PROPOSED NNN STANDARD: QUANTITATIVE RISK ASSESSMENT

Kristin Marano[1], Robinan Gentry[2], and Charlene Liu[1]
[1]RAI Services Company, Winston-Salem, North Carolina; [2]Ramboll Environ, Monroe, Louisiana

Abstract

The US Food and Drug Administration (FDA) has published a proposed product standard for N-nitrosonornicotine (NNN) content in finished smokeless tobacco products. The proposed NNN limit was derived based on a target excess lifetime cancer risk (ELCR). A review of the quantitative risk assessment (QRA) conducted by FDA was undertaken. Results of the review indicated deficiencies in the QRA. First, the methods used to estimate the NNN cancer slope factor are inconsistent with derivation methods preferred by the US Environmental Protection Agency (EPA) and methods supported previously by FDA. In addition, several key input assumptions are inconsistent with the most current EPA recommendations in risk assessment practice, i.e., body weight and lifespan, and the data evaluated by FDA for input assumptions was incomplete, i.e., absorption factor. Further, the estimated ELCR in the proposed rule conveys an unrealistic level of precision, inconsistent with EPA recommendations. Finally, the ELCR is not directly applicable to oral cancer risk. It is not clear that an ELCR calculation is relevant for the establishment of an NNN limit – ELCR is inadequate as a measure of excess cancer deaths in the population, as it does not account for competing mortality. However, if the ELCR is calculated in accordance with current EPA risk assessment guidance, an NNN level in the range of 9-13 ppm dry weight is identified. This range is consistent with or lower than historical NNN levels in the smokeless tobacco products used by Swedish participants in epidemiology studies demonstrating no meaningful increase in cancer risk. Based on an assessment of the available data, there is no evidence to demonstrate the proposed NNN limit in smokeless tobacco products would be protective of public health.

Introduction

The US Food and Drug Administration (FDA) proposed a product standard of 1 microgram per gram (µg/g) dry weight for N-nitrosonornicotine (NNN) content in finished smokeless tobacco products. The proposed product standard was based on a target excess lifetime cancer risk (ELCR). This analysis reviews the quantitative risk assessment (QRA) conducted by FDA to derive the product standard.

The following aspects of FDA's QRA were reviewed:

- NNN Oral Cancer Slope Factor
- Exposure assumptions
- Consistency with current risk assessment guidance and practice
- Applicability

References

Caraway JW and Chen PX. 2013. Assessment of mouth-level exposure to tobacco constituents in US snus consumers. Nicotine & Tobacco Research, 15(3):670-7.
Ebbert JO, Dale LC, Nirelli LM, Schroeder DR, Moyer TP, Hurt RD. 2004. Cotinine as a biomarker of systemic nicotine exposure in spit tobacco users. Addictive Behaviors, 29(2), 349-355.
EPA. 1989. Risk Assessment Guidance for Superfund: Human Health Evaluation Manual, Part A.
EPA. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. March.
EPA. 2011. Exposure Factor Handbook, 2011 Edition.
EPA. 2014. OSWER Directive 9200.1-120. Memorandum, Human Health Evaluation Manual, Supplemental Guidance, Update of Standard Default Exposure Factors.
FDA. 2017. Tobacco product standard for N-nitrosonornicotine level in finished smokeless tobacco. Proposed rule. Docket No. FDA-2016-N-2527. Federal Register / Vol. 82, No. 13. January 23, 2017.
OEHHA. 1992. Expedited cancer potency values and proposed regulatory levels for certain proposition 65 carcinogens. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

FDA's Use of the NNN Slope Factor

- The estimate of the cancer slope factor is based on incidence of respiratory system papillomas, and FDA cites no evidence that the cancer slope factor is predictive of human oral cancer risk.
- The methods to estimate the cancer slope factor for NNN are inconsistent with the state of the science and current regulatory standards.
  - Improper animal to human extrapolation.
- Only one dose concentration was used to estimate the cancer slope factor.

Review of Exposure Assumptions

Exposure assumptions used by FDA are inconsistent with EPA recommendations or the literature (Table 1).

Table 1. FDA's Exposure Assumptions vs. EPA Recommended Values

Exposure Assumptions	FDA Used	EPA or Literature
Adult Body Weight	70 kg	80 kg (EPA 2014)
Lifespan	78 years	70 years (EPA 2014)
Exposure Duration	60 years	51 years (EPA 2014 and FDA 2017)
NNN Extraction Rate	60% (NNK)	30 – 40% (NNN, Caraway and Chen 2013)
NNN Expectoration Rate	None	50% (Ebbert et al. 2004)
NNN Absorption Rate	60%	15 – 20% (Extraction Rate × Expectoration Rate)

In the ELCR calculation, FDA should incorporate parameters that are consistent with the most recent risk-assessment guidance and relevant peer-reviewed literature findings in order to increase applicability and to reduce variability and uncertainty.

Other Inconsistencies

- Inconsistency and lack of transparency in the estimation of NNN concentrations in US smokeless tobacco products.
- The ELCR calculation (FDA 2017) should be clarified:
  - A conversion factor of 1 milligram = 1000 microgram (1 mg = 1000 µg) should be included in the equation.
  - The units for the Cancer Slope Factor should be replaced with $(mg/kg\text{-}day)^{-1}$
- FDA's calculated ELCR conveys an unrealistic level of precision and should be modified to be consistent with current risk-assessment recommendations and practice.

If FDA's ELCR is re-calculated in accordance with current risk assessment recommendations, an NNN limit in the range of 8.6 to 13.4 µg/g dry weight would be more appropriate (Tables 2 and 3).

The following equation is used, consistent with FDA's proposed rule.

$$C\left(\frac{\mu g}{g} wet\ weight\right) = \frac{ELCR \times BW \times AT}{CF \times TC \times AB \times EF \times ED \times CSF}$$

where

$$C\left(\frac{\mu g}{g} dry\ weight\right) = \frac{C\left(\frac{\mu g}{g} wet\ weight\right)}{1 - MC}$$

Table 2. Input Parameters for ELCR Calculation

Parameter	Abbreviation	Units	Value	Source
NNN Level	C	µg/g dry weight	to be determined	--
Excess Lifetime Cancer Risk	ELCR	unitless	1×10^{-4}	"All cancer risks should be expressed as one significant figure only" (EPA 1989).
Body Weight	BW	kg	80	EPA 2011 and 2014.
Averaging Time	AT	days	25550	EPA 1989 and 2014.
Conversion Factor	CF	mg/µg	0.001	--
Absorption Factor	AB	percent	20	Based on a conservative extraction rate of 40% (Caraway and Chen 2013), an expectoration rate of 50% (Ebbert et al. 2004), and an absorption rate of 100%.
Exposure Frequency	EF	days/year	365	Maximum value.
Exposure Duration	ED	years	51	Based on an average life span of 70 years (EPA 2014) and tobacco use initiation at or near 19 years of age (FDA 2017).
Tobacco Consumption	TC	g/day	12	FDA 2017.
Oral Cancer Slope Factor	CSF	$(mg/kg\text{-}day)^{-1}$	0.83	Cal EPA CSF (OEHHA 1992) adjusted to be consistent with methods supported by EPA (2005) and FDA.
Moisture Content	MC	percent	40	FDA 2017.

Table 3. ELCR and NNN Levels

ELCR (n in 10,000)	ELCR (n in 10,000) (EPA 1989)	NNN Level (µg/g wet weight)	**NNN Level (µg/g dry weight)**
0.95×10^{-4}	1×10^{-4}	5.14	**8.6**
1.49×10^{-4}	1×10^{-4}	8.06	**13.4**

Conclusions

- FDA's proposed product standard for NNN is calculated in a manner that is inconsistent with current risk assessment recommendations and practices.
- Appropriately conducted QRA does not support an NNN limit of 1 µg/g in smokeless tobacco products.