

ORIGINAL ARTICLE

Health Risk Assessment of Electronic Cigarette Use among Adults in Klang Valley, Malaysia

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ABSTRACT

Introduction: The electronic cigarette (EC) usage has raised public health concerns; whether its advantages to smokers as a potential smoking cessation aid have outweighed its negative health impacts among EC users. This study aims to estimate health risks associated with chemical exposures to nicotine, propylene glycol (PG) and selected Tobacco-Specific Nitrosamines (TSNAs) namely 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN) in e-liquids locally-manufactured in Malaysia. **Methods:** The health risk assessment (HRA) was performed using established guideline by the Environmental Protection Agency (EPA). The average daily dose (ADD) and lifetime average daily dose (LADD) were calculated using previously published data on chemical concentration of selected compounds and local EC usage topography data. Next, the non-carcinogenic risk (nicotine and PG) and carcinogenic risk (NNK and NNN) were calculated and denoted as total hazard quotient (HQ_T) and total lifetime cancer risk (LCR_T) value, respectively. **Results:** For non-carcinogenic risk, the mean of HQ_T was 78.9 which falls under "unacceptable" risk as demonstrated by HQ_T value of more than 1. While for carcinogenic risk, the mean of total LCR_T value was $1.54E-04$ which may place EC users at risk of developing cancer resulted from exposure to selected TSNAs. **Conclusion:** Comprehensive HRA using currently available data of local EC usage topography and chemical evaluation of Malaysian-made e-liquids have revealed that the exposure to nicotine, PG and selected TSNAs are expected to be a significant health concern for local EC users. This finding supports the local health authority to issue a stringent health policy in considering EC as a tool for smoking cessation among heavy smokers.

Keywords: Electronic cigarette, E-cigarette, Health risk, Health risk assessment, Cancer risk

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INTRODUCTION

The emergence of electronic cigarette (EC) or electronic nicotine delivery system (ENDS) in the market has called upon the public health concerns pertaining to its safety and potential harm to health. Despite the uncertainty on its health effects, there are evidences of its potential use as a smoking cessation aid for smokers to quit smoking (1,2). Nevertheless, there are reports in Canada that the EC has become an experimenting device for young adults who never smokes (3) and a report in Malaysia reported similar findings (4). A previous multi-country study reported that Malaysia had among the highest percentage of current EC users (14%) (5). The finding also showed that there were 15% smokers who were dual-users who also use conventional cigarettes in addition to EC. A small sub-community study in Malaysia

has shown that most EC users believed vaping was safer than using conventional cigarettes (87%) and existing tobacco smokers stated the reason for vaping was to reduce tobacco consumption (81%) (6). A small fraction of the sample population was previously non-smokers (3.9%) (6) which reinforce previous findings about EC usage not limited to existing traditional tobacco users only (7).

E-liquids locally produced are widely available in the Malaysian market (6). E-liquids are easily accessible and can be either purchased from physical vape shops, online shops or night markets with loose restriction. In addition, it has been sold without quality assurance, particularly on the accuracy of labelling of its chemical contents. Currently, e-liquids that contain nicotine are regulated under Section 9(1) Poison Act 1952 (8). Under the law, nicotine is categorised as a poison in Group C in which it should only be sold as "dispensed medicine" by licensed pharmacists and the sale of products are regulated by Ministry of Health. While, the Ministry of Domestic Trade, Cooperatives and Consumerism is

responsible to regulate and enforce the safety standards of EC device as well as the labelling of nicotine-free e-liquids. However, the restriction and e-liquid products' terms of sale are still unclear.

The acceptance of the EC and the use of locally-manufactured e-liquids among the public have created the need to perform health risk assessment. Existing study has shown that e-liquids contain TSNA (9) which are the most potent chemical classified as Group 1 human carcinogen by International Agency for Research on Cancer (IARC) (10) while nicotine is the most addictive agent in tobacco products. The selected TSNA have been detected in e-liquid samples in the range from 0.22 to 9.84 µg/L for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and 0.34 to 60.08 µg/L for N'-nitrosonornicotine (NNN) (9). In addition, there is the issue with labelling discrepancies on nicotine content which has previously been reported in literature [range of percentage difference between the labelled-and measured concentration of nicotine = -27% to -73% difference (11) and -32.2% to 3.3% difference; (12)]. All these evidences demonstrate the ability of EC to pose detrimental health effects of either carcinogenic or non-carcinogenic impact to its users.

The knowledge gap on the health risk assessment (HRA) in regards to EC use, incorporated with an increasing number of users among Malaysian populations have warranted further investigation on this public health issue. Assessment of health risks performed using local EC topography data is important because data on estimated risk may be used in health promotion activities or in conveying or communicating information on the potential hazards arising from EC use especially among younger population. There is the need to address health promotion activities according to its hierarchical importance; the first is that e-liquids with labelling discrepancies may expose younger population who uses EC for experimenting purposes become addicted to nicotine and may end up as conventional cigarette smokers in the future (13). This is followed by the need to continue to reduce the prevalence of current smokers as specified in the Framework Convention of Tobacco Control (14). No other studies have attempted to estimate the risks associated with the use of locally-manufactured e-liquids, especially the products most-favoured among local users. Therefore, this study aims to assess human health risk for non-carcinogenic and carcinogenic effects resulting from the exposure to nicotine, PG and selected TSNA contained in the locally-manufactured e-liquids. It is expected that the findings of this study will assist the authority to develop an evidence-based policy and a framework on EC regulation.

MATERIALS AND METHODS

This health risk assessment (HRA) study was a part of larger study of a survey on the use of EC conducted

among 86 adult tobacco users in several areas in the Klang Valley, Malaysia. Being one of the most concentrated areas of EC users (15), the selection of Klang Valley as a study location was the most relevant. The results of the survey were previously published elsewhere (6). To recap briefly, a survey on EC use has been conducted among 226 tobacco users who purposively sampled among selected populations of adults in Klang Valley area. Three survey dissemination approaches have been applied in order to obtain the sufficient number of respondents, namely the university-based, company-based and online-based approach. The data on EC usage topography was collected among 86 of EC users who identified during the survey. The EC usage topography data consisted of i) usage duration (median: <1 year); ii) volume of e-liquid used per month (60 mL/month); and iii) no. of puff per day (50 puffs/day). The study also was able to identify 17 most-favoured locally manufactured e-liquids. The e-liquids were analysed using previously established methods (9,16) to determine the concentration of nicotine, PG and selected TSNA and were previously published in the literature (11).

HRA was performed using an established method proposed by United States Environmental Protection Agency (17). This method has been applied in other studies to estimate health risks resulting from exposures to selected chemicals at the population level (18,19). In this study, the probability of detrimental health effects occurring as a result of the exposure to selected chemicals contained in locally-manufactured e-liquids determined in a separate study (11) were calculated based on the approach established by the United States of Environmental Protection Agency (USEPA) (20). This method integrates analytical measurements of chemicals with topography data to come out with population-based health risks.

For the health risks associated with the 17 e-liquids, estimations were made on i) non-carcinogenic health effects due to exposure to nicotine and PG content and ii) carcinogenic health effects due to exposure to NNK and NNN. Non-carcinogenic health effects include cough, dry mouth and throat, throat irritation, nausea, dizziness, and emphysema.

In order to estimate the health risks of non-carcinogenic health effects resulted from nicotine and PG exposures, the average daily dose (ADD) were calculated using equation 1 for individual compounds.

$$ADD = \frac{C_p \times IR \times ED \times EF}{BW \times ATNC}$$

[Equation 1]

In equation 1, C_p is average concentration of chemical in e-liquid (mg/mL); IR is ingestion rate (mL/day); ED is exposure duration (year); EF is exposure frequency (day/

year); BW is average of body weight of respondents (kg); ATNC is averaging time (EDx365 days/year) for non-carcinogenic effects. The HQ value was determined using equation 2. The RfD values for nicotine and PG were as established value by European Food Safety Authorities (20) and Agency for Toxic Substances and Disease Registry (22), respectively.

$$HQ = \frac{ADD \text{ (mg/kg/day)}}{RfD \text{ (mg/kg/day)}} \quad [\text{Equation 2}]$$

In equation 2, ADD is the average daily dose of population (mg/kg/day) and RfD is the reference dose for particular non-carcinogenic chemical constituents (mg/kg/day). The final outcome of the HRA for non-carcinogenic health effect is the characterisation of HQ value. The value would determine whether the exposure to the compound was; i) not likely to attribute to non-carcinogenic health effect which interpreted as “acceptable risk”/ (HQ value was less than 1) or ii) likely to contribute to non-carcinogenic health effect which interpreted as “unacceptable risk” when the HQ value was more than 1. The sum of individual HQ of nicotine and PG exposures would be expressed as total HQ (HQ_T).

For carcinogenic health risk, lifetime average daily dose (LADD) values were estimated as the result of respondents’ exposure to NNK and NNN contained in locally-manufactured e-liquids. Equation 3 was applied to determine the LADD values.

$$LADD = \frac{Cp \times IR \times Ed \times EF}{BW \times ATC} \quad [\text{Equation 3}]$$

In equation 3, Cp is the average concentration of chemical in e-liquid (µg/L); IR is the ingestion rate (L/day); ED is the exposure duration (year); EF is the exposure frequency (day/year); BW is the average body weight of respondents (kg); ATC is the averaging time (70x365 days/year) for carcinogenic effects. The LCR calculation in equation 4 considers the value of respective cancer slope factor (CSF) for each carcinogenic compound which were derived from the California Office of Environmental Health Hazard Assessment (23).

$$LCR = LADD \times CSF \quad [\text{Equation 4}]$$

In equation 4, LADD is the lifetime average daily dose (µg/kg/day); CSF is the cancer slope factor for each carcinogenic chemical constituents. The carcinogenic health risk which was denoted by LCR value would be interpreted as; i) clearly acceptable if the value was less than 1.0E-6; ii) acceptable if the value fall within 1.0E-6 to 1.0E-4 and iii) clearly unacceptable when the value was more than 1.0E-4. Total LCR (LCR_T) would be the sum of individual LCR value of NNN and NNK exposures. Table I shows the parameters used for the calculation of ADD, LADD, HQ and LCR.

Table I: Parameters used in the estimation of ADD^a, LADD^b, HQ^c, and LCR^d

Parameter	Value	Reference
Measured concentration (Cp) mean (standard deviation)	i) Nicotine = 3.26 (1.04) mg/mL	(11)
	ii) PG= 484.10 (98.24) mg/mL	(11)
	iii) NNK ^e = 0.085 (0.057) µg/L	(11)
	iv) NNN ^f = 0.0377 (0.289) µg/L	(11)
Ingestion rate (IR)	2 mL/day	(6)
Exposure duration (ED)	1.04 year	(6)
Exposure frequency (EF)	260 day/year	(6)
Body weight (BW)	73.86 kg	(6)
Averaging Time (AT)	Non-cancer ^g = 379.6 Cancer ^h = 25550	-
Reference dose (RfD)	i) Nicotine = 0.0008mg/kg/day	(21)
	ii) PG = 25mg/kg/day	(22)
Cancer slope factor (CSF)	i) NNK = 1.81 x 10 ⁻⁵ µg/kg/day	(23)
	ii) NNN = 1.4 mg/kg/day	(23)

^aAverage daily dose; ^bLifetime average daily dose; ^cHazard quotient; ^dLifetime cancer risk
^eNNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; ^fNNN = N'-nitrososornicotine; ^gAT for non-cancer risk = ED*365; ^hAT for cancer risk = 70 years*365

RESULTS

The assessment of health risks related to EC usage resulting from the exposure to nicotine, PG and selected TSNAs contained in the locally manufactured e-liquids were performed according to the EC usage topography information and selected chemical analysis data as published previously (6,11). Prior to step of risk characterization, the dose of exposure (ADD & LADD) to chemicals was calculated as described in Table II using equation 1 and 3.

Table II: Dose of exposure to selected chemicals

No.	Compound	ADD ^a (mg/kg/day)	LADD ^b (µg/kg/day)
	Nicotine	0.063	NA*
	PG	9.338	NA
	NNN	NA	1.098E-7
	NNK	NA	2.45994E-08

*Not applicable; ^aADD (average daily dose) = (refer equation 1); ^bLADD (lifetime average daily dose) = (refer equation 3)

The mean value of LCR_T was 1.54E-04 which slightly exceeds the acceptable risk threshold of 1E-4. Figure 1 presents the box plots of (a) individual LCR of NNK; (b) individual LCR of NNN; and (c) Total LCR of NNN and NNK. Based on Figure 1, it was estimated that the population will be at risk of developing cancer due to exposure to selected TSNAs (NNN and NNK). Total LCR value has exceeded the acceptable value of more than 1E-4. Specifically, according to the total LCR value (LCR_T), a ratio of 2 persons over 10,000 of user population will be at risk of cancer.

Figure 2 demonstrates the box plots of (a) individual HQ of PG; (b) individual HQ of nicotine; and (c) total HQ of PG and nicotine. For non-carcinogenic health risks, the HQ_T was 78.9 (Figure 2 (c)) which exceeded the acceptable level of 1. It is estimated that the population were at risk of experiencing non-carcinogenic health

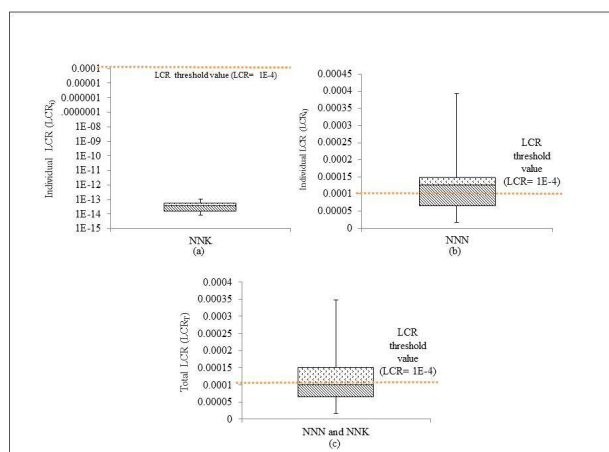


Figure 1: Box plots of (a) individual LCR of NNK; (b) individual LCR of NNN; and (c) Total LCR of NNK and NNN

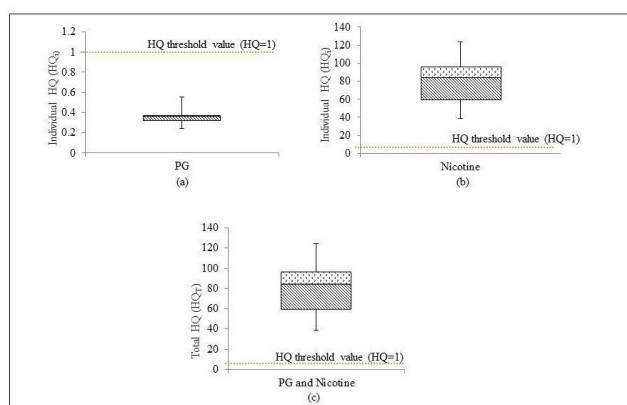


Figure 2: Box plots of (a) Individual HQ of PG; (b) Individual HQ of nicotine; & (c) Total HQ of PG and Nicotine
effects due to exposure to nicotine and PG contained in e-liquids.

DISCUSSION

This study aimed to estimate the carcinogenic and non-carcinogenic health risks arising from the exposure to nicotine, PG and selected TSNAs related to the use of EC and locally-manufactured e-liquids. This study estimates that two out of 10,000 EC user populations will be at risk of experiencing cancer effects due to cumulative exposure to NNN and NNK identified in the locally-manufactured e-liquids. The study shows that the total exposure to nicotine and PG contained in e-liquids were able to expose EC users to the risk of non-carcinogenic health effects.

In order to estimate the risk of EC, multiple approaches have been applied (24). However, many of previous studies (25,26) have presented the finding on the chemical constituents contained either in the e-liquid or vapor, without emphasizing on the carcinogenic or non-carcinogenic health risk that could be attributed from the exposure to selected chemical contents. In the present study, the health risk of local population was estimated based on their EC usage topography data and included the chemical analysis of the most-favoured locally-

manufactured e-liquids. The methodology of performing health risk estimation has provided an advantage in the present study to stand as a comprehensive HRA in order to address the health risk encountered by local population.

Despite being advertised as harmless (27,28), this study has added the evidence of the potential non-cancer health effects of EC that could be experienced by the users due to cumulative exposure of nicotine and PG in e-liquid. Within the Malaysian context, the EC has not only been used among smokers, but it was also smoked by previously never-smokers who initially used EC for enjoyment purposes. The entry of EC into the Malaysian market has contributed to the involvement of never-smokers as a new group of tobacco users which may have prevented the reduction in the number of local smoking population. As reported in the 21,410 representative Malaysian populations-based survey, National Health Morbidity Survey (NHMS), smoking-related diseases have contributed about one-fifth of disability adjusted life years (DALYs) and one-third of years of life lost (YLL) among Malaysian (29,30). Therefore, the use of EC including dual-users and those who never previously smoke may indirectly contribute to the national burden of tobacco/smoking-related diseases in Malaysia. Multiple health effects, particularly symptoms related to the respiratory system have been reported such as dry mouth and throat, and cough among EC users (31,32). The occurrence of these symptoms may be due to the hygroscopic property of PG where this relates to the ability of PG absorb moisture in its surroundings causing the dryness of mouth and throat once the vapour was inhaled by users (33). Equally important, the findings suggest that there is the probability of TSNAs in e-liquids posing cancer risks to EC users in a ratio of 2 persons over 10,000 of EC user populations. As reported in pre-clinical studies, the exposure to NNK has been related to lung cancer risk (34,35) while NNN exposure has posed a risk of esophageal and oral cavity cancer (36). Therefore, the use of EC, especially among the group of users who previously have never smoked is of significant concern.

Although the device has been deemed as a harm-reduction tool (37), it has been surrounded by controversial issues such as its potential in promoting tobacco use among the younger population. The trend of youth smoking since 2003 (19.9%) (38) to 2006 (6.1%) (39) has been on the decline, but from the data, it clearly shows that there was a large incline of percentage from 2012 (11.5%) (40) to 2017 (13.8%) (41) with reasons not explained. The emergence of EC as a new-technology in delivering nicotine may to some extent contribute to that increment. Other studies have reported that the younger population may be keen to try EC due to curiosity and the myriad varieties of e-liquid flavours currently available in the market (42,43) which later may facilitate initiation of nicotine dependence among

non-smokers (31,44). Thus, scientific-based evidence as provided in this study is deemed important, especially as a platform to provide evidence on the need to develop health promotion that reaches the target population, in this case the younger generation on the potential health risks that they may encounter due to the use of EC. It is essential to distribute accurate information to this vulnerable population as they are being exposed to misconception regarding EC usage. Therefore, it is important for related authorities to oppose the claims made by EC manufacturer which states EC as harmless device. It can be done by strategizing proactive health promotions among younger population, such as school-based programs which can be understood and is reachable by the public particularly younger generation in order to prevent tobacco use and its initiation. Furthermore, this finding is able to be used as an evidence for the current EC users or dual users on the health risk that they are encountering while using EC. Even though there are users using EC as a smoking cessation aid (45), the debate on that issue continues and at the time being, there is an inconclusive statement by WHO on the capability of EC in assisting smokers to quit due to limited and inconsistent evidences (46). Despite the estimation method used to represent the potential health as seen in this study, the outcomes can to an extent be used by the government to challenge the unproven health claims made by EC manufacturer.

To the best of our knowledge, this is the first study that addresses the health risk estimation of EC usage. This study considers the Malaysian usage topography of EC as well as chemical analysis of most-favoured locally-manufactured e-liquid. Furthermore, the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) is the international treaty introduced by WHO. This modern public health framework emphasized on the impact of tobacco use within the context of social, economic and environment. Subsequently, "MPOWER" was introduced. MPOWER is a policy package intended to assist in the country-level implementation to reduce the demand for tobacco products (47). The components of MPOWER includes i) M for monitor tobacco use and prevention policies, ii) P for protect people from tobacco smoke, iii) O for offer help to quit tobacco use, iv) W for warn about the harmful effect of tobacco, v) E for enforce bans on tobacco advertising, promotion and sponsorship and vi) R for raise taxes on tobacco. In line with the FCTC MPOWER strategies (48), the present study has supported two strategies, including i) "M" for monitoring and surveillance of local EC usage and chemical constituents in e-liquids and ii) "W" for warning about the potential risk of EC to the users and a younger population.

Within the local context, the Ministry of Health, Malaysia has announced the target of for the Tobacco End Game to build a smoke-free nation by 2045 (49). However, the emergence of EC as another kind of nicotine-tobacco

delivery device has challenged the government's approach to accomplish the mission of having less than 15% of smoker by 2045. The acceptance of EC use among the public (5,50) interrupts the health promotion objectives performed by the government to de-normalise smoking habit, thus, it may contribute to initiation of tobacco use among non-smokers.

The limitation of this study includes the fact that the health risk assessment was performed based on oral ingestion rather than inhalation exposure. At present, there are no existing HRA data published involving local EC products and there was no access to smoking machine at the commencement of this study. As such, this is the best available local data produced to represent the potential adverse health effects to EC users; which is the main concern in the area of public health. Due to this limitation, data should be interpreted with caution. Further assessment using inhalation exposure data should be performed in the future once data are made available. Notwithstanding the limitation, the estimation of the health risks was performed based on the real EC usage topography of this population and the chemical analysis was conducted for the most-favoured locally manufactured e-liquids. Thus, this study has been conducted in a comprehensive approach in evaluating the potential human health risk as an outcome of exposure to nicotine, PG and selected TSNAs from the use of EC.

CONCLUSION

This study estimates that EC use has the potential to contribute to non-cancer and cancer risk to the health of its users. The findings of this study will assist the local related authority to come out with evidence-based policies on EC, in order to combat the rising of tobacco-related morbidity and mortality and prevent tobacco use initiation among the population to reach the national goal of End Game for tobacco by 2045.

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