TOX/2021/21

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

First draft Addendum to the statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): presence and pharmacokinetics of nicotine salts.

Background

1. At the December 2020 COT meeting, the committee reviewed published data on the presence of nicotine salts in ENDS products and effects of inhaling nicotine in the salt form from ENDS products on internal exposure to nicotine. A draft addendum to the COT Statement on electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes) has been prepared summarising this discussion which is attached at Annex A.

2. In addition, the Committee requested for an overview to be provided of a publication on 'nicotine flux' co-authored by Eissenberg. This publication is summarised below, and a Figure provided in Annex B.

Shihadeh A, Eissenberg T (2015). Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine & Tobacco Research, 17, 158-162.

3. The publication of Shihadeh and Eissenberg addresses the question of the regulation of nicotine delivery from electronic nicotine delivery systems (ENDS), comparing and contrasting this with the situation for conventional cigarettes (CC). A conceptual framework intended to provide an approach for evaluating and regulating the nicotine emitted from ENDS is proposed.

4. In considering the potential for both nicotine toxicity and drug abuse, total dose and speed of delivery are key variables. For a CC, usage characteristics lie within a relatively narrow range – a single cigarette is typically consumed over approximately 5 min, with 8-15 puffs taken. Nicotine yield may be described as total dose per CC and/or as the speed of delivery (yield per 5 min). In the case of ENDS devices, the situation is more complicated, given the wide range of possible product designs, operating conditions, and individual user parameters.

5. Instead for ENDS devices, Shihadeh and Eissenberg suggest that it is the overall 'nicotine flux' which should be considered to be the important factor in evaluating the balance between utility and safety. Individual metrics to be taken into account in the consideration of nicotine flux include design, heating element features, e-liquid contents, and user behaviour (puff topography).

6. The publication of Shihadeh and Eissenberg defines nicotine flux, $\dot{m}_{nic}$, as the mass obtained from an ENDS device per puff second (mg/s). The nicotine dose can be computed per puff, use episode, or day, by integrating the nicotine flux over any of these defined periods. Dose = $\int \dot{m}_{nic}(t)dt$.

7. Nicotine flux depends on 'design efficacy index' (Z_d), which represents the effect of product characteristics on nicotine flux, and 'puffing intensity parameter' (Z_p), which represents the ways that puff topography can influence nicotine flux. Guided by dimensional analysis, Z_d and Z_p can be chosen in a manner that the nicotine fluxes from all ENDS design and operating condition combinations collapse onto a single universal surface[1] relating flux, Z_d and Z_p. This surface could allow regulators to compute possible nicotine flux span for a given product over a range of potential use scenarios.

Figure representing potential use of nicotine flux as a regulatory tool

8. A figure is provided in the paper illustrating a theoretical nicotine flux surface plot over a range of three hypothetical ENDS products/usage conditions, and this figure is reproduced in Annex B. The figure plots 'Puffing intensity' (Z_p) versus 'Design efficacy' (Z_d), and nicotine flux is represented over a range of 0-65 µg/s by colours representing hypothetical categories that the authors suggest could be defined by a regulatory agency: ranging from dark blue to light blue ('ineffective') through green and yellow ('target') to orange, red, and dark red ('unsafe'). The hypothetical regulatory target range for product effectiveness in this example is given as 25-45 µg/s.

9. Product A is a variable-voltage device that the user can fill with their own e-liquid. This product has an inefficient heater, leading to poor aerosolization, and thus nicotine flux mostly spans the dark blue to light blue area, only achieving yellow to green at the highest available voltages and e-liquid nicotine concentrations. The product occupies a large nicotine flux surface, but mostly with an unacceptably low nicotine flux.

10. Product B is a fixed voltage device sold with prefilled disposable cartridges of fixed nicotine concentration. The nicotine flux surface for this product spans a wide area from light blue to red, with long puff durations allowing potentially unsafe nicotine fluxes.

11. Product C is identical to product B except that it contains a microchip that switches off power to the heater coil on reaching a pre-set puff duration; at this point, a minimum timespan must elapse before another puff can be taken. Thus, the nicotine flux surface of product C covers a subset of that for product B, mostly spanning the green to yellow region.

[1] This concept is illustrated in Figure 1 at Annex B.

12. Overall, in consideration of a regulatory framework for safety and effectiveness, products A and B would raise cause for concern based on their design features and knowledge of plausible ranges of user puff topography. Product A is likely to be ineffective in preventing nicotine cravings (and hence CC use) in individuals attempting to quit smoking, while product B is of concern in terms of the potential for nicotine toxicity (including short-term effects such as nausea and vomiting and longer-term effects) and/or the promotion of addiction in nicotine-naïve users. Product C is considered to represent the middle ground, allowing users to function within a nicotine flux surface that spans an area including absence of toxicity and a sufficiently high nicotine intake to provide suppression of nicotine cravings.

Questions for the Committee

13. Members are invited to review the information provided in this paper and to consider the following questions:

i. Does the Committee have any comments on the addendum to the E(N)NDS statement provided in Annex A?

ii. Is there any information on nicotine flux that would be helpful to add to Annex A?

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Abbreviations

CC	Conventional cigarette
ENDS	Electronic nicotine delivery system
E(N)NDS	Electronic nicotine (and non-nicotine) delivery system

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Addendum to the statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): presence and pharmacokinetics of nicotine salts. – First Draft

Draft text on the presence and pharmacokinetics of nicotine salts, to be included as an addendum to the COT statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes).

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Introduction

1. Although the nicotine present in electronic nicotine delivery system (ENDS) products has predominantly been in the 'freebase' form, some more recent products contain organic acids in the e-liquid, leading to the presence of a proportion of the nicotine in the protonated form, as a salt. Nicotine salts are less volatile than freebase nicotine and are reported to produce a less harsh experience when inhaled. Narrative relating to the history of development of combustible tobacco products suggests that tobacco production procedures such as 'flue-curing' that allow higher levels of retention of leaf sugars, the precursors of organic acids in tobacco smoke, have led to products that are less harsh to smoke and thus more likely to be inhaled into the lungs rather than kept in the mouth. Information from internal tobacco industry documents that have been made available to the public also indicates that during the second half of the twentieth century, organic acids were tested/used as tobacco additives to reduce pH and enhance smoothness of conventional cigarette (CC) smoke. Thus, it could be expected that, under similar puffing conditions, the use of ENDS products containing nicotine salts might lead to a higher delivery of nicotine to the lungs rather than the mouth and buccal cavity compared with the use of E(N)NDS containing only freebase nicotine. The presence of nicotine salts might, thus, have the potential to alter the bioavailability of nicotine inhaled in the aerosol.

2. In order to address this aspect, the COT reviewed published data on the presence of nicotine salts in ENDS products and effects of inhaling nicotine in the salt form from ENDS products on internal exposure to nicotine. Literature searches conducted to 09/10/2020 identified a small number of studies that had analysed the presence of nicotine salts in ENDS products and a few small-scale clinical studies that had investigated the pharmacokinetics of nicotine on inhalation from these types of products.

Presence of nicotine salts in ENDS products

3. Information provided by the UK Medicines and Healthcare products Regulatory Agency (MHRA) as of November 2020 indicated that there were a total of 1409 unique notified e-cigarette products which listed a nicotine salt in their ingredients. The most commonly reported of these was nicotine salicylate, present in over 700 products on the published list, followed by nicotine lactate and nicotine benzoate, each present in around 300. Notifier submissions were noted to record the

ingredients of the product(s) either as the nicotine salt or with the nicotine and acid reported as separate ingredients. In some cases, the acids may be used as ingredients with other functions in the final product, for example citric acid is commonly used as a flavouring.

4. Analytical studies of e-liquids from ENDS products marketed in various countries indicated the presence of various organic acids in commercially available e-liquids, including acetic, citric, lactic, benzoic, levulinic, salicylic, malic, and tartaric acids (El-Hellani et al. 2017, Duell, Pankow and Peyton 2019, Harvanko et al. 2019, Talih et al. 2019, Mallock et al. 2020). Available data indicated that the majority of nicotine in such products is in the protonated form, with only a small fraction of freebase nicotine.

Pharmacokinetic studies of ENDS products containing nicotine salts

5. Clinical studies, mostly conducted by product developers, have evaluated the pharmacokinetics of inhaled aerosolised nicotine salt-containing products in comparison with inhalation of products providing nicotine in the freebase form, in small cohorts of regular CC smokers (Rose et al. 2010, Teichert et al. 2018, O'Connell et al. 2019, Jay et al. 2020). These studies have generally indicated higher and/or faster nicotine delivery to the user from products containing nicotine and organic acids than from products containing equivalent concentrations of nicotine in the freebase form. However, the identified evidence base available for evaluation was small.

Synthesis and COT opinions

a. Some more recently marketed ENDS products contain nicotine in the form of a salt, owing to the inclusion in the e-liquid of an organic acid, for example benzoic acid or lactic acid. This lowers the pH of the e-liquid, leading to a shift of nicotine towards the protonated rather than freebase form. Protonated nicotine is reported to be less harsh and bitter on inhalation than freebase nicotine, and less irritating to the throat and lungs, and thus it may be predicted that a higher proportion of the inhaled nicotine would reach the lungs.

b. The COT considered the published literature to early October 2020, with an aim to evaluate whether there is evidence to indicate that the inclusion of nicotine salts in ENDS products can modify the level of internal exposure to nicotine that is achieved by use of these products, in comparison with use of ENDS products containing nicotine in the freebase form.

c. The Committee agreed that the use of ENDS products containing nicotine salts is likely to be associated with increased bioavailability of nicotine to users. However, it is not currently possible to quantify any effects, given the limited availability of pharmacokinetic data and the additional factor of the role of vaping topology in nicotine exposure.

d. From a general point of view, increased nicotine delivery may be helpful in that it could aid the user attempting to quit CC smoking to attain adequate

exposure to nicotine from the substitute ENDS product. The presence of nicotine salts in e-liquids may also have an impact on acceptability of the product to the user. However, products that have a higher capacity for nicotine delivery may have a concomitant increased risk of promoting addiction and for any potential health effects related to higher levels of nicotine exposure. The committee noted that some reports have indicated that experienced ENDS users are able to 'self-titrate' nicotine intake according to individual requirement. This is a complex behavioural area which is beyond the scope of the COT evaluation. The committee noted that higher capability for nicotine delivery and potential for 'self-titration' might be associated with a lower level of exposure to other constituents present in ENDS liquids and/or aerosols, due to decrease in overall exposure to the aerosol.

e. The Committee has reviewed the potential effect on nicotine toxicity as a result of use of nicotine salts (protonated nicotine) instead of freebase nicotine in ENDS liquids. Risk assessment of any products should include assessment of the salts or acids used in the product, which have not been considered here.

COT

April 2021; Addendum to COT statement 2020/04

Abbreviations

CC	Conventional cigarette
E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ENDS	Electronic nicotine delivery system
MHRA	Medicines and Healthcare products Regulatory Agency

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Figure 1 of Shihadeh & Eissenberg (2015). Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux.

Reference:
Shihadeh A, Eissenberg T (2015). Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine & Tobacco Research, 17, 158-162.

This figure is attached. It is not being made publicly available for copyright reasons.

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Figure 1. Nicotine flux versus product design and topography parameters for three hypothetical products. Colour represents nicotine flux. Hypothetical regulatory target range for product effectiveness is chosen as 25-45 µg/s. Enclosed areas (per product) represent ranges of possible nicotine fluxes given the possible product characteristics and puff topography.

Reproduced from Figure 2 of Shihadeh A, Eissenberg T (2015). Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux.