



## Editorial

# Are e-cigarettes beneficial for public health: Hume's guillotine – The debate continues?



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## ABSTRACT

Cigarette smoking is the most common preventable cause of death which has led to a search for healthier alternatives to tobacco smoke. Electronic cigarettes are devoid of many harmful constituents found in cigarette smoke and are therefore being positioned as safer alternative to tobacco smoke. The carcinogenic potential may be of lower magnitude compared with cigarette smoke, but it is still there. The use of e-cigarettes, however, is fairly new, so its long-term effects are still unknown. Moreover, they continue to possess the cardiovascular side-effects and are certainly as addicting. Thus on one hand while their substitution could lead to reduction of some side-effects of tobacco smoke, its use may be just shifting the modality of addiction and will be unlikely to lead to total abstinence from tobacco products. On the other hand there is a fear that its use could lead to loosening of the taboo currently associated with use of tobacco products and so the benefits of years of advocacy to ban tobacco products might be lost. Thus currently the scientific community is divided about role of e-cigarettes.

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“Smokers smoke for the nicotine, but are killed by the tar”

## 1. Background

Smoking is the leading risk factor for mortality, accounting for 12% of male deaths and 6% of female deaths worldwide.<sup>1</sup> Smoking cessation (and other lifestyle measures) is one of the most important ways to increase life-expectancy.<sup>2</sup> The belief that nicotine is generally safe and it is the tar in the smoke that is harmful led to evolution of smoke free, nicotine-containing alternatives like nicotine patches and gums, since 1970s.<sup>3</sup> Four decades later, e-cigarettes have become popular with individuals addicted to smokable cigarettes, who view using e-cigarettes (vaping) less harmful than smoking. The basis for this assumption is that while tobacco smoke contains thousands of constituents, it is nicotine that is responsible for the crave while other constituents (of smoke) are responsible for the flavor and provide a physical milieu in the form of an aerosol properties, allowing for rapid absorption into the pulmonary circulation. The exact mechanism of nicotine addiction is unclear but it operates via inducing an initial sensation of reward, followed by development of tolerance and dependence, so that over long-term smokers root for tobacco products primarily to relieve the symptoms of nicotine withdrawal. Besides, nicotine use also increases a sense of belonging to a group in under-confident individuals with “role play acts” such as unwrapping, sharing, handling or smoking in a particular fashion.<sup>4</sup> However, leave aside dependence, on its own, nicotine is not a very

hazardous chemical. It does have some cardiovascular effects (it increases heart rate and blood pressure) and is a local irritant but has only weak carcinogenic effect, if any.<sup>5,6</sup> Further, the risks associated with other constituents of the smoke (tar) such as lung cancer from pro-carcinogens in tobacco smoke, COPD from the irritants and vascular congestion and other cardiovascular diseases due to pro-inflammatory chemicals in the smoke are unlikely with mere use of nicotine. Thus if nicotine could be delivered effectively and acceptably to smokers it could be a viable alternative to tobacco smoking. Indeed in 2015, a Public Health England report stated that e-cigarettes could be 95% less harmful than smoking.<sup>7</sup>

## 2. E-cigarettes/electronic nicotine delivery systems

Electronic nicotine delivery systems (ENDS) or e-cigarettes are battery based devices which have 3 basic components: a battery or an energy source, a liquid (nicotine containing compressed aerosol) containing cartridge, and an atomizer (a chamber with a heating element to vaporize the aerosol). In addition it may have a micro-chip for controlling the heating element (and thus regulating the aerosol quantity formed), an airflow sensor to monitor the flow during inhalation and even diode light at tip which lights up when the device is operative and gives a sense of burning cigarette to the user. In-built are air holes to generate the pressure drop which propels the aerosol which is puffed. The device may be manually activated or be automatic i.e. activated by

a drag/inward puff. Newer ENDS may have refillable reservoirs (tankmizers) and longer battery life, programmed pumps for delivery of a specific amount and indicators for amount use as well as safety warnings.<sup>6</sup>

The liquid mixture is composed of nicotine dissolved in water, propylene glycol, glycerine, flavorings and other chemicals. However, unlike tobacco smoke, the aerosol (which is inhaled and then exhaled) does not contain smoke, tar or carbon monoxide but may contain metallic (tin, nickel, copper, silver, iron, cadmium) and nano-particles (originating from the heating coil such as lead, nickel and chromium), tobacco alkaloids (nicotine, anatabine, anabasine) and traces of tobacco-specific N-nitrosamines (NNK), polycyclic aromatic hydrocarbons and other volatile organic compounds. Besides, there may be materials derived from ceramic, plastic, rubber, filament fiber and foam.<sup>6</sup>

### 3. Health concerns with e-cigarettes

E-cigarettes may produce 31 or so harmful chemicals, including some that may predispose to cancer, albeit in smaller amounts. There is growing evidence on health-hazards of vaping. Olfert and co-workers using intravital microscopy and Doppler ultrasonography in mice found that vaping caused increased reactivity of arterioles acutely, causing a constriction in nearly 1/3rd and increased aortic stiffness ( $\times 2\ 1/2$  times) on long-term basis. Thus use of e-cigarettes may have serious consequences on cardiovascular health.<sup>8</sup> In another study, Middlekauff and co-workers revealed that individuals who use e-cigarettes almost every day have elevation of biological markers known to be associated with increased the risk of heart disease just as in tobacco users; an increase in adrenaline levels in the heart, increased oxygen free radicals which can contribute to development of acute myocardial infarction acutely and atherosclerosis on long term basis.<sup>9</sup> The main cardiovascular effects of vaping seem to be co-related with nicotine which acts by releasing catecholamines, contributing to hemodynamic effects; increase in heart rate, blood pressure, vasoconstriction of both coronary and extra-coronary circulation, adverse effect on lipid profile, insulin resistance but it can also cause endothelial dysfunction and contribute to fetal teratogenicity. Regarding the risk of cancer, nicotine can inhibit apoptosis and enhance angiogenesis in animal studies. However, the most important risk associated with nicotine is that of addiction. Acute nicotine toxicity is a rare but manifest risk and could occur due to accidental or suicide motivated ingestion or dermal exposure.<sup>6</sup> On the other hand, tobacco-specific nitrosamines like NNK, although present in traces are highly carcinogenic. Likewise, thermal degeneration of propylene glycol can generate propylene oxide, a known carcinogenic agent. Furthermore, acrolein can be generated consequent to heating of glycerol and is an irritant and oxidizing agent which can partly explain the cardiovascular and pulmonary effects of vaping. Extreme heating can also generate formaldehyde, a known carcinogen. Propylene glycol (also used to generate theatre fog) by itself is relatively non-toxic but is known to be pulmonary irritant and therefore can exacerbate asthma and COAD. However the data on human health subjects is rather controversial; some studies suggesting pulmonary toxicity in terms of increased dynamic airway resistance and a decrease in exhaled nitric oxide but another retrospective study found no adverse effects, rather improved pulmonary functions, decreased severity of asthma symptoms when conventional smokers with asthma switched to e-cigarettes. Vaping is also associated with generation of low levels of metal with uncertain health risks.<sup>6</sup> Contrary to popular perception the aerosol contains particulate matter, the health-effects of which again are uncertain but particulate matter in environment has been co-related with short and long term CVS effects.<sup>10</sup> Finally, some flavoring agents, while

they seem innocuous, are known to be cytotoxic (cinnamaldehyde, butterscotch, balsamic flavor).

### 4. Other smokeless tobacco

Smokeless tobacco use in form of chewed tobacco or gutka is high in countries of South Asia (~20% in India) but also in Southeast Asia, Africa and Northern Europe (snus in Scandinavia). The simplest form of smokeless tobacco in Indian sub-continent is a betel quid (tobacco is added to the betel leaf plus areca nut and slaked lime), however, currently gutka (tobacco pan masala) consumption has become even more popular.<sup>11</sup> While oral cancers are well known with tobacco chewing, meta-analyses of prospective studies of smokeless tobacco users performed by Boffetta and Straif revealed an increased risk of 13% for fatal CAD and 40% for fatal stroke.<sup>12</sup> In another meta-analysis performed in Asian countries (China, Taiwan and India) the increased CAD death risk was 26%.<sup>13</sup> There was a greater prevalence of hypertension and metabolic syndrome in users of smokeless tobacco and the risk of accelerated athero-thrombosis was also higher – 26% (similar to smokers).

INTERHEART study evaluated nearly 30,000 individuals for association of cardiovascular risk factors with AMI world-wide (52 countries). They found that current smoking was associated with a nearly three-fold greater risk of non-fatal MI (OR 2.95, 95% CI 2.77–3.14), smoking beedies (cottage cigarette, indigenous to South Asia) alone also conferred a similar risk (OR 2.89, 95% CI 2.11–3.96), while risk associated with chewing tobacco was only marginally lower (compared to cigarette smoking), a two-fold increased risk (OR 2.23, 95% CI 1.41–3.52) but those who were smokers and who also chewed tobacco had the highest, more than four-fold risk (OR 4.09, 95% CI 2.98–5.61) compared to non-smokers.<sup>14</sup>

### 5. Comparison between smoking and e-cigarette use

Tobacco cigarettes are very addictive and are known to have extremely serious long-term health effects ranging from cancers, heart disease, stroke, emphysema, hypertension and diseases of reproductive system. As a matter of fact they have the greatest potential for preventing death globally, being directly accountable for majority of cancers world-wide. Health effects of e-cigarettes, particularly long-term effects are largely unknown, as there is a general lack of hard data on the subject, it being a relatively new product. They are, however, considered safer and less destructive to health than traditional cigarettes although equally addictive. The carcinogenic effects of smoked cigarettes are largely related to presence of carcinogenic substances in tar particularly polycyclic aromatic hydrocarbons and nitrosamines, but overall there could be nearly 50 chemicals that can be considered cancer causing. E-cigarettes may also contain some carcinogens like nor-nicotine, nitrosamines, aldehydes and propylene oxide but in much lower amounts (9- to 450-fold less) so that their health risk is uncertain.<sup>15</sup>

The second major health-effects related to smoked tobacco are cardiovascular effects; hypertension, increased atherosclerosis on long term basis and transient activation of sympathetic system resulting in precipitation of myocardial infarction. This effect is mainly due to nicotine content of smoked cigarettes although several other constituents like carbon monoxide, hydrogen cyanide, nitrogen oxide and even particulate matter in smoke may contribute. E-cigarettes contribute to nearly similar level of serum nicotine elevation (although it is devoid of other CVS effecting constituents) and therefore have similar cardiovascular effects.

Cigarette is also known to worsen the chronic obstructive airway disease as a result of several chemicals; 4-aminobiphenyl, formaldehyde, acetaldehyde, acrolein, and particulate matter in

the smoke. E-cigarettes also contain formaldehyde, acetaldehyde and acrolein but in much lower amounts. Further, particulate matter (aerosol) generated by e-cigarettes seems to be much more benign and has only uncertain effects on respiratory symptoms. On the other hand, propylene glycol and plant glycerol present in e-cigarette aerosol (and not tobacco smoke) are known respiratory tract irritants. Finally, some of the flavoring agents in e-cigarettes are known cytotoxic. Comparison of cigarette smoke and e-cigarettes is shown in Table 1.

## 6. Policy matters and e-cigarettes regulation

In an ongoing search for safer alternatives evermore smokers are turning to electronic-cigarettes in the belief that it is a safer alternative to conventional tobacco-based cigarettes. Furthermore, many are promoting this approach in the fond hope that it will lead to cessation of use of tobacco products. On the other hand anti-tobacco advocates are concerned that this modality represents just another source of tobacco addiction. In June 2014, the Royal College of Physicians (RCP) advised the UK government to promote use of e-cigarettes and other nicotine replacement methods. They stated that, "On the basis of available evidence, the RCP believes that e-cigarettes could lead to significant falls in the prevalence of smoking in the UK, prevent many deaths and episodes of serious illness, and help to reduce the social inequalities in health that tobacco smoking currently exacerbates."<sup>16</sup> Recently, in July 2017 even FDA announced a sweeping change in its policy regarding use

of e-cigarettes and vaping products: the administration outlined its plan to focus on reducing usage of combustible cigarettes and tobacco but in turn loosening restrictive rules concerning e-cigarettes (laid out just 2016) stating that "without smoke, most if not all of the harm of smoking could probably be avoided."<sup>17</sup> However, other organizations including some anti-tobacco advocacy groups remain vehemently opposed to use of e-cigarettes. Recently, US Centers for Disease Control and Prevention stated there was no credible evidence that e-cigarettes work as a smoking cessation tool.<sup>9</sup> There certainly is an ongoing controversy as to usefulness of e-cigarettes health-wise; being associated with less side-effects and possible role in smoking cessation versus known CVS harm, uncertain long-term effects and also representing another form of addiction. However, even more damagingly could be the possibility of social acceptance of this form of tobacco abuse and thus losing all the benefits of decades of anti-tobacco advocacy. Accidental poisoning is another concern especially with children because of bright colorful containers, it can even be fatal. Finally, explosions, fires and malfunctions all related to lithium battery remain a distinct possibility. US Federal Aviation Administration issued a safety alert to air carriers that e-cigarettes should not be allowed in checked baggage after a review of fire safety issues, including two fires caused by e-cigarettes in checked baggage.<sup>18</sup> There is also a risk that some may misuse the devices to administer other drugs like cannabis, alcohol and other contaminants which may not only make product more toxic but also increase risk of explosion.<sup>19</sup> However, the reality is that any

**Table 1**  
Comparison of cigarette smoke with e-cigarettes.

	Smoked cigarettes		E-cigarettes	
	Content in smoke from 1 cigarette	Health effects	Content in 14 puffs of inhaled aerosol	Health effects
Polycyclic aromatic hydrocarbons (Tar constituent)	≈50 mg	Highly Carcinogenic, COAD, Atherosclerosis	–	–
4-Aminobiphenyl	≈10 ng	Bladder cancer, COAD, pregnancy	–	–
Benzene	≈10 μg	Leukemia	Traces	±
1,3-Butadiene	≈200 μg	Carcinogenic	Traces	±
Isoprene	≈3 mg	Carcinogenic	Traces	±
N-Nitrosornicotine	≈14 μg	Carcinogenic	Minor amounts	Minor carcinogens
Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	≈4 μg	Cancers of the lung, larynx, esophagus, and pancreas	Minor amounts	Minor carcinogens
N-Nitrosodiethanolamine	≈30 ng	Cancers of the lung, larynx, esophagus, and pancreas	–	–
N-Nitrosodimethylamine	≈30 ng	Cancers of the lung, larynx, esophagus, and pancreas	–	–
N-Nitrosodiethylamine	≈5 ng	Cancers of the lung, larynx, esophagus, and pancreas	–	–
N-Nitrosodi-n-butylamine	≈3 ng	Cancers of the lung, larynx, esophagus, and pancreas	–	–
N-Nitrosodi-n-propylamine	≈13 ng	Cancers of the lung, larynx, esophagus, and pancreas	–	–
Acetaldehyde	≈1 mg	Potential carcinogenic, COAD	≈0.5 μg	Minor carcinogens, COAD
Formaldehyde	≈20 μg	Carcinogenic, COAD	≈0.5 μg	Minor carcinogens, COAD
Hydrazine	≈30 μg	Carcinogenic	–	–
Beryllium	≈0.5 ng	Carcinogenic	–	–
Cadmium	≈1 μg	Carcinogenic	0.2 ng	±
Acrolein	≈100 μg	COAD, respiratory tract irritation	≈2 μg	Minor COAD, irritation of respiratory tract
Nicotine	≈1 mg	CVS; AMI, pregnancy	<1 mg	CVS; AMI, pregnancy
Carbon monoxide	≈15 mg	CVS, pregnancy	–	–
Hydrogen cyanide	≈0.5 mg	CVS, pregnancy	–	–
Nitrogen oxide	≈0.1 mg	CVS	–	–
Total particulates	≈10 mg	CVS & COAD	≈10 mg	±
Propylene glycol	Nil	–	–	Respiratory Irritant
Glycerol	Nil	–	–	Respiratory Irritant
Propylene oxide	Nil	–	Minor amounts	Minor carcinogens
Flavoring agents	Nil	–	–	Cytotoxicity
Nickel	Nil	–	0.02 ng	±
Lead	Nil	–	0.04 ng	±

technology, like any knowledge is by nature neutral, it can be used for harm or good. Everything depends on the context. Nuclear power can be used to generate “green” energy, or a nuclear weapon. Thus if this technology is used in those already addicted to tobacco smoke it might be useful by substituting it with a less harmful product and possible role in smoking cessation but if it used to enroll new, particularly younger adherents, by making this modality more socially acceptable, then it can be extremely harmful.

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