Quantitative Risk Assessment of Combustible Tobacco Products: Two Approaches to Inhalation Exposure Assessment

Charlene Liu, Sc.D and Kristin Marano, Ph.D, MPH, CPH

RAI Services Company, Winston-Salem, North Carolina, USA

Quantitative risk assessment (QRA) may inform regulatory decisions regarding tobacco products (TP). In general, QRA is a five-step process that includes problem formulation, hazard identification, dose-response assessment, exposure assessment, and risk characterization. Evaluation of human health risks from cigarette smoking requires an adequate assessment of the exposure, which is a challenging task because the concentration of toxicants in the respiratory tract and exposure duration are not constant. No regulatory guidance currently exists for exposure assessment of tobacco products, although examples exist in the peer-reviewed literature. The U.S. Environmental Protection Agency (USEPA) provides guidance that addresses methods for quantitative evaluation of exposure and risk, which is useful and can be reasonably applied to tobacco products. Importantly, USEPA guidance defers to the risk assessor to make modifications to the exposure assessment, as appropriate and as relates to, e.g., the exposure pathway and the receptor.

Two different methods were developed to quantify inhalation exposure with machine-generated smoke yields from a market survey of U.S. cigarettes. The first method treats exposure to a chemical in smoke as a continuous process and estimates an exposure concentration by averaging the yields of the chemical from cigarettes consumed over the average daily volume of air inhaled by a user. The second method treats exposure to the chemical as discrete smoking sessions and estimates a respiratory concentration of the chemical via summation of discrete smoking sessions over the course of a day. Both methods incorporate standard exposure parameters to derive a lifetime average exposure to the chemical. For simplicity and conservatism, both methods assume 100% retention of the chemical in the smoker's body.

Results indicate the two methods provide QRA estimates that were <2X different; the first method was more conservative (i.e., risk-maximizing). Exposure assessment of TP should be consistent with available evidence, guidance, and state of the science for risk assessment. These findings indicate that incremental modifications to exposure input assumptions do not materially affect the QRA results.

Problem Formulation

- establish risk assessment scope

In 2009, the Family Smoking Prevention and Tobacco Control Act granted the U.S. Food and Drug Administration (USFDA) authority to regulate tobacco products, with the intention of protecting public health. USFDA has identified 93 harmful and potentially harmful constituents (HPHC) in cigarette smoke (USFDA 2012a).

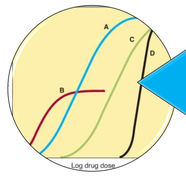
Evaluation of human health risks from cigarette smoking requires an adequate assessment of the exposure, which is challenging because the concentration in the respiratory tract and exposure duration are not constant.

The objective of this evaluation was to estimate potential health risks for a set of U.S. cigarette products using two different exposure assessment approaches.

Hazard Identification

- identify adverse health effects

According to USFDA, HPHC may be considered carcinogens, respiratory toxicants, cardiovascular toxicants, and/or reproductive or developmental toxicants (USFDA 2012a). This evaluation was limited to an abbreviated list of HPHC which are considered representative of different chemical classes, with potential for different health effects, and for which analytical methods are widely available (USFDA 2012b).



Dose Response

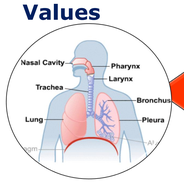
- characterize adverse health effects

Toxicity values were obtained from USEPA recommended hierarchy sources:

- **Tier 1—USEPA's Integrated Risk Information System**
- **Tier 2—USEPA's Provisional Peer Reviewed Toxicity Values**
- **Tier 3—Other Toxicity Values**

Table 1. Toxicity Values

Constituent	Reference Concentration (RfC) (mg/m^3)	Inhalation Unit Risk (IUR) $(\mu g/m^3)^{-1}$
Acetaldehyde	9.0E-03	2.2E-06
Acrolein	2.0E-05	NA
Acrylonitrile	2.0E-03	6.8E-05
2-Aminonaphthalene	NA	5.1E-04
4-Aminobiphenyl	NA	6.0E-03
Benzene	3.0E-02	7.8E-06
Benzo(a)pyrene	2.1E-06	1.1E-03
1,3-Butadiene	2.0E-03	3.0E-05
Carbon Monoxide	2.3E+01	NA
Crotonaldehyde	1.0E-02	NA
Formaldehyde	9.8E-03	1.3E-05
NNK	NA	5.2E-03
NNN	NA	4.0E-04



Exposure Assessment

- determine to whom, when, where, and how exposure occurs

Mean HPHC machine-generated smoke yields using the Health Canada smoking regimen were obtained from a market survey of U.S. cigarettes (Bodnar *et al*. 2012).

Table 2. Average Yields of HPHC of Samples from the 2009 U.S. Cigarette Market

HPHC	Mean Yield	HPHC	Mean Yield
Acetaldehyde, µg/cig	1393	1,3-Butadiene, µg/cig	105
Acrolein, µg/cig	177	Carbon Monoxide, mg/cig	32.3
Acrylonitrile, µg/cig	28.4	Crotonaldehyde, µg/cig	55.4
2-Aminonaphthalene, ng/cig	19.9	Formaldehyde, µg/cig	99
4-Aminobiphenyl, ng/cig	4.45	NNK, ng/cig	166
Benzene, µg/cig	89.3	NNN, ng/cig	280
Benzo(a)pyrene, ng/cig	20.2		

General Assumptions:

- **Exposure Frequency (EF) – 365 days/year**
- **Exposure Duration (ED) –Initiation of smoking at 12.5 years of age (SAMHSA 2015) for a lifetime of 70 years (USEPA 2014). The total ED is 57.5 years: 54 years as an adult and 3.5 years as an adolescent**
- **Cigarette Consumption per Day (CpD) - 20 cig/day (CDC 2014)**
- **Averaging Time (AT) – 255,50 days (Method 1) or 613,200 hours (Method 2)(70 years) for cancer and 20,987.5 days (Method 1) or 503,700 hours (Method 2) (57.5 years) for noncancer (USEPA 2014)**
- **100% Retention of the chemical in the smoker's body**

Method 1 – Inhalation Rate Method

- **Exposure to smoke is a continuous process**
- **Exposure concentration (EC) is estimated by averaging chemical yields per cigarette (D) over the average daily volume of air inhaled**
- **Method Specific Assumption: Inhalation Rate (IR) - 20 m^3/day (USEPA 2014)**

$$EC\ \left(\frac{mg}{m^3}\right) = \frac{D \times CpD \times EF \times ED}{IR \times AT}$$ (USEPA 1989)

Method 2 – Concentration in the Respiratory Tract Method

- **Exposure to smoke is a series of discrete smoking sessions**
- **Respiratory concentration (C_{inh}) is estimated *via* summation of discrete smoking sessions over the course of a day**
- **Method Specific Assumptions:**
  - **Puff Count (PC) 11 puffs, Duration (DT) 1.8 second, Puff Volume (PV) 0.043 L (Zacny and Stitzer 2012)**
  - **Tidal Volume (VT) 0.545 L (USEPA 2011)**
  - **Exposure Time (ET) 0.11 hour = CpD×PC×DT**

$$C_{inh}\left(\frac{mg}{m^3}\right) = \frac{D}{(PV+VT)PC} \times \frac{10^3 L}{m^3}$$ (Bos *et al.* 2012)

$$EC\ \left(\frac{mg}{m^3}\right) = \frac{C_{inh} \times ET \times EF \times ED}{AT}$$ (USEPA 2009)

Risk Characterization

- assess health risks from cigarette smoking

Noncancer Health Hazard (USEPA 2009):

$$Hazard\ Quotient = \frac{EC}{RfC}$$

Excess Lifetime Cancer Risk (USEPA 2009):

$$ELCR = EC \times IUR$$

Table 4. Predicted Health Risks*

Constituent	Method 1 Inhalation Rate Method		Method 2 Concentration in the Respiratory Tract Method	
	Noncancer Hazard Quotient	Excess Lifetime Cancer Risk	Noncancer Hazard Quotient	Excess Lifetime Cancer Risk
Acetaldehyde	2E+02	3E-03	1E+02	2E-03
Acrolein	9E+03	--	6E+03	--
Acrylonitrile	1E+01	2E-03	1E+01	1E-03
2-Aminonaphthalene	--	8E-06	--	6E-06
4-Aminobiphenyl	--	2E-05	--	2E-05
Benzene	3E+00	6E-04	2E+00	4E-04
Benzo(a)pyrene	1E+01	2E-05	7E+00	1E-05
1,3-Butadiene	5E+01	3E-03	4E+01	2E-03
Carbon Monoxide	1E+00	--	1E+00	--
Crotonaldehyde	6E+00	--	4E+00	--
Formaldehyde	1E+01	1E-03	7E+00	7E-04
NNK	--	7E-04	--	5E-04
NNN	--	9E-05	--	7E-05
Total	9E+03	7E-03	6E+03	5E-03

*The risk presented herein does not equate with absolute risk or hazard but rather it is a comparative risk and hazard assessment between the two methods.

Results and Conclusions

- **Both methods are consistent with USEPA RAGS Part F guidance.**
- **Two methods provide risk estimates that were <1.5X different; Method 1 was more conservative (i.e., risk-maximizing).**
- **Exposure assessment of tobacco products should be consistent with available evidence, guidance, and state of the science for risk assessment practice, especially considering uncertainties already associated with QRA estimates.**
- **These findings indicate that incremental modifications to exposure input assumptions do not materially affect the QRA results.**

References

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