PROBABILISTIC RISK ASSESSMENT TO COMPARE HEALTH RISKS OF ORAL TOBACCO PRODUCTS

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ABSTRACT

In the evaluation of substantial equivalence (SE) for tobacco products for submission to the US Food and Drug Administration (FDA), differences in harmful and potentially harmful constituents (HPHCs) may necessitate the determination of whether a new tobacco product raises different questions of public health. Quantitative risk assessment (QRA) is a useful tool for evaluating public health concerns, informing regulatory decisions, and developing approaches for risk-benefit analyses. Traditional health-risk QRA approaches typically begin by screening available data in a deterministic QRA intended to be protective of human health. This approach uses mathematical models to produce point estimates of risk (e.g., average or reasonable worst-case) from which risk estimates may then be compared for individual chemicals, chemical mixtures, consumer products, or remediation approaches. If questions about comparative risks remain, a probabilistic risk assessment (PRA) may be conducted. PRA utilizes tools to identify, characterize, and quantify the key input factors that impact risk estimates. As such, PRA provides information regarding uncertainties and variabilities, and ultimately informs the risk management decision-making process. PRA uses mathematical modeling approaches that rely on distributions of data as inputs, resulting in calculated probability distributions of the relationship between exposure and risk. This presentation will include an example of a PRA conducted on a smokeless tobacco product to estimate and compare noncancer and cancer health risks between two products. The PRA will focus on the 8 HPHCs required to be reported to FDA for smokeless tobacco products. The presentation will include a description of the data and methods available for conducting the PRA, the potential uncertainties/challenges with each step, and how variability in the toxicity and exposure parameters impact the comparative risk estimates.

HAZARD IDENTIFICATION & DOSE RESPONSE

In March 2012, the FDA published a draft guidance that listed 9 harmful and potentially harmful constituents (HPHCs) in smokeless tobacco that are to be reported to the FDA under section 904(a)(3) of the Federal Food, Drug and Cosmetic Act (FDA 2012). The HPHCs are considered to be carcinogens, respiratory toxicants, cardiovascular toxicants, and/or reproductive/developmental toxicants. Although nicotine is included in the list of 9 HPHCs, it was not evaluated in the PRA analysis because it is addressed separately by FDA.

Noncancer oral reference doses (RfDs) or oral reference values (ReVs) developed by the U.S. Environmental Protection Agency (EPA) or the Texas Commission on Environmental Quality (TCEQ), respectively, were used as the basis to calculate noncancer risk (Table 1). Cancer oral slope factors (CSFo) developed by EPA, California Environmental Protection Agency (CalEPA), or available from published studies were used as the basis to calculate cancer risk (Table 1).

Table 1 – HPHC Noncancer and Cancer Toxicity Values

HPHC	Noncancer RfD (mg/kg-day)	Source	Cancer CSF_O $(mg/kg\text{-}day)^{-1}$	Source
Acetaldehyde	1.0E-01	TCEQ	NA	NA
Arsenic	3.0E-04	EPA	1.5E+00	EPA
Benzo(a)pyrene	3.0E-04	EPA	1.0E+00	EPA
Cadmium	1.0E-03	EPA[a]	NA	NA
Crotonaldehyde[b]	1.0E-03	EPA PPRTV	1.9E+00	EPA HEAST[c]
Formaldehyde	2.0E-01	EPA	2.1E-02	CalEPA
NNK	NA	NA	1.8E+01	Naufal et al. 2009
NNN	NA	NA	8.3E-01[d]	CalEPA

[a] Based on RfD for cadmium in food
[b] Based on a Provisional Peer-Reviewed Toxicity Value (PPRTV)
[c] EPA Health Effects Summary Table (HEAST)
[d] The CalEPA oral cancer slope factor (CSF_O) that was derived from animals to humans using a surface area approach was adjusted by Rimkus based on body weight cross species scaling ($BW^{3/4}$) using EPA methodology for such extrapolations
NA = not applicable

The HPHC concentrations in two hypothetical smokeless tobacco products and the percent differences in the HPHCs were calculated as shown in Table 2. The HPHCs are higher in Product 1 than Product 2; therefore, a deterministic quantitative risk assessment (QRA) was conducted to compare cancer and noncancer risks of the two hypothetical products. A probabilistic risk assessment (PRA) was also conducted to incorporate the full range of model factors (e.g., tobacco consumption, exposure duration, and body weight) in addition to HPHC concentration ranges. This approach characterizes the relative risk between two products and identifies and quantifies those model factors that most directly relate to estimates of risk (e.g., sensitivity analysis).

Table 2 – Rank Order of Percent Differences in Mean HPHC Concentrations

HPHC	Mean Concentration (C) ng/g		% Difference
	Product 1	Product 2	
Acetaldehyde	4,494	3,481	25.4%
NNN	1,959	1,657	16.7%
NNK	558	482	14.6%
Benzo(a)pyrene	82	73	12.2%
Cadmium	638	565	12.2%
Formaldehyde	630	584	7.5%
Arsenic	118	112	5.5%
Crotonaldehyde	62	69	-11.5%

EXPOSURE ASSESSMENT

Exposure model factors selected to estimate chronic daily intake (CDI mg/kg-day) in the PRA are detailed in Table 3. Model parameters were based on published exposure and risk assessment guidance and represent reasonably expected ranges of population parameters and oral tobacco use behavior. The mean HPHC concentrations and exposure parameters were used in the deterministic QRA.

Table 3 – Exposure Factors

Factor	Definition	PRA Range (minimum, mean, maximum)	PRA Assumption Distribution	Reference
C	HPHC Concentration (nanogram per gram of smokeless tobacco, ng/g)	Variable	Normal	HPHC data (Table 2)
CF	Conversion factor: 10^{-6} milligram per nanogram (mg/ng)	NA	Discrete	Calculated
TC	Tobacco consumption rate (g/day)	(0.62, 15.2, 102)	BetaPERT	Hatsukami et al. 1988 NHANES 2003-2004
ED	Exposure Duration (years)	(1, 20, 61)	BetaPERT	CDC 2005
EF	Exposure Frequency (days/year)	365	Discrete	Conservative assumption of daily exposure
BW	Body Weight (kg)	(20, 80, 116)	BetaPERT	EPA 2011
AT	Averaging Time (days) ED Years x 365 days/year	(365, 7,300, 22,265)	BetaPERT	CDC 2005 EPA 2011

$$CDI = \frac{C \times CF \times TC \times EF \times ED}{BW \times AT}$$

RISK CHARACTERIZATION

The QRA and PRA were conducted to compare estimated relative noncancer and cancer health risks between two hypothetical smokeless tobacco products, not to determine absolute human health risk estimates. The individual and composite HPHC noncancer and cancer risks were calculated using the following equations.

Oracle "Crystal Ball" software (Release 11.1.2.3.500) was used to conduct the PRA based on the full range of reasonable values for each model variable (e.g., consumption rate, HPHC values, toxicity values). Noncancer and cancer risks were calculated using Monte Carlo simulations run with 100,000 iterations. Output noncancer and cancer risks were rendered as probability plots.

Noncancer Hazard Quotient (HQ) for Each HPHC:
Hazard Quotient, HQ = CDI ÷ RfD
Where,
HQ = Constituent Specific Noncancer Risk (unit less)
CDI = Constituent Specific Chronic Daily Intake (mg/kg-day)
RfD = Constituent specific Reference Dose (mg/kg-day)

Composite Noncancer Risk (Hazard Index, HI):
The composite noncancer risks were estimated for the two products by summing individual noncancer HQ estimates as per the National Research Council (NRC) and the EPA (NRC 2009; EPA 1989; EPA 2009). According to EPA, "When the evaluation involves multiple chemicals assessed via HQs, risk assessors typically first calculate the HQ for each substance, and then sum the individual HQ values" (EPA 2009).

$$HI = \sum_{n=i}^{i} HQ_1 + HQ_2 + \cdots + HQ_i$$

Excess Lifetime Cancer Risk (ELCR) for Each HPHC:
ELCR = CDI x CSFo
Where,
ELCR = Constituent Specific Excess Lifetime Cancer Risk (unit less)
CDI = Constituent Specific Chronic Daily Intake (mg/kg-day)
CSFo = Constituent Specific Oral Cancer Slope Factor $(mg/kg\text{-}day)^{-1}$

Composite ELCR:
The composite ELCR values were estimated for the two products by summing individual cancer risk estimates as per the NRC and EPA. According to EPA, "When evaluating predicted cancer risks from multiple contaminants, risk assessors should estimate the cancer risk for each substance and then sum these risks. This yields an estimate of total cancer risk, which represents the cumulative predicted cancer risk for the chemicals at a site" (EPA 2009).

$$ELCR = \sum_{n=i}^{i} ELCR1 + ELCR2 + \ + ELCRi$$

Deterministic QRA Results
Table 4 presents the results of the QRA analysis of individual and composite HPHC noncancer risks and ELCRs. QRA data showed a 10% difference in composite HI (noncancer risk) and a 16% difference in composite ELCR (cancer risk).

Table 4 – DQRA Noncancer and Cancer Risk Estimates

HPHC	Mean HPHC Concentration (C) ng/g		Chronic Daily Intake (CDI) mg/kg-day		Hazard Quotient (HQ)		Excess Lifetime Cancer Risk (ELCR)	
	Product 1	Product 2	Product 1	Product 2	Product 1	Product 2	Product 1	Product 2
Acetaldehyde	4,494	3,481	6.7E-04	5.2E-04	6.7E-03	5.2E-03	--	--
Arsenic	118	112	1.8E-05	1.7E-05	5.9E-02	5.6E-02	2.7E-05	2.5E-05
Benzo(a)pyrene	82	73	1.2E-05	1.1E-05	4.1E-02	3.6E-02	1.2E-05	1.1E-05
Cadmium	638	565	9.6E-05	8.5E-05	9.6E-02	8.5E-02	--	--
Crotonaldehyde	62	69	9.3E-06	1.0E-05	9.3E-03	1.0E-02	1.8E-05	2.0E-05
Formaldehyde	630	584	9.4E-05	8.8E-05	4.7E-04	4.4E-04	2.0E-06	1.8E-06
NNK	558	482	8.4E-05	7.2E-05	--	--	1.5E-03	1.3E-03
NNN	1,959	1,657	2.9E-04	2.5E-04	--	--	2.4E-04	2.1E-04
					Composite HI		Composite ELCR	
				Difference	2.1E-01	1.9E-01	1.8E-03	1.6E-03
					10%		16%	

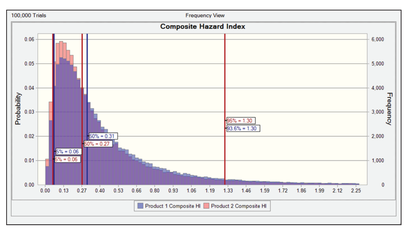
PRA Risk Characterization Results
Table 5 presents the results of the PRA analysis of individual and composite HPHC noncancer risks and ELCRs. Comparisons of the 50th percentile risk for Product 1 to the 5th and 95th percentile risk for Product 2 indicates that with a 90% degree of certainty individual and composite noncancer and cancer risks are equivalent.

Table 5 – PRA Noncancer and Cancer Risk Estimates

HPHC	Product 1 HQ Range		Product 2 HQ Range		Product 1 ELCR Range		Product 2 ELCR Range	
	5%	95%	5%	95%	5%	95%	5%	95%
Acetaldehyde	1.8E-03	4.8E-02	1.3E-03	3.6E-02	--	--	--	--
Arsenic	1.6E-02	4.2E-01	1.4E-02	3.8E-01	6.6E-06	1.8E-04	5.9E-06	1.6E-04
Benzo(a)pyrene	1.1E-02	2.9E-01	9.6E-03	2.6E-01	3.0E-06	8.1E-05	2.7E-06	7.1E-05
Cadmium	2.6E-02	6.8E-01	2.2E-02	5.9E-01	--	--	--	--
Crotonaldehyde	2.4E-03	6.7E-02	2.5E-03	6.8E-02	4.2E-06	1.2E-04	4.3E-06	1.2E-04
Formaldehyde	1.3E-04	3.4E-03	1.1E-04	2.9E-03	4.9E-07	1.3E-05	4.2E-07	1.1E-05
NNK	--	--	--	--	3.7E-04	9.9E-03	3.2E-04	8.4E-03
NNN	--	--	--	--	6.0E-05	1.6E-03	5.0E-05	1.3E-03
	Composite HI		Composite HI		Composite ELCR		Composite ELCR	
	6.4E-02	1.5E+00	5.6E-02	1.3E+00	4.8E-04	1.2E-02	4.0E-04	1.0E-02
% Difference	3.1%	3.1%			4.1%	4.2%		

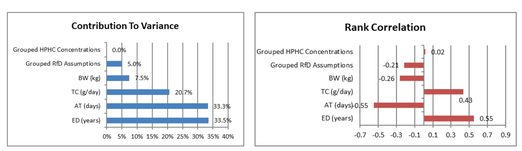
PRA Composite HI
Probability distribution of composite noncancer HI in Figure 1 suggests that at the 95th percentile, Product 1 noncancer risk differs from Product 2 noncancer risk by 1.4 percentiles.

Figure 1 – Probability Distribution of the Composite HI for Products 1 and 2



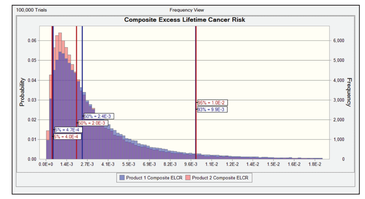
PRA Composite HI Sensitivity Analysis
As shown in Figure 2, sensitivity analysis of Product 1 demonstrates that HPHC concentration is weakly correlated with the composite HI (i.e., rank correlation 0.02). The most significant correlates with noncancer risk are years of exposure (0.5), tobacco consumption (0.4), and grouped RfD assumptions (0.3). The variance in grouped HPHC concentrations are small (<0.1%) compared to duration of tobacco usage (33%), daily tobacco consumption (21%), body weight (8%), and grouped RfD assumptions (5%).

Figure 2 – Sensitivity Analysis of the Composite HI for Product 1



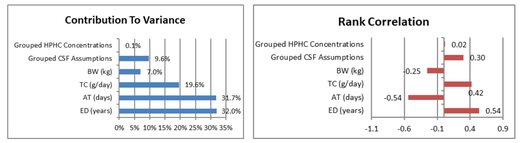
PRA Composite ELCR
Probability distribution of ELCR depicted in Figure 3 suggests that at the 95th percentile, Product 1 ELCR differs from Product 2 ELCR by 2 percentiles.

Figure 3 – Probability Distribution of the Composite ELCR for Products 1 and 2



PRA Composite ELCR Sensitivity Analysis
As shown in Figure 4, sensitivity analysis of Product 1 demonstrates that grouped HPHC concentrations are weakly correlated with composite ELCR (i.e., rank correlation 0.02). The most significant correlates with ELCR are years of exposure (0.5), tobacco consumption (0.4), and grouped CSF assumptions (0.3). The variance in grouped HPHC concentrations of Product 1 are small (<0.1%) compared to duration of tobacco usage (32%), daily tobacco consumption (20%), body weight (7%), and grouped CSF assumptions (10%).

Figure 4 – Sensitivity Analysis of the Composite ELCR for Product 1



CONCLUSIONS

- QRA analysis suggests a 10% difference in composite HI (noncancer risk) and 16% difference in composite ELCR (cancer risk).
- PRA demonstrated that at the upper tail of the probability distributions (i.e., 95th percentile) of composite noncancer and cancer risks of Product 1 and Product 2 differed by no more than 2 percentiles.
- Sensitivity analysis of composite noncancer and cancer risk suggests that variability in lifetime smokeless tobacco consumption, body weight, and uncertainty associated with grouped HPHC toxicity values represent more than 99% of PRA model variability compared to differences in grouped product HPHC concentrations.
- PRA data suggests that noncancer and cancer risk is comparable between the two hypothetical smokeless tobacco products.

SUMMARY

- Comparative risk assessment of two tobacco products may require varied levels of analysis to better understand the relationships between exposure factors and health risk.
- Deterministic QRA is an excellent tool to obtain a general understanding of exposure and health risk. PRA expands on deterministic QRA and estimates the probability of an outcome based on the full range of selected model factors. In addition, PRA identifies and quantifies those model factors that most directly relate to estimates of risk (e.g., sensitivity analysis).
- The PRA results demonstrate that the estimated noncancer and cancer health risks associated with the two smokeless tobacco products are strongly correlated with tobacco usage (e.g., consumption rate and duration) and weakly correlated with minor differences in product HPHC concentrations.