Meta-Analysis on the Health Effects of Primary and Secondary Exposure to Electronic Cigarette Vapor

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ABSTRACT

Electronic cigarette (e-cig) smoking or vaping is a major method of tobacco smoking cessation. Independent studies from several different groups have shown contradictory evidence on the effects of vaping on the user and bystanders. The rate of e-cigs usage and associated health effects have increased rapidly mostly due to misleading information on the safety of e-cig components. The current study has been conducted to critically evaluate the health effects of e-cig vaping on the primary user, secondary smoker (bystander) who undergoes passive vaping and the process of addiction in both primary and secondary smokers.

I have proposed a concept of *'health effects cycle of electronic cigarettes'* which describes how e-cig components (both liquid and vapor) can cause health conditions and ultimately lead to addiction in both the primary smoker and the secondary smoker. This cycle describes that the mainstream vapor inhaled and e-liquid components cause cancer, asthma/respiratory conditions, heart diseases and dental/oral conditions in primary smoker. Long-term vaping cause nicotine addiction as well. The secondary smokers are exposed to both sidestream and mainstream vapor, and this passive smoking cause mainly respiratory health conditions and addiction. Accidental exposure to e-cig products are common in secondary smokers. The e-cig vaping by both primary smoker and newly addicted secondary smoker contribute to poor indoor air quality.

By meta analysis of the studies conducted on the toxic constituents of the side stream and mainstream vapor and the e-cig liquid, I have summarized that e-cig usage can be a health hazard to a wide range of primary and secondary smokers, leading to respiratory conditions, asthma, cancer, cardiovascular conditions, and oral/dental conditions. Moreover, accidental exposure to

e-cig components was shown to damage mainly the pediatric population of less than 5 years old, but also adolescents older than 20 years old. My study concludes that while vaping could be a comparatively less harmful alternative for tobacco smoking, poses great health risks to both primary smoker and bystanders of a wide range of ages.

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LIST OF ABBREVIATIONS

CDC	Centers for Disease Control
CEH	Center for Environmental Health
CNS	Central Nervous System
E-cigarettes or E-cig	Electronic Cigarettes
ENSA	Electronic Nicotine Delivery Systems
FDA	Food and Drug Administration
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TSNAs	Tobacco-Specific Nitrosamines
US	United States
VOCs	Volatile Organic Compounds

CHAPTER 1: INTRODUCTION

1.1 Background

Cigarette smoking is a global health hazard. The current primary and secondary tobacco smoker death toll is approximately 6 million per year (WHO, 2015). Moreover, smoking is one of the leading causes of cancer, asthma, cardiovascular diseases and addiction (Health and Services, 2014). Passive smoking or second-hand smoking, which is caused by the inhalation of sidestream vapor from the cigarette and/or mainstream vapor exhaled by the cigarette user, may lead to severe health conditions in the secondary smoker (Cao et al., 2015). Even though, there are regulations restricting the smoking indoors or at public places, passive smoking remains a global health concern, as it causes approximately 600,000 deaths per year (Oberg et al., 2011, Arora and Kumar, 2011).

Electronic cigarettes (***e-cigarettes*** or ***e-cig***) were introduced mainly for mitigation or cessation of tobacco smoking, as well as to reduce passive smoking (Bullen, 2014). E-cigs are 'recreational nicotine devices' which are designed to mimic the 'act of smoking' (*vaping*) (Cahn and Siegel, 2011a). Apart from the primary health consequences caused by nicotine and toxic by-products of vaping, the continuous act of smoking may lead to addiction. Increasing rate of adolescent addiction to vaping and subsequent chronic smoking has also been a great concern (Fillon, 2015b, Klein, 2015).

While the global health consequences of tobacco smoking are well established and being addressed, the studies of e-cigarette vaping are rather controversial and inconclusive. Therefore, there is an urgent need for critical evaluation of primary and secondary health hazards and addictive effects of vaping.

1.2 Literature Survey

Primary smoking health consequences: In contradiction to the popular claim that e-cigs are healthier alternatives for tobacco smoking and an effective smoking cessation approach (Adkison et al., 2013, Goniewicz et al., 2013), studies have reported higher levels of toxic chemicals, carcinogens, nicotine by-products in e-cig vapors, which may lead to primary health hazards (Farsalinos et al., 2015a, Etter, 2009, Cavico et al., 2014).

Secondary smoking health consequences: Many of the promoting studies of e-cigs have implied that no toxic vapor is produced from them (Long, 2014, Tayyarah and Long, 2014). However, recent reports suggest that e-cigs do produce both sidestream and mainstream toxic vapors that may cause severe health consequences in bystanders, especially vulnerable populations such as pregnant women and children (Protano et al., 2015, Ballbe et al., 2014).

E-cigarette nicotine addiction: There is an alarming rise in news on e-cig addiction in non-smokers, especially young adolescents and school children. This addiction has been attributed to the misleading commercials from e-cigarette companies (Dufort and Owila, 2014). Regulations are in place to ban or control selling e-cigarettes to minors to avoid addiction in adolescents and school children (Tremblay et al., 2015, Kmietowicz, 2014).

Knowledge gap: Currently available information of e-cigarette safety, their efficacy as a tobacco cessation approach, and primary and secondary harmful health hazards are mostly inaccurate, inconsistent or controversial (Peralta and Guntur, 2014, Drummond and Upson, 2014). Albeit the lower toxin levels found in e-cigs as opposed to tobacco cigarettes, a growing body of literature provides evidence of carcinogens, additives and flavors in e-cigs. However, another set of reports contradict these studies implying the e-cigs are indeed user- and environment-friendly.

Therefore, there exists a knowledge gap regarding critical evaluation of these studies to assess the real-time health effects of vaping.

1.3 Rationale for the proposed project

There are highly controversial studies performed on the health hazards of e-cigs. Yet the effects of e-cigs on this 'cycle of primary and secondary health hazards and addiction' have not be systematically reviewed before. Due to the controversial nature of the reported health hazards of e-cigs, the community may continue using e-cigs while the rate of new users increases rapidly. Therefore, a comparative and systematic evaluation of the primary, secondary and addictive effects of e-cigarettes is essential.

1.4 Research Questions

Three research question have been chosen to be addressed based on the literature survey conducted above. The questions are as follows;

1. What are the health effects of electronic cigarettes on primary smokers (user)?
2. What are the types of toxic compounds released from e-cigarettes and what are the health consequences of these compounds on secondary smokers (bystanders)?
3. Does e-smoking/vaping cause addiction in both primary and secondary smokers?

1.5 Hypothesis

The mainstream vapor inhaled into the primary smoker leads to health effects such as cancer, asthma, heart diseases and dental/oral conditions. Long-term usage of e-cigarettes by primary smokers lead to nicotine addiction. Both sidestream vapor released from the e-cigarette

and mainstream vapor exhaled by e-cigarette user are inhaled by the bystander (secondary smoker) and this passive smoking cause health conditions as well as addiction. Therefore, I hypothesize that there is a '*health effects cycle*' of electronic cigarettes **(Figure 1. 1)**.

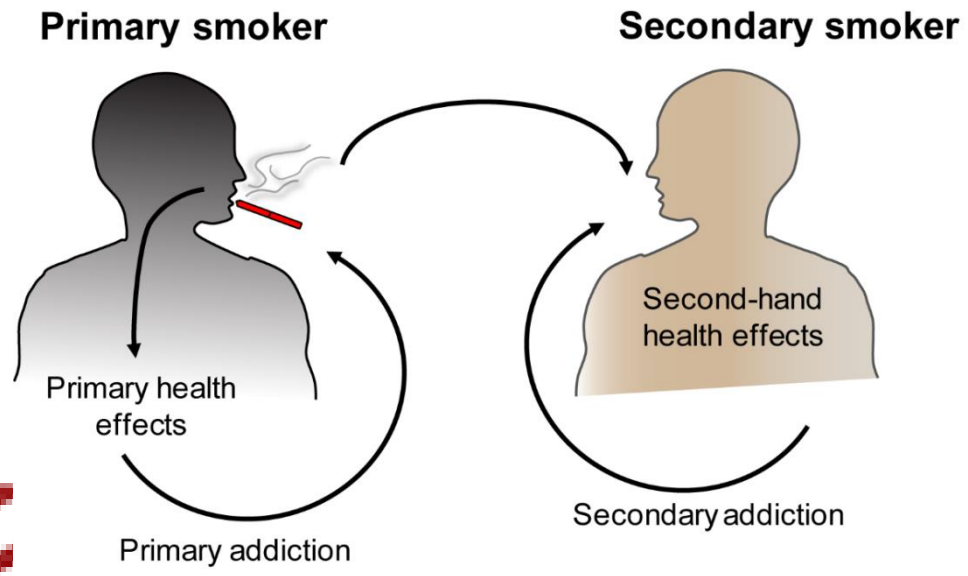


Figure 1. 1 Proposed health effects cycle of electronic cigarettes.

The smoking by the primary smoker leads to primary health effects such as cancer, asthma, heart diseases and dental/oral conditions. Long-term smoking further leads to primary addiction of the primary smoker. The sidestream vapor released from the e-cigarette as well as mainstream vapor exhaled by e-cigarette user can cause health effects in a nearby person (secondary smoker). This may lead to addition in secondary smoker as well.

1.6 Research Objectives

In order to test these hypotheses, I propose the following three research objectives;

Aim 1: Evaluation of the health effects of electronic cigarettes on primary smokers.

Aim 2: Assessment of the effects of second-hand exposure to toxic compounds released from electronic cigarettes.

Aim 3: Investigation of potential addictive effects of electronic cigarettes

CHAPTER 2: MATERIALS AND METHODS

2.1 Ethics statement

No human subjects were used in the study. All the information and data were collected from published studies with proper acknowledgement. To avoid ethical concerns, studies with conflicts of interest were excluded from the study.

2.2 Data collection and analysis strategy: PRISMA

To collect data/information relevant to the study and analyze them, I have used the "Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). This method of systematic review of e-cigs have been done before and the methods of two of such studies were adapted and modified to fit into the aims of the current study (Farsalinos and Polosa, 2014, Pisinger and Dossing, 2014). Further insights on the meta analysis were obtained from similar studies (Wang et al., 2016, Stroup et al., 2000).

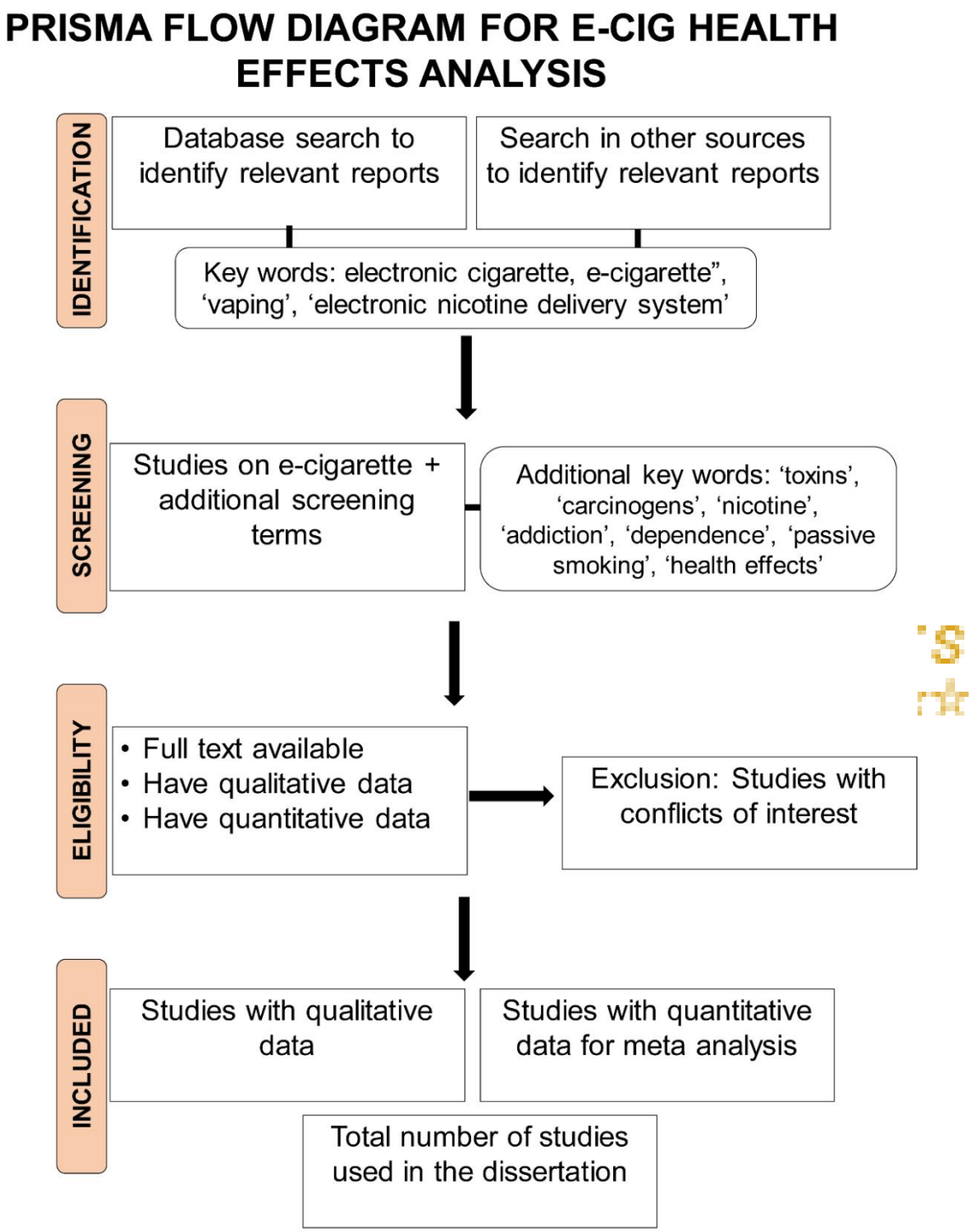


Figure 2. 1 A PRISMA flowchart for the publications/studies included in the systematic review of health effects of electronic cigarettes (e-cig).

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) approach was modified to screen the studies to be included in the metal analysis of health effects of e-cigs.

2.3 Literature survey strategy

Identification of studies: Comprehensive literature survey was performed using two major databases namely, PubMed and Google Scholar. The articles published in between 2000-2016 were taken into consideration to be included in the PRISMA. The basic key words used in the first step of the PRISMA approach were 'electronic cigarette', 'e-cigarette", 'vaping' and 'electronic nicotine delivery system'. To further expand the articles used in the study, the bibliographical reference lists in selected articles were also surveyed to identify any study which was missed by the aforementioned search terms.

Additionally, qualitative information on e-cig usage was extracted from a wide range of media websites, blogs which were not included as an article but a source of data collection.

Screening strategy: The selected articles were further screened for the presence of following key words: 'toxins', 'carcinogens', 'nicotine', 'addiction', 'dependence', 'passive smoking' and 'health effects'.

Inclusion and exclusion strategy: The studies were limited to full texts. Review articles were excluded in the meta analysis. Several of the studies had to be excluded as they expressed conflict of interest as either they were funded by e-cig manufacturing companies and/or authors being expressed conflicts of interest due to their roles as consultants in tobacco smoking cessation approaches using e-cigs. Among the articles which fulfilled the identification and screening strategies, only the articles with either qualitative and/or quantitative data on toxins, chemicals, carcinogenic substances were included in meta analysis.

2.4 Data extraction strategy

Quantitative data on toxin levels, threshold levels and percentage users and incident rates were extracted. Raw data was extracted whenever possible from government statistics and case studies. In studies where concentrations of toxic or chemical substances were investigated, the results were separated based on the nature of the vaping product used, vapor or fluid.

2.5 Qualitative data and information extraction

Review articles were used to gather qualitative information and concepts. Moreover, several review articles were used to verify the research studies included in the Meta analysis and to include any study that was missed during the database search using selected set of key words. Several blogs sites were used to gather insights on attitudes of e-smokers, general population and health care providers.

The blog sites consulted were as follows; http://info-electronic-cigarette.com/blog/ and http://sfata.org/resources/e-cig-blogs/.

Also many science or health related news websites were used. They include https://www.sciencedaily.com/releases, http://www.medicalnewstoday.com/, http://www.cbc.ca/ and http://www.webmd.com/news/.

2.6 Limitations of the study

The heterogeneity of the studies available on e-cigarettes might influence the conclusions. The limited use of search terms may also omit or cause a bias in studies included in

the study. The literature on the electronic cigarettes are vast. With the available time and resources, only a limited set of literature was used to derive the conclusions of the study.

CHAPTER 3: RESULTS

3.1 Aim 1: Evaluation of the health effects of electronic cigarettes on primary smokers.

3.1.1 Electronic cigarettes as an alternative for tobacco smoking

Cigarettes smoking is extremely harmful and a global health hazard. For this reason, many smokers have been persuaded to either quit smoking or bear the consequences of continued smoking while damaging themselves and endangering others lives. The annual deaths caused by smoking exceeds 6 million, projecting its harm to increase up to 8 billion per year by 2018 (Organization, 2011, Tobacco, 2014). Over 600 000 of this 6 million death are second-hand smokers, which will be discussed in the section 3.2. Among many of the tobacco smoking cessation therapies, the tobacco harm reduction program implemented electronic cigarettes smoking or 'vaping' in 2004. Since then e-cig vaping has been very popular among ex-tobacco smokers. Several survey results conducted support the success of e-cigarettes as a better cessation approach compared to other tobacco replacement therapies (Siegel et al., 2011, Etter and Bullen, 2011b).

It is admissible that as compared to the health hazards caused by tobacco smoking, e-cig usage provides several health benefits to the ex-smoker. One major benefit of vaping is that it mimics the act of smoking and thereby provides satisfaction to the tobacco addicts and provide ways of calming themselves without much harming (Cahn and Siegel, 2011b). Many ex-smokers preferred e-cigs over nicotine replacement therapies (Etter and Bullen, 2011b). This has also led to prevention of smoking relapse in ex-smokers (Etter and Bullen, 2014).

As many health organizations have questioned the safety of e-cigarettes, many research groups compared the levels of different toxins or components in between tobacco smoke and the e-cigarette vapor. Below are projections from some of the studies which imply safety of e-cigarettes based on aforementioned comparisons. Considering the reduced levels of major pollutants and toxic compounds listed in the table, the e-cigs seem to be safer than tobacco cigarettes.

Table 1. Comparison of major toxin/compounds in between Tobacco cigarette and Electronic cigarette

Chemical compound	**Tobacco cigarette**	**Electronic cigarette**	**References**
Formaldehyde	1.6-52 µg	0.20-5.61 µg/15 puffs	(Goniewicz et al., 2014)
Toluene	1400 µg/m3	4 µg/m3	(Marco and Grimalt, 2015)
Nicotine	1300 µg/m3	4 µg/m3	
Carbonyls	31865.2 ng/L	797.7 ng/L	(McAuley et al., 2012a)

3.1.2 Assessment of toxic compounds in electronic cigarettes_ Evaluation of health hazards

The e-cig user is exposed to both vapor and the liquid components of the cigarette. This concept was introduced in my hypothesis as reasons for health effects in the user as well as a probable cause for primary addiction. In order to evaluate the toxins-found in e-cigarette that can harm the primary user, I have chosen few published studies to compare their levels of toxins reported. The major toxic additive in e-cigs is nicotine, hence the name ‘Electronic Nicotine Delivery Systems (ENDS).

Some of the ex-smokers or new smokers prefer e-cigarettes due to the availability of nicotine-free systems. The labels of e-cigs either mention that the nicotine content is zero or do not mention any amount as an indication of the absence of nicotine. Unfortunately, many of the e-cigs perceived as nicotine-free were found to contain lower levels of nicotine. I have shown percentage of products tested in two studies which were shown to be misleading (Cheah et al., 2014, Hutzler et al., 2014). My comparison study indicated that approximately 70-80% of the products showed misleading information on nicotine content (**Figure 3. 1**).

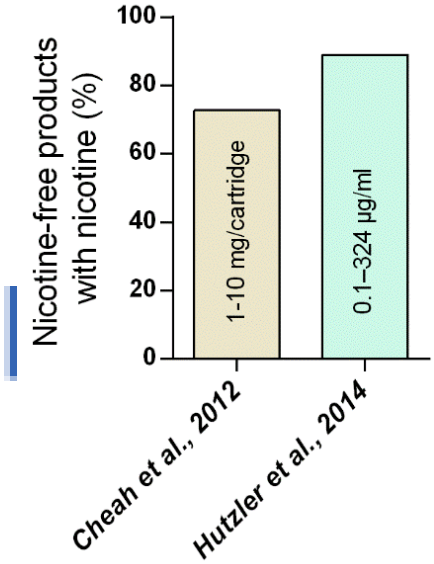


Figure 3. 1 Percentage of products perceived as nicotine-free but contained nicotine.

Two studies were used in analysis of the percentage of electronic cigarette products with the labels either mentioned 0 mg of nicotine or no mention of nicotine content, but reported nicotine presence (Cheah et al., 2014, Hutzler et al., 2014). The range of nicotine found in these products is indicated within each column.

Even though nicotine-free e-cigs are considered to be safer, some evidence has surfaced to contradict this theory. The explanation was that, the levels of propylene glycol and glycerol in nicotine-free e-cigs might be higher than nicotine containing e-cigs. The below comparison suggest that the propylene glycol was higher only in one nicotine-free e-cig product as compared to the two nicotine-positive products (**Figure 3. 2**). The same was true in the case of glycerol. In the study in which it was shown that shisha-pen (type of e-cig) containing 0 mg of nicotine, the levels of propylene glycol and glycerol were above the levels of that can harm humans and cause airways irritation (Kienhuis et al., 2015). Therefore, there is a possibility that some of the e-cig products use more propylene glycol and glycerol to make them more potent, yet could be harmful to human health.

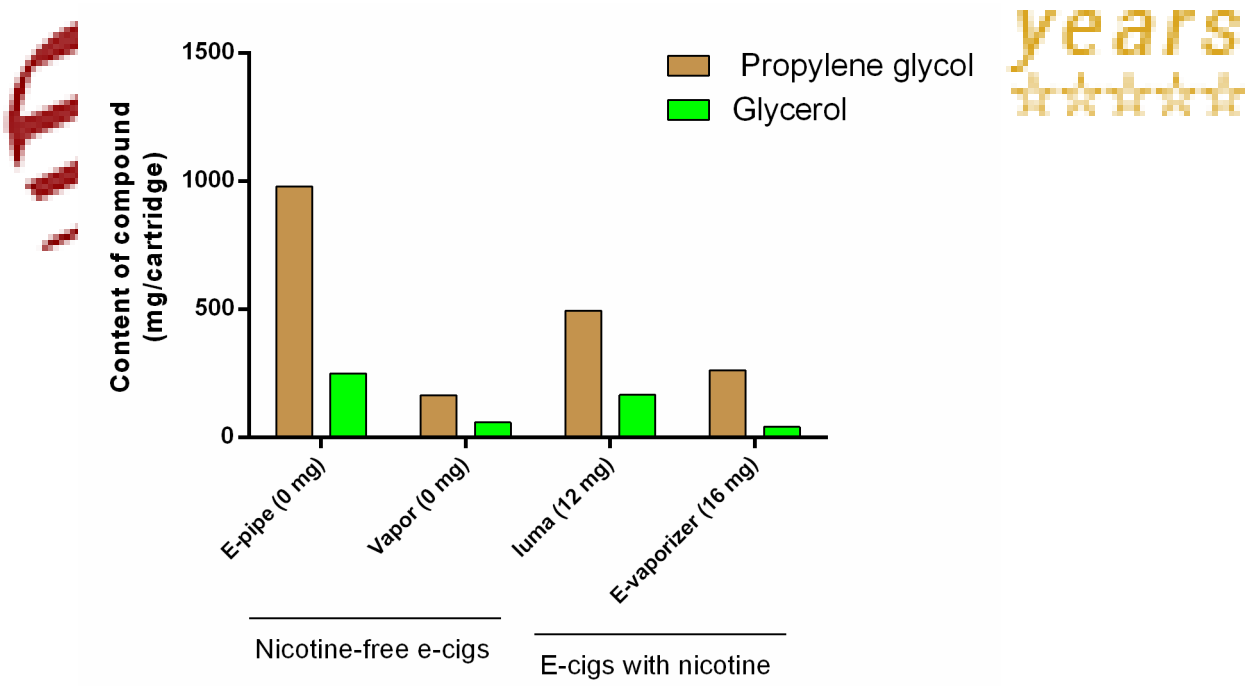


Figure 3. 2 Comparison of propylene glycol and glycerol in nicotine-free and nicotine containing electronic cigarettes.

The concentrations of propylene glycol and glycerol were compared in two nicotine-free e-cig products and two nicotine containing e-cig products. Data extracted from (Cheah et al., 2014).

Moreover, smokers prefer different levels of nicotine in their e-cigs. However, unfortunately, many of the labels do not convey the truth. Analysis of nicotine content actually present in the liquid and what is mentioned in the label suggested that many of the labels are misleading (Cheah et al., 2014).

As propylene glycol and glycerol were suggested as potential toxicity causing contents of e-cig liquid contents by (Kienhuis et al., 2015), I further looked into their presence in e-cigs and links to health conditions reported in the literature. Propylene glycol and glycerine are two major vaping products or vaporizing agents. Ethylene glycol is also used as a vaporizing agent in many e-cig products. Therefore, I analysed three studies which used 28, 2 and 20 types of e-cigarettes in their studies, respectively, to identify the major components of the vaporizing agents (Hutzler et al., 2014, Pellegrino et al., 2012, Cheah et al., 2014).

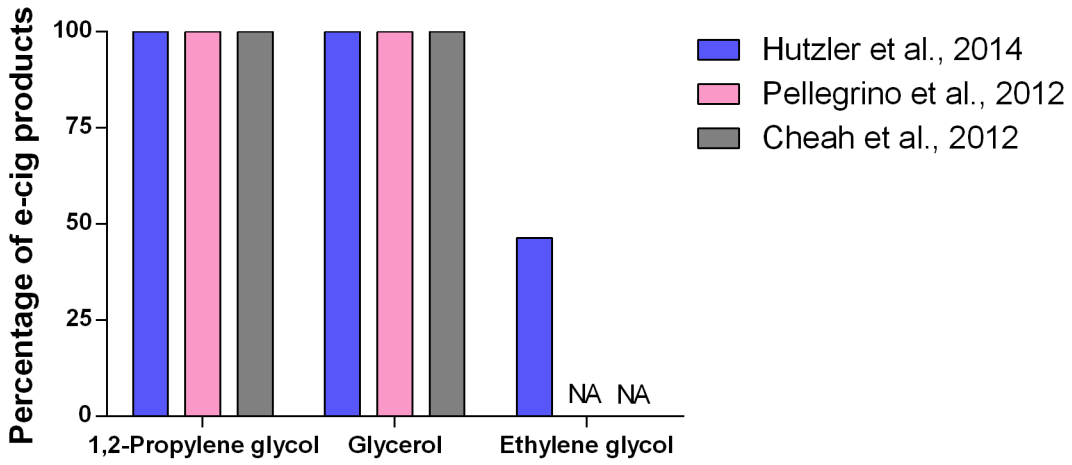


Figure 3. 3 Percentage of electronic cigarette products containing propylene glycol, glycerol and ethylene glycol

Three studies were used in analysis of the percentage of electronic cigarette products containing propylene glycol, glycerol and ethylene glycol (Hutzler et al., 2014, Pellegrino et al., 2012, Cheah et al., 2014). The number of e-cig products tested in each study are 28, 2 and 20, respectively.

The results of my comparison are shown in **Figure 3. 3**. Interestingly, 100% of the e-cig products used in all three studies contained propylene glycol and glycerol. However, ethylene glycol was reported only in one study, and 46% of the 28 e-cigs tested in this study contained ethylene glycol. According to some reports on e-cigs, ethylene glycol is much more toxic than propylene glycol and glycerol (Hutzler et al., 2014). This might explain the reason that it was not found in many of the e-cig products tested.

Additionally, e-cigs with glycerin have been linked to lipoid pneumonia (McCauley et al., 2012). Other than these substances, formaldehyde, acetaldehyde and acroleins have also been found among the common toxins in e-cigs (Farsalinos et al., 2015c, Kosmider et al., 2014b, Geiss et al.). In a later section, I will be discussing potential of formaldehyde as a carcinogen found in e-cigs. Additionally, several metal vapors such as nickel, chromium and lead have also been constituents of e-cig vapor. Moreover, two studies indicated that the levels of metals in e-cigs are higher than tobacco cigarettes (Goniewicz et al., 2014, Williams et al., 2013). Even though the exposure to trace amounts of metals in e-cig may not pose a great health concern for regular smokers, non-smokers may find these metal vapor hazardous to their health (Farsalinos et al., 2015b). For instance, these heavy metals found in e-cigs have been linked to oxidative stress in lungs (Lerner et al., 2015), which may contribute to lung-associated disease conditions.

3.1.3 Health conditions associated with e-cigarette usage

3.1.3.1 Asthma and other respiratory conditions

Lungs and rest of the respiratory system are the primary target of any smoking effort. E-cigs have been recommended/suggested for ex-smokers with severe respiratory conditions. Improvements of respiratory outcomes due to cessation of tobacco smoke while using e-cigs have been reported (Polosa, 2015). Switch to e-cig usage in asthma patients, who has used tobacco cigarettes before showed reduction in asthmatic symptoms and improvements in respiratory physiology (Polosa et al., 2014).

However, approximately 1% of such cases, e-cig usage have aggravated the respiratory conditions in the user. For example, a case report on a 43-year-old new e-cig user on tobacco smoking cessation strategy showed development of bronchial syndrome after e-cig usage (Hureaux et al., 2014). However, his case is a complicated one, as he has a history of primary lung adenocarcinoma and brain metastasis. E-cig using tests in health participants have shown alterations in pulmonary function test parameters, including reduction in total respiratory impedance and fraction of exhaled nitric oxide in e-cig users within 5 mins of smoking (Vardavas et al., 2012). A study which compared plasma cotinine levels in between tobacco smokers and e-cig smokers showed similar plasma cotinine levels between the two groups (Flouris et al., 2013). Cotinine is a product of nicotine metabolism and its levels in plasma is generally used as a biomarker for tobacco smoking (Koru-Sengul et al., 2011). The active e-cig users had a 3% reduction in lung function as compared to 7% lung function reduction in active tobacco smokers. Moreover, lipoid pneumonia, fever, cough and dyspnea were reported in a female e-cig user who used e-cigs for 7 months. Her symptoms disappeared after cessation of e-cig usage (McCauley et al., 2012).

Respiratory symptoms seen in e-cig users are mostly attributed to the airways irritations caused by propylene glycol vapor (Wieslander et al., 2001). However, e-cig vapor contains hundreds of other toxins and contaminants which may irritate the airways in many ways (Jimenez Ruiz et al., 2014). Moreover, nicotine content also seems to be a factor contributing to respiratory damage by e-cigs (Flouris et al., 2013). Yet, it should be taken into consideration that majority of these studies are biased and are not properly controlled. It would require much larger e-cig user cohorts and well controlled experiments, measurement of other health parameters to conclude direct association of e-cigs with respiratory deterioration. Regardless of the evidence pro- and against- the respiratory hazards of e-cig vapor, Spanish Society of Pneumology and Thoracic Surgery recommends proper regulation of e-cigs in medicinal use for tobacco cessation (Jimenez Ruiz et al., 2014).

3.1.3.2 Cardiovascular or Heart conditions

Increased heart rate was identified as a common heart condition visible immediately after using an e-cig containing 26 mg/mL, 11mg/mL or 14 mg/mL nicotine (Nides et al., 2014, Farsalinos et al., 2014, Czogala et al., 2012). Increased blood pressure and heart rate were observed in e-cig smokers who used e-cigs with nicotine (1.6-2.4%), glycerin (50-75%), propylene glycol (20%), glycerin menthol (75%) (Yan and D'Ruiz, 2015, Farsalinos et al., 2014). An interesting but terrifying correlation was found between increase risk of heart diseases in e-cig users who also use hormonal contraceptives. The risk of stroke, myocardial infarctions, coronary heart diseases as well as arterial disease have been reported in women using both e-cigs and hormonal contraceptives (Riley et al., 2016)

These studies provide implications whether constituents of e-cig liquid including nicotine, glycerin, propylene glycol and glycerin menthol contribute to the heart conditions in e-

cig users. It has been well established that tobacco containing smoking is a cause of cardiovascular diseases. The concept of “no safe level of exposure to tobacco smoke” has been shown to be quite accurate for tobacco smoke (2014). Comparing the levels of nicotine and other compounds available in the e-cigs analyzed above suggest that there are no safe levels of e-cigarette exposure as well. Not only human studies, but also several animal models of nicotine exposure have demonstrated that nicotine can increase the chance of atherosclerotic disease (Heeschen et al., 2001)

3.1.3.3 Cancer

Direct reports of cancer in e-cig users are rare. It is challenging to determine whether e-cig usage specially caused cancer, mostly due to the complex etiology of cancer as well as the history of e-cig user in terms of other substance abuses including tobacco usage. Mouse models of lung cancer and atherosclerosis demonstrated that nicotine exposure in mice induced angiogenesis, capillary and collateral growth, and thereby contribute to increased lung cancer lesion growth (Heeschen et al., 2001). Even though this study was not directly related to e-cig usage, nicotine as a major addictive compound found in e-cigs, it is an important correlation between nicotine and lung cancer growth. This study also indicates that lung cancer patients who are on a cessation program through e-cig usage may have increased risk of cancer relapse. In support of this concept, some doctors do recommend cancer patients to be away from e-cigs (Cummings et al., 2014).

Common carcinogenic compounds found in e-cigs are quinolone, diethyl carbonate, benzoic acid, butyl acetate, dioctyl phthalate 2,6-dimethyl phenol. Due to the presence of these carcinogens, e-cigs have been declared to be another public health concern in terms of cancer

risk (Cobb et al., 2010). In a study conducted by the Center for Environmental Health (CEH), e-cig was referred to as ‘a smoking gun’, mostly due to the presence of carcinogenic compounds in them (Cox, 2015). It is the general belief of many e-cig users that e-cigs are devoid of cancer-causing toxins and therefore has no cancer risk. In the 2015 CEH report, they tested 97 e-cig varieties for carcinogens and discovered that many e-cig products contained both or at least one of acetaldehyde and formaldehyde. Moreover, they reported that the presence of any carcinogen in e-cigs is a violation of the California’s consumer protection law (Proposition 65) [or Safe Drinking Water and Toxic Enforcement Act, 1986], which states a list of chemicals that can cause cancer, birth defects, and/or reproductive defects. Moreover, propylene glycol and glycerol are ‘formaldehyde-releasing agents’. The presence of propylene glycol and glycerol in e-cigs and their contribution to health outcomes are repeatedly discussed in this dissertation. It should be noted that formaldehyde is a group 1 carcinogen based on the International Agency for Research on Cancer (Kosmider et al., 2014a). Inhalation of formaldehyde or formaldehyde-releasing agents was proposed to increasing lifetime cancer risk (Jensen et al., 2015). Moreover, the authors reported that using high voltage e-cigs seem to increase the release of formaldehyde and formaldehyde-releasing agents approximately by 14-15-fold, which would account for the increased cancer risk.

E-cig usage was shown to become increasingly common in patients with lung cancer who were recommended to cease smoking (Lucchiari et al., 2016). The conclusions from some studies suggest that e-cig usage help in reducing clinical symptoms seen in lung cancer patients such as cough, phlegm and breath shortness. However, e-cigs with nicotine may trigger aggravation of lung cancer (Rowell and Tarran, 2015), Moreover, the same study speculates that

as e-cig contents may increase airway inflammation and it may increase development of lung cancer.

A study based on patient evaluation in Memorial Sloan Kettering Cancer Center summarized a very high use of e-cigs in many cancer patients (Borderud et al., 2014). For example, according to this study following percentage of patients were identified to use e-cigs during the study period; Breast cancer (23.42%), Colorectal cancer (31.25%), Genitourinary cancer (29.41%), Gynecological cancer (27.12%), Head and neck cancer (33.98%), Hepatobiliary cancer (24.62%), Thoracic cancer (31.90%) and Urology-related cancer (18.18%). Interesting observation of gender specificity of e-cig usage in cancer patients was also made where majority was female patients (56.5%), while only 43.5% of patients were male. The common concept that e-cigs are harmless may have led these cancer patients to use e-cigs over tobacco smoking.

3.1.3.4 Dental/oral conditions

Tobacco smoking is a major reason for many oral health concerns including oral cancer, poor oral/dental hygienic conditions, bad breath, teeth discoloration, tartar buildup, mouth/gum sores, jaw bone loss and burns. It is the belief of many e-cig users that e-cigs have no risk on oral health. Due to the increasing demand of e-cig usage and the projected oral health risk, many organizations have promoted campaigns to determine the effects of e-cigs on oral health and demands allocation of more funding to explore this regard (Tomar et al.). Moreover, many ex-smokers who have severe oral health conditions including oral cancer, have increased tendency to use e-cigs, assuming it would have no harm while still providing the pleasure of act of smoking (Holliday).

One major way e-cig can harm the user is the explosion of e-cigs inside the mouth. For example, (Rogér et al.) reported explosion of his e-cig inside the mouth causing loss of teeth, tooth fracture and oral lacerations. Moreover, e-cig components have the ability to damage the periodontal epithelial cells and mucosal cells within the mouth. Studies suggest that e-cig components can cause mutations, increased cell proliferation and cell death which may contribute to many oral health conditions include oral cancer (Branch, 2014). E-cig usage have also been shown to cause mouth and throat dryness, oral irritations as well as dry cough in more than 20% of the users tested (Polosa et al., 2011, Etter and Bullen, 2011a).

Collectively, e-cigs seem to be less harmful than tobacco smoking in terms of oral health. But there is increasing evidence piling up to demonstrate the oral health concerns caused by e-cig usage.

3.1.3.5 Accidental exposure of the primary smoker

Health hazards caused by accidental exposure to the e-cig contents have been reported. The accidental exposure of non-smokers especially pediatric population will be discussed in section 3.2. However, careless handling of the e-cig liquid or explosion of the e-cig have caused damage to the user in many cases. Combining the incident reports from two studies conducted in Texas poison centers and United States (US) poison centers showed that approximately 41-42% of the reported incidents were from adults older than 20 years old (Ordonez et al., 2015, Chatham-Stephens et al., 2014). Some of these accidents were due to explosion of e-cig batteries and subsequent burns or fires (Farsalinos and Polosa, 2014). Moreover, there are risks of e-liquid spills and leaks, and subsequent skin irritations as well (Yang et al., 2014). Considering the high risk of fires cause by e-cig explosion, US Fire Administration and US Department of

Transportation together have worked to ban e-cigs in checked-in hand luggage while traveling through airplanes (Roger et al., 2016).

3.1.4 Is e-cigarettes a lesser devil?

Studies discussed here along with many other studies support that, in comparison to tobacco smoking, vaping is 'less harmful'. However, less harmful is not 'harmless'. Many studies summarized in this chapter point out that e-cig using also cause many health conditions. The reduced health effects in ex-tobacco smokers seem to be an advantage. However, if electronic cigarettes are used by new users or people who have stopped smoking a while ago, the odds are not so great. The assessment of the health effects on secondary smokers and indoor air quality in the next section will also agree that the e-cigs are harmful, regardless of the comparisons to tobacco smoking. It is understandable that complete cessation of smoking of any kind is a nearly impossible task. Therefore, e-cigs can be considered as a lesser devil. However, e-cigs are nor approved by Food and Drug Administration (FDA) as therapeutic intervention (Corey et al., 2013), but are recommended as an approach for smoking cessation. Therefore, the users and as well as the society must be well aware of the benefits and the health risks of using e-cigs. They should also understand the health limits of e-cig usage as a smoke cessation tool.

3.2 Aim 2: **Assessment of the effects of second-hand exposure to toxic compounds released from electronic cigarettes.**

3.2.1 Is second-hand vaping harmless?

Tobacco smoking is extremely harmful to the smoker and to the environment while posing a greater health risk. Therefore, many clinical programs have organized and recommended smoking cessation programs and secondary smoking reduction methods. Electronic cigarette usage is one such approach. Several surveys conducted by many organizations suggest that the smokers' point of view being the e-cigs are harmless to the smoker and bystanders (McRobbie et al., 2014). Some studies conducted on e-cigs have shown evidence supporting that the contents of e-cigs are indeed harmless and pose no treat to the general population. On the contrary independent research carries out by other groups have shown otherwise. In this section, I will be critically comparing the studies that are conducted to show either safety of e-cigs or vice versa.

Certain studies have suggested that the vapor produced from e-cigarettes have lesser half life (19-20 minutes) which is not sufficient to cause passive vaping (Bertholon et al., 2013). Moreover, vapor content comparison between e-cigs and tobacco cigarettes by (McAuley et al., 2012b) showed that while several pollutant such as volatile compounds, carbonyls, nicotine, and glycols were detected in e-cig vapor, none of them pose a cancer risk or harm to human health.

Considering many of these contradicting studies, it is justifiable to hypothesize that the e-cigs are safer than tobacco smoking, however contain many harmful products that can cause human health risk. Therefore, in subsequent sections, I will be presenting a critical evaluation of the available literature on the contents of vapor from electronic cigarettes. The data analysis

below will add to the growing evidence that second-hand e-cig smoking (passive paving) has the ability harm populations of different ages.

3.2.2 Mechanism of e-cigarette operation and its effects on passive vaping

Investigation of the public health concerns arising from passive vaping is addressed in this section. There is enough conflicting evidence on either exposure of bystanders to sidestream vapors from e-cigs being harmful or adverse effects being minimal. One critical factor that is brought up into light in this regard is the mechanism of e-cigarette operating, which determines whether any harmful sidestream or mainstream vapor is generated that can harm the bystanders.

Each e-cig contains, a rechargeable lithium battery, a vaporization chamber and a cartridge, as illustrated in **Figure 3. 4A**. The vaporizing chamber is where an atomizer is located which generates the vapor for smoking or in this case vaping. The cartage carries the nicotine liquid or "smoke juice", which basically contains propylene glycol. The inhalation by the e-cig user activates the atomizer and the liquid nicotine is converted to vapor. The vapor generated here is called the sidestream vapor or inhaled aerosol. When the user exhales, mainstream vapor is also exhaled which can be harmful to bystanders. The LED light at the end of many e-cigs simulate an artificial flame when the user inhales similar to a normal cigarette. This way the user experiences ‘the act of smoking’, with considerably reduced damage. The liquid nicotine may contain several flavors added by the manufacturer and examples of flavors are tobacco and menthol flavor to mint, apple, chocolate, coffee, caramel and cherry. The significance of these flavors in terms of addiction will be discussed and evaluated in section 3.3.

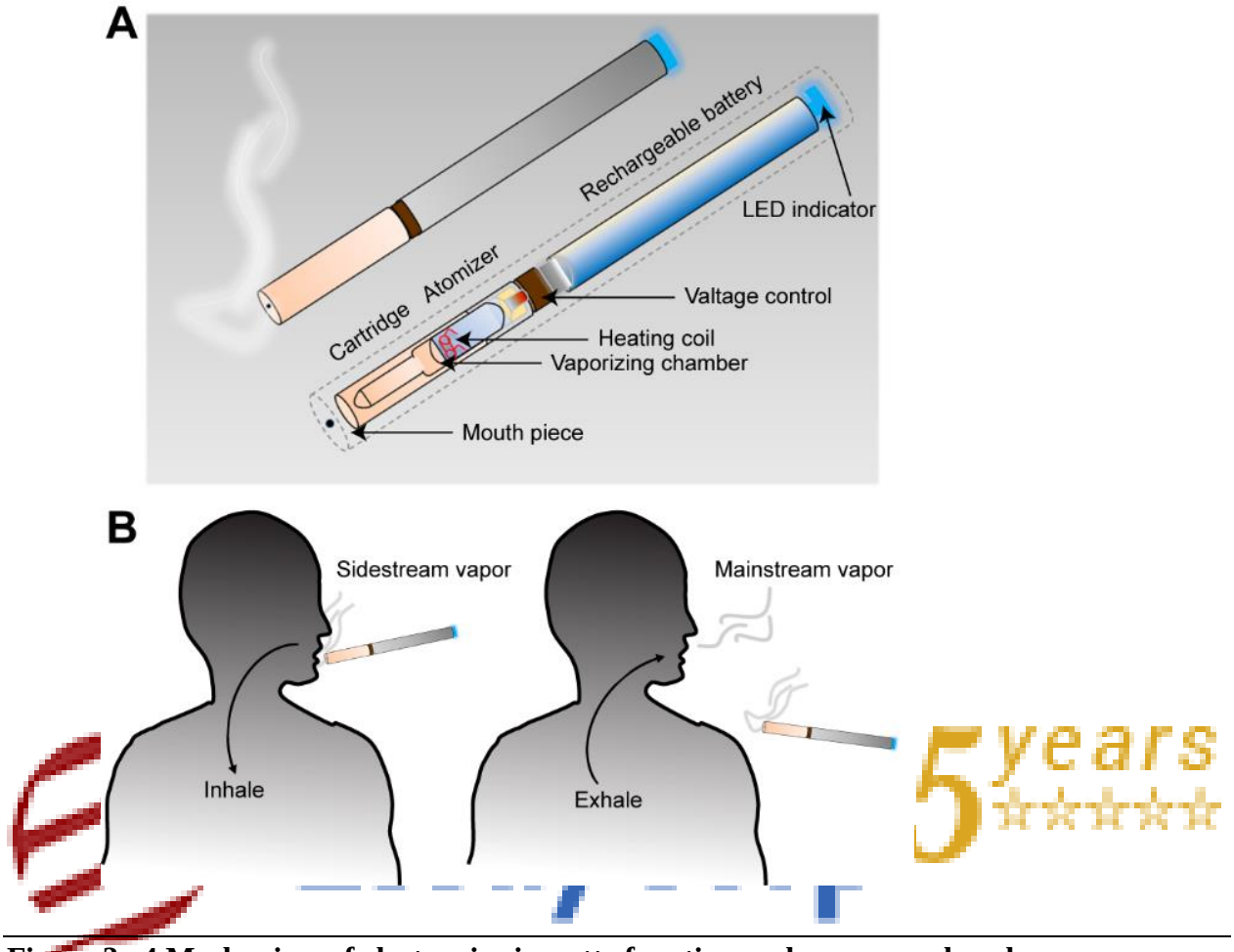


Figure 3. 4 Mechanism of electronic cigarette function and vapor produced

A) Components of e-cigarette required for its mechanism of operation. B) Generation of sidestream and mainstream vapor from electronic cigarettes.

It is a common misconception that aerosol generated during e-cig mechanism is called 'vapor' (gaseous substance) and an e-cig emits harmless water vapor (Arnold, 2014). The aerosol is actually composed of fine particles mixed in a gas which also contains nicotine and toxins. Due to this misconception, it is mentioned in many reports that e-cigs do not generate vapor that can harm bystanders. However, the second-hand aerosols are very much capable of harming vulnerable populations, if exposed enough (Czogala et al., 2014a).

3.2.3 E-cigarette sidestream aerosol contains carcinogens and respiratory chemical hazards

Thorough analysis of the literature points out that the mainstream smoke as well as sidestream smoke may contain toxic and carcinogenic compounds that can harm bystanders through passive vaping. These aerosol compounds include nicotine, fine particles and toxins. Many of these constituents of vaping have been declared as harmful and potentially harmful constituents in cigarette filler and smoke by the FDA, under 2009 Family Smoking Prevention and Tobacco Control Act, section 904(a)(3) (FDA et al., 2012). In this section, I have done a through survey to identify major players of health hazards, specifically cancer and respiratory system associated health conditions such as asthma.

I have averaged the data obtained from three types of cigarettes reported in (Schripp et al., 2013). They were fairly comparable as they were made from similar casing of stainless steel and were filled with one type of apple flavored liquid containing 3-Methylbutyl-3-methylbutanoate and no nicotine. The analysis showed higher levels of 1,2-Propanediol, 1,2,3-Propanetriol and 3-Methylbutyl-3-methylbutanoate and minute traces of Diacetin, Triacetin, Nicotine, Formaldehyde, Acetaldehyde and Propanal (**Figure 3. 5**). Additionally, three other studies reported Glycerol, Ethylene glycol, Thujone and Ethyl vanillin as other harmful constituents of e-cig aerosol (Hahn et al., 2014, Hutzler et al., 2014, Chatham-Stephens et al., 2014). Another interesting observation was that, even though the label indicated that the liquid is devoid of nicotine, the testing showed the presence of nicotine. This has been shown to be true by many other studies, where nicotine-free liquids actually contain low levels of nicotine (Food and Administration, 2012, Cheah et al., 2014).

As the highest levels of mass per puff was generated by 1,2-Propanediole, I further searched for any link of this compound and any associated constituent of e-cigarettes with known

health hazards. As 1,2-Propanediol is also named as Propylene glycol, I also used that term to expand the search. Interestingly, a vast range of literature was found with regard to respiratory hazards of ,2-Propanediol/Propylene glycol which are summarized in Table 2.

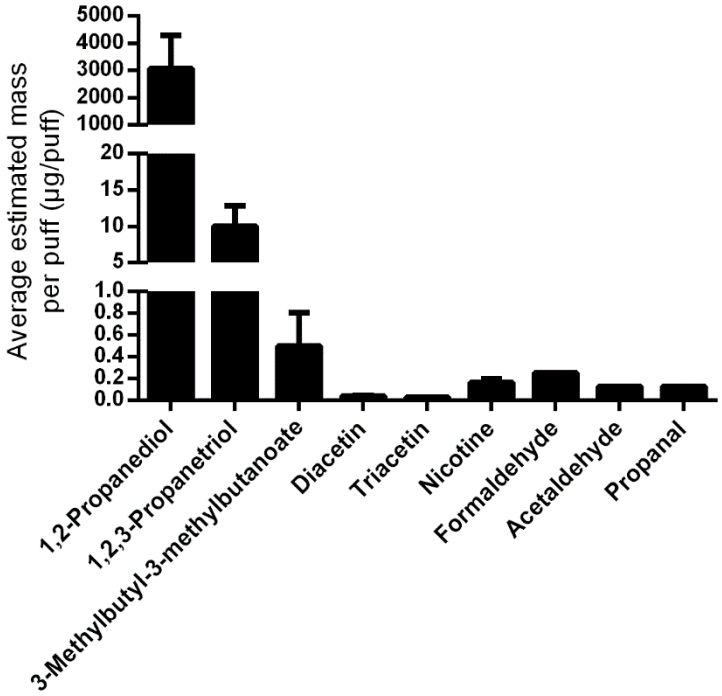


Figure 3. 5 Average estimated mass per puff (µg/puff) of known toxins of electronic cigarette second-hand vapor.

The toxic compounds released from three different e-cigs. The data was extracted from (Schripp et al., 2013) and averaged. N=3.

The table below summarises the concentrations of aerosol compounds detected in e-cigs studied it two studies and health hazards, specifically respiratory health conditions associated with these compounds.

Table 2. Electronic cigarette sidestream vapor/aerosol constituents and their link to respiratory health conditions				
	Concentrations of the compound in aerosol		**Health condition associated**	
Aerosol compound	**Reference**	**Information**	**Reference**	**Information**
1,2-Propanediol	(Schober et al., 2014b)	547,000-673,000 mg/l in nicotine free liquids and 529,000-546,000 mg/l in nicotine containing liquids	(Schober et al., 2014b).	activate inflammation, mucus production and oxidative stress
	(Hahn et al., 2014)	57 g/100g in 94% of the liquids	(Spreux et al., 1996, Choi et al., 2010, Wieslander et al., 2001, Al-Khudhairi et al., 1982)	Asthma and coughing, Respiratory conditions/irritations
Glycerol	(Hahn et al., 2014)	37 g/100g in 94% of liquids	(Fluhr et al., 2008)	Oral and skin exposure may cause irritation.
Ethylene glycol	(Hahn et al., 2014)	10 g/100g in 91% of liquids	(Brent, 2001, Catchings et al., 1985)	Poisoning, respiratory distress
Thujone	(Hahn et al., 2014)	6.7 mg/l in 26% of liquids	(Brown and Rosenthal, 1997)	Airway rack irritation/respiratory irritant
Ethyl vanillin	(Hahn et al., 2014)	30 mg/l in 26% of liquids	(Sax and Bruce, 1975)	Irritation of airway mucosal cells

Lung and respiratory diseases in second-hand smokers

Components emitted during vaping causes poor indoor air quality (Colard et al., 2015, Farsalinos and Voudris, 2014), which is another reason for lung and respiratory system associated diseases. Other than asthma, these volatile compounds have been shown to activate inflammation, mucus production and oxidative stress (Schober et al., 2014b). The 1,2-propanediol vapor that was recognized to be highly available in the sidestream vapor in the analysis above is among the most damaging respiratory hazard. It can get deposited in the lungs. Nicotine in its vapor or aerosol form can induce inflammation. A study was described in section 3.1 which showed comparable levels of plasma cotinine in between tobacco smokers and e-cig smokers (Flouris et al., 2013). In the same study, they showed similar levels of plasma cotinine in experimental subjects exposed to tobacco and e-cig vapor in a passive manner (passive exposure), which is an indicative of tobacco exposure that may cause lung associated irritations.

3.2.4 Airborne markers of second-hand exposure to e-cigarette vapor and poor indoor air quality

The vaping process generate many aerosol compounds that can reduce the indoor air quality. Due to the increasing awareness of second-hand vaping, several studies have evaluated the quality of the secondary smoke generated or in other words the mainstream and sidestream vapor/aerosols from e-cigs. By careful examination of many reports that I have summarized the compounds identified in these studies. Some of these compounds include 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavorings, nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, flavours and solvent carriers.

Few studies have identified a handful of aerosols generated by e-cigs as 'airborne markers of second-hand exposure to e-cig vapor'. They include, nicotine, aerosol particles such as $PM_{(2.5)}$, carbon monoxide, and volatile organic compounds (VOCs) (Czogala et al., 2014b). The study concludes nicotine as a major component emitted by e-cigs that can be considered as an airborne marker for second-hand vaping. Similar studies have recognized nicotine and salivary cotinine as markers for secondary vaping (Ballbè et al., 2014).

Studies discussed above as well as in section 3.1 highlight that e-cigs emit numerous air pollutants and thereby reduce the quality of indoor air. Based on Consumer Product Safety Commission and American Conference of Governmental Industrial Hygienists regulation, the maximum amount of nicotine that is allowed in a work place is 0.5 mg/m^3 (500 $\mu g/m^3$) (Association, 2014). The amount of nicotine released by e-cigs in (Czogala et al., 2014b) ranged from 0.82 to 6.23 $\mu g/m^3$ suggesting that it is considerably low. However, combined with other aerosol compounds, even small amounts of nicotine may harm the vulnerable populations. Moreover, air quality is also disrupted by unpleasant smells and irritants which are obvious parts of smoking. The ultrafine particles emitted from e-cigs seem to be a major components of air pollutants that can cause poor air quality (Schober et al., 2014a).

Recent studies also show the possibilities of third-hand exposure to e-cig vapor. Even though literature with regard to third-hand exposure is very rare, one study on deposition of aerosols from e-cigs on different surfaces including floors, glass, windows, walls, wood, and metal showed a vast degree of nicotine deposition on these surfaces that may cause third-hand exposure (Association, 2014).

3.2.5 Accidental exposure to nicotine and chemical hazards from electronic cigarettes

Exposure to nicotine by accident is another health hazard that is caused by e-cigs to the bystanders. The accidental exposure to nicotine occurs mainly in children. The ways that e-cigs can cause a health hazard may occur through accidental ingestion, skin or eye contact with the nicotine liquid or burns caused by battery explosion (Chen, 2013). The symptoms of accidental nicotine exposure reported are oral irritation, nausea, vomiting, dizziness, heart failure, pneumonia, hypotension, seizures and burns and skin irritations.

In order to demonstrate the rates of accidental exposure to e-cig contents, two studies summarising the reports of accidental nicotine exposure to poison centers or emergency center or call centers were evaluated and the incident rates were compared. The first report indicated incident repots from Texas poison centers during the period of 2009 to February 2014 (Ordonez et al., 2015). The second study was conducted by Centers for Disease Control (CDC) in the U.S. poison centers covering a wide range of US including the District of Columbia, and U.S. territories (Chatham-Stephens et al., 2014). The period that was included in the study was September 2010 to February 2014.

The age of exposed patients as well as mode of exposure were compared in between the two poison report centers (**Error! Reference source not found.A**). Combined analysis of the data collected from both poison report centers suggests that the accidental exposure is common in children of age lower than 5 years (52%). But surprisingly high exposure rates were also identified in adolescents older than 20 years (41.5%). There was a significant difference in between exposure of children of age lower than 5 years and adolescents older than 20 years ($P<0.05$) (**Error! Reference source not found.B**). Moreover, combined data from both poison centers showed the percentage of ingestion reports were higher in a statistically significant way

than incidents of inhalation, dermal or ocular exposures (P<0.001) (**Error! Reference source not found.C**).

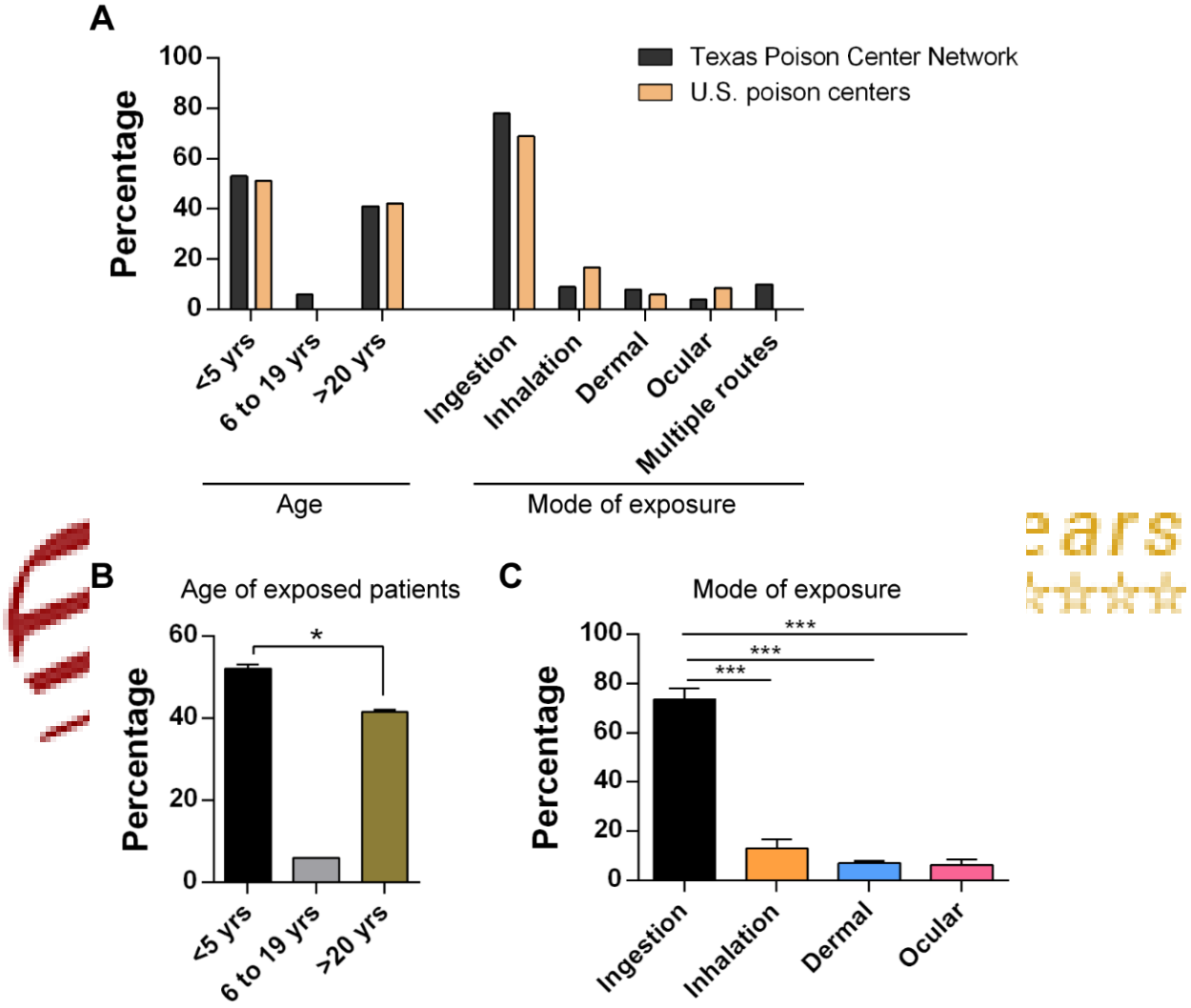


Figure 3. 6 Incidents of accidental exposure to electronic cigarette components in two poison report centers in US.

A) Comparison of the ages of patients and modes of exposure in Texas Poison Center Network and U.S. poison centers. B) Comparison of ages of exposed patients. C) Comparison of modes of exposure. N=2 (poison centers). Statistical significance was determined by P<0.0001**,

P<0.001***, P<0.01** or P<0.05*. Data extracted from (Ordonez et al., 2015) and (Chatham-Stephens et al., 2014).

The higher incident rate of accidental exposure in children younger than 5 years of age was further confirmed by another study focused on the Texas poison centers for the period of January 2010-June 2014 and specifically reported pediatric exposures (Forrester, 2015) confirming that majority (~42%) of the accidental reports were from children of 2 years of age, while 32% was from children of 1 years of age.

Considering the higher rate of accidental exposure in adolescents aged more than 20 years suggests that it is no longer an issue for accidental pediatric exposure but carelessness and/or not knowing the risks of using e-cigs might have caused this an adolescent health hazard.

3.2.6 Populations vulnerable to passive vaping

I have discussed in detail above that passive vaping is harmful to bystanders. The bystanders exposed to e-cig vaping may include workers in the workplace, cafeteria, school class rooms and public washrooms, restaurants and bars. The effects of e-cig vapor may depend on many factors including the space, current air quality, ventilation, current health condition of the bystander, type of e-cig, amounts of toxins and voltage of the e-cig. However, regardless of these factors, there are many vulnerable populations to e-cig and tobacco cigarettes such as children, pregnant women and patients with many other health conditions including cardiac and respiratory diseases (Czogala et al., 2014b).

In the section 3.2.4, I discussed that pediatric population is highly vulnerable to e-cig-associated accidents. Not only accidental exposure by spills or explosions, but also inhalation (passive vaping) can be harmful to this population. The above studies also showed children in

between 6-19 are also exposed to e-cig components and get harmed. This group mainly include school children adolescents who still undergoes important stages of their brain development and learning. Therefore, this group is highly susceptible to nicotine exposure (Health and Services, 2014). Addiction to e-cigs in school children has become a severe problem which will be discussed in section 3.3.

Pregnancy is a period when mothers and the growing fetus are highly susceptible to the adverse effects of smoking. Therefore, passive vaping can be quite harmful to pregnant women. Nicotine once again seem to be the major culprit that can harm a fetus (Ginzel et al., 2007). Unfortunately, e-cigarette smoking is very common in pregnant women. Among the e-cig using pregnant women, ~40% believed that vaping is harmless to the fetus (Mark et al., 2015). For this reason, pregnant women belong to both primary and secondary smokers and the fetus can be considered as the secondary smoker in both cases who faces the most adverse effects of vaping.

Psychiatric patients and schizophrenic patients also belong to vulnerable e-cig passive vaping populations and may have high rate of smoking-related mortality (Brown et al., 2000).

However, unfortunately, there are no proper regulations settled to protect these vulnerable populations from e-cig vaping or tobacco smoking. There are notices indicating that smoking is harmful and non smoking in public places or indoors. However, these notices are barely effective and there must be tighter regulations to reduce the incidents of e-cig vaping indoors and outdoors.

3.3 Aim 3: **Investigation of potential addictive effects of electronic cigarettes**

3.3.1 Addiction in primary smokers

Nicotine addiction is the most pronounced addiction seen in primary smokers. In almost all cases, the e-cig users are previous tobacco smokers who were put on the cessation program by switching to e-cig vaping. Vaping of e-cigs allows the ex-tobacco smoker to experience the act of smoking' by all means ('hand-to-mouth habitual'). Therefore, maintenance of the nicotine or tobacco addiction at a controlled level could be a challenge for e-cig users. However, there are concepts supporting as well as against the addictive potential of e-cigs.

The usage of e-cigs as a nicotine replacement approach has not been validated by multiple studies (Bullen et al., 2013). Some studies suggest that the addiction potential of e-cigs by themselves are considered low, owing to the slower rate of nicotine entry to the body (Dawkins and Corcoran, 2014, Nowak et al., 2014). For the new generation of e-cigs, Central nervous system (CNS) exposure to nicotine takes minutes, as compared to conventional smoking, wherein CNS exposures occurs in 20 minutes. This significantly contributes to the low addiction potential of e-cigs. Thus, even though e-cigs have not been proven to be more effective than already available nicotine replacement methods, they do not pose a significant threat of being an addictive agent. This has relevance from a separate perspective, since previous reports have shown e-cigarette consumption are also related to personal identity, much like a 'smokers' identity, which is not necessarily formed by use of other nicotine replacement products (Barbeau et al., 2013). Another significant factor was demonstrated by a separate study, which reported that both nicotine-containing and nicotine-free e-cigarettes were able to reduce the urge to smoke as well as nicotine withdrawal symptoms (Dawkins et al., 2012). Approximately 99% of

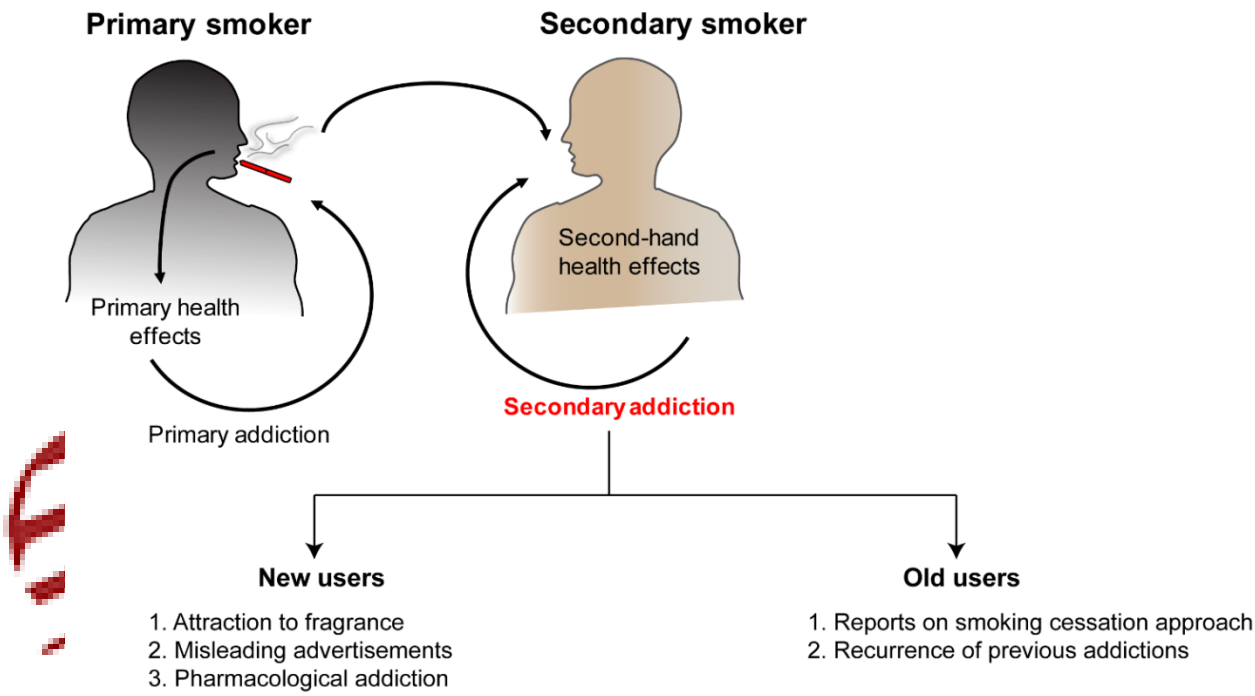
manufactured e-cig products contain nicotine, and the aforementioned study highlights the significance of exploring the benefits of nicotine-free e-cigs.

For nicotine to be affective as an addictive agent, it should be in the bioavailability form, which can be easily diffused through epithelial cells. Free-base (Nic) is the most bioavailable form of nicotine. One study showed that, in many of the e-cig products available, nicotine is found in the form of Nic (El-Hellani et al., 2015). However, this also makes the e-cigs users vulnerable to the same consequences of nicotine toxicity as conventional cigarette smokers, including increased cardiovascular and cancer risk (2014). As an unfortunate result of introduction of e-cigs to cease the tobacco smoking, many smokers use both tobacco and e-cigs (Lee et al., 2014). They smoke tobacco outdoors while vaping e-cigs indoors. This occurs mainly due to addiction to smoking and continuation of the addiction through vaping. Due to this reason, the nicotine intake and nicotine addiction in the user may elevate (Crotty Alexander et al., 2015). Certain survey studies also conclude that some of the ex-smokers who were addicted to tobacco smoking show increased dependence to e-cigs (Etter and Eissenberg, 2015). Another study used higher nicotine contents in e-cig liquid to achieve higher satisfaction in tobacco addicts, and these subjects showed a higher dependence and craving for these high-nicotine e-cigs (Etter, 2015, Etter and Eissenberg, 2015).

3.3.2 Addiction in secondary smokers/bystanders

As proposed in my hypothesis, the exposure to aerosols from e-cig vaping may trigger a craving to use e-cigs in the secondary smoker and eventually lead to addiction (**Figure 3. 7**). The largest vulnerable group for second-hand vaping and addiction are the school children and young adolescents. Adult females and school kids who were not smoking before can also get

attracted to vaping due to pharmacological stimulation of brain for nicotine. Moreover, especially in the case of adult females, lack of significant smell after vaping, different flavors and availability of low nicotine or nicotine free e-cig product may contribute to addiction. Likewise, the perception of e-cigs being safer have led to increased e-cig usage in pregnant



women, exposing the fetuses to e-cig contents (Baeza-Loya et al., 2014).

Figure 3. 7 Secondary addiction in second hand smokers

Exposure to vapor from primary smoker's e-cigarette, the secondary smoker may get brain stimulating cues to use e-cigarettes by himself/herself. These secondary users can be new users who has not smoked before. The second category are the ex-smokers who are on smoking cessation methods as well as ex-smokers whose nicotine addiction is relapsed.

The secondary smokers who may get addicted to e-cig vaping can be of two types. First, new user who has never smoked before. Initially craved by the pharmacological nicotine drive

they may get into smoking. Studies have shown that secondary smoking increased blood nicotine levels similar to tobacco smoking and therefore, nicotine addiction caused by secondary/passive vaping may be as strong as tobacco smoking (Flouris et al., 2013, Crotty Alexander et al., 2015). Misleading advertisements, other's misleading concepts, many myths on e-cigs being harmless could be driving factors for addiction to e-cigs in new users (Duke et al., 2015, Ramamurthi et al., 2015, Duke et al., 2014).

The second category of second-hand addicts for e-cig are the ex-smokers. They might have been on other tobacco-cessation approaches and due to exposure to nicotine from e-cigs, they may get back to e-cig usage as well as tobacco usage relapse. For the ex-smokers, the stimulation by e-cig nicotine may cause increased addiction to nicotine and/or tobacco.

Once the secondary smoker becomes addicted to e-cigs, he/she becomes the provider of polluted sidestream and mainstream aerosols to third-hand smokers. In other words, the secondary smokers may acquire the role of primary smokers and re-start 'the health cycle'.

3.3.3 Pharmacological nicotine addiction

Pharmacological nicotine addiction is a chemical reaction controlled by the brain. Many studies have demonstrated the nicotine addiction in general and mostly related to tobacco smoking (Benowitz, 2010). Many of the e-cigs contain nicotine and it is used as the major addictive agent in them. For the same reason, e-cigs are also referred to as 'Electronic nicotine delivery systems' or ENDS. Few scientists have shown their concerns on the nicotine addiction through e-cig usage, specially in younger populations (Fillon, 2015a, Crotty Alexander et al., 2015, Klein, 2015). Therefore, pharmacological stimulations and brain signalling pathways could be the same for both nicotine addictions in the case of tobacco smoking and e-cig vaping, since

most e-cigs do have nicotine. Therefore, I adapted the general nicotine addiction pathways to describe a potential nicotine addiction pathway in e-cig vaping.

I assume that it occurs at 4 basic steps which are shown in detail in the **Figure 3. 8**.

1) Craving for nicotine: At this stage the nicotine levels in the blood has gone down. Therefore, the e-cig user craves for more nicotine. This can be further affected by other cues such as act of smoking.
2) E-cig vaping: The act of smoking, increased nicotine levels in the blood and the nicotine entrance in to the system activates brain molecular signalling pathways to enjoy the vaping. This act calms the e-cig user down, relaxes him/her and give pleasure due to Dopamine release in the brain.
3) Nicotine withdrawal: Due to prolonged exposure to nicotine, the nicotine receptors are no longer receptive to nicotine and become desensitized. Because of this nicotine levels drop again and the user undergoes nicotine withdrawal symptoms. These symptoms lead to the craving for another e-cig vaping and the cycle repeats.
4) Long-term vaping and increased craving: The reduced nicotine sensitive receptors drives the user to crave for more nicotine and thus vaping. When this occurs long term, new nicotine receptors are generated and the cycle continues. Moreover, the e-cig user may get tolerance to nicotine.

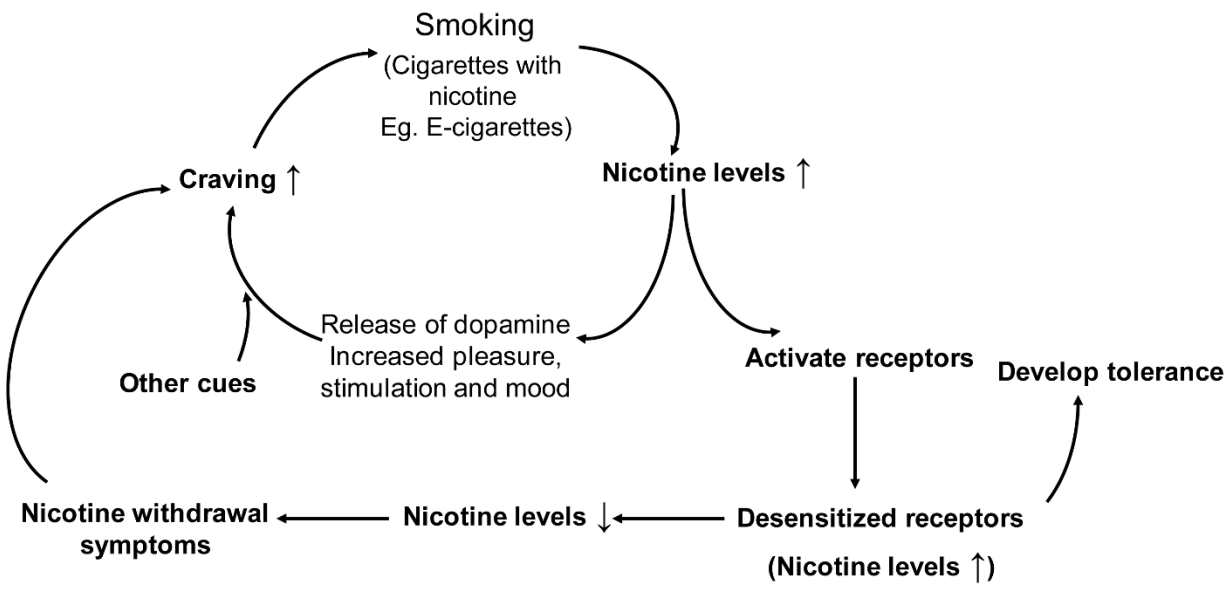


Figure 3. 8 Potential pathway of pharmacological nicotine addiction in electronic cigarette user.

A pathway of pharmacological nicotine addiction is shown. As the electronic cigarette contain nicotine, it is possible that e-cig users may also undergo similar addiction pathway. Figure designed based on the concepts extracted from (Benowitz, 2010).

3.3.4 Increased e-cig usage in school children

A host of studies have demonstrated associations between e-cig usage and eventual conventional cigarette smoking, especially among the young adults (Primack et al., 2015, Soneji et al., 2015, Leventhal et al., 2015, Coleman et al., 2015). These studies lend support to the theory that e-cig consumption is a 'gateway' for future conventional cigarette smoking. This is especially troubling in light of reports stating that 1 in 5 teenagers in US have used e-cigs (Arrazola et al., 2015). The significance of these reports are exacerbated by a major disadvantage of e-cigs over other nicotine replacement methods, the incidence of second-hand exposure. This

is in addition to the dangers of second-hand exposure to nicotine through e-cigarettes. Studies have shown that even though e-cigarettes are a source of second-hand exposure to nicotine, they do not convey combustion toxicants. In the section 3.2, I elaborated on the contents of e-cig vapor and their effects on secondary smoker's health.

To prove the high usage of e-cigs in school children (youth) and young adults, I extracted the cigarette use information from Canadian Tobacco, Alcohol and Drugs Survey (CTADS) for 2013, to show the use of e-cigs in different ages of users. The comparison indicated that, in Canada, the e-cig usage among young adults were as frequent as the conventional smoking. Moreover, e-cig usage was seen in youth (15-19 years) as well as young adults (20-24). There was no information available on e-cig usage in adults of older than 25 years.

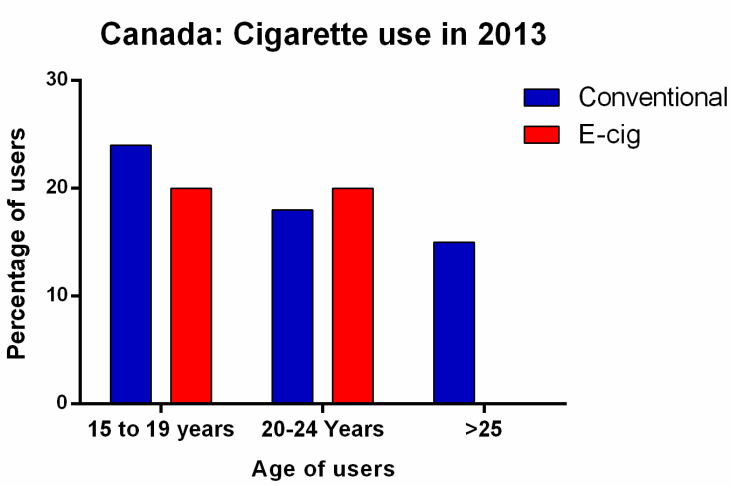


Figure 3. 9 Comparison of electronic cigarette and conventional cigarette usage in Canada in 2013.

Data available through Canadian Tobacco, Alcohol and Drugs Survey (CTADS). Accessed http://healthycanadians.gc.ca/science-research-sciences-recherches/data-donnees/ctads-ectad/summary-sommaire-2013-eng.php on 2016/03/06.

3.3.3.1 Additives in e-cigs and their role in addiction

A survey of additives which may cause addiction was done to determine the contribution of these additives in increasing the chance of addition in e-cig users. The literature survey suggested Pyrazines to be a major additive which belong to this category. Examples of Pyrazines found in e-cigs include 2,3,5,6-tetramethyl-pyrazine, 2,3,5-trimethylpyrazine and acetylpyrazine (Alpert et al., 2015). Pyrazines have shown to increase the nicotine intake into the lungs as well as reduce the irritating and noxious effects of cigarette contents, working through the pharmacological addiction described in the section above (Alpert et al., 2015). Such additives may cause it difficult for a smoker to quit smoking, even in the case of e-cig vaping. Moreover, this may cause relapse of ex-tobacco smokers into smoking and/or increase use of e-cigs. These additives may also cause addiction in new users such as in the case of young school kids.

3.3.3.2 Effects of flavor compounds in passive vapor on addiction

It has been hypothesized that the flavors added to the e-cigs have become one of the reasons for increased addiction to them. However, studies conducted in understanding the addiction to e-cigs are only a handful. There are 5 main categories of flavors used in e-cigs. They are; tobacco flavors, menthol flavors, fruit flavors (apple, blueberry, peach,), sweet flavors (candy, vanilla, chocolate) and other flavors (tea, coffee, wine). By design, these flavored additives are used to attract more users and drive frequent use. Here in this section, I have

attempted to investigate any link between the frequency of flavored compounds being used in known e-cig liquids with the addiction to e-cigs.

Hutzler and colleagues tested e-liquid from 28 electronic cigarettes to identify flavored compounds and they found 141 flavor compounds from (Hutzler et al., 2014). To understand their relevance in addiction to e-cigs, I studied this report thoroughly extract any information on flavors that may lead to addiction.

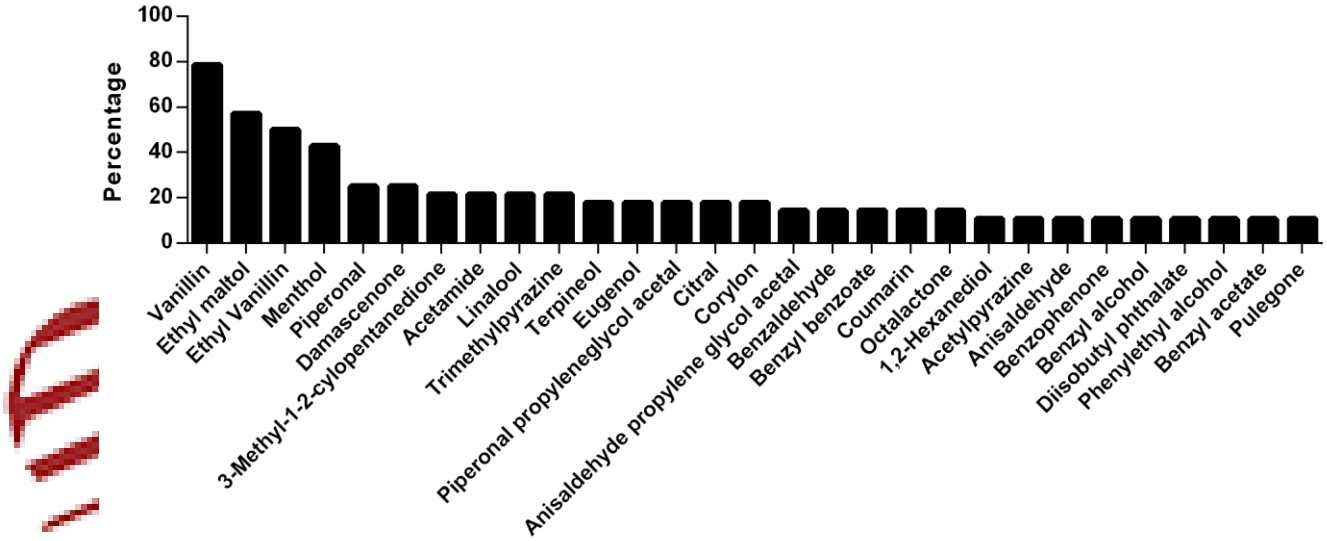


Figure 3. 10 Volatile flavor compounds detected in e-liquids of electronic cigarettes.

The frequency of 141 compounds found in (Hutzler et al., 2014) were analyzed to calculate percentage frequency in 28 electronic cigarette liquids. The compounds which had more than 10% frequency are shown here. Data extracted from (Hutzler et al., 2014)

First, I filtered them based on the percentage/frequency of each compound in 28 e-cig liquids and chose the compounds which showed more than 10% frequency. Among them, four compounds were identified to be found in 40-80% of the e-cigs tested. They are Vanillin, Ethyl

maltol, Ethyl Vanillin and Menthol (**Figure 3. 10**). Vanillin is a compound which showed in ~80% of the e-liquids and it is a very common flavor used in ice cream, baked goods and other sweet snacks such as Nutella. Interestingly, vanillin and ethyl-vanillin are additives used in flavoring tobacco (Fowles et al., 2000). The last compound menthol, is also a very common flavor and interestingly, constitutes approximately 0.71% by weight of a traditional cigarette (Fowles et al., 2000). Studies show that addition of addictive flavors such as Vanillin and Menthol are quite common in cigarette science to alter the brain chemistry to take more of it and thereby lead to addiction (Fowles and Shusterman).

One study was conducted to investigate whether flavors in e-cigs increase appeal for e-cig usage in school children. The results of this study demonstrated that in contrast to the non-flavored e-cigs, candy flavored e-cigs increased interest in buying e-cigs as well as trying them in school kids (Vasiljevic et al., 2016). Moreover, this study was conducted based on watching the advertisements for e-cigs. Therefore, this study clearly indicates that misleading advertisements and use of flavors are major factors that can attract young school kids to the habit of smoking and thereby lead to addiction.

CHAPTER 4: DISCUSSION

For decades, cigarettes smoking has been a major public health hazards. Now, the alternative which was introduced to replace tobacco smoking has become a health concern. In the chapter 3, I discussed in detail how e-cigs can be harmful to both the primary smoker and secondary smoker.

4.1 Reasons for electronic cigarettes have become a health hazard

There are several factors that contribute with this regard including myths associated with e-cigs, misleading advertisements and concepts and easier availability.

Myths associated with e-cigs: 'E-cigs are harmless'. This is the major myth associated with e-cigs and had been the major challenge in regulating the use of e-cigs. This 'safe' concept usually comes from ex-tobacco smokers who are addicted to either the act of smoking or the contents. In cases where patients are being recommended to switch to less harmful e-cig products, they believe that e-cigs are safer, when severe symptoms of tobacco poisoning is reduced. Another reason that most people think e-cigs are safe is the 'no visible smoke'. Evnthough e-cigs do generate aerosol particles or vapor, most people believe no smoke is generated from e-cigs. Therefore, it is challenging to convince the harmful effects of a smoke/vapor that is barely visible.

Misleading advertisements: Unregulated and misleading marketing, limited or misleading information available on the safety issues and health hazards caused by e-cigs, frequent use of e-cigs by adults at home, artificial flavors used have been listed as the high ranking risk factors which may drive e-cig consumption and addiction specially in young children and adolescents

(Vasiljevic et al., 2016, Pepper et al., 2014). In many cases, e-cigs are manufactured and marketed using methods that are not regulated or approved by FDA.

Easier availability: One reason that e-cigs could be much more dangerous than tobacco smoking is they are readily available for purchase over the internet. In the case of tobacco-containing cigarettes, a proof of age is required for purchase. In contrast, in most cases of e-cig purchase, no proof age is requested during the purchase, especially over the internet. Therefore, even under-aged children have access to e-cigs.

4.2 E-cigs usage in minors/adolescents:

The e-cig usage in minors and adolescents is a critical problem as exposure to nicotine and any other toxic compounds discussed in this thesis may affect the brain development of these kids while causing many other health hazards.

In many of the US states, e-cig selling to minors is not restricted or regulated. Fortunately, the increasing awareness of the harmful effects of e-cigs have led to banning e-cig purchase and usage by children under age 18 in many countries or provinces. CDC has been active in assessing the laws of e-cig sale to minors and controlling indoor e-cig usage. As a projection of this assessment, in 2014, e-cig sales to minors was banned in 40 states in United states, which included major states such as California, Florida, New York, Virginia and Washington (Marynak et al., 2014). However, not all states agreed to ban the e-cig usage in indoor spaces such as restaurants and bars. Unfortunately, these places can be some of the most vulnerable places for the minors to be exposed to e-cig vapor. Imposing tax is also a factor that

can restrict youth access to e-cigs and currently Minnesota acts in applying taxes for e-cigs (Gourdet et al., 2014).

The flavors found in e-cigs have been another attractant of children. The flavors such as candy, fruit, soda and caramel can be more attractive to adolescents and young school children.

4.3 Second-hand/passive exposure is harmful in many ways

In many countries there are no specific regulations to protect vulnerable populations from e-cig or tobacco-cig exposures. A survey performed in 192 counties in 2011 reported that the population of children exposed to passive smoking/vaping exceeded 40% (Oberg et al., 2011). The pediatric health concerns brought up in chapter 3.2 further agrees with the Oberg's findings on the fact that children are a high risk population of vaping.

4.4 Accidental exposure of pediatric population to e-cigarettes

The reasons for accidental exposure to e-cigarette liquid or vapor being a serious pediatric health concern are mostly attributed to the parental use of e-cigs at houses (Forrester, 2015, Garbutt et al., 2015). This reasoning was confirmed by the report of 96% of the accidental exposures of pediatric cases at Texas poison center being occurred at the patient's residence (Forrester, 2015). The basic reason for the higher accidental exposure of young kids to e-cigs is the carelessness of the parents in storing the e-cig liquids and the producds are not being childproof. A recent study indicated the 34% of parents store e-liquids in a drawer or cupboard while 22% and 13% parents stored in a purse or open counter, respectively (Cox, 2015). However, unfortunately, many parents are unaware of the health risks of using e-cigs, especially

pediatric issues. The accidental exposure of these children were mostly due to improper storage of the e-liquid by the parents (Garbutt et al., 2015). The seriousness of such accidental exposure of young children to e-liquid was further emphasized by the report of the death of 1 year old child in US (Korioth, 2015).

4.5 Do e-cigarettes support smoking cessation?

My meta analysis of health effects on both the users and the bystanders ask the question whether e-cigarettes were a proper smoking cessation approach. Soon after the introduction of e-cigs there was a rapid decline in tobacco smoking. However, recent studies suggest that the rate of smoking cessation has slowed down while use of e-cigs have elevated overtime. My meta analysis along with the plethora of studies support that e-cigs cause public health concerns to a level which was not anticipated during the time of e-cig invention.

CHAPTER 5: CONCLUSION

5.1 Conclusions

The aim of this dissertation was to explore and identify the health effects caused by electronic cigarettes on the user, secondary smokers or bystanders and finally on primary and secondary addiction. The below '*health effect cycle of electronic cigarettes'* concept was proposed in the hypothesis for my study.

"*The mainstream vapor inhaled into the primary smoker leads to health effects such as cancer, asthma, heart diseases and dental/oral conditions. Long-term usage of e-cigarettes by primary smokers lead to nicotine addiction. Both sidestream vapor released from the e-cigarette and mainstream vapor exhaled by e-cigarette user are inhaled by the bystander (secondary smoker) and this passive smoking cause health conditions as well as addiction. Therefore, we hypothesize that there is a* ***'health effects cycle' of electronic cigarettes****."*

The conclusions of the study which provided positive evidence to support the hypothesis are summarized in the figure below. My findings based on a broad literature survey and meta analysis provide evidence against the long perceived concept of 'harmless electronic cigarettes'.

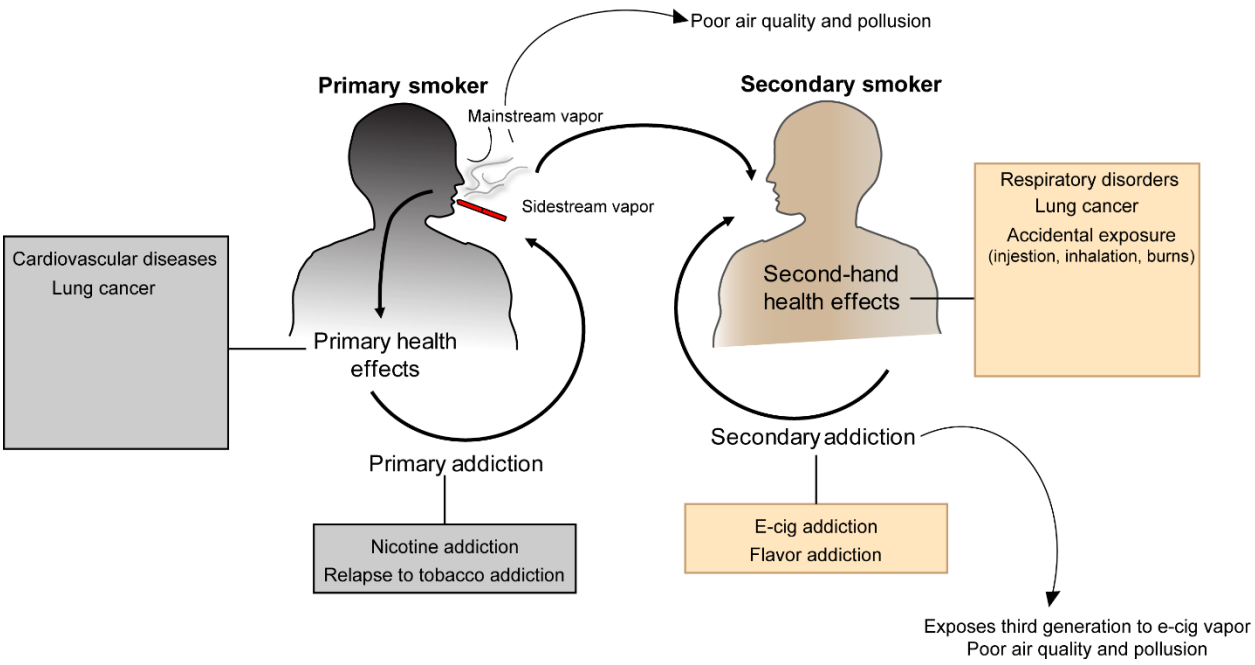


Figure 5. 1 Summary and conclusion of the study.

The *'health effects cycle' of electronic cigarettes'* was proven by the data and literature provided in this study.

The addiction and usage of e-cigs by the secondary smoker or the bystander, generates e-cig vapor, creating another cycle of health effects involving a third generation. This added concept is illustrated in the summary **Figure 5. 1**.

Another interesting and important finding of my study is the recognition of vulnerable groups. While pediatric population of less than 5 years old have been exposed to e-cigs accidentally or passively, a striking feature was that there was relatively higher adolescent population affected by e-cigs. The population of young adults around 20 years of age have been reported to be accidentally exposed to e-cig components or got addicted to using e-cigs.

5.2 Significance of the study

The findings and conclusions of the study will contribute significantly to the knowledge of health effects of e-cigarettes. The major significance of the study is establishment of the '*health effects cycle*' of electronic cigarettes, which is able to describe almost all the health effects caused by e-cigarettes. Moreover, the current study provided a critical comparison of the available data pro- and against- the safety of e-cigarettes. The studies on e-cigarette addiction are very limited. Therefore, this study has contributes significantly to the knowledge of e-cigarette addiction as well.

5.3 Future directions and recommendations

Based on the conclusions obtained from the current study, recommendations could be made to establish laws to regulate indoor and outdoor e-smoking. The use of filters in e-cigarettes to reduce the health hazard could be evaluated as a future project.

As the e-cigs were introduced as an alternative tobacco smoking cessation approach and telemarketing approaches and misleading reports have already established e-cigs deep into our life. However, there is still room to implement regulations and guidelines to minimize the health concerns caused by e-cigs. It will be challenging to change the opinion of the e-cig users to cease the e-cig usage as well. However, if proper regulations are implemented to reduce the indoor and outdoor e-cig and tobacco consumption; to launch proper advertisement of health hazards of e-cigs; to restrict or ban selling e-cigs or related products to minors and to provide education of parents and young adolescents about all aspects of e-cigs, the damage done by e-cigs and associated products could potentially be reduced in the future.

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