Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

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

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.

2. Freebase nicotine is volatile, with a tendency to deposit in the mouth and upper respiratory tract. Nicotine salts are less volatile than freebase nicotine and are reported to produce a less harsh experience when inhaled. Absorption of nicotine across biological membranes is pH dependent. Nicotine is a weak base with pKa 8.0 and in the ionised state (in acidic conditions) does not rapidly cross membranes. Absorption in the mouth is thus dependent on the pH of the smoke or aerosol inhaled; at alkaline pH, a considerable proportion of nicotine is in the freebase form, which is well absorbed through the mouth. Nicotine that reaches the small airways and alveoli is rapidly absorbed at the lung fluid pH of 7.4

3. During the development of combustible tobacco products, tobacco production procedures such as 'flue-curing' that allow higher levels of retention of leaf sugars, the precursors of organic acids in tobacco smoke, were introduced, which led to products that are less harsh to smoke and thus more likely to be inhaled deep 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 the 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 deep into the lungs 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 systemic bioavailability of nicotine inhaled in the aerosol.

4. 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

5. 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 that 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.

6. 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

7. 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

- 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. Thus, it may be expected that although nicotine flux across the lipid membrane is reduced at a lower pH, a higher proportion of the inhaled nicotine would be delivered deep into the lungs due to increased tolerability resulting in more intense inhalation of the product.

- The COT considered the published literature to early October 2020, in order to evaluate the consequences of the inclusion of nicotine salts in ENDS products on 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.

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

- From a general point of view, increased bioavailability of nicotine might 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 nicotine bioavailability 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. However, as yet there is no direct evidence for this.

COT
August 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

References

Duell, A. K., J. F. Pankow & D. H. Peyton (2019) Nicotine in tobacco product aerosols: It's déjà vu all over again'. Tobacco Control.

El-Hellani, A., R. El-Hage, R. Salman, S. Talih, A. Shihadeh & N. A. Saliba (2017) Carboxylate Counteranions in Electronic Cigarette Liquids: Influence on Nicotine Emissions. Chem. Res. Toxicol., 30**,** 1577-1581.

Harvanko, A. M., C. M. Havel, P. Jacob & N. L. Benowitz (2019) Characterization of Nicotine Salts in 23 Electronic Cigarette Refill Liquids. Nicotine Tob Res.

Jay, J., E. L. Pfaunmiller, N. J. Huang, G. Cohen & D. W. Graff (2020) Five-Day Changes in Biomarkers of Exposure Among Adult Smokers After Completely Switching From Combustible Cigarettes to a Nicotine-Salt Pod System. Nicotine Tob Res, 22**,** 1285-1293.

Mallock, N., H. L. Trieu, M. Macziol, S. Malke, A. Katz, P. Laux, F. Henkler-Stephani, J. Hahn, C. Hutzler & A. Luch (2020) Trendy e-cigarettes enter Europe: chemical characterization of JUUL pods and its aerosols. Archives of Toxicology.

O'Connell, G., J. D. Pritchard, C. Prue, J. Thompson, T. Verron, D. Graff & T. Walele (2019) A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. Intern Emerg Med, 14**,** 853-861.

Rose, J. E., J. E. Turner, T. Murugesan, F. M. Behm & M. Laugesen (2010) Pulmonary delivery of nicotine pyruvate: sensory and pharmacokinetic characteristics. Exp Clin Psychopharmacol, 18**,** 385-94.

Talih, S., R. Salman, R. El-Hage, E. Karam, N. Karaoghlanian, A. El-Hellani, N. Saliba & A. Shihadeh (2019) Characteristics and toxicant emissions of JUUL electronic cigarettes. Tobacco Control, 28**,** 678-680.

Teichert, A., P. Brossard, L. Felber Medlin, L. Sandalic, M. Franzon, C. Wynne, M. Laugesen & F. Lüdicke (2018) Evaluation of Nicotine Pharmacokinetics and Subjective Effects following Use of a Novel Nicotine Delivery System. Nicotine Tob Res, 20**,** 458-465.