Discrepancies in reported *versus* measured nicotine content of e-cigarette refill liquids across 9 European Countries before and after the implementation of the EU Tobacco Products Directive

Charis Girvalaki, Manolis Tzatzarakis, Alexander Vardavas, Christina Kyriakos, Katerina Nikitara, Polychronis Stivaktakis, Aristidis Tsatsakis, Constantine Vardavas

Please cite this article as: Girvalaki C, Tzatzarakis M, Vardavas A, et al. Discrepancies in reported *versus* measured nicotine content of e-cigarette refill liquids across 9 European Countries before and after the implementation of the EU Tobacco Products Directive. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00941-2019).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©ERS 2019
Discrepancies in reported vs. measured nicotine content of e-cigarette refill liquids across 9 European Countries before and after the implementation of the EU Tobacco Products Directive.

Charis Girvalaki\(^1\), Manolis Tzatzarakis\(^1\), Alexander Vardavas\(^1\), Christina Kyriakos\(^1\), Katerina Nikitara\(^1\), Polychronis Stivaktakis\(^1\), Aristidis Tsatsakis\(^1\), Constantine Vardavas\(^1\)

\(^1\)Laboratory of Toxicology, Faculty of Medicine, University of Crete, Heraklion, Greece

**Article type:** Research Letter

**Corresponding author:** Constantine Vardavas,

Laboratory of Toxicology, Faculty of Medicine, University of Crete, Heraklion, Greece

Email: vardavas@tobcontrol.eu
Dear Editor,

During the past years, the e-cigarette market across European countries has grown extensively [1,2], as 15% of Europeans reported having tried e-cigarettes, representing a 7.0% increase since 2012 [3]. E-cigarettes are regulated across the 28 European Union Member States (EU MS) [4] under Article 20 of the Tobacco Products Directive (TPD), a legislative document whose aim is to regulate the internal European market and to harmonise the safety and quality of e-cigarette products through design specifications, including but not limited to the volume of the refill container, nicotine content, the existence of child-resistant refill containers amongst other parameters. In order for e-cigarette refill vials to be placed onto the market under the TPD, electronic cigarettes must deliver nicotine doses at consistent levels under normal conditions of use (Art20;3f); must not contain nicotine in excess of 20 mg/ml (Art20;3b); and only ingredients of high purity are to be used in the manufacture of the nicotine-containing liquid (Art20;3d) [4]. Research performed before the TPD was implemented indicated that there were wide inconsistencies between the labeled and the actual nicotine concentration of the products, with production impurities commonly noted [5-9].

In light of the above we aimed to evaluate potential impurities and the discrepancy between the reported and the measured nicotine concentration of the most popular brands of e-cigarette refill liquids in 9 EU MS so as to assess if the implementation of the TPD has led to the improvement in production quality and standards of e-cigarette refill liquids.

Within the context of a European Respiratory Society project, EUREST-PLUS, funded by the European Commission Horizon 2020 programme, we sampled the most popular e-cigarette refill liquids from 9 EU MS (France, Poland, Germany, Netherlands, United Kingdom, Spain, Romania, Hungary and Greece) at two time intervals, once before (pre TPD in early 2016) and once after (pre TPD in early 2018) the implementation of the EU TPD [10]. At baseline (pre-TPD), Euromonitor Reports on sales data was used to identify the top-selling companies in each EU MS. For two EU MS (the Netherlands and Romania) the 2016 Euromonitor Report did not contain detailed data regarding the top selling e-liquids and hence the most top selling companies were identified based on ALEXA rankings (website traffic rankings) as a proxy of their popularity in that national market. After identifying the “top 5” selling companies per EU MS, we randomly selected three products from each top selling company (15 products from each of the 9 EU MS, n=135, of which n=122 were available for purchase).

In the post TPD phase -using only Euromonitor 2018 sales reports- we identified 107 matching products still on the market and also included 30 new products that now represented products
randomly selected from new companies in the “top 5” in 2018. In total 259 products were purchased. From the analysis we excluded 4 samples from the pre TPD phase as the content of nicotine was not reported on the vial while we did not further assess 3 samples from post TPD phase in which zero nicotine was reported, and traces were detected. A discrepancy threshold was applied so as to take into account potential nicotine degradation post-production, based on both the European Commission Joint Research Center (JRC) report (±10%) and the draft of the Technical Committee of the European Standardization body for EC and e-liquids (CEN TC437) [11,12]. The latter sets a discrepancy level at ±15% for liquids with a nicotine concentration of 0.50-5.99 mg/ml, at ±10% for concentrations of 6.00-12.99 mg/ml and ±7% for concentrations 13.00-20.00 mg/ml.

In total, 252 e-liquid refills were analyzed for their concentrations of nicotine, nitrosamine and Polycyclic aromatic hydrocarbons (PAHs) content was performed by gas chromatography-mass spectrometry (GCMS) and liquid chromatography-mass spectrometry (LCMS) [13].

Our results indicated differences between the measured vs. reported nicotine content in both the pre-TPD and post-TPD evaluation. Overall, more than half of the top selling products in the EU market were measured to have a discrepancy in nicotine concentration that was greater than ±10% of the amount labelled on the product (Figure 1) – an indicator of the lack of quality control in production of e-cigarette refill liquids [11]. From the 118 products of the pre TPD phase, 57.6% (n=68) were above the threshold of 10% in nicotine discrepancy while from the 134 products of the post TPD phase, 53.7% (n=72) were above the threshold of 10% noted by the JRC report. Only one product exceeded the legislated limit of ≤20mg/ml of nicotine in the post-TPD phase in comparison to 8 samples in the pre-TPD implementation. Applying the CEN TC437 thresholds, for samples with a nicotine concentration <5.99mg/ml, there was an increase in discrepancy (50% pre TPD vs. 81.8% post TPD). For samples with a nicotine concentration from 6.00-12.99 mg/ml, and samples with a nicotine concentration from 13.00-20.00 mg/ml there was a slight decrease in discrepancy (59.7% vs. 50.6%; and 71.0% vs. 60.9% respectively)

Moreover, all products in both the pre and post-TPD phase were tested negative for nitrosamines and (PAHs), indicating an absence of impurities, contrary to earlier research which had led to concerns related to the production and quality control process of these substances, hence indicating that improvements in quality control should now focus primarily on nicotine concentrations [14,15].
Our findings are higher than those identified through pilot research performed by the European Commission JRC which identified a discrepancy in almost one in three products among 39 EU refill liquids – lower than the discrepancy of 57.6% in our study, however our sampling and sample size was extensively larger (255 e-liquids vs. 39) [11]. This is the first assessment of discrepancies in nicotine content within e-cigarette refill liquids across multiple EU MS before and after implementation of the TPD using data from the most popular brands across the EU MS (n=255), which would have the largest impact on consumers. However, as we tested only a randomly selected sample of the most popular e-liquids and we were not able to test all liquids available in Europe our results may not be generalizable to the entire EU market but to the 9 selected EU MS.

Our findings indicate the need for close monitoring of the nicotine concentration of electronic cigarette refills, marketed in the EU as discrepancies exist between the actual nicotine content in the vial as compared to that stated on the label, even after the implementation of the TPD. These observed discrepancies may impact consumers by leading to a higher or lower nicotine uptake which could impact their real or perceived level of addiction.

As mandated in the TPD, products that do not meet the strict quality criteria set under the Directive and “are not safe or are not of good quality or are otherwise not in conformity with this Directive”, are then subject to corrective actions as manufacturers should “bring the product concerned into conformity with this Directive, to withdraw or to recall it, as appropriate” [4]. In light of the above, improvements in the production process and implementation of quality control mechanisms for the nicotine content of e-cigarette refill vials in Europe are still needed, for the protection of consumer health.

**Funding:** This work was supported by a grant from the European Commission (Horizon2020 HCO-6-2015; EUREST-PLUS: 681109; Vardavas)

**Conflict of Interest:** None to declare
References


12. Technical Committee of the European Standardization body for EC and e-liquids (CEN TC437). General principles and requirements for testing for quality and nicotine levels of e-liquids, 2015.


**Figure 1:** Discrepancies in the measured vs. reported nicotine concentration among popular e-cigarette refill liquids across 9 EU MS before and after the implementation of TPD.