



Nicotine pharmacokinetics of electronic cigarettes: experimental data and a review of the literature

Ian M. Fearon, Alison Eldridge, Nathan Gale, Mike McEwan

Paul R. Nelson, Mitch Stiles, Elaine Round

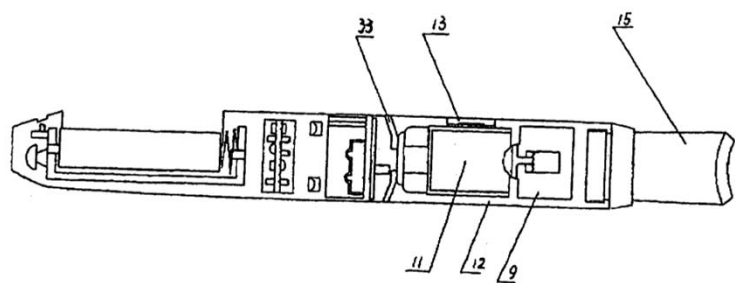
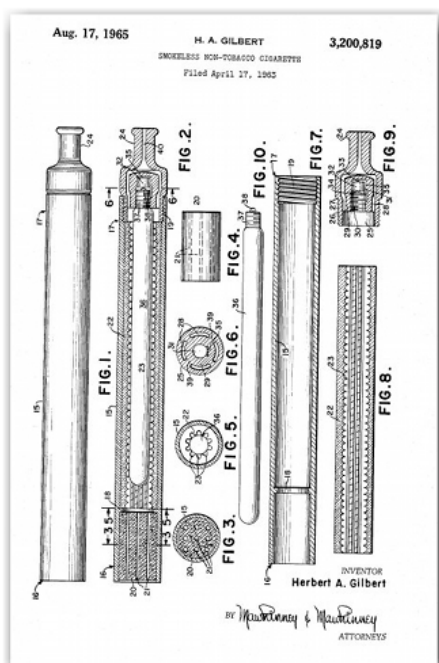
71st Tobacco Science Research Conference. 30th November 2017, Bonita Springs, Florida, USA

Content

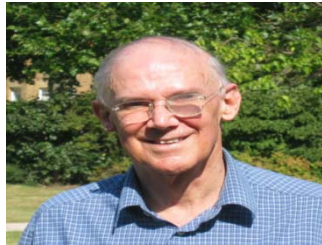


- E-cigarettes and public health
- E-cigarette evolution
- Nicotine pharmacokinetic studies
- A review of the literature
- Is there a need for standardisation?
- Alternatives to pharmacokinetic studies
- Summary

A very brief history of e-cigarettes



Why might e-cigarettes provide public health benefit?



Professor Michael Russell brought recognition that cigarette smoking is a classic drug dependence behaviour, underpinned by nicotine addiction

People smoke for nicotine but they die from the tar.

British Medical Journal, 1976, **1**, 1430-1433

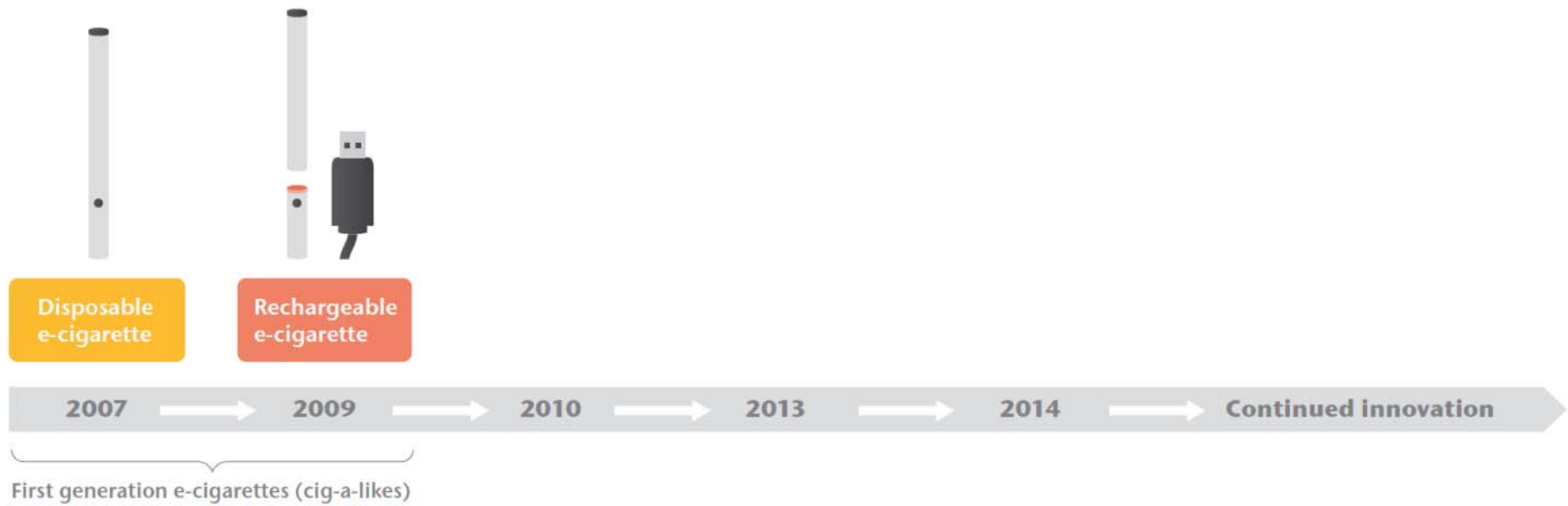


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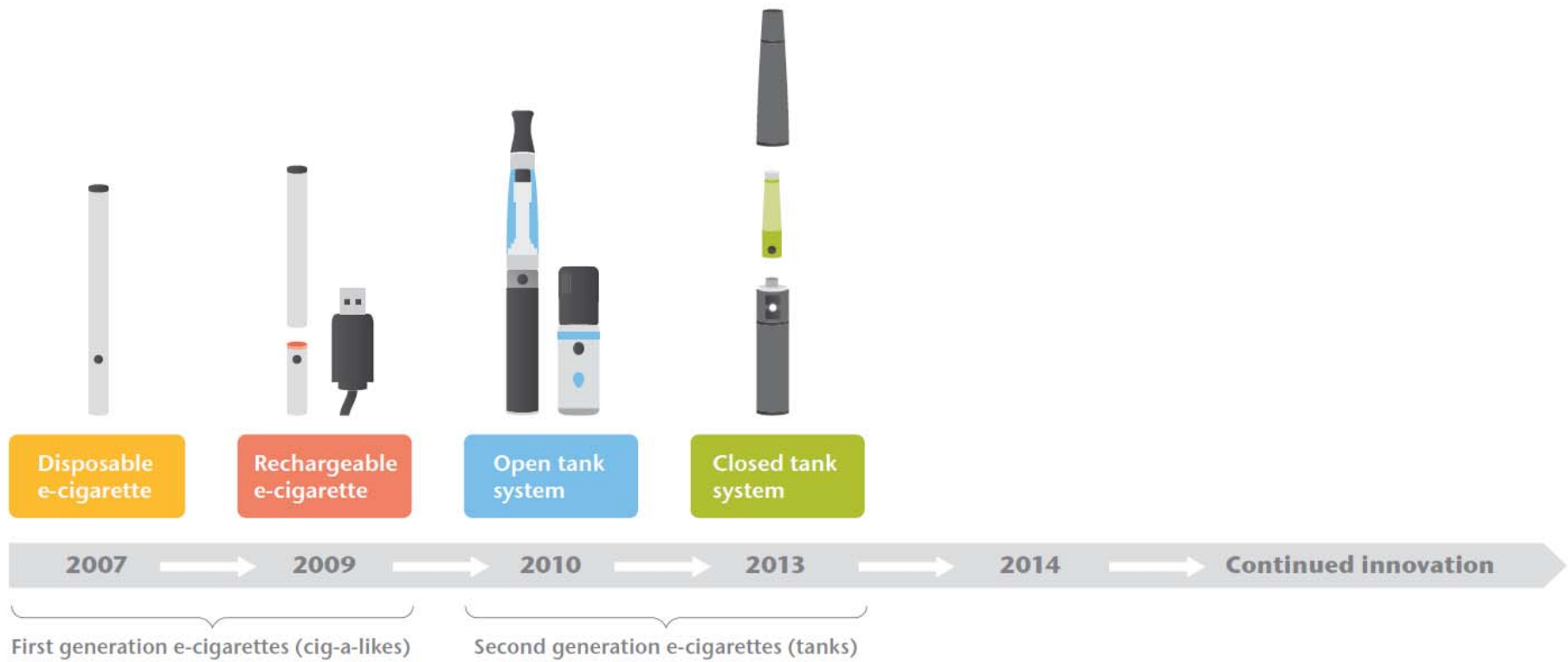
“...demonstrate that smokers smoke predominantly for nicotine, that nicotine itself is not especially hazardous, and that if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives could be saved” (2007).

“...the RCP believes that e-cigarettes could lead to significant falls in the prevalence of smoking in the UK, prevent many deaths and episodes of serious illness....” (2014).

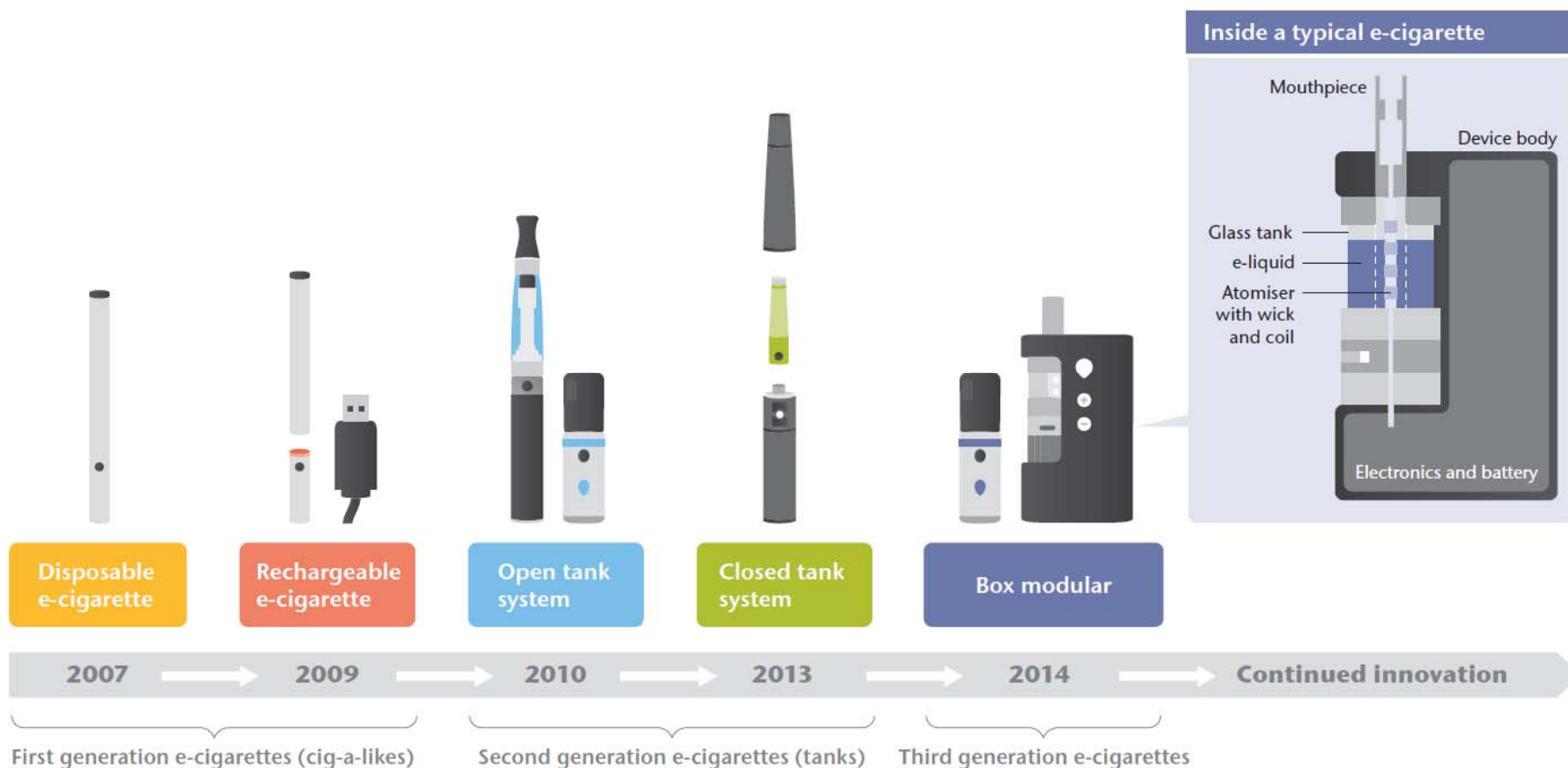
E-cigarette evolution



E-cigarette evolution



E-cigarette evolution



Nicotine pharmacokinetic studies

Why are they important?



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Nicotine without smoke
Tobacco harm reduction

- > Nicotine regulatory approaches should therefore be designed to encourage as many smokers as possible to either quit all nicotine use, or switch completely from smoking to an alternative source of nicotine.
- > Products are regulated to ensure that they are safe and fit for purpose. Regulation of e-cigarettes and other similar products should therefore aim to minimise potential exposure to harmful vapour constituents, ensure that those that deliver nicotine do so in doses that smokers find satisfying, and encourage substitution for smoked tobacco.

Nicotine pharmacokinetic studies

Why are they important?



Guidance for Industry

Applications for Premarket Review of New Tobacco Products

Your studies in adult human subjects should provide the following evaluations of your tobacco product:

Abuse liability and addictiveness

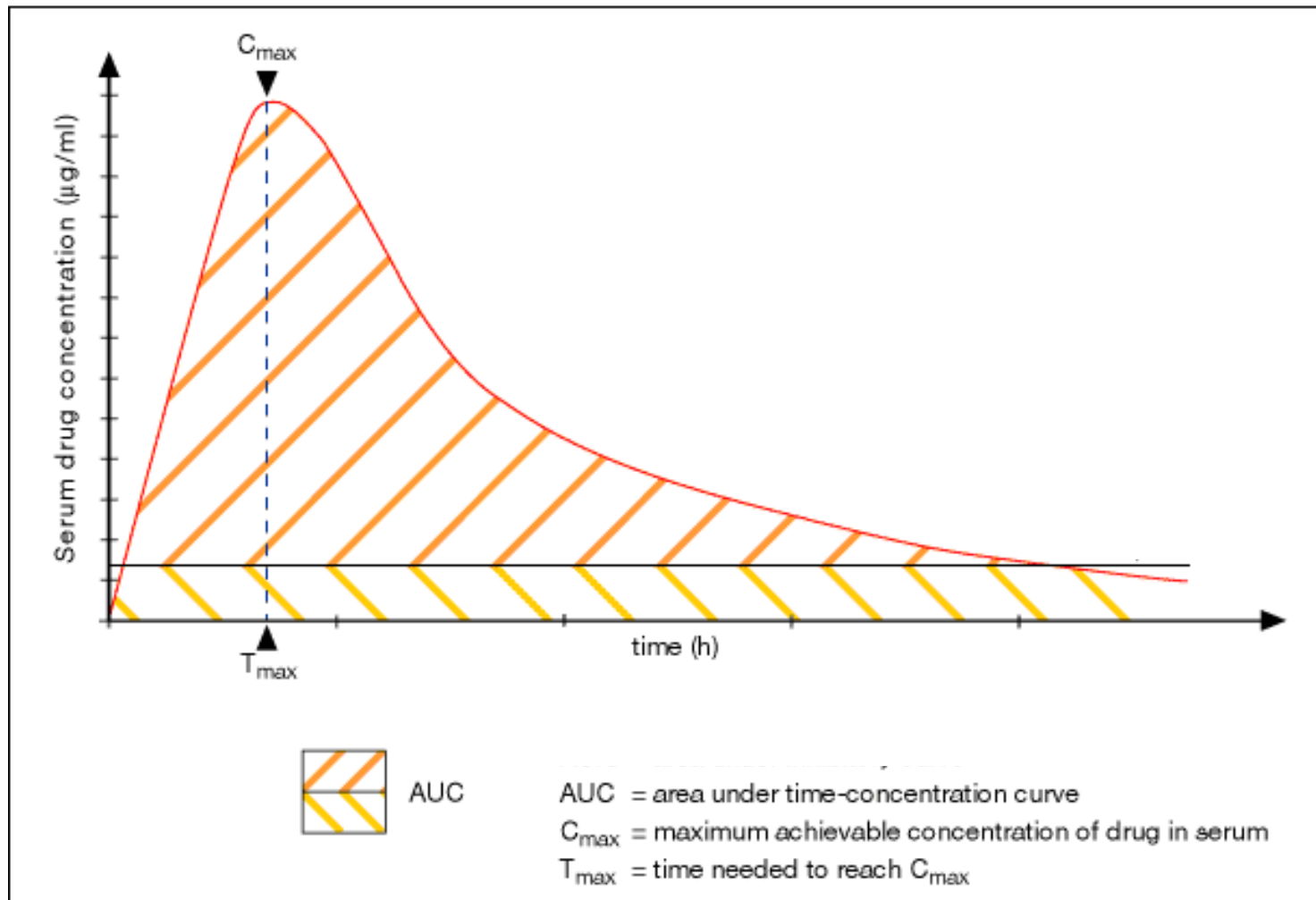
Guidance for Industry

Modified Risk Tobacco Product Applications

“FDA recommends that applicants conduct human abuse liability studies to assess the impact of various features of the product on the speed and efficiency of nicotine delivery and the formation of unprotonated nicotine”.

Nicotine pharmacokinetic studies

Interpreting PK data

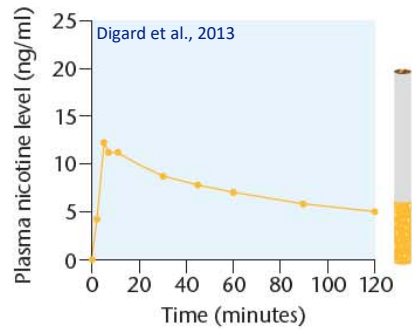


A review of the literature

Nicotine pharmacokinetics have evolved over time



Cigarette

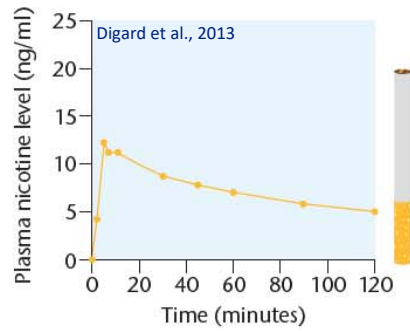


A review of the literature

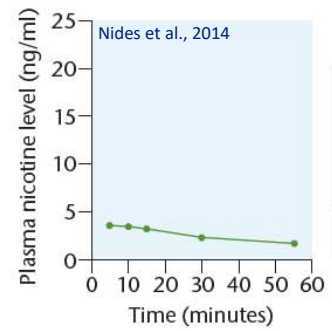
Nicotine pharmacokinetics have evolved over time



Cigarette



Disposable e-cigarette

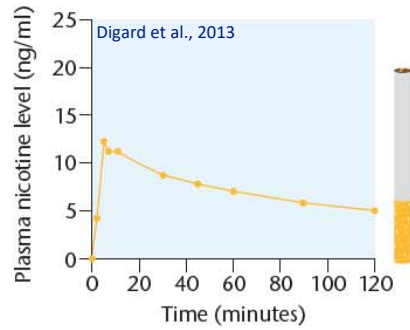


A review of the literature

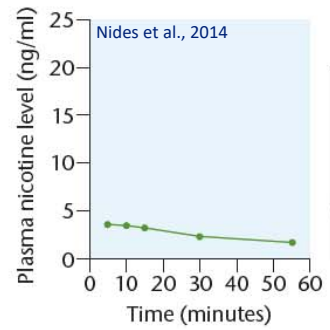
Nicotine pharmacokinetics have evolved over time



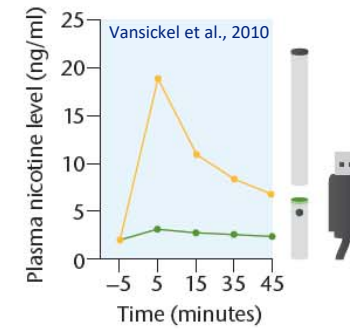
Cigarette



Disposable e-cigarette



Rechargeable e-cigarette

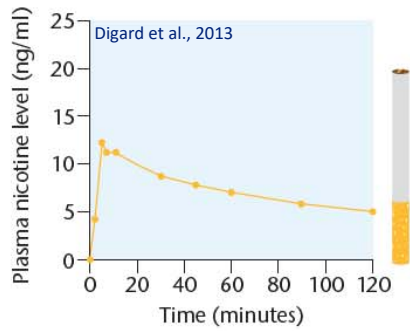


A review of the literature

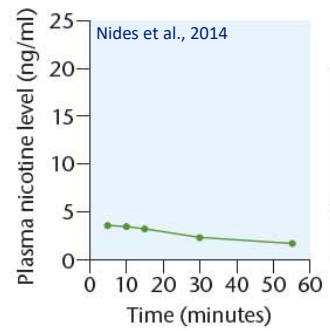
Nicotine pharmacokinetics have evolved over time



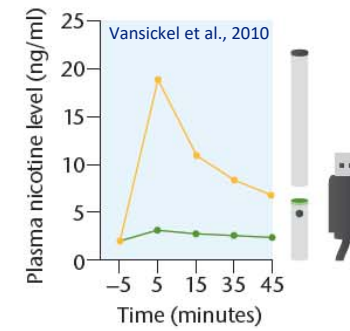
Cigarette



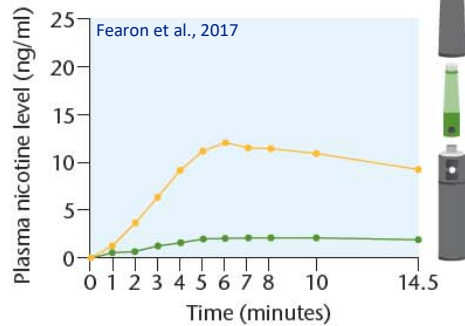
Disposable e-cigarette



Rechargeable e-cigarette



Closed tank system

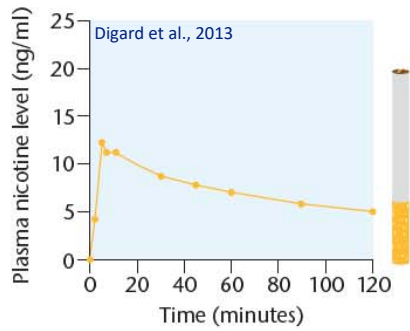


A review of the literature

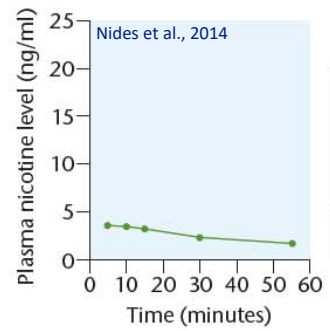
Nicotine pharmacokinetics have evolved over time



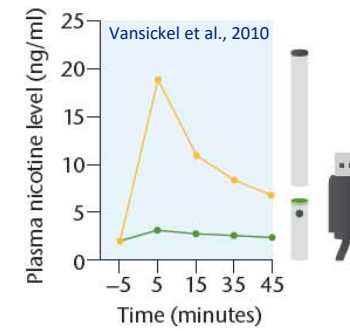
Cigarette



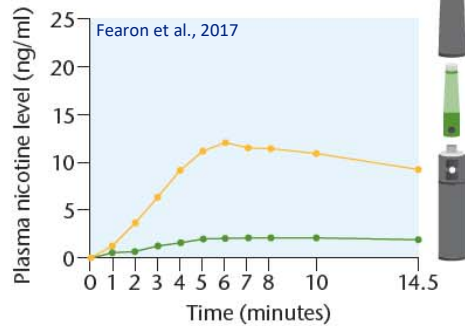
Disposable e-cigarette



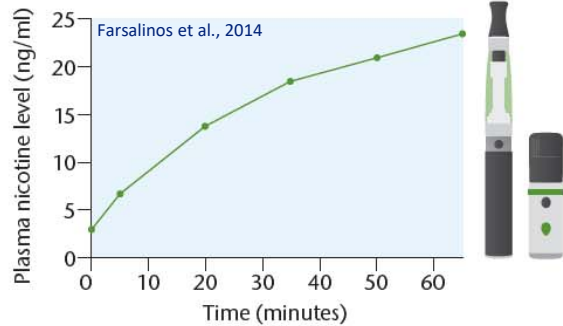
Rechargeable e-cigarette



Closed tank system



Open tank system

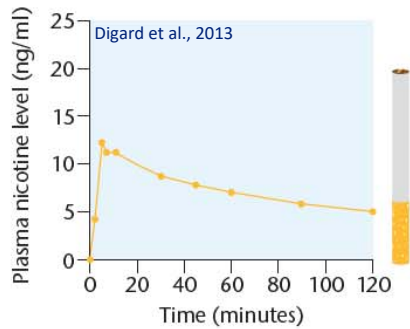


A review of the literature

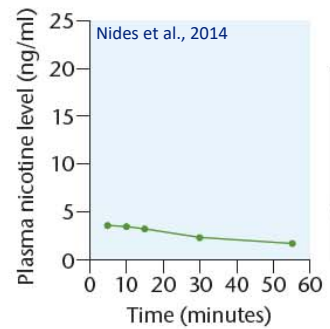
Nicotine pharmacokinetics have evolved over time



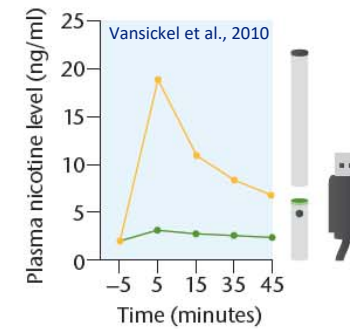
Cigarette



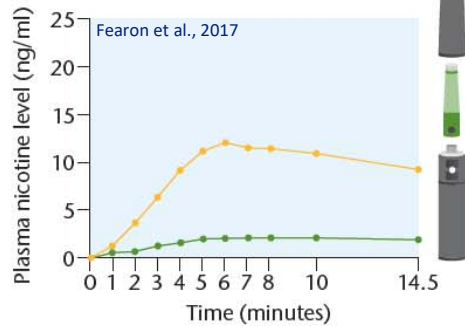
Disposable e-cigarette



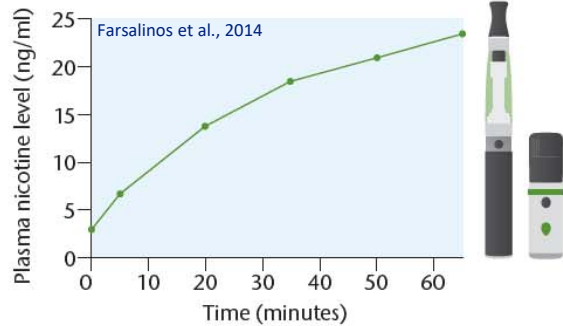
Rechargeable e-cigarette



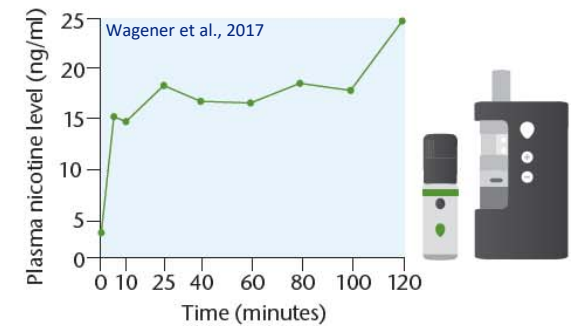
Closed tank system



Open tank system



Box modular



A review of the literature

Nicotine pharmacokinetics have evolved over time



First-generation

Study	E-cigarette C _{max}
Bullen et al., 2010	1.3 ng/ml
Vansickel et al., 2010	Not reported due to insignificant change from baseline
Dawkins & Corcoran, 2014	6 ng/ml (defined) 13 ng/ml (<i>ad libitum</i>)
Hajek et al., 2014	4.6 ng/ml
Nides et al., 2014	3.5 ng/ml
Farsalinos et al., 2014	2 ng/ml (defined) 13 ng/ml (<i>ad libitum</i>)
D’Ruiz et al., 2015; Yan & D’Ruiz, 2015	10-17 ng/ml (defined) 14-22 ng/ml (<i>ad libitum</i>)
St. Helen et al., 2016	9.1 ng/ml (V2 cigs) 4.4 ng/ml (blu)
Walele et al., 2016	2.5 and 3.6 ng/ml during fourth repeat of puffing regime
Fearon et al., 2017	4.7 ng/ml
Hajek et al., 2017	7.5-13.6 ng/ml
Stiles et al., 2017	3.0-5.4 ng/ml

Newer-generation

Study	E-cigarette C _{max}
Vansickel & Eissenberg, 2013	8 ng/ml (defined) 16 ng/ml (<i>ad libitum</i>)
Farsalinos et al., 2014	4 ng/ml (defined) 21 ng/ml (<i>ad libitum</i>)
Farsalinos et al., 2015	Smokers 2.7 ng/ml (defined) and 12.2 ng/ml (<i>ad libitum</i>) E-cigarette users 12.8 ng/ml (defined) and 22.0 ng/ml (<i>ad libitum</i>)
Dawkins et al., 2016	22.0 ng/ml (low nicotine e-liquid) 43.6 ng/ml (high nicotine e-liquid)
St. Helen et al., 2016	2-20 ng/ml
Wagener et al., 2016	Second-generation 7.3 ng/ml (defined) and 23.5 ng/ml (<i>ad libitum</i>) Third-generation 17.5 ng/ml (defined) and 24.8 ng/ml (<i>ad libitum</i>)
Hajek et al., 2017	9.9 ng/ml (open tank) 11.9 ng/ml (modular)

What else did the review tell us?

Experienced users get more nicotine than naïve users



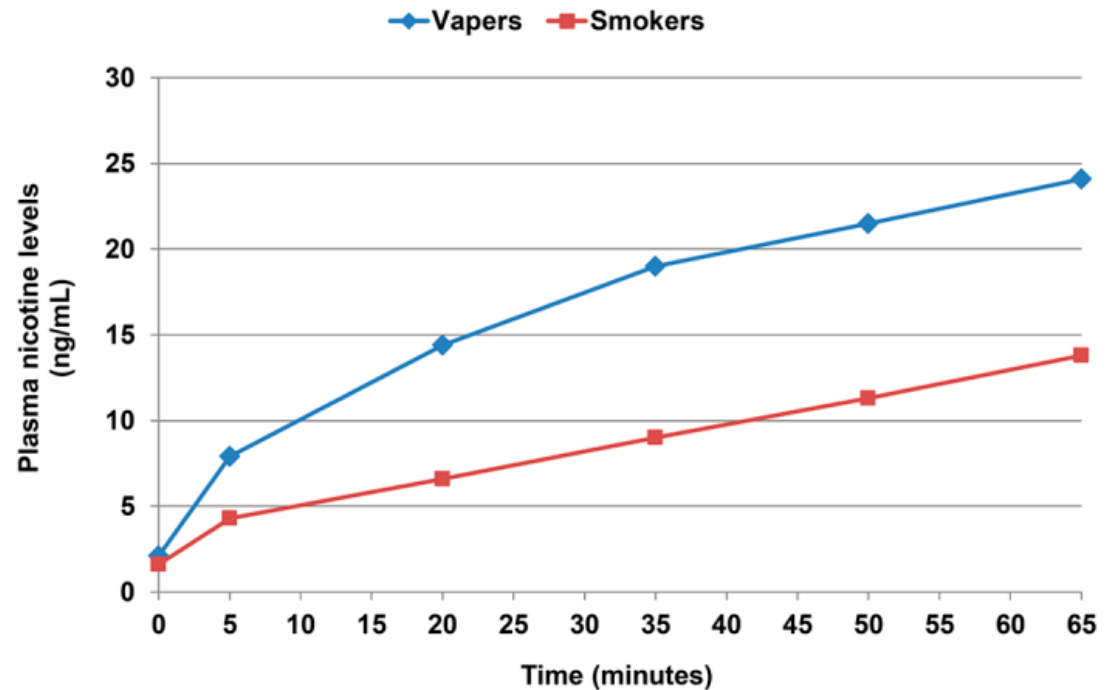
SCIENTIFIC REPORTS

OPEN

Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naïve users (smokers)

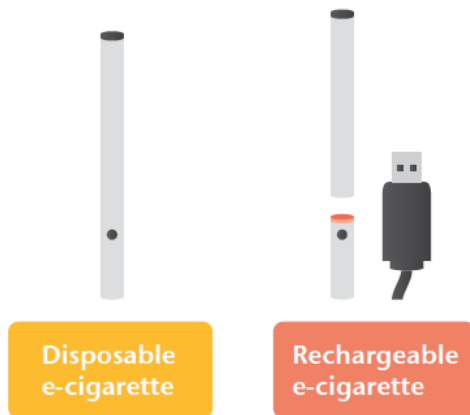
Received: 14 January 2015
Accepted: 23 April 2015
Published: 17 June 2015

Konstantinos E. Farsalinos^{1,2}, Alketa Spyrou¹, Christos Stefanopoulos¹, Kalliroi Tsimopoulou¹, Panagiota Kourkouveli¹, Dimitris Tsiapras¹, Stamatios Kyrzopoulos¹, Konstantinos Poulas² & Vassilis Voudris¹



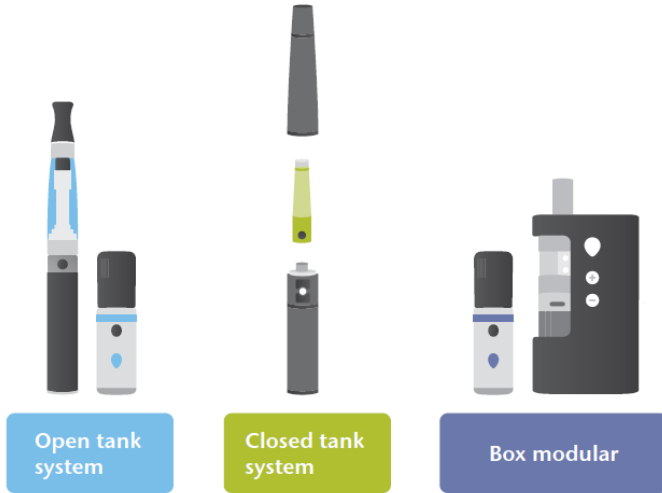
- Other studies (Hajek et al., 2015; Fearon et al., 2017) support this finding

Is there a need for standardisation?



Study	Subjects	Product use regimen
Bullen et al., 2010	Exclusive smokers	<i>Ad libitum</i> for 5 minutes
Vansickel et al., 2010	Exclusive smokers	10 puffs, 30 seconds apart, for 5 minutes
Dawkins & Corcoran, 2014	Regular e-cigarette users	10 puffs in 5 minutes, followed by <i>ad libitum</i> for 1 hour
Hajek et al., 2014	Exclusive smokers	<i>Ad libitum</i> for 5 minutes
Nides et al., 2014	Exclusive smokers	10 puffs in 5 minutes
Farsalinos et al., 2014	Regular e-cigarette users	10 puffs in 5 minutes followed by <i>ad libitum</i> for 1 hour
D’Ruiz et al., 2015; Yan & D’Ruiz, 2015	Exclusive smokers	50 5-second puffs, 30 seconds apart for 25 minutes <i>Ad libitum</i> for 1 hour
St. Helen et al., 2016	Regular e-cigarette users	10 puffs, 30 seconds apart, for 7.5 minutes
Walele et al., 2016	Exclusive smokers	10 4-second puffs, 30 seconds apart for 5 minutes; four repeats, each an hour apart
Fearon et al., 2017	Regular e-cigarette users	<i>Ad libitum</i> for 5 minutes
Hajek et al., 2017	Regular e-cigarette and conventional cigarette dual-users	<i>Ad libitum</i> for 5 minutes
Stiles et al., 2017	Exclusive smokers	<i>Ad libitum</i> for 10 minutes

Is there a need for standardisation?



Study	Subjects	Product use regime
Vansickel & Eissenberg, 2013	Regular e-cigarette users	10 puffs in 5 minutes, followed by <i>ad libitum</i> for 1 hour
Farsalinos et al., 2014	Regular e-cigarette users	10 puffs in 5 minutes followed by <i>ad libitum</i> for 1 hour
Farsalinos et al., 2015	Exclusive smokers and experienced e-cigarette users	10 puffs in 5 minutes followed by <i>ad libitum</i> for 1 hour
Dawkins et al., 2016	Regular e-cigarette users	<i>Ad libitum</i> for 60 minutes
St. Helen et al., 2016	Regular e-cigarette users	10 puffs, 30 s apart for 7.5 minutes
Wagener et al., 2016	Regular e-cigarette users	10 puffs in 5 minutes, followed by <i>ad libitum</i> for 115 minutes
Hajek et al., 2017	Regular e-cigarette and conventional cigarette dual-users	<i>Ad libitum</i> for 5 minutes

Alternatives to PK studies



Commentary

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

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Abstract

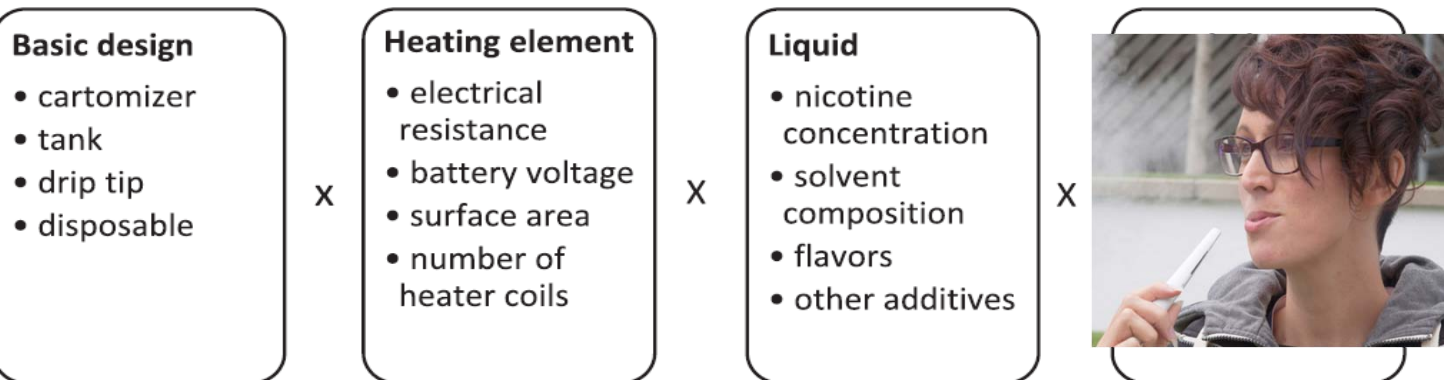
Electronic cigarettes (ECIGs) comprise an aerosolized nicotine delivery product category that provides consumers with probably unprecedented control over extensive features and operating conditions, allowing a wide range of nicotine yields to be obtained. Depending on the combination of such ECIG variables 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.

Nicotine & Tobacco Research, 2015, 158–162

doi:10.1093/ntr/ntu175

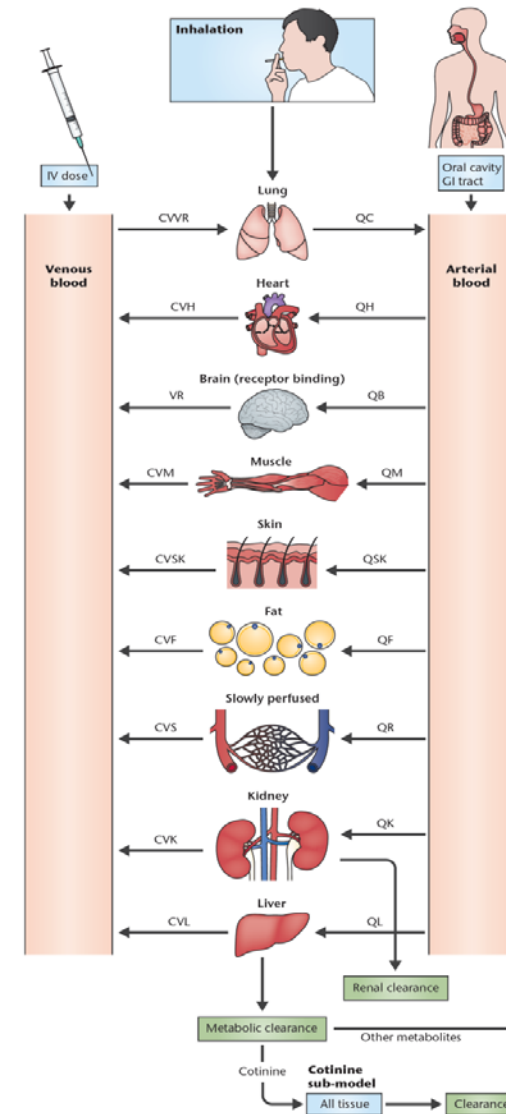
Advance Access publication September 1, 2014

Commentary



Alternatives to PK studies

- Physiologically-based pharmacokinetic (PBPK) modelling
- Multi-compartment nicotine model
- Three routes of exposure; IV dosing, inhalation and oral (from chewing gum; Teeguarden et al, 2012)
- Cotinine sub-model
- Renal and metabolic clearance applied to kidney and liver



Alternatives to PK studies

Predicting blood nicotine from PK study



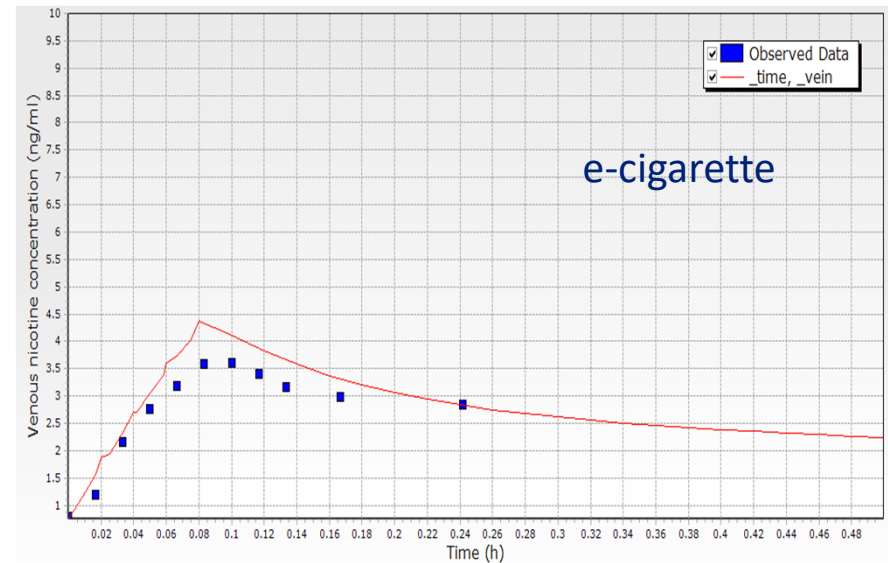
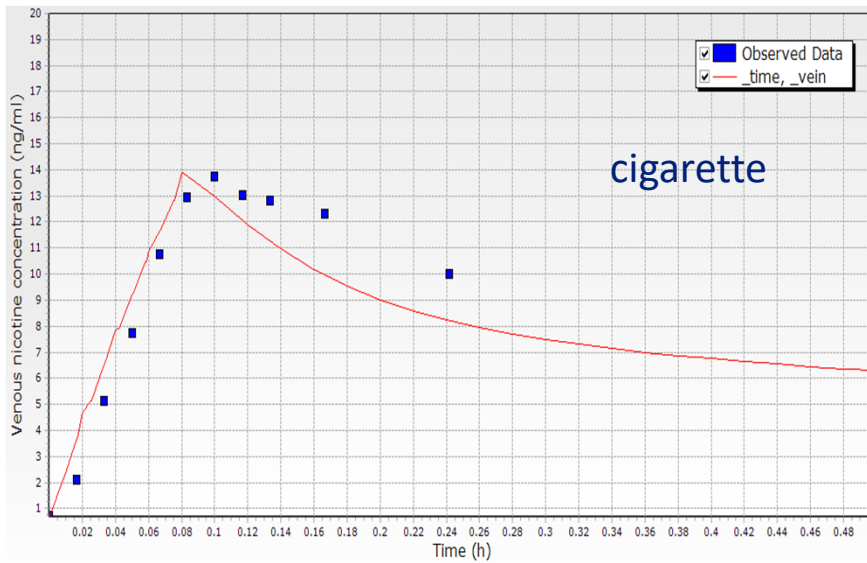
Inputs (Fearon *et al.*, 2017):

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

Assumptions:

30% mouthspill

— modelled ■ actual

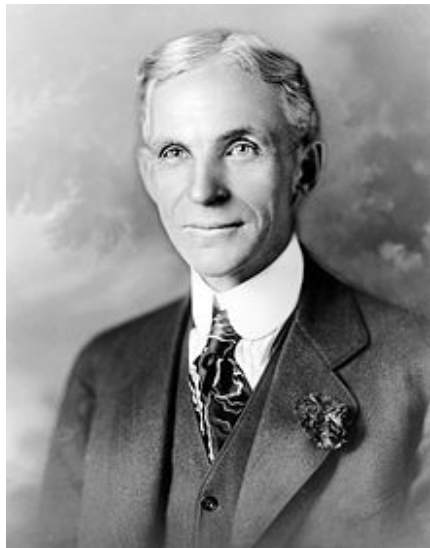


Nicotine PK data from Fearon *et al.*, 2017

Summary



- Nicotine pharmacokinetics proposed eg. RCP to be an important determinant in smoking displacement
- E-cigarettes and nicotine pharmacokinetics have co-evolved over time
- Protocol standardisation may facilitate better comparisons
 - Product use definition
 - Smokers vs e-cigarette users
- Alternatives to pharmacokinetic studies may be useful
 - Nicotine flux approach limited
 - PBPK models may be more appropriate



Coming together is a beginning,
staying together is progress, and
working together is success.
Henry T. Ford

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