Quantitative Risk Assessment (QRA) of Compounds Generated from Electronic Nicotine Delivery Systems (ENDS) and Cigarette Smoke

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Abstract

Assessing the relative toxicity of electronic nicotine delivery systems (ENDS) and conventional cigarettes remains a pressing challenge in risk analysis and mixtures toxicology. The US Food and Drug Administration (FDA) draft guidance (2016) for Premarket Tobacco Product Applications (PMTA) for ENDS products recommends that the submitter characterize the constituents in the e-liquid that may impact the constituents in the aerosol (including HPHCs – Harmful and Potentially Harmful Constituents - and other toxic chemicals). To adequately characterize the HPHCs and other potential toxicants, a range of analytical techniques may be applied to identify and quantify compounds. These methods include gas- or liquid-chromatography combined with mass spectrometry to identify organic compounds and inductively coupled plasma-mass spectrometry to evaluate metals. The objective of this presentation is to propose a method for comparison of individual and composite (i.e., whole-product) risk of analytes present in ENDS product aerosol to reference cigarette smoke constituents. This effort is consistent with FDA's Predictive Toxicology Roadmap initiative that includes topics such as "determining the comparative toxicity of tobacco products, which are inherently toxic," and "quantitative risk assessment (QRA) addressing the complex mixtures of tobacco products." Whole-product risk is estimated for both cancer (i.e., Excess Lifetime Cancer Risk – ELCR) and non-cancer (i.e., Hazard Index – HI) risk which provides a means to assess relative risk of one product to another. The presentation provides a general overview of the approach that includes hazard identification, exposure assessment and risk characterization using toxicity values sourced from established regulatory agencies (e.g., EPA IRIS values). ELCR and HI for each product type are calculated per EPA guidelines. The underlying assumptions and methodological limitations of this approach are also addressed.

Background & Methodology

- The U.S. Food and Drug Administration (FDA) defines Harmful and Potentially Harmful Constituents (HPHCs), as "chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers." U.S. FDA draft guidance recommends reporting the HPHCs in tobacco products, and addressing the contributions of HPHCs to the public health risk of the product.
- Marano, et al. 2018, demonstrated that US Environmental Protection Agency risk assessment guidelines (US EPA 1989) can be used to compare two different tobacco cigarettes on the basis of HPHCs.
- US FDA draft guidance for Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS) Under Section 910 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387j), recommends a list of HPHCs to be considered for analysis in e-cigarette e-liquids and aerosols.
- We adapt the previously employed methods to generate a whole product comparison between a conventional tobacco cigarette and aerosol from an ENDS device on the basis of FDA's HPHC lists. Briefly:
    1. Regulatory values for cancer and non-cancer hazards were sourced for each HPHC on both the cigarette smoke and ENDS aerosol list. The priority tier for sourcing the compounds was:
        - A. United States Environmental Protection Agency (US EPA)
        - B. International Conference on Harmonization (ICH Q3D) [considered for metals only], or California Environmental Protection Agency (Cal EPA) [for non-metals]
        - C. Other regulatory authorities (ACGIH, ECHA, OARS, TCEQ, WHO)
        - D. Primary literature
        - E. Threshold of Toxicological Concern (TTC)
    2. Exposure assumptions were sourced from US EPA and FDA regulatory guidance as well as CDC epidemiological data.
    3. With these values, the exposure to and risk of each HPHC can be estimated.
    4. Per US EPA and the Agency for Toxic Substances and Disease Registry (ATSDR, 2018) guidelines, these individual estimates were aggregated on the assumption of dose addition to obtain a final cumulative ELCR and Hazard Index (HI) for each product.
    5. These whole product estimates can serve as a basis for understanding the relative risk of conventional cigarette smoke and ENDS aerosol with respect to the listed HPHCs.

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Hazard Identification

The following HPHC's appear on either the abbreviated HPHC list for cigarette smoke or the HPHC list for ENDS aerosol. Values were sourced from regulatory agencies to evaluate the cancer risk or non-cancer hazard of each HPHC.

HPHC	FDA Classification[1]	HPHCs in E – cigarette Aerosol	HPHCs in Cigarette Smoke (Abbreviated)	Cancer		Non-Cancer	
				Inhalational Unit Risk (IUR) ($\mu g/m^3$)$^{-1}$	Source	Reference Concentration (RfC) (mg/m^3)	Source
Acetaldehyde	CA, RT, AD	✓	✓	2.20E-06	US EPA, 1988	9.00E-03	US EPA, 1991
Acetyl Propionyl	NA	✓	x	NA	NA	7.50E-05	TTC[2]
Acrolein	RT, CT	✓	✓	NA	NA	2.00E-05	US EPA, 2003
Acrylonitrile	CA, RT	✓	✓	6.8E-05	US EPA, 1987	2.0E-03	US EPA, 1991
4-Aminobiphenyl	CA	✓	✓	6.0E-03	Cal EPA, 1992	NA	NA
1-Aminonaphthalene	CA	✓	✓	5.1E-04	Cal EPA, 1992	NA	NA
2-Aminonaphthalene	CA	✓	✓	5.1E-04	Cal EPA, 1992	NA	NA
Ammonia	RT	✓	✓	NA	NA	5.00E-01	US EPA, 2016
Anabasine	AD	✓	x	NA	NA	NA	NA[3]
Benzene	CA, CT, RDT	✓	✓	7.80E-06	US EPA, 1998	3.00E-02	US EPA, 2003
Benzo[a]pyrene	CA	✓	✓	6.00E-04	US EPA, 2017	2.00E-06	US EPA, 2017
1,3-Butadiene	CA, RT, RDT	✓	✓	3.00E-05	US EPA, 2002	2.00E-03	US EPA, 2002
Cadmium	CA, RT, RDT	✓	x	1.80E-03	US EPA, 1987	2.00E-05	Cal EPA, 2008[4]
Carbon monoxide	RDT	x	✓	NA	NA	7.00E+00	WHO, 2010
Chromium	CA, RT, RDT	✓	x	1.20E-02	US EPA, 1998[5]	8.00E-06	US EPA, 1998[5]
Crotonaldehyde	CA	✓	✓	4.8E-04	Cal EPA, 2018[6]	4.00E-03	Cal EPA, 2018[7]
Diacetyl	NA	✓	x	NA	NA	0.04	ACGIH, 2012[8]
Diethylene glycol	NA	✓	x	NA	NA	12	ECHA, 2017
Ethylene glycol	NA	✓	x	NA	NA	0.4	Cal EPA, 2008[4]
Formaldehyde	CA, RT	✓	✓	1.30E-05	US EPA, 1988	9.00E-03	Cal EPA, 2008
Glycerol	NA	✓	x	NA	NA	33	ECHA, 2018[9]
Isoprene	CA	✓	✓	2.2E-08	TCEQ, 2018	1.20E-01	TCEQ, 2018
Lead	CA, CT, RDT	✓	x	1.20E-05	Cal EPA, 2011	2.50E-04	ICH, 2014[10]
Menthol	NA	✓	x	NA	NA	6.4	OARS, 2014[11]
Nickel	CA, RT	✓	x	2.60E-04	Cal EPA, 2011	3.00E-04	ICH, 2014[10]
NNK	CA	✓	✓	5.20E-03	Naufal et al. (2009)[12]	NA	NA
NNN	CA	✓	✓	4.00E-04	Cal EPA, 1992	NA	NA
Propylene glycol	NA	✓	x	NA	NA	10	ECHA, 2018[9]
Toluene	RT, RDT	✓	✓	NA	NA	5.00E+00	US EPA, 2005

[1]Key: Addictive (AD), Carcinogen (CA), Cardiovascular Toxicant (CT), Respiratory Toxicant (RT), Reproductive or Developmental Toxicant (RDT), Not Available (NA)
[2]No RfC for Acetyl Propionyl . Calculated using the Threshold of Toxicological Concern (TTC), of 1.5 µg/day, and inhalation rate of 20 m^3/day (ICH M7, 2014, ISO 18562-1)
[3] Not included in this RA, will be assessed using the "ICH Guidance Q3B (R2) – Impurities in New Drug Products, July 2006, Revision 2"
[4]Chronic Reference Exposure Levels, OEHHA, 2008
[5]IUR of Cr(VI) and RfC for Chromic acid mists and dissolved Cr(VI) aerosols are used
[6]No IUR for Crotonaldehyde. Route extrapolation from an oral slope factor of 1.9(mg/kg-day)$^{-1}$ to IUR assuming body weight of 80kg and inhalation rate of 20 m^3/day (Health Effects Assessment Summary Tables - Human Health Risk Assessment (HHRA) Note, OEHHA 2018)
[7]No RfC for Crotonaldehyde. Route extrapolation from reference dose of 1.00E-03 to RfC assuming body weight of 80kg (provisional peer-reviewed toxicity value - (HHRA) Note, OEHHA 2018)
[8]No RfC for Diacetyl. Threshold Limit Value–Time-Weighted Average (TLV–TWA) based on a 8-hour workday and a 40-hour workweek from The American Conference of Governmental Industrial Hygienist (ACGIH) is used in place of RfC
[9]No RfC for Glycerol or Propylene glycol. Derived no-effect levels (DNEL) from European Chemical Agency (ECHA) are used as toxicity value
[10]Derived using the Q3D Elemental Impurities, International Conference On Harmonization, inhalational permitted daily exposure value and an inhalation rate of 20 m^3/day
[11]Workplace Environmental Exposure Level derived Occupational Alliance for Risk Science (OARS) (OARS 2014)
[12] No IUR for NNK. IUR derived by Naufal et al., 2009, by extrapolation from CSF assuming a body weight of 70 kg and an inhalation rate of 20m^3/day

Exposure Assumptions

Exposure values were sourced from US EPA and FDA regulatory guidelines and CDC epidemiological data.

Parameter	Symbol	Value	Unit	Source
HPHC Concentration in Product	C	varies	µg/product	Analytical Data
Consumption Rate, cigarette	CR_C	14.1	product/day	CDC (2018)
Consumption Rate, ENDS	CR_E	2	product/day	Internal Data
Exposure Frequency	EF	365	days/year	Maximum value
Exposure Duration	ED	57.5	Years	USFDA (2013)
Inhalation Rate	IR	20	m^3/day	USEPA (2011)
Averaging Time, noncancer	AT_{NC}	20,988	days	USEPA (2014)
Averaging Time, cancer	AT_C	25,550	days	USEPA (2014)

Calculating Exposure Concentration

An estimated exposure concentration was generated per US EPA guidance on estimating chemical intakes (USEPA 1989). For each individual HPHC, the concentration per unit of product (cigarette or ENDS cartridge) was multiplied by an estimate of consumption rate of product per day, the number of days per year, and an estimate of years spent using tobacco products. This value was then averaged over an estimate of total inhaled air for either the duration of exposure (for a non carcinogen risk) or lifetime (for carcinogen risk) to generate a final estimated exposure concentration (EC) in µg/m^3. This is expressed by the equation:

$$EC = \frac{C \times CR \times EF \times ED}{IR \times AT}$$

Calculating ELCR and HQ

After an estimated exposure concentration was generated, published regulatory values were used to calculate an estimated lifetime cancer risk (ELCR) or hazard quotient (HI) for each individual HPHC.

$$ELCR = EC_{cancer} \times IUR \qquad HQ = \frac{EC_{noncancer}}{RfC}$$

where:

- IUR is the inhalation unit risk, the upper bound risk estimate of continuous exposure to 1 µg/m^3 of a given HPHC
- RfC is the reference concentration, a concentration under which adverse effects are considered unlikely

Per US EPA and the ATSDR, individual ELCR and HQs for each HPHC can be added together to produce a whole product cumulative ELCR or Hazard Index (HI).

$$cumulative\ ELCR = \sum_i^n ELCR_i \qquad HI = \sum_i^n HQ_i$$

Results

- Analytical data were obtained from a sample conventional tobacco product and a sample ENDS product.
- Data were masked by extrapolating to values through a pseudorandom map. The final values presented here are within the range of real products, but are not representative of any one product.
- The following table shows the limited cumulative ELCR and HI for conventional cigarette smoke or ENDS aerosol, based only on the HPHC's previously listed.

Quantitative Risk Assessment	ENDS Aerosol	Conventional Tobacco Cigarette Smoke	% Difference[1]
ELCR	2×10^{-5}	2×10^{-2}	-99.90%
HI	3×10^{0}	6×10^{3}	-99.95%

[1](ENDS Aerosol – Cigarette Smoke)/(Cigarette Smoke) x 100

Challenges and Considerations

We have adapted the Marano et al. (2018) approach to evaluate relative risk of conventional cigarette smoke and ENDS product aerosol. This method could potentially be used to cross compare any type of tobacco product. However, there are several limitations of this approach that warrant further consideration:

- A relative risk comparison is dependent on the HPHCs included in the assessment.
    - The underlying assumption of the presented approach is that the ENDS HPHC list and the abbreviated HPHC list for cigarettes are representative of whole-product risk. There may be additional HPHCs unique to ENDS products that should be considered in the overall evaluation (e.g., glycidol or chemical profiling data).
    - The current evaluation excludes analytes that are below the limit of detection (BLD) or quantification (BLQ). Future work will evaluate the most appropriate approach for consideration of these analytes.
- In the absence of acceptable regulatory values for risk assessment (e.g., Acetyl Propionyl), a Threshold of Toxicological Concern (TTC) of 1.5 µg/day (associated with an excess lifetime cancer risk of 1 in 100,000) is applied.
    - Comparison to a TTC can be included in the HI (for non-cancer hazards); however, it cannot be converted to an IUR and included in the ELCR estimate. Including potential carcinogenic HPHCs in the HI could skew estimates of both non-cancer and cancer risk.
- Approaches are currently lacking for evaluation of HPHCs that are classified by FDA as carcinogens but lack an established IUR.
- On-going work will focus on addressing the above issues to ensure relative risk between two products is appropriately represented.

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