Use of Quantitative *In Vitro* to *In Vivo* Extrapolation (QIVIVE) for the assessment of Non-Combustible Next Generation products

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1. INTRODUCTION

With the use of *in vitro* new approach methodologies (NAMS) for the assessment of non-combustible next generation products, new extrapolation methods are required to interpret and contextualize the physiological relevance of these results. Quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) can translate *in vitro* concentrations into in-life exposures with physiologically based pharmacokinetic (PBPK) modelling and provide an estimate of the likelihood of harmful effects from expected exposures.

In the present study, we combined a PBPK model with a lung deposition model (MPPD) to better understand the pharmacokinetics of nicotine in non-combustible next generation products and combustible cigarettes. We ran the MPPD model to characterize particle deposition in the respiratory tract and developed a PBPK model for nicotine that was validated with human clinical trial data. Finally, we estimated a Human Equivalent Concentration (HEC) and predicted blood concentrations based on the minimum effective concentration (MEC) derived after acute exposure of BEAS-2B cells to cigarette smoke (1R6F) or heated tobacco product (HTP) aerosol at the air liquid interface.

The objective of this project was to use computational tools to better understand the pharmacokinetics of HTP and cigarettes components (using nicotine) and to interpret and contextualize the in vitro assay results (MECs) in terms of expected corresponding human blood concentrations.

2. METHODS

2.1 MPPD modeling

Lung deposition with different particle sizes was calculated using the MPPD model (MPPD version 3.04) available from the Applied Research Associates webpage (https://www.ara.com/mppd/). In the simulations presented here, the stochastic model was used with upright body position and oral breathing at constant exposure conditions. Different inhalation scenarios were also tested, including normal or deep breathing at resting with same inhalation/exhalation time or shorter inhalation and extended exhalation as well as no breath hold, short breath hold and extended breath hold.

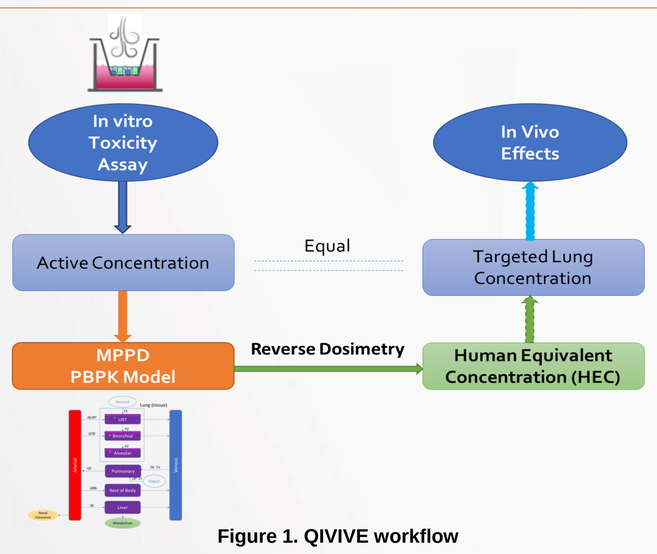

Figure 1. QIVIVE workflow

2.2 Quantitative In Vitro to In Vivo Extrapolation (QIVIVE)

Three steps were followed to derive a blood concentration equivalent to an AC_{50} from an *in vitro* assay (Figure 1):

- Estimate the fraction deposited for a scenario type with MPPD.
- Use the fraction deposited from MPPD in the PBPK model and by reverse dosimetry derive the exposure concentration that matches the estimated *in vitro* deposition POD.
- Derive the blood concentration using the PBPK model.

3. RESULTS

3.1 Dosimetry and Lung *in vitro* assay

The Figures below show the minimum effective concentration (MEC) after exposure of BEAS2B to 1R6F diluted smoke whole aerosol (1:5) with filtered air, subsequent recovery of 24 hours and the nicotine mass (captured on glass plates), corresponding to the MEC that was measured using High Content Screening (Fig 2a). The corresponding nicotine dose equivalent to the MEC is shown in Figure 2b and the same experiment was repeated with undiluted HTP aerosol too see Figure 2c.

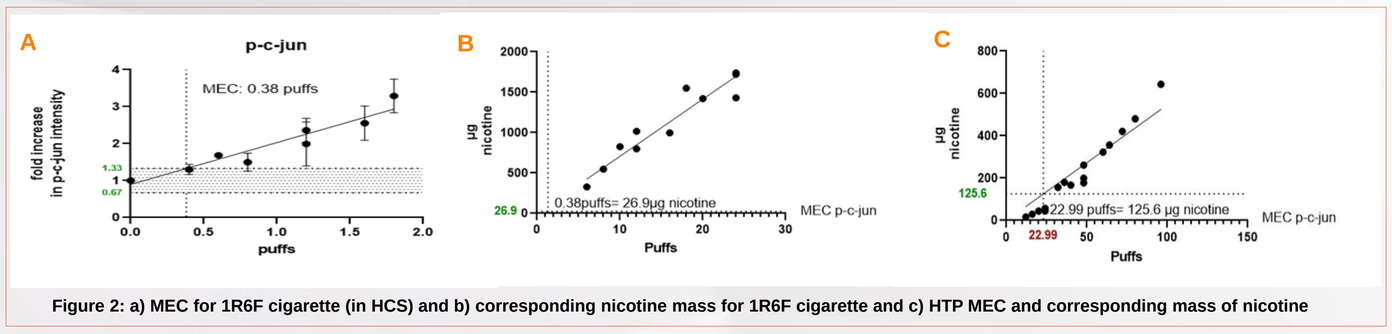

Figure 2: a) MEC for 1R6F cigarette (in HCS) and b) corresponding nicotine mass for 1R6F cigarette and c) HTP MEC and corresponding mass of nicotine

3.2 Development and validation of a human PBPK model

The PBPK model schematic for nicotine shows the representation of the main organs considered with various sub-compartments in the lung for inhalation exposure (Fig 3A). The performance of the model was evaluated using *in vivo* pharmacokinetic (PK) data. Blood nicotine PBPK simulations were compared to inhalation exposure data of McEwan *et al*. (2019); (Fig 3B) and Picavet *et al*. (2016), (Fig 3C). For figures 3B and 3C the solid lines are the simulated venous concentration (ng/ml), with the red circles being measured PK data (ng/ml).

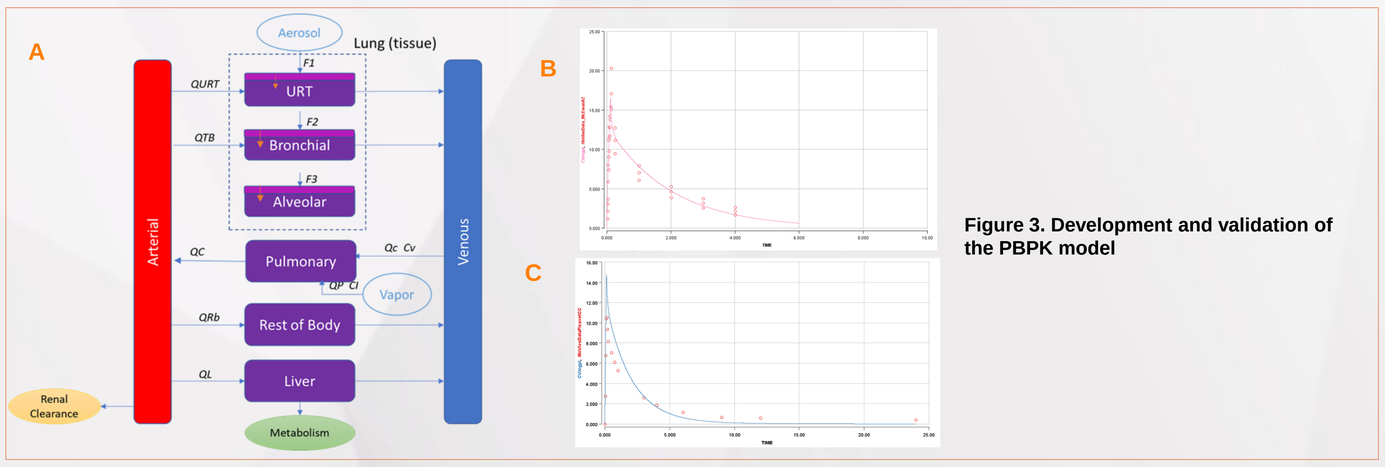

Figure 3. Development and validation of the PBPK model

3.3 Quantitative In Vitro to In Vivo Extrapolation (QIVIVE)

The exposure concentration necessary to reach the MEC as well as the margin of exposure (MOE) are in Table 1. The PBPK model was used to predicted the dose of nicotine per cigarette necessary to reach the MEC for both 1R6F and HTP. The margin of exposure (MOE), which is the ratio between the nicotine content necessary to reach the MEC and the classic nicotine content of each cigarette is also shown. Results show that after smoking less than a ¼ of a 1R6F cigarette, the MEC is already reached. In contrast, it would be necessary to puff 2.5 HTP sticks at the same time to reach the MEC.

	MEC (µmol)	HEC (mg nicotine/cig)	Classic nicotine concentration (mg nicotine/cig)	Margin of Exposure (MOE)
1R6F	0.072	0.245	1.85	0.13
HTP	0.77	2.60	1.03	2.5

Table 1: Human equivalent exposure concentrations (HEC) based on PBPK modeling and MEC values

To derive blood concentrations (Table 2), we used two scenarios, one where only one cigarette is smoked (at the HEC and at 1.03 mg nicotine for comparison with nicotine content in cigarettes or 1.85 mg nicotine for HTP) and a second where 10 cigarettes are smoked over time (at the HEC×10 for the total dose of nicotine over the 10 sessions and at 10.3 mg or 18.5 mg nicotine. which means 1.03 mg nicotine per cigarette or 1.85 mg nicotine per HTP×10 sessions). For each session, a cigarette is smoked entirely after 10 puffs every 30 seconds (5 minutes) and cigarettes are smoked every hour.

	HEC (mg nicotine/cig)	Blood concentration after 1 cigarette (ng/ml)	HEC at steady state (mg nicotine/10 cigarettes)	Blood concentration at steady state (ng/ml)
1R6F	0.245	4.35	2.45	8.91
HTP	2.60	46.15	26	94.77

Table 2: Estimated human blood concentrations based on HEC values at steady state

4. CONCLUSIONS

- The MPPD-PBPK model predicted the *in vivo* data from clinical studies for both HTP and combustible cigarettes generally within a factor of two of the data, in keeping with the WHO International Programme on Chemical Safety (2010) guidance. The human blood concentration was calculated using QIVIVE to derive the human exposure concentration (HEC) that matched the estimated *in vitro* deposition POD measured *in vitro* (MEC combustible cigarette = 0.38 puffs or 26.9µg nicotine, HTP = 22.9 puffs or 125.6µg nicotine).
- Results showed that for the 1R6F cigarette, consuming >¼ of a stick would be required to induce the effects seen *in vitro*. Whereas, for HTP it would be necessary to consume 2.5 sticks simultaneously to produce the effects observed *in vitro*. This data further demonstrates the reduced potency of the HTP aerosol compared to cigarette smoke; thereby adding to the weight of evidence that non-combustible next generation products have the potential for reduced harm when compared to cigarettes.
- The QIVIVE approach demonstrates great promise in assisting human health risk assessments, however, further optimization and standardization is required for regulatory acceptance.

REFERENCES

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