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On the Passive Exposure to Nicotine from Traditional Cigarettes Versus e-Cigarettes

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Abstract

This study reports on the measurement and comparison of passive exposures to nicotine from smokers/vapers of conventional and e-cigarettes, respectively. To this end, a smoking machine was constructed whose experimental conditions can be easily changed and in which the nicotine of the produced smoke or aerosol was trapped and further analyzed by HPLC. The main results of the present work were (a) the average value of nicotine delivered per puff, was 42 ± 0.3 µg/puff for the combustion cigarette and 25 ± 0.2 µg/puff for the e-cigarette (b) it was found a drastic reduction to nicotine exposure in the *passive subject* when the *active smoker* was replaced by the *active vaper*. Specifically, at a distance of 100 cm, the passive smoker reduced its exposure to nicotine from 600 ng/puff to five ng/puff when the active subject was vaping an e-cigarette. The main conclusion of the investigation was the drastic reduction to nicotine exposure of the passive subject with the use of the e-cigarettes. instead of conventional cigarettes by the active vaper or smoker, respectively. Finally the present study suggest that the nicotine exposure experienced by the passive subject may follow an inverse quadratic dependence with the distance from the active smoker or vaper.

Keywords

HPLC, E-cigarette, Passive Smoking, Nicotine Exposure

1. Introduction

The rapid development of electronic nicotine delivery systems (ENDS), also called e-cigarettes, as an alternative to tobacco (used in conventional combustion cigarettes) was mainly based on manufacturers' claims of a healthier alternative to conventional smoking as well as on an effective gateway to giving up smoking [1-5]. The former claim appears to be supported by some scientific evidence like the results reported by Goniewicz et al [6] who investigated the content of toxicants in e-cigarette vapors. These authors found toxicant levels in e-cigarettes 9-450 times lower than in cigarette's smoke. They concluded that the substitution of tobacco cigarette by e-cigarettes substantially reduced exposure to selected tobacco-specific toxicants and, consequently, suggested the necessity of further investigations on e-cigarettes as a harm reduction strategy for smokers unwilling to quit.

With respect to the consideration of the e-cigarette as a gateway to quit smoking, it remains unclear since there is nowadays the perception that the advent of e-cigarettes has created an addiction to electronic smoking.

Despite the increasing popularity of e-cigarettes [7-8], partially based on the perception of a reduced health risk [1, 5-8], a debate on their impact on health and indoor air quality persists and is currently of major concern among scientists and public health institutions. This situation is in part motivated by the fact that the e-cigarette produces an aerosol - often called "vapor" - which is not only inhaled by the vaper but also, as in the case of the tobacco smoker, partially exhaled into the environment.

Several reviews have been published on ENDS, covering general aspects [1, 9-11] or specific topics, including health effects [12-15]; nevertheless, few studies (see for example the review article by Glasser et al [1]) have reported on the effects of e-cigarette vaping on passive subjects. To cite some of the most relevant, McAuley et al [3] compared the impact of e-cigarette vapor and cigarette smoke on indoor air quality and Schripp et al [16] measured the volatile organic compounds (VOCs) and ultrafine particles (UFP) released from an e-cigarette while actively vaping in an emission chamber of few cubic meters. In addition, while Geiss et al [17] reported that e-cigarettes are a source of propylene glycol, glycerol, nicotine, carbonyls and aerosol particulate, Gallart-Mateu et al [4] and Czogala et al [18] found that passive exposure to nicotine from e- cigarettes was lower than from conventional cigarettes.

Although the cited studies revealed that non-users are certainly exposed to nicotine (among other compounds) in ENDS vapor, it is still unclear if any level of nicotine exposure is sufficient to be of biological concern to humans [1]. Therefore; more studies are needed before conclusions about harm reduction can be made [19-20]. This necessity is even clearer for systematic studies centered on passive exposure to nicotine from e-cigarettes as a function of the spatial configuration like the relative distance and orientation of the active versus the passive smoker. Indeed, there is a great demand to asset the nicotine impact on passive subjects on a face- to- face configuration simulating the most adverse, real life conditions. In this context, the focus of the present study is on the measurement of passive exposures to nicotine from consumers of conventional and e-cigarettes. Accordingly, this work reports on the active and passive nicotine exposure from conventional and e-cigarettes, respectively in which the distance between passive and active smoker/vaper was changed to simulate real conditions.

Nicotine emission was controlled using a smoking machine whose experimental conditions and puffing regime could be adapted to the selected objective. It will be shown how the systematic analysis of smoke and aerosol can be implemented with high sensitivity using the optimized HPLC methodology and, consequently, how this analytical method can be very useful in assessing the impact of ENDS on humans under real life conditions.

2. Material and Methods

2.1. Materials

The e-cigarettes and conventional cigarettes used in this study were purchased in the market. Nicotine standard with purity higher than 99% and potassium phosphate monobasic (purity > 99.5%) were purchased from Sigma-Aldrich (Steinheim, Germany). Methanol, acetonitrile (ACN) and 2-propanol HPLC grade from Scharlab (Barcelona, Spain) were used. Ultra-pure water was obtained using a Millipore system (Bedford, MA, USA). Stock nicotine solutions (1000 mg/L) were prepared in water. These solutions were stored at 4°C in the dark. Working standard solutions were prepared in the respective mobile phase buffer by diluting the stock solutions as required.

2.2. Smoke/Aerosol Generation and Collection

Figure 1 illustrates a simplified description of the experimental setup employed for smoke and aerosol collection. While Figure 1a refers to the configuration for the active smoker or vaper, Figure 1b corresponds to that of passive smoker or vaper. For the latter configuration the collection distance can be changed within the range 30 cm ≤ d ≤ 200 cm (see discussion below); however, only data taken 30cm and 100cm of distance are reported in the present communication.

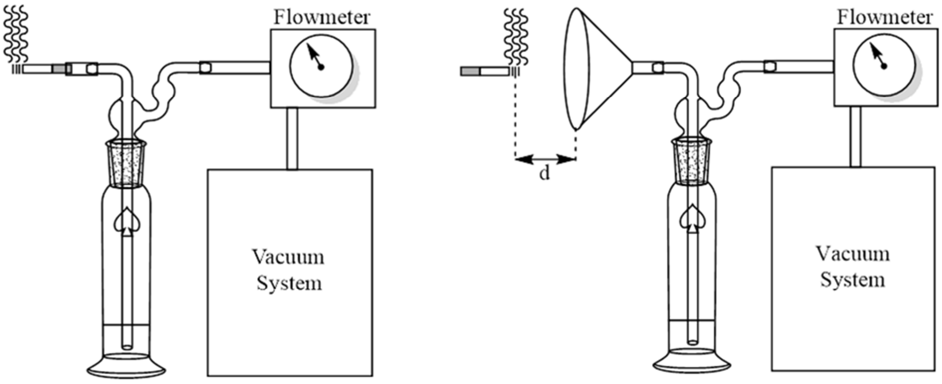

Figure 1. *Schematic layout of the smoking machine with the liquid traps, vacuum unit and flowmeter. a) Active smoker configuration; b) passive smoker configuration. The collector diameter was 20 cm. See text for comments.*

The smoking machine follows the well- established methodology based on liquid traps [see for example Ref. 6] and consists of one or two liquid traps, depending on the experimental conditions, a programmable flowmeter and a vacuum system. In a typical run, the flowmeter set was adjusted at the desired flow rate maintaining the vacuum pump on and using a conventional cigarette. Afterward, the puffing regime was set to the desired values and the run was initiated using a new volume of liquid in the trap and a new cigarette sample, either conventional or electronic.

During the present investigation, all measurements for active smoking or vaping were taken with a puff time of 2 s and a volume of 100 mL, with a time interval of 30 s between successive puffs.

Although the solvent and volume employed in the liquid traps obviously depend on the analyte to be determined, for nicotine quantification a total volume of 300 mL of water (nicotine is highly soluble in water) in only one trap proved to be the optimal conditions. This trapping protocol was selected after several tests were carried out. It was found that one trap and 300 mL volume guaranteed the total collection of the nicotine present in the aerosol, i.e., the use of a greater volume in the same or additional traps hardly changed the total nicotine collection. The use of a liquid trap was also preferred due to the non- volatile character of the nicotine. As already stated, the main goal of the present investigation was the monitoring of nicotine exposure to passive subjects. Thus, the use of other trapping elements like solid filters to collect volatile compounds [21] was not considered to simplify the measured chromatogram, and, hence the analytical method.

The active sampling configuration traps all the nicotine that the smoker collects but it does not monitor the nicotine that he exhales to the air. Hence, the measured values, in principle, should be considered as an upper limit. However, the amount of nicotine exhaled by the active smoker to the air is negligible [see for instance Ref. 4 and discussion below] compared with the total nicotine intake during the puffing. Therefore, this small difference is not of relevance for the main result and conclusions of the present investigation, rather focused on the passive exposure to nicotine.

Under the experimental conditions mentioned above, the nicotine content delivered per puff was determined for both conventional and e-cigarettes purchased from the market. All conventional cigarettes analyzed in this work were selected with a manufacturer`s declared nicotine content of 0.7 mg/cigarette, while each e-cigarette contained a declared nicotine concentration of 7.4 mg diluted in 0.4 mL of liquid with a mixture of propylene-glycol and glycerol.

For passive smoking or vaping, the analytical method and the smoking machine were the same as used for active smoking or vaping. Nevertheless, the following changes were implemented to simulate real life conditions: the flowmeter operating conditions were changed to reproduce the average human breathing rate of 6 L/min; the smokers or vapers were situated first at 30 cm and afterwards at 100 cm in front of the collector (see Figure 1b). Five experienced smokers and five experienced vapers provided their consent after receiving detailed information about the outgoing investigation. The analytical procedure and data analysis were the same as outlined above. It should be remarked that in the passive mode the trapping machine collected either the vapor exhaled by the active vaper, when one uses the e-cigarette, or the smoke delivered by the combustion cigarette to the air plus the smoke exhaled by the active smoker, if a conventional cigarette is employed.

The nicotine measurement campaign for each type of cigarette was implemented as follows*: active and passive smoking with combustion cigarettes*; the smoke from 100 puffs, 10 puffs from each of the 10 cigarettes of the same brand was collected in the liquid trap and its nicotine content determined by the chromatographic method outlined in the next subsection. This procedure was repeated using three different brands with the same declared nicotine content. The nicotine content per puff was estimated for each cigarette and the *average value per puff of the* conventional *cigarette* was obtained together with its RSD (see Table 1).

Active vaping with e-cigarettes: the collection of 100 puffs did not require ten cigarettes as the total number of puffs afforded by each e-liquid was found to be 210 ± 3. As a result, 100 puffs were collected from each of the three e-cigarettes. As in the previous case, the average value of nicotine content per puff was estimated together with its RSD. This protocol was applied for active and passive vaping located at 30 cm between the passive and active vaper. However, when this protocol was applied at 100 cm distance, the total number of puffs was increased to 600, i.e. 200 puffs were used from each of the three e-cigarettes to guarantee that the nicotine signals were well above the LOQ.

2.3. Instrumental

Chromatographic system consists of a Star LC Workstation V.6.41/VARIAN INC. (Walnut Creek CA., USA) using a Tracer Excel 120 C-8 (150 x 4.6 mm, 3µm) column from Teknokroma (Barcelona, Spain).

The mobile phase composition was optimized based on Patel *et al.* [22] with minor changes using single variable modifications due to the different nature of the stationary phase. The resulting mobile phase was ACN/phosphate buffer 20 mM pH 3.5 (5/95). Before use, the mobile phase was filtered daily using a vacuum pump Millipore filtration device and a 0.45 nm nylon filter. Column eluents were monitored for UV absorbance at 260 nm using a single wavelength detector. Indeed, the lack of UV-VIS absorption combined with the high polarity of Propylene glycol and Glycol make HPLC not suitable for their analysis unless one derivatization is employed. Hence, the use of UV absorption at 260 nm significantly simplifies the chromatogram of the e-cigarettes since these specimens basically contain the two mentioned alcohols and, the substance here investigated, nicotine.

2.4. Nicotine Determination by HPLC

A volume of 20 µL of the smoke/aerosol extract containing nicotine (or standard) was injected in the chromatographic system, the mobile phase flow rate being 1.0 mL/min. Nicotine identification was made by comparison of retention time with the standard. The obtained chromatograms showed the presence of nicotine in both conventional and e-cigarettes. Nicotine quantification was made using a calibration curve.

3. Results and Discussion

3.1. Nicotine Calibration and Test

Figure 2 (Upper level) shows a typical chromatogram of the smoke extract of 30 puffs from a conventional cigarette. As mentioned further above the use of liquid traps rules out the trapping of volatile compounds. The selection of the 260 nm as the working wavelength and the appearance of the main peak at 3.7 min of retention time, as confirmed by the nicotine standard, allow us to assign it to nicotine. In addition, the other small peaks may be assigned to aromatic compounds. Their specific identities are under investigation using GC-MS techniques and will be the subject of a forthcoming paper. Figure 2 (Lower panel) illustrates a typical chromatogram from a 30 puffs extract of an e-cigarette in which the only relevant feature is the nicotine peak. This is not surprising since the use of the wavelength at 260 nm rules out the observation of the two main components of the e-liquids alcohols, namely, propylene glycol and glycol because, as already mentioned, they do not absorb in the UV-VIS range of the spectrum. As stated further above their investigation in currently outgoing in our laboratory by GC-MS methodologies which will be most adequate even to analyze small traces of aromatic compounds which might be present in concentrations below the LOQ.

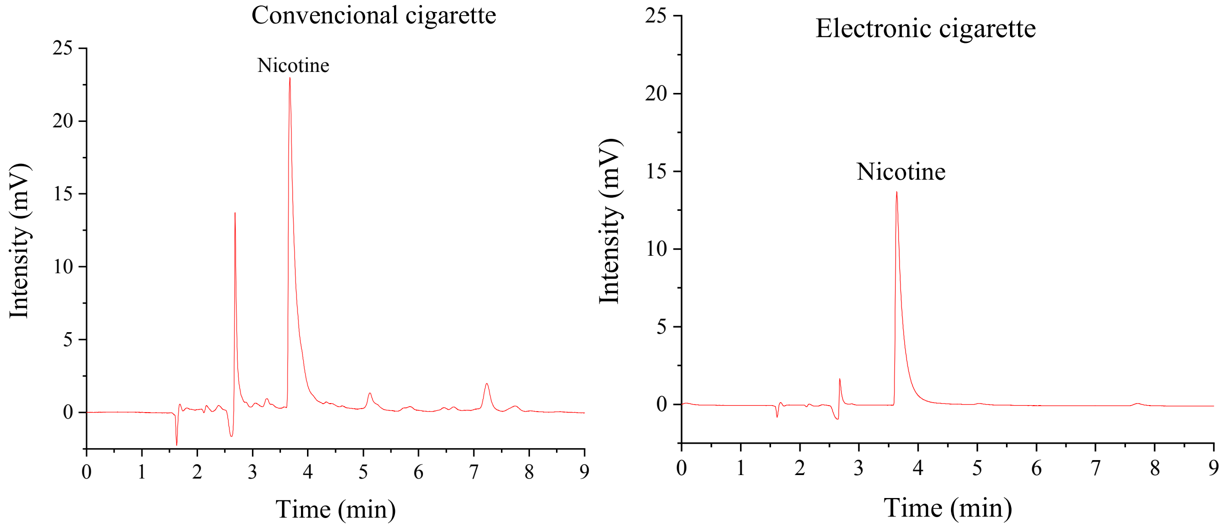

Figure 2. *Chromatograms of nicotine (t_R=3.7 min). (Upper panel) conventional cigarette extracts corresponding to 30 puffs. (Lower panel) e-cigarette extracts corresponding to 30 puffs. Notice the simplicity of the chromatogram showing the nicotine peak only. See text for discussion.*

The nicotine calibration plot was linear from 0.2 mg/L up to 12 mg/L, the determination coefficient, R^2, being 0.99997 for 8 points. A LOD value of 60 µg/L and a LOQ value of 0.2 mg/L were found based on the criterion used in chromatography (LOD = 3×σ/s. LOQ = 10×σ/s). Here σ and s stand for the standard deviation and slope of the calibration curve. The linear fit of the calibration is given by Peak *area (mV·min) = 2.60·*10^{-4} *[Nicotine] (mg/L) + 1.94·*10^{-5}.

To test the method accuracy, the nicotine content of the 3R4F reference cigarette (from the University of Kentucky (Lexington, KY, USA) was determined to be Mean ±$CI_{95\%}$: 2.26 ± 0.06 mg/cigarette, which compares satisfactorily with the value of 2.09 ± 0.14 mg/cigarette published in Schaller et al [23]. Similar satisfactory results were obtained using other samples proving the accuracy and consistency of our analytical method.

3.2. Active Smoking and Vaper

Following the analytical procedure outlined above, the average value of nicotine delivered per puff and therefore, inhaled by the active smoker or vaper, was determined for both conventional and e-cigarettes, respectively. The results listed in Table 1 were 42 µg/puff ± 0.3 µg/puff for the combustion cigarette and 25 µg/puff ± 0.2 µg/puff for the e-cigarette. These results deserve some comments given below.

The first one concerns the total nicotine value estimated for the conventional cigarette. The collected value from a total number of 10 puffs which, under our experimental conditions, was the maximum number of puffs available from a cigarette containing nicotine, amounts to 42 µg/puff × 10 puffs = 0.42 mg/cigarette; that is, only 60% of the declared nicotine content of the cigarette. Hence, one may conclude that a significant part of the remaining nicotine is either adsorbed in the cigarette filter or delivered into the environment clearly affecting the air quality.

Regarding the nicotine inhaled by the active vaper, it is interesting to compare our result with that obtained by Trehy et al [24] who used e-cigarettes with a similar total content of nicotine, i.e. 7 mg/cigarette in similar experimental conditions. These authors analyzed the nicotine content of the aerosol obtaining 27 µg/puff, a value very close, in order and magnitude, to that determined in this work.

3.3. Passive Exposure to Nicotine from Smokers and Vapers

Using the protocol described in section 2, passive exposure to the nicotine content from active smokers and vapers was measured obtaining the results listed in Table 1.

In first place, the nicotine exposure of the passive subject situated at 30 cm from the active smoker was 6.8 µg/puff which is a non-negligible amount in view of the total amount of 28 µg/puff not inhaled by the active smoker. Thus, one may conclude that despite the amount of nicotine absorbed by the filter or destroyed by combustion the nicotine delivered into the environment *is at least 10%* of the total amount present in the conventional cigarette.

As illustrated in the results in Table 1, nicotine exposure decreases significantly with distance and, even more so, when one compares the passive exposure to nicotine from the conventional and the e-cigarette. Note the drastic reduction in nicotine exposure by the *passive subject* when the *active smoker* is replaced by the *active vaper*. For example, at a distance of 30 cm between the passive and active subject, the nicotine exposure experienced by the passive subject is reduced from 6800 ng/puff to only 50 ng/puff. Likewise, at 100 cm of distance the reduction was from 600 ng/puff to five ng/puff. In other words, the passive exposure to nicotine from an e-cigarette represents two orders of magnitude less than that from a combustion cigarette.

Table 1. *Nicotine content inhaled by the active smoker/vaper and the passive subjects.*

Nicotine exposure of active smoker/vaper				
Smoker/Vaper	**Brand/Cigarette per brand**	**Puff/cigarette**	**Total puff**	**Nicotine average (µg/puff)**
Conventional cigarette	3/10	10	300	42 (± 0.7%)[a]
E-cigarette	3/1	100	300	25 (± 0.8%)[a]

Passive exposure to nicotine from active smokers and vapers				
Smoker/Vaper	**Distance (cm)**	**Puff/cigarette**	**Total puff**	**Nicotine average (µg/puff)**
Smoker	30	100	300	6.8 (± 3.2%)[a]
	100	100	300	0.6 (± 5.1%)[a]
Vaper	30	100	300	$5\cdot10^{-2}$ (± 6.7%)[a]
	100	200	600	$5\cdot10^{-3}$ (± 8.2%)[a]

[a] Relative standard deviation (n=3)

Clearly, the active vaper does not inhale the same amount of nicotine per puff that the active smoker does, However, even if one normalizes, that is, multiplies the five ng/puff by the factor 42/25, according to the values listed in Table 1, the result will be 8.4 ng/puff. This is still two orders of magnitude less than that of obtained from the combustion cigarette. The drastic reduction in nicotine exposure of the passive vaper as well as its very low level, just a few ng/puff, leads us to question about its existence, at least with respect to the nicotine exposure from active vapers.

Gallart-Mateu et al [4] have reported 32 ng nicotine content per puff in the exhaled breath of an e-cigarette vaper. Albeit detailed information on the puffing regime was not given these results are consistent with our measured 50 ng/puff nicotine exposure of the passive vaper located at 30 cm from the active vaper. In addition, these findings support the conclusion that most of the nicotine released into the environment from an active vaper comes from the exhaled breath of the e-cigarette vaper as the ENDS is a closed device, which only releases vapor to the active vapers.

The same authors reported 223 ng of nicotine per puff in the exhaled breath from a conventional cigarette smoker, a result that is far below our results of 6800 ng/puff received by the passive smoker at 30 cm. This nicotine level is in line with the nicotine released into the environment between puffs that we discussed above, confirming that the major contribution to passive nicotine exposure does not come from the nicotine exhaled by the smoker but from the nicotine released by cigarette combustion to the environment.

A final remark is worthy before closing this section. It concerns the nicotine exposure dependence of the passive subject with the distance from the active subject regardless of the type of cigarette employed. A closer inspection of Table 1 results indicates that in both cases, i.e. for combustion and e-cigarettes, the nicotine exposure reduces a factor of ca. 10 when the distance increases a factor of 100cm/30cm = 3.3. This dependence may suggest a D^{-2} dependence being D the distance between the active and passive subject; Interestingly, this functionality resembles that of the solid angle Ω extended by the passive smoker with respect to the active one which is given by $\Omega= S/D^2$ being S is the area subtended by the passive subject with respect to the origin of the coordinate system centered at the active subject. As these results are based on four measurements, the suggested model dependence should only be taken as a working hypothesis for future work which would benefit from a more ample data set.

4. Conclusions

The present study was centered on the investigation into nicotine exposure in active and passive smokers or vapers from conventional and e-cigarettes. A simple smoking machine was constructed whose experimental conditions could be easily changed and in which the nicotine from the produced smoke/aerosol could be efficiently trapped and further analyzed by HPLC.

It was shown how the combination of a simple smoking machine together with the HPLC methodology proved useful in measuring the nicotine exposure of passive subjects from conventional cigarette smoke or e-cigarette aerosol in a "face to face" spatial configuration adopted to simulate the most adverse real-life conditions.

The main conclusion of the investigation was the drastic reduction in nicotine exposure of the *passive subject* when the smoker of a combustion cigarette was replaced by the *vaper of an e-cigarette*. In all cases here analyzed, the average nicotine exposure was reduced by two orders of magnitude. For example, at a distance of 100 cm between the passive and active smoker, an adverse but sometimes realistic spatial configuration, the average nicotine exposure per puff varied from 600ng to five ng when the active subject was vaping an e-cigarette. Thus, according to these results, the passive vaper will require to be surrounded by 100 active vapers to reach the same nicotine exposure, as he would receive from only one active smoker.

Another point of relevance of the present investigation is the finding of an *inverse quadratic dependence of the nicotine exposure with the distance between the passive and active smoker or vape*r. These preliminary results may stimulate future investigations in our field for (short and long range) spatial modelling of toxicant diffusion in both indoor and outdoor environments.

Work is now in progress to extend this investigation to passive exposure to other e-cigarette components, for example, glycols.

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Conflict of Interest

The authors declare none

References

[1] A. M. Glasser, L. Collins, J. L. Pearson, Overview of Electronic Nicotine Delivery Systems: A Systematic Review. Am. J. Prev. Med. 52 (2017) e33-e66.

[2] J. M. Logue, M. Sleiman, V. N. Montesinos, M. L. Russell, M. I. Litter, N. L. Benowitz, L. A. Gundel, H. Destaillats. Emissions from Electronic Cigarettes: Assessing Vapers´ Intake of Toxic Compounds, Secondhand Exposures, and the Associated Health Impacts. Environ. Sci. Technol. 51 (2017) 9271-9279.

[3] T. R. McAuley, P. K. Hopke, J. Zhao, S. Babaian. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal. Toxicol. 24 (2012) 850-857.

[4] D. Gallart-Mateu, L. Elbal, S. Armenta, M. de la Guardia. Passive exposure to nicotine from e-cigarettes. Talanta. 152 (2016) 329–334.

[5] B. A. Majeed, S. R. Weaver, K. R. Gregory, C. F. Whitney, P. Slovic, T. F. Pechacek, M. P. Eriksen. Changing Perceptions of Harm of E-Cigarettes Among U. S. Adults, 2012-2015. Am. J. Prev. Med. 52 (2017) 331-338.

[6] M. L. Goniewicz, J. Knysak, M. Gawron, L. Kosmider, A. Sobczak J. Kurek, A. Prokopowicz, M. Jablonska-Czapla, C. Rosik-Dulewska, C. Havel, P. Jacob, N. Benowitz. Levels of selected carcinogens and toxicants in vapor from electronic cigarettes. Tob Control. 23 (2) (2014) 133–139.

[7] R. E. Bunell, I. T. Agaku, R. A. Arrazola et al. Intentions to Smoke Cigarettes Among Never-Smoking US Middle and High School Electronic Cigarette Users: National Youth Tobacco Survey, 2011-2013. Nicotine Tob. Res. 17 (2015) 228-235.

[8] L. T. Kozlowski, D. Lynn Homish, G. G. Homish, Daily users compared to less frequent users find vape as or more satisfying and less dangerous than cigarettes, and are likelier to use non-cig-alike vaping products. Prev. Med. Rep. 6 (2017) 111-114.

[9] A. B. Breland, T Spindle, M. Weaver, T. Eissenberg. Science and electronic cigarettes: current data, future needs. J Addict Med. 8 (2014) 223–233.

[10] Z. Sanford, L. Goebel. E-cigarettes: an up to date review and discussion of the controversy. W V Med J. 110 (2014) 10–15.

[11] A. Breland, E. Soule, A. Lopez, C. Ramoa, A. El-Hellani, T. Eissenberg Electronic cigarettes: what are they and what do they do? Ann N Y Acad Sci. Online January 15, 2016. http://dx. doi. org/10. 1111/nyas. 12977.

[12] A. A. Lopez, T., Eissenberg. Science and the evolving electronic cigarette. Prev. Med. 80 (2015) 101–106.

[13] N, Campbell-Heider, D Snow. Teen use of electronic cigarettes: what does the research tell us? J Addict Nurs. 27 (2016) 56–61.

[14] A. Marsot, N. Simon. Nicotine and cotinine levels with electronic cigarette: a review. Int. J Toxicol. 35 (2016) 179–185.

[15] A. Zulkifli, E. Z. Abidin, N. Z. Abidin, A. S. Amer Nordin, S. M. Praveena, S. N. Syed Ismail, I. Rasdi, K. Karuppiah, A. A. Rahman. Electronic cigarettes: a systematic review of available studies on health risk assessment. Rev Environ Health. Online April 21, 2016. http://dx. doi. org/10. 1515/ reveh-2015-0075.

[16] T. Schripp, D. Markewitz, E. Uhde, T. Salthammer. Does e-cigarette consumption cause passive vaping? Indoor Air. 23 (2013) 25-31.

[17] O. Geiss, I. Bianchi, F. Barahona, J. Barrero-Moreno. Characterisation of mainstream and passive vapors emitted by selected electronic cigarettes. Int. J. Hyg. Envir. Heal 218 (2015) 169-180.

[18] J. Czogala, M. L. Goniewicz, B. Fidelus, W. Zielinska-Danch, M. J. Travers, A. Sobczak. Secondhand Exposure to Vapors from Electronic Cigarettes. Nicotine Tob. Res. 16 (2014) 655-662.

[19] Royal College Physicians. Nicotine without smoke: Tobacco harm reduction. London April 2016.

[20] A. McNeill, L. S. Brose, R. Calder, S. Hitchman, P. Hajek, E. McRobbie. E- cigarettes: An Evidence Update—A Report Commissioned by Public Health England. London: Public Health England, 2015.

[21] A. Sinjewel, E. L. Swart, H. Lingeman and A. J. Wilhelm. LC Determination of Propylene Glycol in Human Plasma after Pre-Column Derivatization with Benzoyl Chloride. Chromatographia 66 (2007), 66, 103–105.

[22] V. Patel Jinesh, B. Patel Dipti. Development and validation of reverse phase high performance liquid chromatography method for estimation of nicotine in nicotine gum tablet. Int. J. of Pharm. Drug Anal. 2 (2014) 291-295.

[23] J. P. Schaller, D. Keller, L. Poget, P. Pratte, E. Kaelin, D. McHugh, G. Cudazzo, D. Smart, A. R. Tricker, L. Gautier, M. Yerly, R. R. Pires, S. Le Bouhellec, D. Gosh, I. Hofer, E. Garcia, P. Vanscheeuwijck, S. Maeder. Evaluation of the Tobacco Heating System 2. 2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regul. Toxicol. Pharmacol. 81 (2016) S27-S47

[24] M. L. Trehy, W. Ye, M. E. Hadwiger, T. W. Moore, J. F. Allgire, J. T. Woodruff, S. S. Ahadi, J. C. Black, B. J. Westenberger. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. J. Liq. Chromatogr. Relat. Technol. 34 (2011) 1442-1458.