Derivation of Excess Lifetime Cancer Risk via the Oral Route of Exposure

Casandra West, Ph.D.
Reynolds American Services Company, Winston-Salem, NC, USA

Abstract

In 2024, the United States Food and Drug Administration (FDA) published two toxicology memos focusing on the calculation of Excess Lifetime Cancer Risk (ELCR) for ENDS products as part of Premarket Tobacco Application (PMTA) evaluation. ELCR estimates the likelihood of cancer development over a lifetime of exposure to one or more substances (cumulative ELCR). Globally, there are over 300 million users of oral tobacco products such as snus, moist snuff, and nicotine pouches. Unlike combustible and vapor products, smokeless tobacco products are generally placed in the mouth in direct and prolonged contact with the oral mucosa, resulting in a different absorption route for nicotine and harmful and potentially harmful constituents (HPHCs) – oral versus inhalation.

As FDA's memos do not address risk assessments for oral tobacco products, this work presents an approach to calculating ELCR for smokeless tobacco products via the oral route of exposure, utilizing cancer slope factors and average human body weight in lieu of inhalation unit risk factors and inhalation rates. Reference data from CORESTA Smokeless Tobacco Reference Products, along with usage assumptions under "average" and "heavy" consumption scenarios, demonstrate the feasibility and practical application of this method.

Introduction

These 2 memoranda[1,2] appear to have signaled a shift in the FDA PMTA review process from a mixture-based *in vitro* approach to a focus on single chemical substances. The memoranda[1,2] outline the FDA's method for constituent tiering and the calculation of adjusted inhalation unit risk (IUR) factors for estimating ELCR of ENDS products. In addition, FDA states in the ELCR memorandum that "reviewers should keep in mind that ENDS also have non-cancer hazards . . . which will be the subject of a future memorandum". It is thought that FDA is referring to the calculation of the non-cancer hazard quotients (HQ) for individual constituents and the non-cancer hazard index (HI) which is the sum of HQs.

As there are a variety of oral nicotine products on the market, the focus herein is on a method for calculating both non-cancer hazards (HQ/HI) and ECLR for oral tobacco products based on FDA's equations for adjusted toxicity factors and utilizing CORESTA reference product data (CRP1.1 and CRP2.1)[3] for demonstration purposes.

Briefly, the 2 FDA memoranda take the following approach to calculating ELCR for each HPHC which are then summed to give the cumulative ELCR (ELCRc). FDA's method for calculating an adjusted inhalation unit risk (μg/day) is described in the equation below:

$$Adjusted\ IUR\ \left(\frac{ug}{day}\right) = \frac{AT * Target\ Risk}{IUR * ET * EF * ED} * Daily\ Inhalation\ Rate$$

Where;

AT = Averaging Time (EL*365 days/year * 24 hours/day)
EL = Lifetime over which exposure occurs (70 years)
Target Risk = 1E-05 (1 in 100,000 ELCR)
IUR = Inhalation Unit Risk (μg/m^3)$^{-1}$
ET = Exposure Time (24 hours/day)
EF = Exposure Frequency (365 days/year)
ED = Exposure Duration (52 years)
Daily inhalation rate = 20m^3/day

To then calculate the ELCR, daily exposure is divided by the potency value (adjusted IUR).

$$ELCR = \frac{Daily\ Exposure}{Potentcy\ Value}$$

Where;

Daily Exposure = Daily exposure to HPHC (μg/day) under heavy use scenario
Potency Value = Adjusted IUR in μg/day

Methodology

FDA's equation can be modified from the inhalation route of exposure to the oral route of exposure by substituting the IURs for oral cancer slope factors (CSF) and the daily inhalation rate for the average human body weight:

$$Adjusted\ CSF\ \left(\frac{mg}{day}\right) = \frac{AT * Target\ Risk}{CSF * ET * EF * ED} * Body\ Weight$$

The daily exposure can then be divided by the potency value (adjusted CSF) to calculate the ELCR for each HPHC under evaluation.

$$ELCR = \frac{Daily\ Exposure}{Potentcy\ Value}$$

To estimate non-cancer hazards, the chronic daily intake (CDI) for the oral route of exposure can be calculated by using the following equation.

$$CDI = \frac{(C * CF * TC * EF * ED)}{BW * AT}$$

Where;
CDI = Chronic Daily Intake (mg/kg-day)
C = Concentration of given constituent (ng/g)
CF = Conversion Factor 10^{-6} mg/ng
TC = Tobacco Consumption Rate (average use: 12 g/day; heavy use: 25.4 mg/day)
EF = Exposure Frequency (365 days/year)
ED = Exposure Duration (52 years)
BW = Body Weight (80 kg)
AT = Averaging Time (52 years * 365 days/year)

With the CDI, HQ for each HPHC can be calculated with the Reference Dose (RfD). The individual HQ's are then summed to give the HI.

$$HQ = \frac{CDI}{RfD}$$

Where;

HQ = Hazard Quotient (unitless)
RfD = Reference Dose (mg/kg-day)

For demonstration purposes data from CRP1.1 and CRP 1.2 (Table 1) was included in the analysis for the constituents included in FDA's HPHC abbreviated list for smokeless tobacco products[4].

Conclusion

The two toxicology memoranda released by FDA in 2024[1,2] describe a method for toxicity factor tiering and calculation of ELCR for ENDS products in the evaluation of PMTAs via the inhalation route of exposure. Here a method for calculating ELCR for estimation of cancer risk, and HQ/HI for estimation of noncancer hazard of tobacco products intended for use by the oral route of exposure is presented with a demonstration utilizing CRP1.1 (Swedish style snus) and CRP2.1 (American style loose moist snuff) CORESTA reference product data, which could be applied to PMTA evaluations.

References

1. FDA. (2024a). Genotoxicity hazard identification and carcinogenicity tiering of constituents in ENDS premarket tobacco product applications [Memorandum]. Retrieved from https://www.fda.gov/media/180609/download

2. FDA. (2024b). Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications [Memorandum]. Retrieved from https://www.fda.gov/media/180610/download?attachment

3. Jablonski J., Cheetham A, and Martin A. Market survey of modern oral nicotine products: determination of select HPHCs and comparison to traditional smokeless tobacco products. Separations. 2022. https://doi.org/10.3390/separations9030065

4. FDA, Abbreviated List of Harmful and Potentially Harmful Constituents. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-under

5. EPA RAGS Part A, page 8-7 (Exhibit 8-2 footnote b) states that "All cancer risks should be expressed as one significant figure only." (EPA 1989).

6. EPA RAGS Part A, page 8-9 (Exhibit 8-4 footnote a) states that "All hazard indices and hazard quotients should be expressed as one significant figure only." (EPA 1989).

Results

To demonstrate the feasibility of this approach data from CRP1.1 and CRP2.1, CORESTA smokeless tobacco reference products characteristic of Swedish snus and American-style loose moist snuff, respectively were used. Data from each analyte on the HPHC short list (Table 1) taken from Jablonski, et. al. supplementary file for were used to calculate the ELCRc and HQ for each product. Overall, CRP1.1 and CRP2.1 both present a significantly lower estimated cancer risk compared to that of the combustible reference product 1R6F, for which FDA estimates the ELCRc to be 10,000 in a population 100,000.[3] Regarding non-cancer hazards, the hazard indices for both CRP1.1 and CRP2.1 were also below the regulatory level of unity (1), indicating that exposure to the constituents evaluated over the period of a lifetime is unlikely to result in the occurrence of deleterious non-cancer effects.

Table 1. HPHC Data

Constituent	CRP1.1	CRP2.1
Acetaldehyde (ng/g)	5460	3430
Arsenic (ng/g)	49.6	71.4
Benzo[a]pyrene (ng/g)*	0	151
Cadmium (ng/g)	233	735
Crotonaldehyde (ng/g)*	0	0
Formaldehyde (ng/g)	776	3640
NNK (ng/g)	40.2	2104
NNN (ng/g)	177	3380

*Benzo[a]pyrene was below the limit of detection (LOD) in CRP1.1 and crotonaldehyde was below the LOD in CRP1.1 & CRP1.2, as such values of '0' were imputed.

Table 2. Excess Lifetime Cancer Risk

Constituent	CRP1.1 (average use)	CRP2.1 (average use)	CRP1.1 (heavy use)	CRP2.1 (heavy use)
Acetaldehyde	8	5	20	10
Arsenic	20	30	40	50
Benzo[a]pyrene	NA	2	NA	4
Cadmium	30	80	50	200
Crotonaldehyde	NA	NA	NA	NA
Formaldehyde	0.2	1	0.4	2
NNK	20	1000	50	2000
NNN	3	50	6	100
Total ELCR	**80**	**1000**	**200**	**3000**

NA: Not applicable
ELCR is expressed as one significant figure for consistency with EPA guidance.[5]

Table 3. Non-Cancer Hazard Quotients and Indices

Constituent	CRP1.1 (average use)	CRP2.1 (average use)	CRP1.1 (heavy use)	CRP2.1 (heavy use)
Acetaldehyde	8E-03	5E-03	2E-02	1E-02
Arsenic	1E-01	2E-01	3E-01	4E-01
Benzo[a]pyrene	NA	8E-02	NA	2E-01
Cadmium	3E-02	1E-01	7E-02	2E-01
Crotonaldehyde	NA	NA	NA	NA
Formaldehyde	6E-04	3E-03	1E-03	6E-03
NNK*	NA	NA	NA	NA
NNN*	NA	NA	NA	NA
Hazard Index	**0.2**	**0.4**	**0.4**	**0.8**

NA: Not applicable
*: HQs were not evaluated for non-cancer hazards as there are not RfDs available for these constituents and they are not considered non-cancer toxicants by FDA.
Non-cancer hazards are expressed as one significant figure for consistency with EPA guidance.[6]

REYNOLDS
A BETTER TOMORROW

Contacts
Casandra West, westc2@rjrt.com

Point your phone's camera at the QR code to find our library of publications

Follow us:

www.ReynoldsScience.com
@RAI_News