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CLINICAL TRIALS
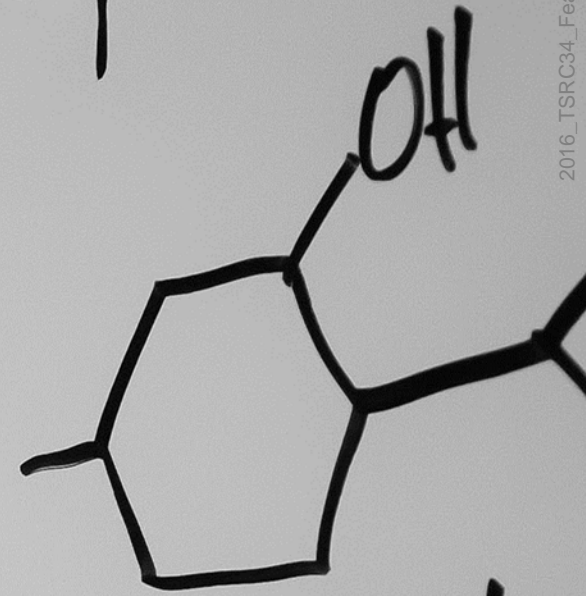
Nicotine delivery from e-cigarettes part II:
data and learnings from two pharmacokinetic studies.

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British American Tobacco (Investments) Limited, R&D, Regents Park Road, Southampton, SO15 8TL, U.K. and Los Angeles Clinical Trials, 4116 W. Magnolia Blvd. Suite 100, Burbank, CA 91505, U.S.A.
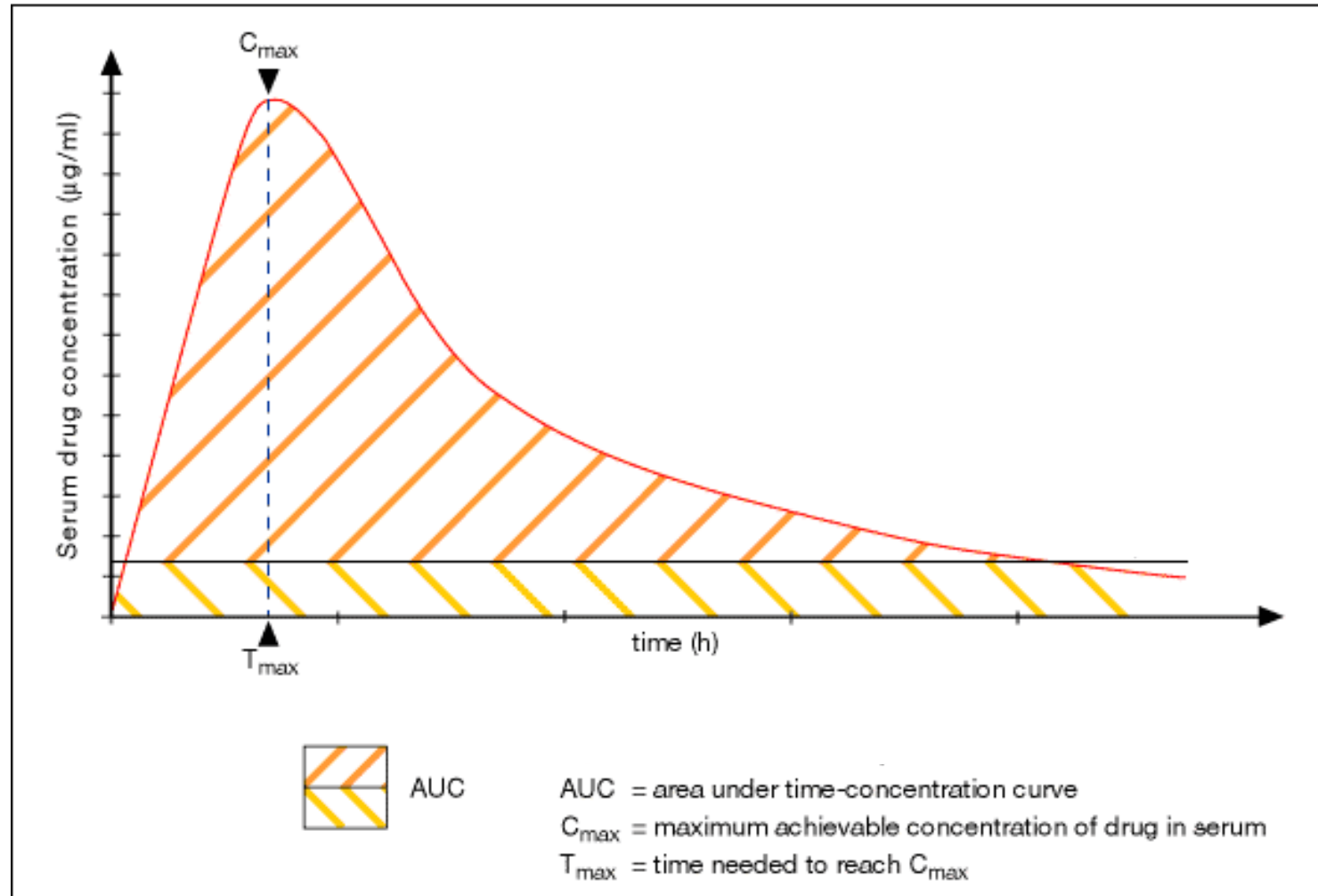
Content

Part I

- E-cigarettes
- Introduction to nicotine PK studies
- Study design for two e-cigarette nicotine PK studies
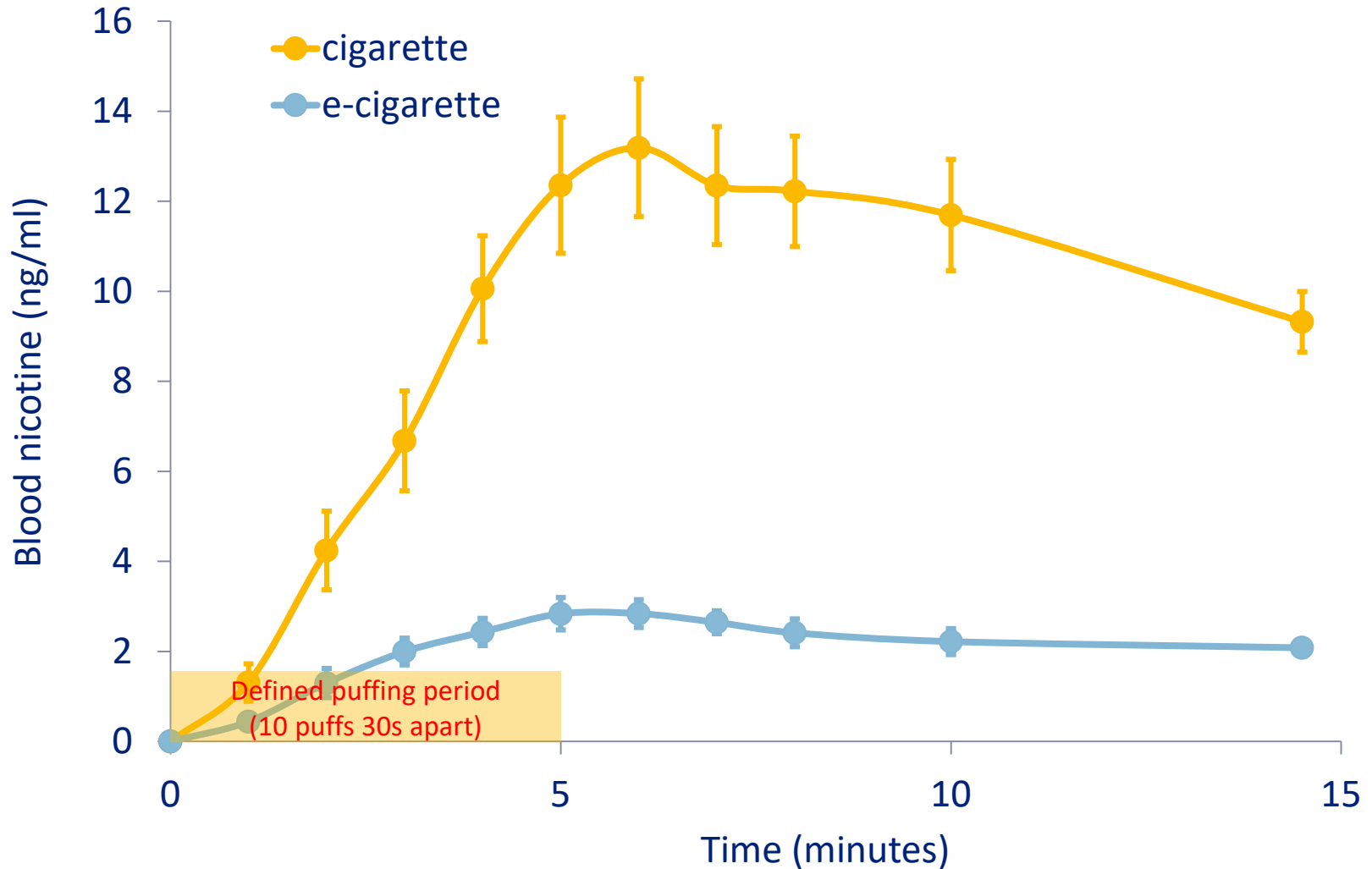 - Belfast, U.K.
  - Burbank, U.S.A.

Part II

- Data from U.K. and U.S.A. nicotine PK studies
- Discussion
  - What do our data tell us about nicotine delivery?
  - How can our data inform future study design?
  - Can we do it differently?

Interpreting PK data 101

AUC = area under time-concentration curve

C_{max} = maximum achievable concentration of drug in serum

T_{max} = time needed to reach C_{max}

BAT PK study #1 – nicotine data

BAT PK study #1 – PK data

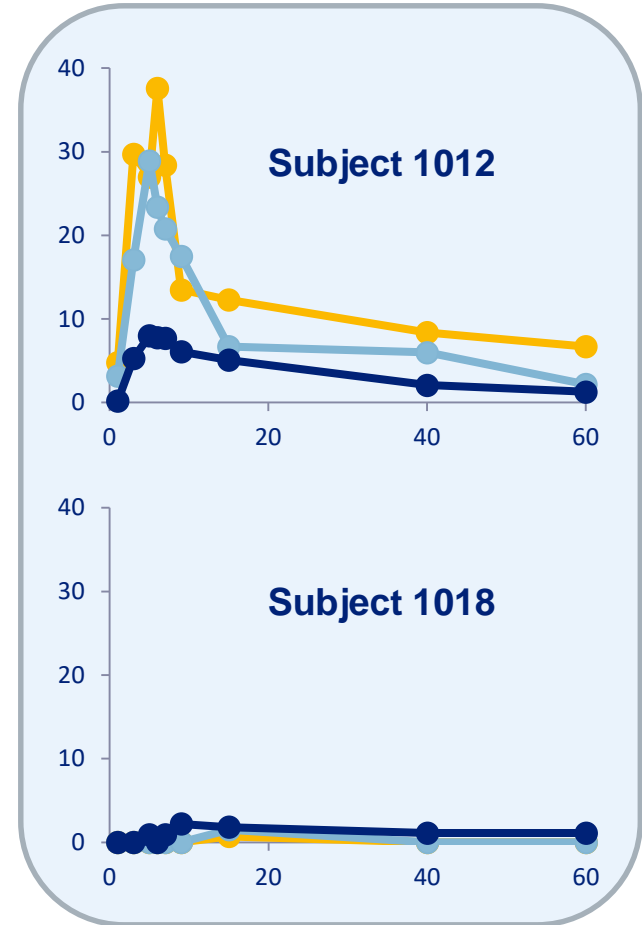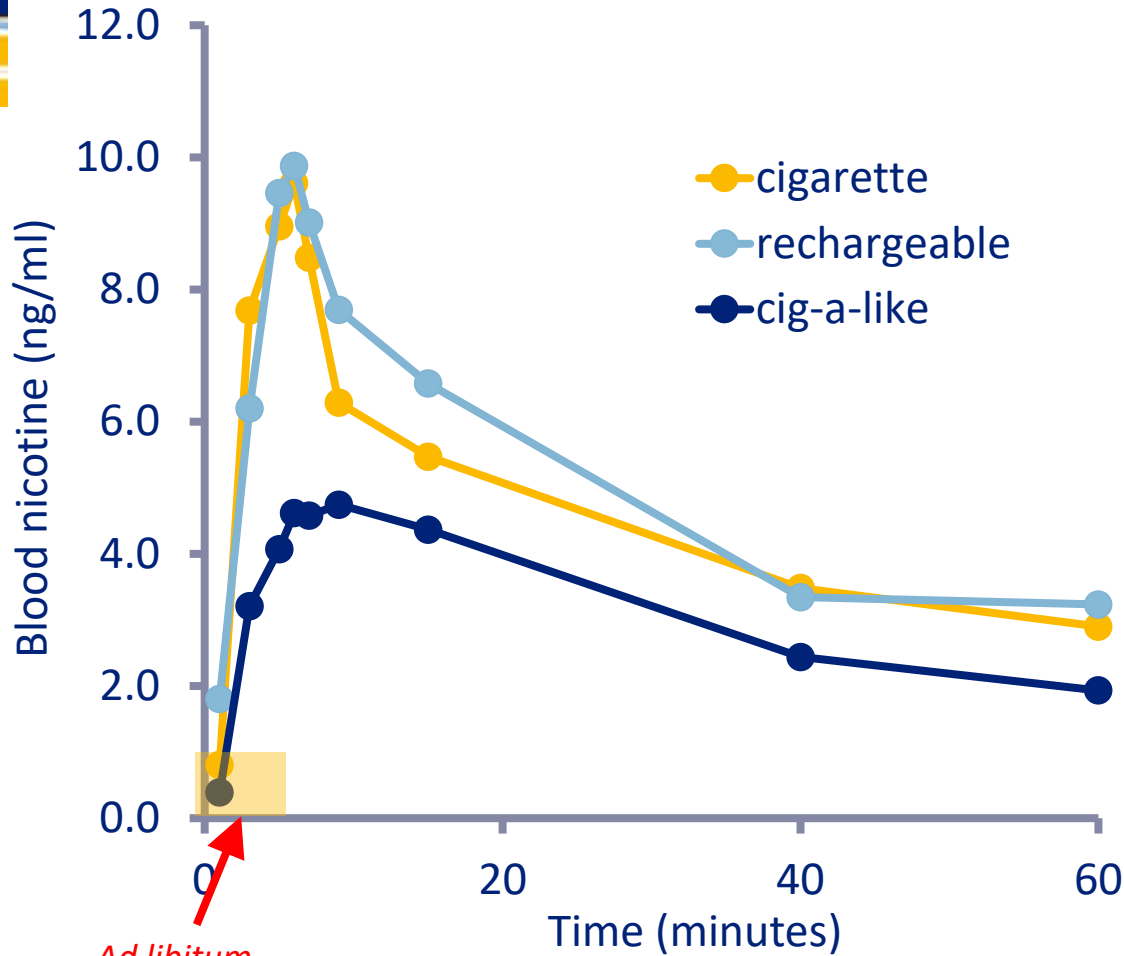| Parameter	Statistic	Period[#]	Cigarette (n=24)	e-cigarette (n=23)
C_{max} (ng/ml)	LS Geometric mean	Controlled	13.0	2.5*
	Geometric mean		13.4	2.5
	Geometric CV (%)		51.4	67.8
	Median		13.5	2.5
	Range (min – max)		5.3 - 35.5	0.5 - 6.9
C_{max} (ng/ml)	LS Geometric mean	Ad libitum	14.1	5.8*
	Geometric mean		14.9	5.9
	Geometric CV (%)		45.7	61.1
	Median		14.7	6.5
	Range (min – max)		6.9 - 40.6	1.6 - 12.5
t_{max} (min)	Median	Controlled	7.0	6.0[NS]
	Median	Ad libitum	75	75
$AUC_{0-14.5}$ (ng.h/ml)	LS Geometric mean	Controlled	2.1	0.4*
	Geometric mean		2.2	0.4
	Geometric CV (%)		45.5	60.5
	Median		2.2	0.5
	Range (min – max)		1.0 - 5.0	0.1 - 1.2

BAT PK study #1 – heart rate data
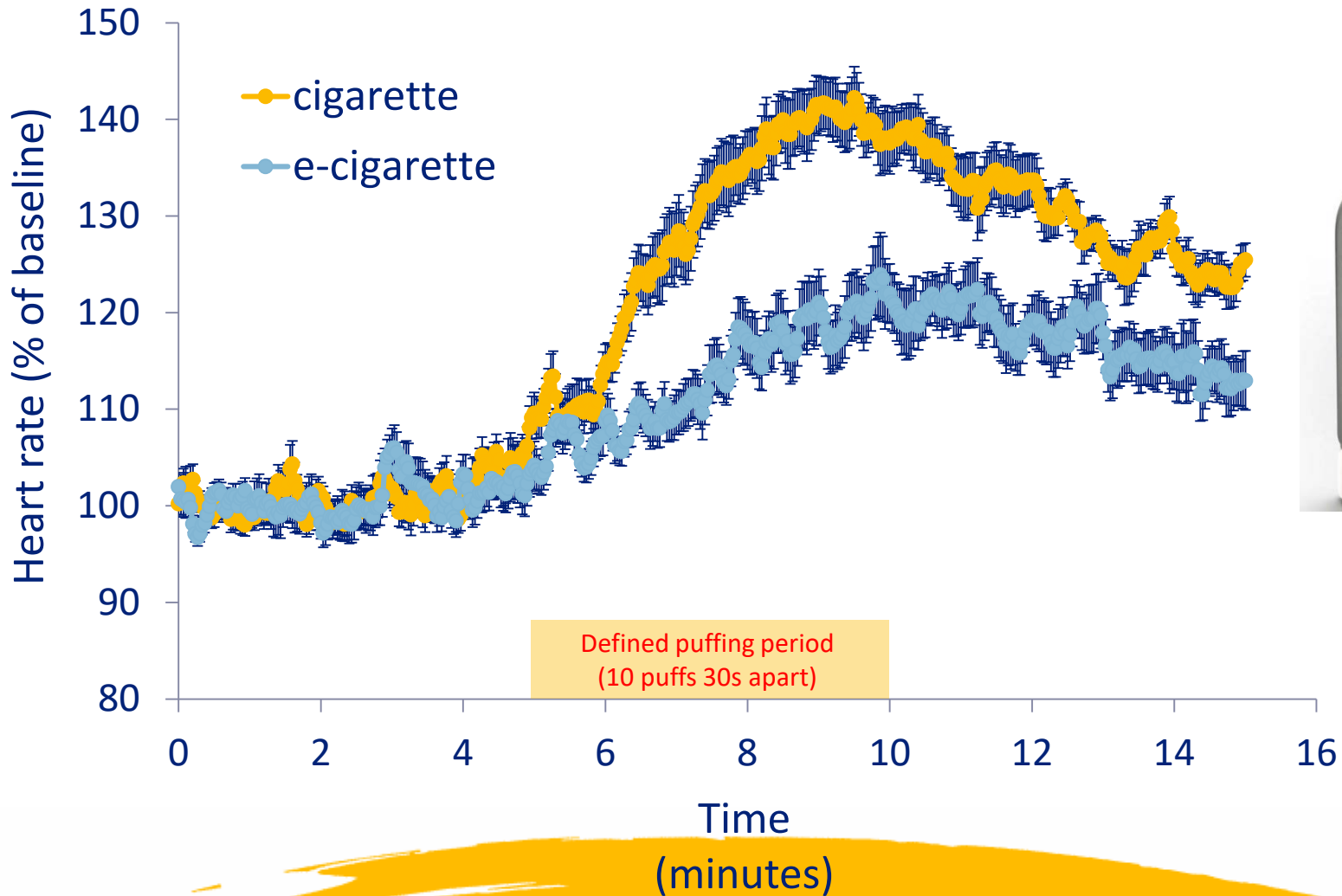
BAT PK study #1 summary

- E-cigarette nicotine delivery much lower than that of a cigarette under defined use conditions

- Potential for heart rate as a surrogate for blood nicotine

- Other data can be gained in these studies – smoking urges, satisfaction, cigarette consumption
  - be wary of subject overload

BAT PK study #2 – nicotine data

BAT PK study #2 – PK data

Parameter	Statistic	Cigarette (n=18)	Vype vPro e-cigarette (n=18)	Nicolites e-cigarette (n=18)
C_{max} (ng/mL)	LS Geometric mean	7.2	8.8[NS]	4.7[#NS]
	Geometric mean	7.2	7.8	4.7
	Geometric CV (%)	130.8	108.2	93.6
	Median	6.2	9.2	5.1
	Range (min – max)	0.7 - 37.6	0.0 - 40.2	1.2 - 18.2
t_{max} (min)	Median	6	6[NS]	9[NS]
$AUC_{0-60.0}$ (ng.h/mL)	LS Geometric mean	3.4	2.9[NS]	2.2[#NS]
	Geometric mean	3.4	2.9	2.2
	Geometric CV (%)	†	†	†
	Median	4.0	4.6	2.9
	Range (min – max)	0.2 - 11.5	0.0 - 15.6	0.0 - 6.3

†, unable to determine

BAT PK study #2 - summary

- Blood nicotine elevation far greater in vapers than in 'naïve' e-cigarette users

- Greater variability seen in this cohort
  - puffing/inhalation behaviour

- Potential need for better screening to ensure subjects meet study criteria

Is there a need for a standardised PK study protocol?

- How you design and run the study will impact the data you generate
    - Subject demographics
    - Product use

- Will this generate a headache for manufacturers and regulators as they try to assess products, potentially against one another?

- **Do we need, therefore, a standardised way of running nicotine PK studies, as far as is practically possible?**

A potential alternative approach using PBPK modelling

- Nicotine PK studies run according to GCP are expensive

- These studies are also resource-intensive

- Heart rate may be a potential surrogate
  - Product assessment
  - Not for regulatory submission
  - Still expensive and time-consuming

- Can we accurately model blood nicotine levels for assessment purposes?

A potential alternative approach using PBPK modelling

Commentary

Electronic Cigarette Effectiveness and Abuse Liability: Predicting and Regulating Nicotine Flux

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Abstract

Electronic cigarettes (ECIGs) comprise an aerosolized nicotine delivery product category that provides consumers with probably unprecedented control over extensive features and operating conditions, allowing a wide range of nicotine yields to be obtained. Depending on the combination of such ECIG variables as electrical power input, geometry, liquid composition, and puff behavior, ECIG users can extract in a few puffs far more or far less nicotine than with a conventional combustible cigarette. These features of ECIG design and use present challenges for public health policy, central among which is the question of how to regulate nicotine delivery. In this commentary, we propose a conceptual framework intended to provide a convenient approach for evaluating and regulating the nicotine emitted from ECIGs. This framework employs nicotine flux to account for the total dose and rate at which nicotine reaches the user, 2 key factors in drug abuse liability. The nicotine flux is the nicotine emitted per puff second (e.g., mg/s) by a given ECIG design under given use conditions, and it can be predicted accurately using physical principles. We speculate that if the flux is too low, users likely will abandon the device and maintain conventional tobacco product use. Also, we speculate that if the flux is too high, individuals may suffer toxic side effects and/or the device may have higher-than-necessary abuse liability. By considering ECIG design, operation conditions, liquid composition, and puff behavior variables in combination, we illustrate how ECIG specifications can be realistically mandated to result in a target flux range.
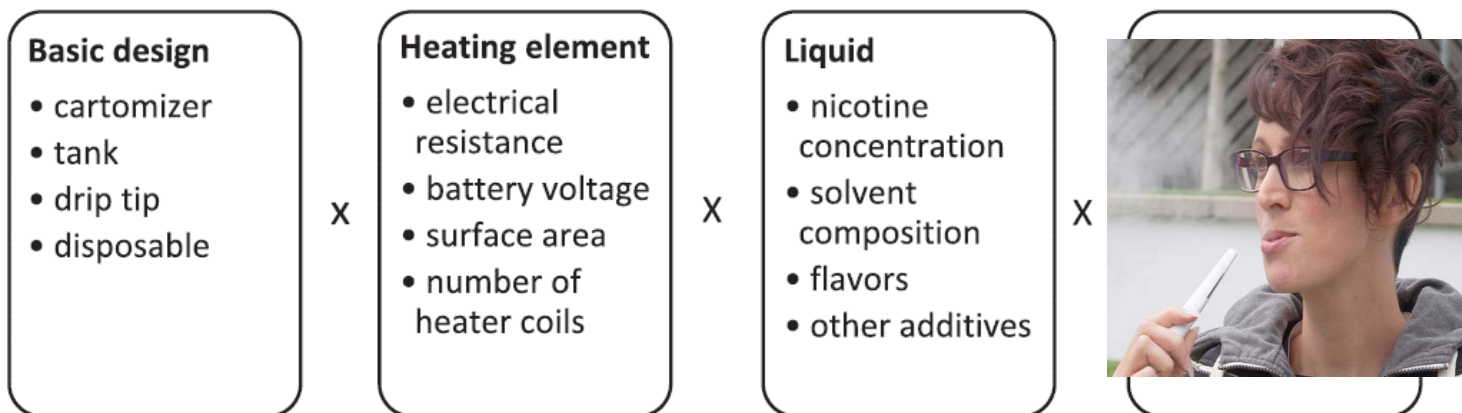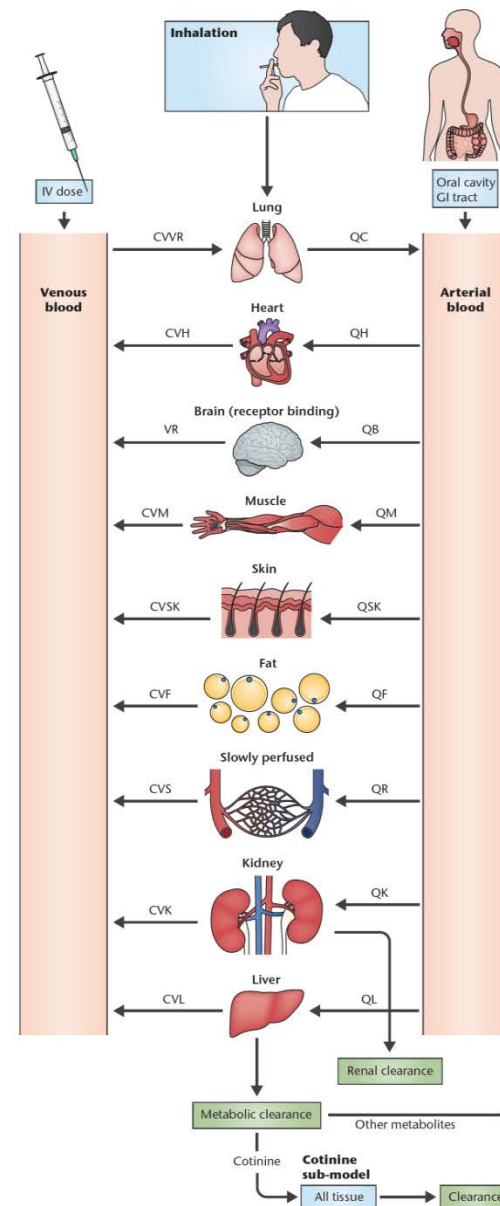
A potential alternative approach using PBPK modelling

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- Multi-compartment nicotine model

- Cotinine sub-model

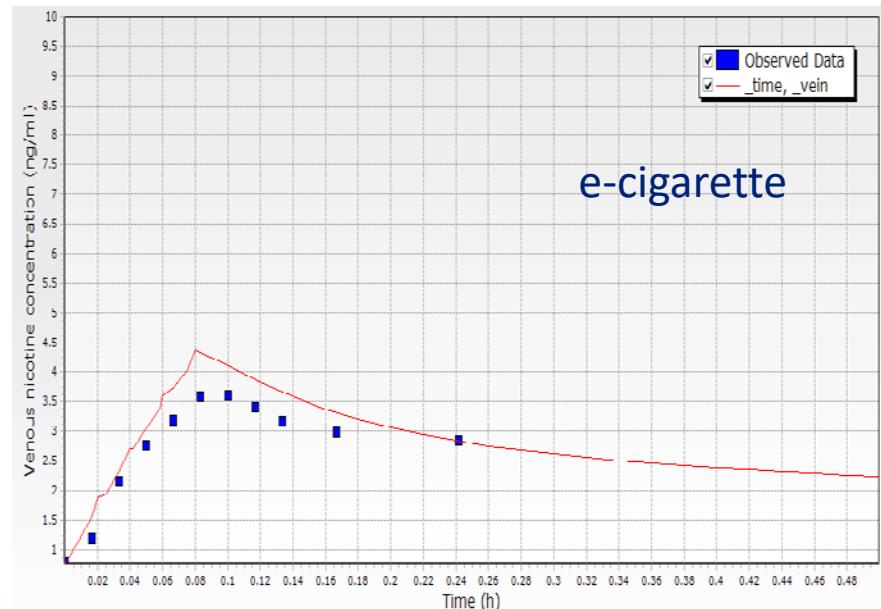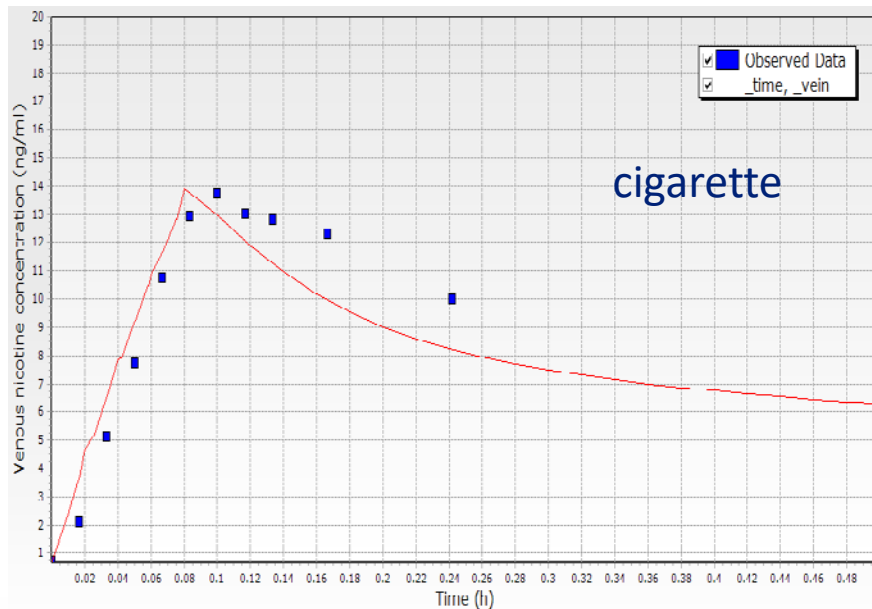- Renal and metabolic clearance applied to kidney and liver

Predicting blood nicotine from PK study #1

Inputs: Estimated puff nicotine yields; puff counts
Average study body weight (76.4 kg)
Nicotine cartridge weights

Assumptions: 30% mouthspill

—— modelled   ■ actual

Summary

- Nicotine PK studies have provided us with a wealth of insight into e-cigarette performance

- Such studies help us understand our products and may be a requirement for regulatory submissions and/or claims

- Standardised protocol will help compare products

- For product development purposes, there might be potential surrogates
  - heart rate
  - PBPK modelling

Acknowledgements

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