerding et al. 2012

Results (Continued)

Figure 1. Comparative risks of oropharyngeal cancer from chewing tobacco, snuff, and non-specified smokeless tobacco



This figure compares relative risks/odds ratios as reported by Lee & Hamling 2009. Study "A" is Broders 1920, "B" is Wynder & Stellman 1977, "C" is Wynder et al. 1983, "D" is Spitz et al. 1988 and "E" is Mashberg et al. 1993. See Table 2 for NNN ranges by US ST product type.

Conclusions

- The relative risk estimate used by FDA in the proposed NNN standard is overstated.
- Swedish epidemiology studies do not support the proposed NNN standard (Table 1).
- The epidemiological evidence does not support NNN as a driver of oral cancer risk (Figure 1).
- In total, the available epidemiological data do not support the proposed standard.

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