Comparative Semi-Quantitative Risk Assessment of Harmful and Potentially Harmful Constituents in Tobacco Products

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Abstract

The US Food and Drug Administration Center for Tobacco Products (CTP) evaluates novel, potentially reduced harm, tobacco products based on an "appropriate for the protection of public health" standard (risks and benefits to the population). An important component is the evaluation of Harmful and Potentially Harmful Constituents (HPHCs) associated with new products in comparison to conventional tobacco cigarettes and other FDA authorized products. CTP has acknowledged that a subset of high magnitude and/or potency HPHCs often drive these comparative risk assessments. To simplify this risk assessment process, we present a semi-quantitative risk assessment (semi-QRA) approach to identify these risk drivers using a heated tobacco capsule (HTC) as an example. Our approach combined the magnitude of difference in HPHC yield and HPHC potency values sourced from authoritative agencies to identify HPHCs with an outsized effect on estimated relative product risk. For instance, when comparing cigarettes to HTC prototypes, the concerns presented by increases in some HPHCs identified through this method (e.g., glycidol and acrylamide) may be off-set by reductions in other HPHCs identified through this method (NNK, ethylene oxide, crotonaldehyde, acrolein, etc.) without resorting to a full QRA. This highlights that despite a lot of analytically non-equivalent increases and decreases in HPHCs between two products, only a few HPHCs with high-magnitude differences and/or high-potency may be significant. As novel tobacco products are developed, both the FDA and industry are proposing new HPHCs to determine whether novel products significantly reduce HPHC exposure and subsequent health risks. Here, we demonstrated a semi-QRA method to identify which HPHC changes can be considered risk drivers to assess the potential health risk of a novel tobacco product prototype.

Background

Cigarette smoke is a mixture that contains more than 7000 individual chemicals. The U.S. Food and Drug Administration Center for Tobacco Products (CTP) 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." CTP identified 93 HPHCs as hazards to represent key toxicants that are believed to drive human health risks from tobacco products.[1] Therefore, HPHC comparisons between two tobacco products is critical in determining whether the two products are likely to have similar or different toxicological outcomes. Use of qualitative or semi-quantitative analyses of HPHC data before quantitative risk assessments (QRAs) is preferred by CTP in the memo of comparing products in the substantial equivalence pathway.[2]

Key considerations of HPHC comparisons identified by CTP are:
- Relevant HPHC yields and likely exposures
- Magnitude and direction of HPHC changes
- The potency of the HPHC
- Cancer and non-cancer endpoints (cardiovascular disease, respiratory effects, developmental and reproductive effects, and addiction) are considered separately.

Key considerations of using reference values identified by CTP[3] are:
- The selection and use of toxicity reference values for the general population should be consistent with the EPA tiering hierarchy.
- Occupational exposure level (OELs) may only inform the toxicity evaluation for non-cancer effects.

Methods

HPHC yields from a reference cigarette (1R6F) and HTC prototype were measured and evaluated to identify analytically non-equivalent. HPHC yield differences are normalized to the weight per nicotine level in the product. The HPHCs were then grouped based on identified cancer and non-cancer endpoints. Potency values such as Inhalation Unit Risk (IUR) or Reference Concentration (RfC) were sourced from authoritative agencies in tiers. The toxicity reference values in the Integrated Risk Information System (IRIS) from US Environmental Protection Agency (EPA), California Environmental Protection Agency (Cal EPA) and Agency for Toxic Substances and Disease Registry (ATSDR), are prioritized as tier 1. Health-based reference values from state and international authorities, such as Texas Commission on Environmental Quality (TCEQ), World Health Organization (WHO) and the Netherlands National Institute for Public Health and the Environment (RIVM), are considered as tier 2. The magnitude of each analytically non-equivalent difference in HPHC yield was evaluated against the corresponding potency of the HPHC. The relative increases and decreases of risk drivers (high magnitude and/or high potency HPHCs) compared to low magnitude and/or low potency HPHCs are highlighted, clearly visualized in a plot, and qualitatively discussed.

Results

Table 1. Cancer Risk Drivers

Cancer Risk Drivers	Weight difference (1R6F – HTC, µg)	IUR $(\mu g/m^3)^{-1}$	Resource
NNK	0.09	1.4×10^{-2}	Cal EPA
Ethylene oxide	8.45	3×10^{-3}	Cal EPA
Crotonaldehyde	22.56	5.4×10^{-4}	Derived from CSF (US EPA)
Acetaldehyde	431.29	2.2×10^{-6}	US EPA
Glycidol	-3.95	3.7×10^{-4}	Cal EPA

Table 2. Non-Cancer Risk Drivers

Non-cancer Risk Drivers	Weight difference (1R6F – HTC, µg)	RfC (mg/m³)	Resource
Acrolein	63.92	2×10^{-5}	US EPA
Acetaldehyde	93.97	9×10^{-3}	US EPA
Carbon monoxide (CO)	366.38	7	WHO

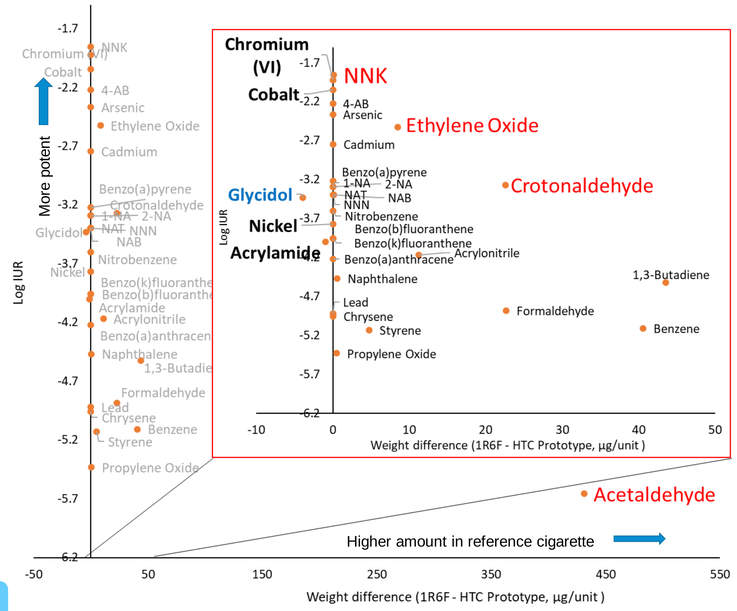

Figure 1. HPHC Comparison to Reference Cigarette (Cancer)
Red font HPHCs are risk drivers in cigarette.
Blue HPHCs are risk drivers in HTC prototype Black bold HPHCs are higher in HTC prototype.

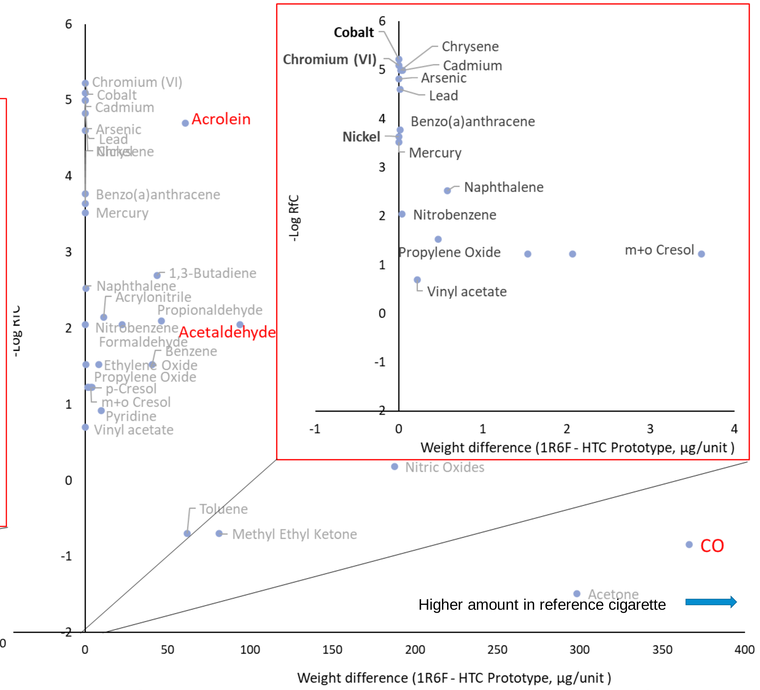

Figure 2. HPHC Comparison to Reference Cigarette (Non-cancer)
Red font HPHCs are risk drivers in cigarette.
Most non-cancer HPHCs are lower in HTC prototype.

Conclusions

1. Applying an offsetting strategy with consideration of HPHCs potency is appropriate to evaluate the differences in risk between two products, when specific HPHCs are identified as risk drivers.
2. The reduction of cancer and non-cancer HPHC yields in HTC prototype, especially risk drivers in reference cigarette (NNK, ethylene oxide, crotonaldehyde, acetaldehyde, acrolein and carbon monoxide), indicates the harm reduction of HTC prototype.

References

1. Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act. 2012.
2. Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports. 2019.
3. Memo: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products. 2019.