Application of the Human Health Risk Assessment Process for the Evaluation of Electronic Cigarettes

Autumn Bernal[1], Charlene Liu[2], Charles Johnson[3] and Richard Young[3]

[1]ToxCreative LLC, CA, USA; [2]RiskWise Solution LLC, NJ, USA; [3]Bibra toxicology advice & consulting Ltd, UK

REFERENCES: Available upon request

ABSTRACT

Electronic cigarettes (e-cigarettes) aerosolize a nicotine-containing e-liquid that is inhaled by the consumer. Compared to combustible cigarette smoke, e-cigarettes typically produce significantly lower levels of inhaled toxicants. The aerosol mixture delivered to the consumer from an e-cigarette contains several components, such as e-liquid ingredients, thermal decomposition/reaction products, and device-derived materials. Exposure to this inhaled mixture is not without health risks that must be evaluated. The human health risk assessment process provides a systematic approach to evaluate the potential adverse effects associated with chemical exposures. However, a comprehensive risk assessment framework for evaluating e-cigarettes has not previously been developed due to the complex nature of the aerosol mixture, variability of toxicological data for the inhaled ingredients (e.g., nicotine, excipients, and flavoring compounds), thermal decomposition/reaction products (e.g., harmful and potentially harmful constituents and non-targeted analytes), and device-derived materials (e.g., leachables), as well as a lack of accepted standards. The objective of this work is to propose a suitable and pragmatic risk assessment process that can be adopted to evaluate the health effects potentially caused by exposure to e-cigarette aerosol mixtures. The framework presented here considers the variability in toxicological data and toxicological prioritization for each aerosol component to incorporate appropriate analytical characterization methods, tools for hazard identification and dose-response assessment, best practices for exposure estimation, and regulatory standards for quantitative and/or qualitative risk characterization approaches. Overall, with consideration of other sources of nonclinical data, a systematic, weight-of-evidence risk assessment process is established for the whole aerosol. This comprehensive framework is the first to be presented for any tobacco product and can be utilized to support risk assessment standardization, product development, regulatory submissions, and inform regulatory decisions.

INTRODUCTION

Based on the potential for reduced exposures to Harmful and Potentially Harmful Constituents (HPHCs) compared to combustible cigarettes and demonstrated cessation effectiveness, e-cigarettes are now used as a tool for smoking cessation in some parts of the world (including the UK and Australia). The FDA Center for Tobacco Products notes that "*switching to lower risk alternatives (e.g., e-cigarettes) has been suggested to reduce smoking-attributable risks*" and "*opportunities exist to educate adult smokers about the relative risks of tobacco products, including e-cigarettes, using evidence-based approaches.*" Therefore, the potential for a new e-cigarette product to raise different questions of public health compared to currently marketed tobacco products must be considered alongside the benefits of e-cigarettes to deliver nicotine with a reduction in HPHCs.

The human health risk assessment process is a systematic approach to evaluate potential health risks associated with exposures. It is widely used by regulatory agencies (e.g. FDA, USEPA) for assessment of various human chemical exposures through foods, water, air, etc. Risk assessment is an integral part of the FDA's Predictive Toxicology Roadmap for evaluating relative health risks of tobacco products during product development, regulatory submissions, and for informing regulatory decisions. Although the techniques employed to evaluate each of these exposures can vary, the risk assessment process routinely comprises of the following key steps: problem formulation, hazard identification, dose-response assessment, exposure assessment, and risk characterization (Figure 1). The application of these steps with respect to e-cigarettes and their key components is described here in an overall risk assessment process.

METHODS

FIGURE 1. SCOPE OF E-CIGARETTE RISK ASSESSMENT

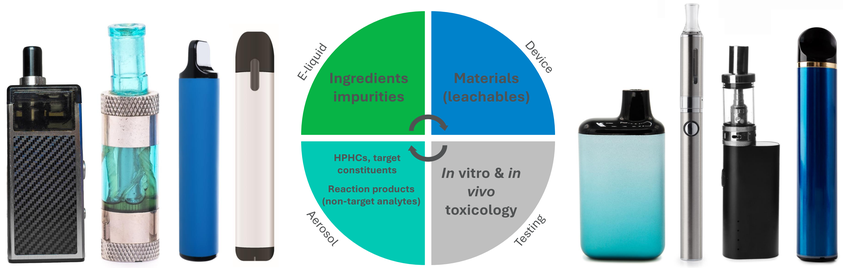


FIGURE 2. METHODS FOR APPLYING A RISK ASSESSMENT FRAMEWORK FOR E-CIGARETTE AEROSOL COMPONENTS

Problem Formulation
- Define risk assessment objectives
- Determine the scope of analyses and techniques for the identification, quantification and risk assessment of HPHCs and target constituents generated in the aerosol, ingredients formulated in the e-liquid, leachables from the device materials, and potential reaction or thermal degradation compounds detected in the aerosol with non-targeted analyses.

Hazard Identification
- Determine the critical toxicological endpoints to be investigated for each component
- Review the available toxicological data (e.g., published literature, read-across, and *in silico* data) and define critical effects, where possible
- Determine aerosol constituents that have the most impact on tobacco-related diseases

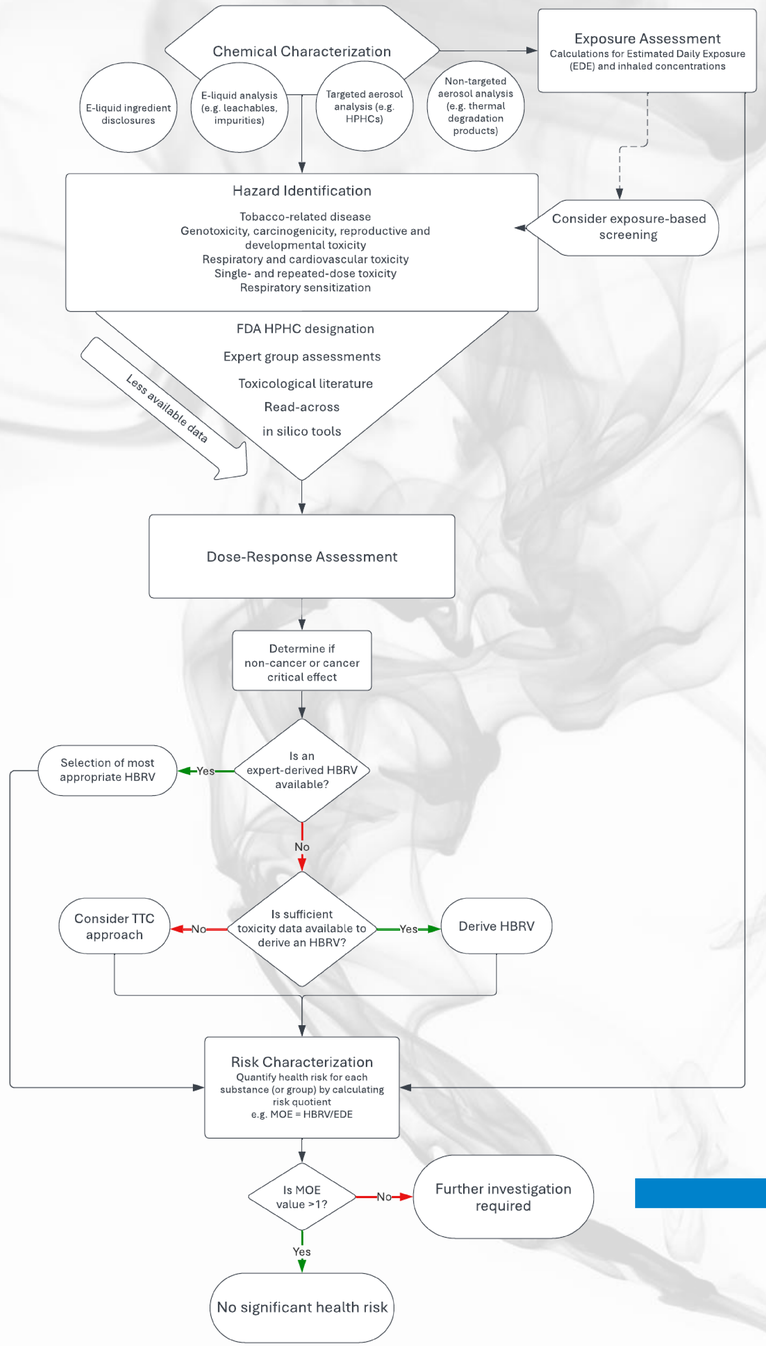
Dose-response
- Develop a systematic approach for identifying the doses at which health effects are anticipated to occur, including Health-Based Reference Values (HBRVs)
- HBRVs may also be derived from good-quality toxicological data, in accordance with appropriate guidance
- Consider the Threshold of Toxicological Concern (TTC), particularly where data are limited

Exposure Assessment
- Estimate daily intakes from inhalation to each constituent
- Considering the accuracy of analytical data
- Integrate human behavior consumption data, where available
- Consider appropriate exposure assessment factors and assumptions to generate Estimated Daily Exposure (EDE) values

Risk Characterization: Estimate appropriate Margins of Exposure (MOE) and/or risk quotient values for each aerosol constituent
Develop tailored approaches for estimating absolute and relative risks

RESULTS

FIGURE 3. RISK ASSESSMENT FRAMEWORK FOR E-CIGARETTE AEROSOL COMPONENTS



EXPOSURE ASSESSMENT CALCULATIONS FOR E-CIGARETTE AEROSOL COMPONENTS

Aerosol constituents (e.g. HPHCs) : $\mathrm{EC}\left(\frac{\mu g}{m^3}\right) = \frac{\mathrm{HPHCY}\left(\frac{\mu g}{puff}\right)\times CR^{*}\left(\frac{puffs}{day}\right)\times \mathrm{EF}\left(\frac{days}{years}\right)\times \mathrm{ED(years)}}{\mathrm{IR}\left(\frac{m^3}{day}\right)\times AT_{NC/C}\,\mathrm{(days)}}$

Equation Key: AT_{NC}= averaging time for noncancer; AT_C= averaging time for cancer; EC= exposure concentration; CR= consumption rate; ED= exposure duration; EF= exposure frequency; IR= inhalation rate; HPHCY= mean yields of HPHCs and target constituents. Note= *Consumption rate was calculated as: pods/day × puffs/pod

E-liquid ingredients: $EDE_i\left(\frac{mg}{day}\right) = \left(Ingredient\ \frac{\%w/w}{100}\times\frac{Purity\ \%}{100}\right)\times PpD\times\left(\frac{g}{pod}\right)\times 1,000\frac{mg}{g}\times 100\%\ BA\times 100\%\ TR$

Equation Key: EDE_i= estimated daily exposure for single chemical constituent; %w/w = weight ratio percentage; PpD = Pods per day (user consumption – heavy or typical use); BA = bioavailability; TR = transfer rate; g = grams; mg = milligrams; g/pod represents the e-liquid weight

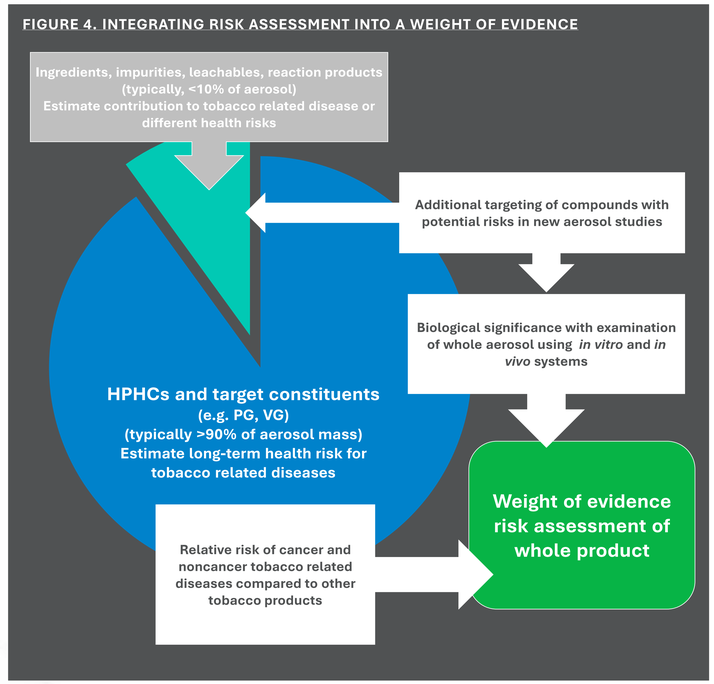
E-liquid leachables: $EDE_i\left(\frac{\mu g}{day}\right) = \left(Concentration\left(\frac{\mu g}{g}\right)\right)\times PpD\times\left(\frac{g}{pod}\right)\times 100\%\ BA\times 100\%\ TR$

Equation Key: EDE_i = estimated daily exposure for single chemical constituent; PpD = Pods per day (user consumption – heavy or typical use); BA = bioavailability; TR = transfer rate; g = grams; mg = milligrams; g/pod represents the e-liquid weight

CONCLUSIONS

- The hazard identification and dose-response phases of the risk assessment process will be mostly dictated by data availability.
- Many HPHCs are well-studied and HBRVs might exist that can be applied during the risk characterization.
- Other constituents of e-cigarette aerosol (e.g., those captured in NTA analyses) may be poorly studied; therefore, the hazard identification and dose-response stages of risk assessment are likely to rely on read-across, *in silico* and/or TTC approaches.
- The risk assessment process can be adapted for each of the various aerosol components potentially inhaled by e-cigarette consumers, to generate initial estimates of risk from exposure to the whole product.
- This process can aid product development by refining products to minimize exposure and risk to certain chemical constituents.
- The combination of chemical risk assessment with other types of non-clinical and clinical data in an overall weight-of-evidence assessment can inform regulatory decision-making processes related to the public health impact of tobacco products.

FIGURE 4. INTEGRATING RISK ASSESSMENT INTO A WEIGHT OF EVIDENCE



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