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REVIEW



Toxicological assessment of electronic cigarette vaping: an emerging threat to force health, readiness and resilience in the U.S. Army

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ABSTRACT

The U.S. Army and U. S. Army Public Health Center are dedicated to protecting the health, and readiness of Department of the Army Service Members, civilians, and contractors. Despite implementation of health programs, policies and tobacco control interventions, the advent of electronic nicotine delivery systems (ENDS), including electronic cigarettes (e-cigs), represent unregulated and poorly defined systems to supplant or substitute use of conventional nicotine products (e.g., cigarettes and pipe tobacco). E-cigs present unique challenges to healthcare officials vested in preventive medicine. The health impact of an e-cig and vaping on an individual's acute or chronic disease susceptibility, performance and wellness, is fraught with uncertainty. Given the relatively recent emergence of e-cigs, high-quality epidemiological studies, and applied biological research studies are severely lacking. In sparsely available epidemiological studies of short-term cardiovascular and respiratory health outcomes, any attempt at addressing the etiology of acute and chronic health conditions from e-cig use faces incredible challenges. Until relatively recently, this was complicated by an absent national regulatory framework and health agency guidance on the manufacture, distribution, selling and use of e-cigs or similar ENDS devices and their chemical constituents. Two key issues underpin public health concern from e-cig use: 1) continued or emergent nicotine addiction and potential use of these devices for vaping controlled substances; and 2) inadvertent sudden-onset or chronic health effects from inhalational exposure to low levels of complex chemical toxicants from e-cig use and vaping the liquid. Herein, the health impacts from e-cig vaping and research supporting such effects are discussed.

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Introduction

The U.S. Army and the U.S. Army Public Health Center (APHC) are dedicated to protecting the health, well-being, operational effectiveness and readiness of U.S. Army active duty Service Members, Department of the Army (DA) civilians, contractors, and their families.

Safeguarding the health and safety of Soldiers, civilians, and the environment is key to public health protection within the U.S. Army. Army Regulation (AR) 600–63 (para. 7-2a) reminds Army personnel that ‘using tobacco products ... harms readiness by impairing physical fitness and by increasing illness, absenteeism, premature death, and health-care costs.’ This regulation further states that ‘readiness will be enhanced by promoting the standard of a tobacco-free environment that supports abstinence from, and discourages the use of any tobacco product’ (DA 2015b). As a unique population, sustaining Soldier Readiness and Resilience is critical.

However, it is also generally appreciated that smoking prevalence among active duty U.S. Military service personnel exceeds average rates of tobacco smoking seen in the general population, where rates as high as 24% of active duty

Military personnel in 2011 reported currently smoking, compared to 19% of civilians at that time (DoD 2013). In active duty Military service personnel, the most commonly cited reasons for conventional cigarette smoking among heavy smokers included provision of a means to help relax and relieve stress. Additionally, heavy cigarette smokers more often reported increased overall stress levels and increased incidences in the symptoms of anxiety and depression (DoD 2013).

The impact of conventional cigarettes on health, fitness and readiness is well-reported (Conway and Cronan 1992, Zadoo *et al.* 1993, Conway 1998). Indeed, Annex C-10 of the Army Medicine 2020 Campaign Plan, Program 3–3.1 entitled ‘Promote Tobacco Free Living,’ presents a clear objective, which is ‘... to substantially decrease tobacco use by changing the Army culture on tobacco.’ Annex C-10 also states that ‘this will reduce morbidity and mortality rates from tobacco-related diseases in Army beneficiaries.’ This objective also seeks to ‘...increase the proportion of Medical Treatment Facility (MTF) campuses and other areas on Army installations that are tobacco-free’ (ACP 2013).

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Challenging the U.S. Army's clear intent of wanting to promote and sustain Resilience, Readiness and combat effectiveness through stamina advocacy programs – as detailed in Annex C-10 of the Army Medicine 2020 Campaign Plan, Program 3–3.1 'Promote Tobacco Free Living,' is the rise in popularity of other tobacco products (OTPs) or 'non-cigarette tobacco product' use (DHHS 2014). In its broadest sense, OTP is a catch-all definition for recreational products other than cigarettes that contain and deliver nicotine to the end-user (CPHSS 2014).

A more recent challenge to the Department of Defense (DoD) and U.S. Army's intent of protecting the health of Military and civilian populations is the emergence and rapid ascendancy of new electronic nicotine delivery systems (ENDS) including electronic cigarettes (e-cigarettes or e-cigs). These devices remain poorly regulated and poorly defined with regard their chemical composition (both of the device and the vaping liquid) and supplementation of the vaping liquid with other additives. E-cigs are purportedly designed to substitute for conventional tobacco products with the intent of satisfying the psychological craving for nicotine (e.g., cigars, cigarettes, and pipe tobacco products).

E-cigs present unique challenges to healthcare officials with long-standing and vested interests in preventive medicine and in protecting individual and population health. Moreover, the public health impact of e-cigs and their likely influence on an individual's disease susceptibility, performance and general wellness remain largely unknown. This is partly due to a paucity of high quality toxicological and epidemiological studies that have explored the health effects of e-cig use in Military or civilian communities over the relatively short existence of the device.

Confounding the lack of knowledge of the potential health effects of e-cig use is a poor understanding of how the constituents that comprise an e-cig impact the long-term health outcomes of an individual. Until quite recently, the situation was further complicated by an absent national regulatory framework, policy, and/or health agency guidance on the responsible use of ENDS to include regulation of the chemical compounds, constituents and supplements from which an individual might be exposed when using an ENDS like an e-cig.

As we shall learn in more detail in the proceeding sections, the aerosol that is liberated from e-cigs and other ENDS devices is far from a harmless water vapor and should not be thought of as just as safe as clean air (CDC 2014). Though it is recognized that e-cigs comparatively emit lower levels of potentially dangerous toxicants than traditional combusive cigarettes, it is also recognized that in addition to nicotine, e-cig aerosols might contain heavy and transition metals, ultrafine or nano-sized particulate matter and metals, and chemicals that are known to promote cancer like acrolein (Goniewicz *et al.* 2014a). E-cig aerosols also contain humectants like glycerin and propylene glycol and perhaps flavorants that add to the appeal of these devices to minors and adolescents. Moreover, some e-cig and other ENDS manufacturers falsely state that including chemicals like glycerin and propylene glycol and food flavorings should be thought of as safe since they meet the FDA definition of what would

be considered 'Generally Recognized as Safe or GRAS'. This claim of GRAS status by e-cig and ENDS manufacturers is grossly misleading because GRAS only applies to those additives for use in foods, and thus oral consumption, and it does not apply to inhalation of those same additives during vaping. The health effects of inhaling those chemical additives is unknown at this time.

Furthermore, despite a growing prevalence of vaping e-cigs in society and the U.S. Military, the health effects of other components found e-cigs, in addition to the unknown effects of flavorant chemicals and their impact on Service personnel readiness, are not only under-appreciated, but they are also misunderstood due in part to a lack of available epidemiological and toxicological data on the demonstrated health impacts of e-cig use. Herein, the health effects of e-cig use are discussed, and experimental evidence supporting such effects are comprehensively reviewed.

The terms e-cigarette and e-cig are the colloquial and more familiar names for ENDS, and the acronym ENDS represents the more formal, scientific and legally accepted name for this device. The terms e-cigarette, e-cig and ENDS are used interchangeably in this review.

Statement of purpose

The purpose of this comprehensive review article is to critically determine the state of current knowledge and the science of e-cig toxicology and health policy as it relates to U.S. Army populations and communities. This article provides a framework for exploring an up-to-date toxicity assessment (TA) and the associated risk analysis of ENDS devices and provides the logic and rationale with which to assess the potential toxicity and likely health effects from e-cig use by the U.S. Army (and other Military Services) personnel. This article seeks to critically determine the known and anticipated health risks of e-cig vaping from the available weight of data and to systematically assess the potential adverse health effects of e-cig constituents. This can include a complex mixture of liquid and aerosolized components and the associated risks from end-user supplementation or customization of those aerosolized components.

Also included in this report is a rational assessment of inhalation and ingestion exposure pathways to the chemical components of e-cigs, particularly the 'vaped' e-liquid constituents. These include a diverse inventory of humectants, nicotine, and an ever-expanding and complex inventory of non-regulated flavorants. In addition, metal components and fibers found in the e-cig cartridge and e-liquid are briefly discussed, and the potential health effects of the entire vaporized aerosol, including fine (defined as particles with an aerodynamic diameter of less than 2.5 μm but greater than 0.1 μm) and ultrafine (defined as particles with an aerodynamic diameter of less than 0.1 μm – otherwise generally referred to as nanoparticles) particulate matter and the known potentially harmful or unidentified chemical substances, are surveyed.

An assessment of the potential health effects following inadvertent secondhand or third-hand exposure to exhaled

aerosols from e-cigs is also provided in this review article. In the absence of established guidelines, science and health policies and regulations on using e-cigs, there is a high degree of uncertainty with regard the heterogeneous and inconsistently-labeled (or frankly inaccurate) content of e-cigs and e-liquids. This uncertainty and inconsistency might translate to unknown subsequent health effects in using e-cigs and e-liquids and possible chronic health outcomes from long-term vaping of the wide variety of e-cigs available on the market today.

This review is drawn from the current literature and seeks to strengthen an understanding of the likely health effects from, and safety of, e-cig use and exposure, particularly the comparative toxicological effects of e-cigs as compared those seen on using conventional combustible tobacco cigarettes and products. This report should also serve as a technical foundation that identifies knowledge gaps that can be addressed through additional study, results of which, could inform policy-makers with responsibilities in e-cig regulation and public health guidance.

History, components, and basic functions of the electronic cigarette

When one considers the historical timeline of e-cigs appearing in the patent office or in public in more general terms, the first documented recording of an e-cig was a patent for an 'electric vaporizer' that was filed on May 3, 1927 in the U.S. and subsequently granted to Joseph Robinson on September 16, 1930 (Number: US 188, 559). This device was not commercialized and it remains uncertain if a prototype was ever manufactured and used in public (Figure 1).

Evidence of the first patented 'smokeless non-tobacco cigarette' appeared in April 1963, when American inventor Herbert A. Gilbert filed a patent (Number: US 3200819A), the application for which stated, 'The present invention relates to a smokeless non-tobacco cigarette and has for an object to provide a safe and harmless means for and method of smoking by replacing burning tobacco and paper with heated, moist, flavored air; or by inhaling warm medication into the lungs in case of a respiratory ailment under direction of a physician.' The patent application also stated, '... A further objective of the invention is to provide a smokeless non-tobacco cigarette in which provision is made for circulating the fluid around the heating element in a turbulent manner to suitably raise the temperature of the inhaled mixture, with the purpose that the temperature of the flavored air may approximate that of cigarette smoke...' The final documented patent for this invention was issued in the state of Pennsylvania on August 17, 1965, and this invention is generally credited as the first device that closely resembles the e-cigs of today (Figure 1).

By 1979 and into the early 1980s, a pioneer of early computers named Phil Ray, collaborated with his personal physician Norman Jacobson, and they invented the first commercialized product that relied on evaporation of nicotine. Though it was not actually an electronic device, they are credited with performing the first recognized research in the field of nicotine delivery. The product was commercialized and reached major retailers, although it never translated to a promising technology for delivering nicotine, due in large part to the device being inherently unreliable. The inventors of this device are largely credited for introducing the verb 'vape' into the vernacular of the English language.

Throughout the 1990s and early 2000s, many patents for so-called nicotine inhaler devices were submitted from both

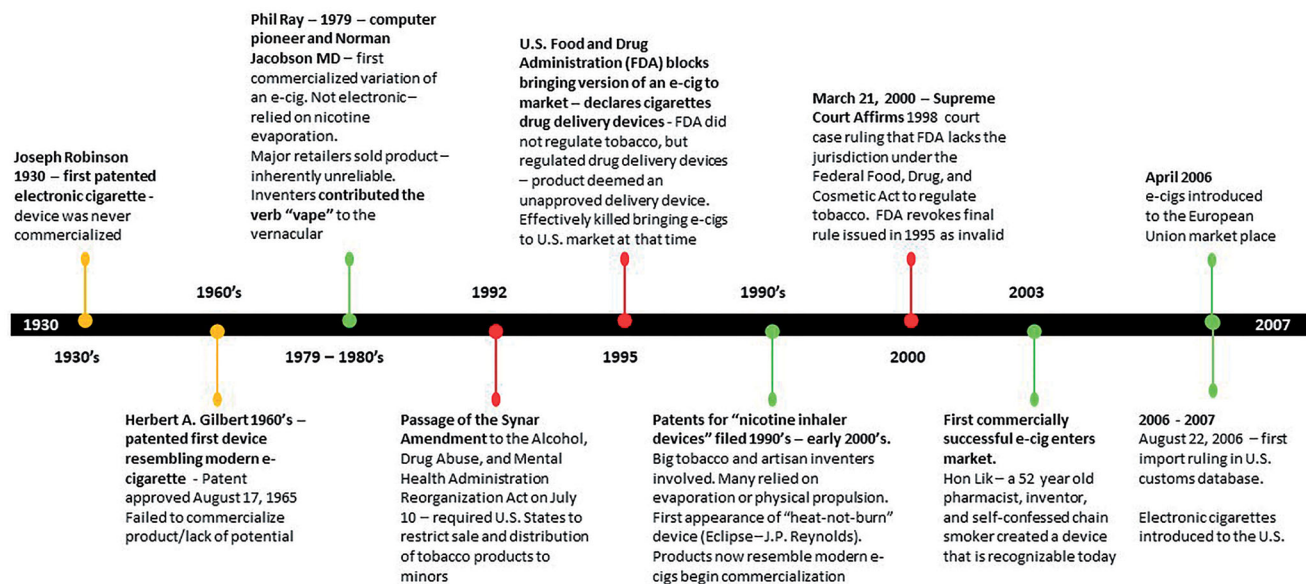


Figure 1. Timeline of electronic cigarette invention, commercialization and emergence of early tobacco regulation, legislation and policy 1930–2007. As this historical timeline shows, although early versions of an E-cig first appeared in Europe in 2006, and the U.S. a year later, these devices have a long history. It was not until 1960 that Gilbert patented the first modern looking device but not appreciating the market for such a device, he failed to commercialize it. Several other attempts through the 1970's and 1990's saw patents filed for various forms of nicotine delivery and inhaling devices, but these were hampered by ongoing attempts at Federal regulation and legislation. Despite this bureaucratic fog, in 2003, a Chinese pharmacist and self-confessed chain-smoker named Hon Lik brought to market the first commercially successful and easily recognizable e-cig that found commercial success in both the U.S. and Europe a few years later.

'big tobacco' and individual inventors. Many devices depended on evaporation or physical propulsion, with some devices very closely resembling the modern e-cig of today. At this time one of the 'big tobacco' companies, R.J. Reynolds, commercialized a product called 'Eclipse,' which was a 'heat-not-burn' device (more on this below) that exhibits a hybrid functioning between that of a nicotine inhalation device and a combusted cigarette. Similarly, Philip Morris brought to the market the 'Accord' device, which heated the tobacco of a specially designed cigarette, and released a flavored smoke that the user then inhaled. As the technology evolved, products that closely resembled the e-cigs of today were moving toward commercialization. Sometime during 1998, the FDA denied a major U.S. tobacco company to bring a version of an e-cig to the market on the grounds that the device represented an unapproved nicotine delivery system. Attempts by other companies to bring similar e-cigs to the market dwindled, and such inventions came and went largely unnoticed until 2003, when Hon Lik, a 52-year old Chinese pharmacist and compulsive cigarette smoker, invented and patented the modern electronic cigarette (Sridi 2013).

Hon Lik's invention overcame the challenges of aerosolization and ensured that the droplets formed were small enough to be inhaled. His device used resistance heating and was sufficiently miniaturized as to mimic a regular cigarette. The device used a high-frequency, piezoelectric ultrasound-emitting element to create an aerosol from a pressurized jet of liquid (known as e-liquid, e-juice, or simply 'juice') containing pure nicotine. The result was a smoke-like aerosol whose inhalation carried nicotine directly to the lungs. In the same year in which the patent was filed, the first e-cig to use this patented ultrasound technology was

manufactured in Beijing, China. The patented e-cig was fully commercialized in 2004 and sold through Hon Lik's company (Dragonite International).

Following the commercial appearance of this device, by April 2006, the modern first-generation disposable e-cig (or cig-a-like) was introduced to European markets, and by mid-2006 through 2007, e-cigs were introduced to the U.S. market. This appearance of the first e-cigs was despite the device not being regulated for either recreational use or as a potential smoking-cessation aid for conventional cigarette/tobacco smoking users (Figure 2).

Modern e-cigs, aerosolize a liquid with a heating element, producing an aerosol that the end-user inhales (or 'vapes'). The aerosol delivers a complex mixture of chemicals, including nicotine, directly to the oral cavity, upper and lower airways, and lungs. The e-cig of today consists of five key components (Figure 2): 1) a battery; 2) a reservoir that contains the e-liquid (typically a complex mixture of the humectants glycerol and propylene glycol, nicotine, flavorants and other (mostly proprietary) additives); 3) a microprocessor; 4) an air-flow sensor or activating button (that emits a colored light-emitting diode (LED) signal at the front end of the e-cig); and 5) a heating element, which is usually a metal wire or rod (e.g., nickel, chromium, or silver-coated copper wire). The majority of the ENDS used today are produced to resemble pens, memory sticks, flash drives, electronic device styluses, or other everyday items.

Unlike conventional cigarettes, e-cigs do not combust processed tobacco *per se*. Instead, when an e-cig user begins to vape, an air flow sensor activates a flow of electricity to the heating element (the atomizing device), which heats and yields an aerosol from the e-liquid-containing cartridge that

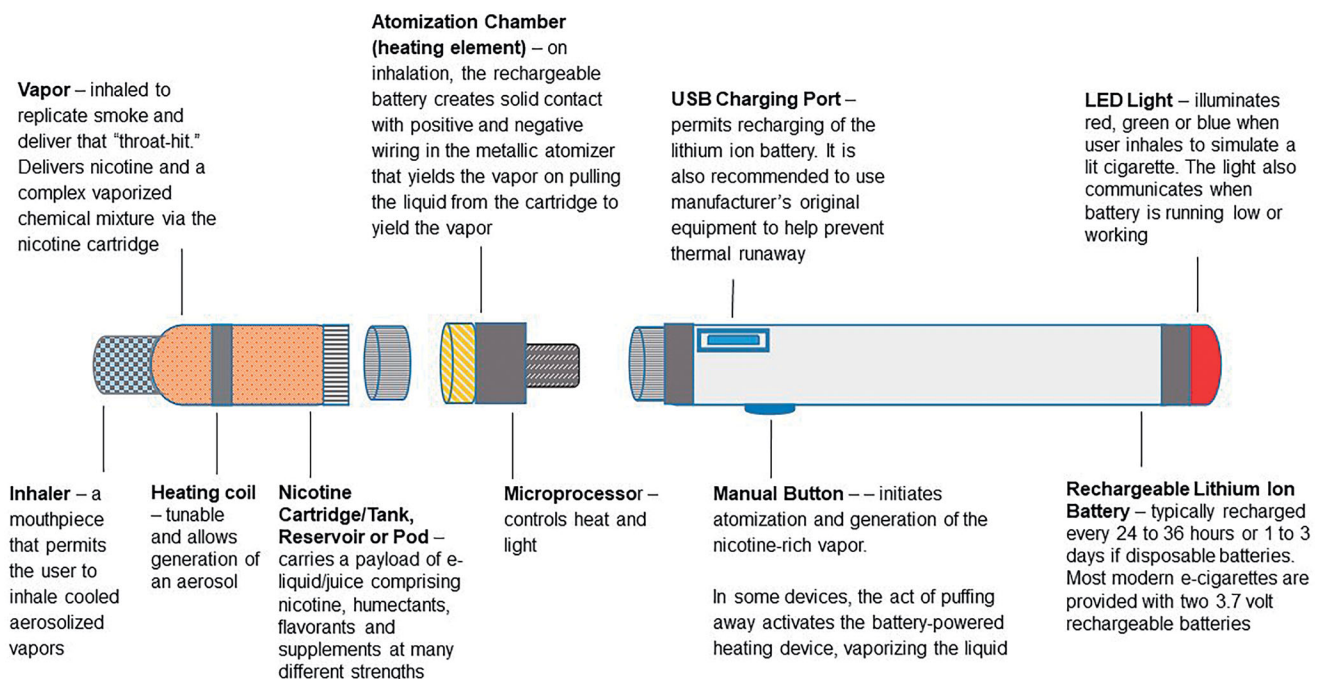


Figure 2. Generic illustration of the basic components found in a first generation rechargeable electronic cigarette. When e-cigs first appeared more than a decade ago, they were largely disposable devices that provided the user about 24h of use before being discarded. Increasingly however, they have evolved to be rechargeable, with high-capacity lithium ion batteries, refillable e-liquid cartridges and customizable formats for content, flavors, the ability to add other supplements to the cartridge or tank – both legal and illegal, and indeed the capacity to deliver varying concentrations of nicotine with its complex chemical payload being delivered to the lungs where they have the opportunity to promote adverse health consequences.

is capable of delivering nicotine without requiring combustion of traditional tobacco products. To e-cig users, this aerosol is analogous to the sensation of inhaling the mainstream smoke of a conventional tobacco cigarette, also known as the 'throat hit' (Brown and Cheng 2014), although its composition differs in comparison to that of an e-cig.

The vaped e-liquid is a complex chemical mixture that typically comprises humectants (e.g., propylene glycol and vegetable glycerin), flavorants (of which several thousand are currently available), water, and nicotine – all of which can be at concentrations that vary significantly between devices and vaping liquids. There is no set standard. The chemical abstract service (CAS) registration number (RN) for each of the growing inventories of flavorants are generally available, but there are simply too many to list here. The mean formulation percentage is thus unknown and there is inherent uncertainty in the concentration, or indeed the presence, of certain components of the e-liquid, which can vary from one batch to another – a fact that is further complicated by the end-user's ability to customize the e-liquid with flavorants and other additives and supplements, including synthetic cannabinoids, other recreational drugs of abuse, and even Viagra or Cialis, depending on the type and design features of the e-cig device.

Unsurprisingly, there are many similarities between e-cig devices and conventional tobacco-burning cigarettes. The most obvious is the highly heterogeneous and complex nature of the chemical constituents found in the nascent e-liquid and in the vaped aerosols that are inhaled to the lung. When coupled with the sensations experienced by the end-user of an e-cig and the familiar behavioral habit of the hand-to-mouth action, it should be no surprise that the aforementioned similarities and 'qualities' have collectively contributed to the rapid rise in e-cig use by society, particularly among adolescent youths, and young adult never-smokers (Caponnetto *et al.* 2013, Bullen *et al.* 2013a, Farsalinos *et al.* 2013a).

Device evolution

The e-cig has transited through a progressive evolution in aerosolization technology (Figure 1). The disposable (cig-a-like) and rechargeable e-cigs that were initially manufactured in 2003–2004 and made widely available through 2007–2009, lacked a modern aerosolization system. Rather, the system that was invented in 2003 (and still used in some devices today) employed heat that was generated by a rechargeable lithium-ion battery to aerosolize the e-liquid and yield an aerosol – a process called atomization (see Figure 2). In addition to evolution of the operating system from a vibratory mechanism to a heating element, the appearance of the devices has evolved dramatically.

The e-cig is now available in five major product types that include: 1) the disposable e-cig or cig-a-like; 2) the rechargeable e-cig type and the related pen-style rechargeable e-cig; 3) the open tank style system; 4) the closed tank-style system; and 5) the box modular system. E-cigs in the pen-style category are manufactured to resemble ink pens, memory

sticks/flash drives, and smartphone styluses, all of which, are thought to be favored by individuals who want to 'vape' unnoticed – a practice otherwise known as 'stealth-vaping.' This practice is also associated with the deliberate supplementation of the vaped liquids with mixtures of flavorants, psychoactive chemicals or drugs, both legal and illegal (Knorst *et al.* 2014, Giroud *et al.* 2015).

Thus, the available ENDS can be conveniently separated into and defined by four generations and five styles of devices whose primary function is to deliver nicotine and/or tobacco to the end-user. These devices are described in turn below.

First generation devices

First appearing on the in the U.S. market at around 2007, the disposable cig-a-like version of an e-cig is modeled and shaped to resemble a traditional cigarette and are the first generation of e-cigs to hit the market. The device comprises a battery and a cartridge that contains an atomizer to heat the e-liquid (with or without nicotine). This model is not rechargeable or refillable and is instead intended to be readily disposed when it no longer produces a respirable aerosol.

The advent of rechargeable e-cig devices, which also fall under the category of first-generation ENDS, are cigarette-shaped devices that comprise a rechargeable battery that is connected to an atomizer that heats replacement or refillable e-liquid that typically contains nicotine at highly variable concentrations. This model, and the subsequent second generation tank models described below, have increased the capacity of the refillable e-liquid tanks, which can be used over much longer periods of time because of the rechargeable battery replacing single-use varieties. It also has an element that regulates puff duration and/or the number of consecutive puffs desired by the user.

A similarly appearing, albeit more sophisticated device, is the medium-sized and pen-shaped rechargeable e-cig. This is an evolving first-generation device that is much larger than either a traditional cigarette or the basic rechargeable e-cig device. It often has a higher-capacity battery and might contain either a prefilled cartridge or a refillable cartridge often referred to as a 'clearomizer.' These devices typically have a built-in manual switch that allows users to regulate the length and frequency of puffs, the output of the battery, and thus the heating element temperature and the nicotine dose delivered to the lung. However, these modifications to the design and functional attributes of the e-cig ultimately affect the chemical composition of the aerosolized vapor and its potential for toxicity.

Second-generation devices

An evolution in the traditional appearing e-cig devices is the tank-style 'personal vaporizers' which are widely regarded as second generation devices. These larger devices do not resemble a conventional cigarette or indeed the original cig-a-like style e-cigs. Instead, these rechargeable e-cigs are designed to generate a high-volume aerosol and a higher

delivery of nicotine (in addition to all the other chemical components present in the vaped product following the aerosolization process). The aerosolizing device is much larger than either a traditional tobacco cigarette or an e-cig, and is equipped with a higher-capacity battery or series of batteries, and typically contains a large, open-tank system. This open-vape tank system design permits the end-user to personally refill and/or supplement a reservoir called the cartomizer, or clearomizer with an e-liquid of choice that can be further customized with flavorants and/or supplements. Other models, known as the closed-vape tank system design, contains the e-liquid in a sealed pod or cartridge that is pre-filled. The end-user simply switches out the spent pod for the new one that is then attached to the device's battery unit.

Both the open- and close-vape models are simply referred to as 'the Tank' and are among the more well-established models of e-cig available. Tank systems have the capacity to deliver nicotine more effectively, and they are rapidly gaining popularity, particularly among younger e-cig users (Farsalinos *et al.* 2014, Herzog 2014). Their market share is also increasing as compared to so-called 'cig-a-likes,' which are the more 'regular,' combustible cigarette-appearing devices. The 'Tank' often contains manually adjustable switches as well as a battery casing that permits end-user customization of battery capacity. Due in part to the Tank's larger e-liquid reservoirs, it does not have the appearance of a typical e-cig. Tank e-cigs remain popular today, due in part to modification of earlier designs like the Mig 21 Clear Fusion (marketed by Mig Vapor) with a higher voltage rechargeable battery and the use of large capacity e-liquid reservoir for vaping.

Moreover, Tank systems can be easily modified, and is thus more likely to be customized for use beyond its intended purpose. For example, since inhalation is the most popular means of consuming cannabis or recreational and pharmaceutical agents on DEA's Controlled Substance lists, the e-cig has emerged as a popular delivery system for such substances (Giroud *et al.* 2015, Brown and Cheng 2014).

Third-generation devices

The modular 'Mod' device represents a third generation model of ENDS and does not resemble a cigarette at all. Modular e-cigs are typically characterized by the inclusion of a separate high-powered and rechargeable battery, an e-liquid reservoir and an atomizer, and resemble a rectangular-shaped device with a vaping mouth-piece resembling a chimney or funnel stack. The modular device is a near fully-automated electronic system, complete with an end-user computerized interface that provides electronic data to the user including the quantified puff count, an estimate of the remaining battery life of the device and resistance (in ohms), the user-regulated temperature and applied power (in watts) and the applied voltage that can regulate the amount of nicotine-containing aerosol delivered to the user's lungs. Modular devices represent the most flexible ENDS on the market, which permit the end-user to experiment with a diverse customizable delivery of products that vary by

nicotine concentration, added flavors, a variable ratio of propylene glycol and vegetable glycerin, and a modular design that permits virtually unlimited user customization, where additional supplements and additives, both legal and illegal, can be introduced into the e-liquid reservoir.

Fourth-generation devices

With continued evolution of the nicotine-delivering capability of ENDS, the advent of devices like the T-vapor, JUUL™ and IQOS (I-Quit-Ordinary-Smoking) was only a matter of 'when and not if' a tobacco and nicotine-containing product (TNCP) would be manufactured. Some of these devices use real tobacco to deliver nicotine to the user in a so-called 'heat-not-burn (HNB)' tobacco product. Such devices arguably represent the fourth generation or true 'next-generation' of e-cigs to hit the market.

The JUUL™ device is somewhat unique in that it resembles a USB flash drive and is not a HNB device. Instead, JUUL™ is a type of e-cig that uses a variety of replaceable flavored cartridges or pods to deliver liquefied nicotine salts or crystals that are found in leaf-based tobacco as its key ingredient (Stahr 2015). The JUUL™ e-cig was introduced in 2015, and is very popular in the U.S., having a greater than 70% market share by most estimates that were published in 2018 (King *et al.* 2018). The JUUL™ device has an extensive appeal among youth and adolescents (Richtel and Kaplan 2018). Like many e-cig and other ENDS devices, JUUL™ is supplemented with the humectants propylene glycol and glycerin and a choice of flavorants that are particularly attractive to teenagers (Huang *et al.* 2019). The JUUL™ device delivers a rapidly absorbed concentration of dissolved nicotine and claims to deliver a nicotine peak within five minutes of use, and an experience closely resembling that of smoking a conventional cigarette. However, the amount of nicotine that is absorbed into the blood is considerably higher than that possible from smoking conventional tobacco cigarettes (Chaker 2018, Unger and Unger 2018). Each JUUL™ pod contains an amount of nicotine that approximates one pack of conventional cigarettes. Each pod contains about five percent or 59 mg/ml of nicotine, which exceeds the amount found in most cigarettes available on the market today (Chaker 2018).

With regard to the JUUL or heated-tobacco products, the major devices on the market today attempt to authenticate the behavioral aspects of smoking conventional cigarettes. Unlike the JUUL™ device, which is not a HNB device, HNBs heat tobacco to high temperatures, in the absence of any combustion and burn-off. Thus, these fourth-generation devices yield an inhalable aerosol, and unlike first, second, or third-generation e-cigs, these devices use real tobacco and the conventional flavored e-liquid found in other vaping devices. The available products share similar functional attributes with conventional tobacco cigarettes, but heat tobacco to a lower temperature than a conventional tobacco-containing cigarette to produce a smoke that contains nicotine, and 100's to 1000s of other chemicals and particulate matter.

A number of HNBs are now available. The 3T system (Vapor Tobacco Manufacturing) that was made available in late 2014 employs a patented aqueous system in which the vaped components are extracted into water and this water extract is mixed with glycerin to facilitate an aerosolized smoke-like vaped product without combustion (Tuinstra 2014). Earlier that same year, IQOS (Philip Morris International) was released onto the market as another HNB product delivering nicotine to the end-user via heated tobacco (Felberbaum 2014). The smoke generated from an IQOS device contains chemicals that are released as by-products of pyrolysis and heat-sensitive degradation of the tobacco-rich paste that is subjected to HNB.

Other variants on the HNB theme are currently available, and include the iSmoke OneHitter (iSmoke) that was introduced in 2015 as a loose-leaf tobacco vaporizer that can be filled with as much as 800 mg of tobacco (iSmoke 2015; Consumer-Centric Vaping 2015). Similarly, the Pax2 device is also a loose-leaf tobacco vaporizer that has four temperature options to a maximum of 455 °F (235 °C). In addition, the V2 Pro vaporizer (released by V2 in the summer of 2014) originally marketed a product called the V2 Pro Series 3 (which simply meant it had three cartridges, including a loose-leaf cartridge). The loose leaf tobacco is heated by conduction (Kahn 2016) and like most e-cigs it is equipped with an independent charging station for the rechargeable battery, and a USB charger cable and an assortment of other accessories. A variant of the V2 Pro called the V2 Pro Series 3X uses dry material, which has three optional and adjustable air flow settings (Silver 2017). The Pro Series 7 is the latest development in products that V2 markets that permits the user of the device to modulate the burn temperature by depressing a single button on the device.

Finally, another product that falls into the remit of a HNB device is available in two unique types that also use conventional loose leaf tobacco. The first product is the HNB T-vapor, and the second is the infused T-vapor – both of which, use loose leaf tobacco. Over the next decade, the market for T-vapor devices is expected to grow by 60% (Unger and Unger 2018). Part of the attraction in using the T-vapor device is its ability to deliver rapidly absorbable concentrations of nicotine that are higher than standard conventional cigarettes, thus increasing the likelihood of rapid addiction to the nicotine-delivering product.

E-cigarettes – a system capable of delivering a complex chemical mixture

To determine the health effects of the chemical compounds and mixtures that typically constitute an e-cig formulation, each compound present in the aerosol from the unit ideally needs to be correctly identified, and the physical, chemical, and toxicological properties need to be accurately determined. Although this approach can be useful for well-defined formulations, in the case of e-cigs, the components are largely ill-defined, highly complex, and inherently heterogeneous – especially in the context of products purchased ‘on the street’ or from obscure online vendors over the internet

that conduct business as unregulated and unmonitored virtual retail outlets with a global reach and captive market.

Online businesses, and others that are more visible with a recognizable marketed identity (e.g., JUUL™, Blu, Mig 21 and MarkTen), have allegedly vested interests in targeting children, adolescents and young adults, with their slick advertising and marketing strategies that are aimed at appealing to those sub-populations of society. They do so by introducing a wide-variety of attractively named, brightly-colored and flavored e-liquids that are vaped via an e-cig. It represents a layered marketing strategy that is appealing to youth and adolescents with interests in new technology with e-cig products names like JUUL™, V2 Pro Series 3 and IQOS (as described above) and of course attractively named flavors.

In the vernacular, anyone that uses a JUUL™ is said to be ‘JUUL™ing’ and use of the term ‘vaping’ appears to have been supplanted (or oftentimes used interchangeably) by the new language. Use of the term JUUL™ing has thus largely replaced the term vaping in the context of adolescent teenagers and minors that have a dependence on and affinity for using the JUUL™ ENDS device.

The formulation of e-cigs is largely proprietary and highly variable, a state further complicated by the lack of an ‘industry standard’ or ‘manufacturing reference e-cig’ that would provide a defined ‘standard’ inventory of the complex chemical mixture that comprises an e-cig, and against which, the myriad of manufactured e-cigs could be compared. Further complicating an appreciation of e-cig formulation is the ability of e-cig users to manually alter and customize the constituents of the e-liquid. As noted previously, E-cig users can supplement the e-liquid with non-regulated herbal extracts, supplements, and both legal and illegal drugs/chemicals, many of which are currently unapproved for inhalational exposure during ‘vaping.’

The origins and quality of ingredients that constitute the e-liquid are generally unknown. However, some manufacturers indicate their use of Good Manufacturing Practices (GMP) to generate e-liquids, a misleading claim since no specific standards are available or currently mandated. It is thus possible that e-cigs will also contain undisclosed additives or supplements, and some claiming to be nicotine-free might contain trace or higher levels of it. This carries the unfortunate risks of inadvertently exposing individuals to nicotine against their intended wishes with potentially adverse consequences should these e-cig devices be accidentally vaped by children or adolescents. Moreover, new formulations are continuously being introduced to the market both from U.S.-manufactured e-cigs and from products that are imported predominantly from China or Western Europe (Goniewicz *et al.* 2014a, Walton *et al.* 2015).

Variability among the components can be attributed to the supplier of a particular e-cig and whether or not its users manipulate the constituents or supplement the constituents of the vaped e-liquid, particularly by adding ‘herbal’ and/or flavorant components that are ill-defined and not intended for inhalational exposures and consumption. Nonetheless, through a detailed chemical analysis of the components found in the e-liquid of a range of e-cig products, the identity of some of the more common constituents found in both

Table 1. Summary of the major formulation components in vaped e-liquid.

Chemical substance	CAS RN	Mean formulation Percentage (g/100g) ^a
Glycerin/Glycerol	56-81-5	37
Propylene Glycol	57-55-6	57
Ethylene Glycol	121-32-4	<5
Trimethylene Glycol	504-63-2	Highly variable ^b
Nicotine	54-11-5	Highly variable ^c
Ethyl Vanillin (a flavorant)	121-32-4	Highly variable ^d
Thujone	546-80-5	Highly variable ^e
Other Flavorants	Too many to list	Highly variable/Unknown ^f

^aData described above are derived from analyzing 54 e-cig fluids (Hahn et al., (2014). The Chemical Abstracts Service (CAS) registry numbers (CAS RN) were derived from the Department of Health and Human Services (DHHS) Agency for Toxic Substances Disease Registry (ATSDR; DHHS 2015). Mean formulation percentages for those chemicals identified by (b–f) were not determined due in part to the highly variable presence or absence of those chemicals in the e-liquid samples.

^bPresent in 13% of samples (mean [C] 0.6 g/100g).

^cPresent in 65% of samples (mean [C] 11 mg/ml).

^dPresent in 26% of samples (mean [C] 30 mg/L).

^ePresent in 4% of samples (mean [C] 6.7 mg/L).

^fPresent in highly variable/unknown concentrations as single (disposable e-cig) or multiple (reusable form of e-cig) added flavorants (Tierney et al. 2016).

the e-liquid and the respirable aerosol of commonly used e-cigs was possible. For a summary of the major formulation components of e-cigs; see Table 1 above.

Although nicotine exposure from e-cig use is a primary concern, there are other exposures to consider. This includes the potential for secondhand exposure, the potential for e-cigs to serve as a gateway to tobacco use or recreational cannabis or other drug use, and a resurgence in smoking (and thus combustible tobacco products) being considered socially acceptable – all of which follows the remarkable gains made in educating the U.S. public of the potential health consequences of conventional cigarette smoking (Trehy et al. 2011, Long 2014, Bell and Keane 2014, Girou et al. 2015, McMillen et al. 2015, Brown et al. 2014, Gostin and Glasner 2014).

The toxicant intake, and particularly that of nicotine, from vaping an e-cig is largely dependent on the vaping device that is selected. As discussed above, e-cig evolution has seen a wide variety of first, second, third and fourth generation devices brought to the market, each of which is capable of either being a completely closed system that cannot be modified by the user, or devices that are fully customizable and capable of delivering both high concentrations of nicotine and a potentially toxic cocktail of a complex chemical mixture as discussed below.

In the following sections, the potential health hazards and concerns regarding the major chemical components of e-cigs will be discussed, with a particular focus on the emerging recognition of the potential adverse health effects from consuming humectants, and the many flavorants currently available. This includes the recognition that e-cigs can be abused for the purpose of consuming cannabis and other psychoactive drugs.

E-cigs and nicotine

The original intent of e-cigs, or at least, the perception, was to help serve as a nicotine delivery system to the user as an alternative to igniting leaf tobacco products and inhaling a smoke-rich cocktail of thousands of chemicals, particulates and additives known or suspected to have adverse health

effects in the short and long term. Electronic liquids contain various quantities of nicotine, which is the highly addictive (DHHS 2014) component of both conventional tobacco products and their e-cig counterparts (Neuberger 2015, Cameron et al. 2014, Pissinger and Dossing 2014).

Nicotine found in e-liquids is present at concentrations as high as 70 mg/mL. E-liquid nicotine, and that derived from smoking conventional combustible cigarettes, is derived from the same cultivated tobacco plant (*Nicotiana tabacum*) that can also efficiently bioaccumulate many environmental pollutants, including heavy and transition metals like lead from its immediate growing area (Boonyapookana et al. 2005, Dunbar et al. 2018). The major concern here is that heavy metals like lead might inadvertently be introduced to the nicotine-containing e-liquid during extraction process (Dunbar et al. 2018). Lead is also introduced into the e-liquid from the device itself (e.g., the heating coil, soldered joints, the wick, or other components), representing another mode of toxic metal exposure from vaped e-liquid aerosol by the end-user. The potential for health effects from inhalational exposure to heavy metals and metallic nanoparticulate toxicants is discussed below in more detail.

On using e-cigs and other ENDS devices, several factors influence the extent to which nicotine is absorbed from the lung to the bloodstream and thus the brain. Clearly the concentration of nicotine present in the e-cig or ENDS e-liquid pod or cartridge is important, and is highly variable between devices and products. The use of additives that might influence nicotine absorption and their capacity to stimulate the nicotinic receptors in the brain and thus promote nicotine addiction also contribute to the concentration of nicotine that is absorbed into the blood. In addition, with each engineered modification and successive generation in the design features of an e-cig device, there are associated improvements to the effectiveness of the aerosolization process and its capacity to transfer nicotine from the reservoir into the aerosol (Kosmider et al. 2014). Finally, in the context of e-cig user puff topography, including inhalation frequency and depth, the bioavailability of the inhaled nicotine can be modulated – use behaviors that are supported by automation

of an e-cig device, and inclusion of long-life rechargeable batteries and high volume, high efficiency e-liquid pods or tanks. Clearly, the heterogeneity inherent in the e-cig device design, the concentration of nicotine present in static e-cig devices containing a defined volume of e-liquid, and rechargeable e-liquid pods and tanks are all major concerns.

The nicotine content of e-cigs has changed considerably since their first introduction in the U.S. in 2007. The big three tobacco companies (and smaller manufacturer's) that include Reynolds American, Lorillard, and the Altria Group entered the e-cig market during 2012 and 2013, and have progressively dominated the open market on e-cig supply and sales (DHSS 2016). In terms of the strength of nicotine found in e-cigs and other ENDS, others have found that devices available from big tobacco-companies do not offer the same number or types of options as compared the smaller vape shop sold products and devices (Hsu *et al.* 2018). Additionally, the big tobacco companies were found to be less likely (lower than half) to manufacture devices or products with nicotine-free options as compared their counterpart competitors manufacturing and selling their products through internet retail outlets and vape stores or cafes, wherein the vast majority offered nicotine-free options to the consumer (Hsu *et al.* 2018). Additionally, the vape cafes and high street stores have increased the numbers and types of nicotine options, including nicotine-free and variations in the levels of nicotine-containing devices (Hsu *et al.* 2018). Assisting the flexibility of vape stores and cafes marketing and selling e-cigs, is their capacity to make open-system models (as discussed above) available, which not only offer a wider range of nontraditional flavor options than their big-tobacco company counterparts, but critically offer a greater range of nicotine options, including nicotine-free e-liquid (Hsu *et al.* 2018). However, claims of e-cig or e-liquid pods/tanks being nicotine-free have often proven to be false since low to moderate levels of nicotine were found in products claiming to be nicotine-free (Hadwiger *et al.* 2010, Trehy *et al.* 2011, Cheah *et al.* 2014).

The nicotine content of the e-cig or refillable e-liquid pod is one of many factors that contributes to, and influences nicotine delivery to the lung. Other crucial factors include puff topography (described below under 'Knowledge Gaps and Data Interpretation'), which is directly associated with the rate and area of absorption of nicotine throughout the upper and lower airways (Zhang *et al.* 2013, Vardavas and Agaku 2015). In the context of first-generation e-cigs and cig-a-likes, peak nicotine levels were found comparable to the low end of oral nicotine replacement therapy products, and thus clearly much lower than could be delivered by conventional tobacco cigarettes (Zhang *et al.* 2013). However, with the advent of newer e-cig models that include the second, third and fourth generation devices described above, nicotine delivery and uptake might proceed via mucosal absorption – a process that is much slower than the relatively quicker arterial mode of nicotine absorption that is associated with conventional tobacco cigarette smoke inhalation, and might instead resemble the absorption kinetics of smokeless tobacco use. The key reason for this comparatively accelerated deposition of conventional cigarette tobacco smoke is

its absorption throughout the respiratory tree and particularly at the deeper sites of the apical pulmonary airways (Zhang *et al.* 2013, Goniewicz *et al.* 2013a).

The major concern with nicotine as a key ingredient in many e-cig devices is the danger that it poses to pregnant women, the developing fetus, and of course children and adolescents, where nicotine is known to be toxic to the developing fetus and can severely disrupt both fetal brain and lung development (DHHS 2014, England *et al.* 2015). In addition, there is a risk of poisoning among users and non-users of e-cigs due to inadvertent or intentional ingestion of liquid nicotine, or via absorption through the skin and of course inhalation of high nicotine doses (CDC 2014). Indeed, calls to national poison centers across the U.S. from e-cig use were found to have increased from one per month in September 2010, to 215 cases per month by February 2014 (CDC 2014). Alarming, more than half of those reported cases involved poisonings of children under the age of five years (CDC 2014). An emerging realization from nicotine exposure via e-cig use is the impact of nicotine intoxication on the still developing adolescent brain, in which critical neuronal circuits that modulate attention, learning capabilities, problem solving and susceptibility to addiction are collectively disrupted (England *et al.* 2015).

As of May 2016, the European Union (EU) Tobacco Product Directive limits nicotine in e-cig refills to 200 mg per 10 ml; however, 1–10 mg/kg of nicotine could be lethal for a child (Neuberger 2015). In addition, in the adult population, an oral dose of 50–60 mg/kg is equivalent to a 70 kg man or woman being exposed to approximately 30–40 mg/m³ nicotine for 30 mins. Therefore, it was suggested that e-cig refill bottles be handled in the same manner as other dangerous (restricted use) drugs. Poison information centers, which have observed an increase in reported intoxications by e-cig refills, also warn against skin absorption. In the field of pediatrics, accidental nicotine poisoning is well described, with low concentrations of nicotine provoking adverse effects and admission to pediatric emergency departments (Mowry *et al.* 2013, Forrester 2015, Gill *et al.* 2015). The emergent concern has prompted the Surgeon General's office to warn of the growing evidence, which is now considered sufficient to caution women of reproductive age, pregnant women and adolescents against nicotine-containing product use, including smokeless tobacco, dissolvables and ENDS as safer alternatives to smoking combustible tobacco cigarettes (DHHS 2014).

As mentioned in the section above, nicotine is a powerful gateway drug that alters brain development and dependency in minors, adolescents and adults – an effect that is likely to occur equally whether nicotine exposure is derived from smoking conventional tobacco cigarettes, from passive tobacco smoke, or from e-cigs; including HNB devices (Fillon 2015). There is also concern that nicotine-containing refill cartridges or e-liquid tanks for e-cig devices can be used to facilitate suicide attempts by means of deliberately ingesting the compound by the general public or consumption by susceptible populations with preexisting psychiatric conditions (Eberlein *et al.* 2014, Schipper *et al.* 2014).

E-cigs, constituent humectants and acrolein

The purpose of an e-cig is to deliver nicotine to the user's lungs efficiently and promptly via a respirable aerosol that is liberated from the e-liquid. In most e-cigs, the nicotine is dissolved in the humectant, which is usually a mixture of propylene glycol with or without glycerol (glycerin). Several studies have focused on the chemical components found in e-cigs in addition to the concern with regard the presence of nicotine (Goniewicz *et al.* 2014a, Schober *et al.* 2014a, 2014b, McRobbie *et al.* 2015, Herrington and Myers 2015). These studies have collectively asserted that e-cig users are exposed to carbonyl compounds, formaldehyde and other aldehydes, heavy and transition metals, volatile organic compounds (VOCs), fine and ultrafine particulate matter and humectants among a myriad of other chemical constituents (Pellegrino *et al.* 2012, Bekki *et al.* 2014, Williams *et al.* 2013, Jensen *et al.* 2015, Uchiyama *et al.* 2013, Orr 2014, Callahan-Lyon 2014, Cheng 2014).

Humectants commonly found in e-cigs include combinations of glycerol, propylene glycol, trimethylene glycol and, to a lesser extent, ethylene glycol – exposures to which, exceeded the minimal risk level thought to be protective of human health as defined by the DHHS-ATSDR (DHHS 2010), and compounds that are not currently listed on the FDA's list of chemicals that are recognized as GRAS (see Table 1; Hahn *et al.* 2014). Others have attempted to determine the toxicity of diethylene glycol (DEG) in 18 brands of e-cig cartridges (e.g., the Smoking Everywhere 555 High brand), but its quantities were not provided, thus limiting an evaluation of its potential toxicity (FDA 2009). As others have indicated (Orr 2014), it is noteworthy that the U.S. Code of Federal Regulations (CFR) (2011) permits up to 0.2% of DEG in polyethylene glycol when polyethylene glycol is used as a food additive (see 21CFR172.820, 2013). However, this regulation applies to oral, and not inhalational exposure.

One example of a humectant commonly used to generate an e-cig aerosol is propylene glycol (1, 2-propanediol). In several studies, high levels of this compound and glycerin were found in e-cigs, with a mean concentration of approximately 57 grams (g) per 100 g (57 g/100 g) (Cheah *et al.* 2014, Etter 2010, Pellegrino *et al.* 2012, Schripp *et al.* 2013, Uryupin *et al.* 2013). Propylene glycol is FDA approved as a food additive (e.g., as a solvent for colors and flavors) in cosmetics and certain medicines (Walton *et al.* 2015). Propylene glycol is also present in some anti-freeze and deicing agents for vehicles, commercial airplanes, and boats. Other instances of propylene glycol and glycerol aerosol use occur in the entertainment industry (fog/smoke machines) and aviation emergency training, which were used both as obscurants and to mimic 'smoky' semi-visible environments (Teschke *et al.* 2005, Tayyarah and Long 2014).

However, glycols are known respiratory and upper airway irritants. Individuals exposed to the theatrical use of propylene glycol-derived fog or smoke mists have suffered from combinations of respiratory, throat, and nose irritation (Moline *et al.* 2000). In July 2001, the Dow Chemical Corporation, which manufactures propylene glycol, issued 'Propylene Glycol – Consideration Against use in Theatrical

Fogs,' which stated, in part, '... use of propylene glycol in theater fogs is impractical ...' However, many manufacturers continue to include propylene glycol despite clear warnings, and there is no governing body that regulates fog fluid ingredients. Moreover, short-term exposure to, or contact with, glycol aerosols can dehydrate the mucus membranes and eyes, and irritate the throat and upper airways (Raymond 1997, Wieslander *et al.* 2001, Vardavas *et al.* 2012, Callahan-Lyon 2014, Grana *et al.* 2014). Short-term exposures to propylene glycol 'fog' are associated with headache, dizziness and drowsiness. Choi *et al.* (2010) have suggested that long-term exposure to propylene glycol might provoke the development of asthma in children. In adults, long-term exposures to smoke-like and fog aerosols were associated with both upper airway and voice symptoms (Teschke *et al.* 2005, Tayyarah and Long 2014). A summary of the material safety data sheet (MSDS, October 2010) for propylene glycol purports it can form explosive gas mixtures but is considered GRAS for oral intake—although this may not be the case when it is heated and inhaled.

Glycerol (or glycerin) is another humectant found in e-cig liquid formulations with many other uses across a variety of products that include pharmaceutical and nutritional supplement products, food and beverages, personal-care products, oral care products and other agricultural, industrial and laboratory uses (Dow Chemical Company 2014). Glycerol is classified by the U.S. FDA as 'generally regarded as safe or GRAS'. Glycerol is used therapeutically to augment the efficacy of inhalants and is an approved food additive in the European Union where it is registered as E 422 (Dow Chemical Company 2014). Although the U.S. FDA views glycerol as relatively safe to ingest, and safe when used as a solution carrier for flavorants, prolonged exposure to glycerol might cause end-organ damage (Callahan-Lyon 2014).

Glycerol displays hygroscopic effects in that it draws water into bronchial secretions and dampens their viscosity. Dow also indicates it can cause irritation if inhaled (Dow Chemical Company 2014). In laboratory studies, glycerol and propylene glycol did not cause cytotoxic effects when human embryonic or mouse neural stem cells or human pulmonary fibroblasts were exposed to several e-cig refill solutions (Bahl *et al.* 2012). Further, as with all components of an e-cig, these compounds are not formally regulated for inhalational consumption in an e-cig or similar device. As an e-cig humectant, glycerol is used in place of, or in combination with, propylene glycol in e-liquid to produce an aerosol (mean concentration approximately 37 g/100g; see Table 1). In addition, it is important to realize that the repeated and potentially long-term inhalational exposure of glycerol aerosol that is associated with e-cig use differs from the exposure levels encountered in the entertainment industry; thus, current available data are insufficient to determine long-term safety with confidence.

Propylene glycol and glycerin have a default (precautionary) eight hour Threshold Limit Value (TLV) of 10 mg/m³ (OSHA 2015), the TLV that is set for all organic aerosol mists. For example, a prior study that associated exposure of theatrical fogs (containing propylene glycol) to respiratory symptoms (Varughese *et al.* 2005) found a mean personal

inhalable aerosol concentration of 0.70 milligrams per cubic meter (mg/m^3) (range 0.02–4.1 mg/m^3). Personal exposure to propylene in the propylene glycol aerosol suggested 3–4 mg/m^3 in the personal breathing zone over an eight hour period (Pellegrino *et al.* 2012, Burstyn 2014). During e-cig vaping, if one assumes moderate to heavy daily use of the device, this amount would equate to vaping 5–25 milliliters per day (ml/day) and 50–95% propylene glycol in the liquid, which is concordant with previous reports (Etter 2010, Burstyn 2014).

In addition, while glycerol is stable at normal storage and recommended use temperatures, this chemical decomposes when subjected to temperatures exceeding 54 °C (130 °F), which are commonly found during the heating/pyrolysis reaction on vaping an e-cig. On decomposition during vaping of an e-cig, glycerol breaks down to the reactive electrophilic compound acrolein – also known as propenal, and yields the formation of formaldehyde and acetaldehyde (Uchiyama *et al.* 2013, Goniewicz *et al.* 2013b, Geiss *et al.* 2015), which accounts for its relative high toxicity and use as a biocide/herbicide in several industrial applications. This is an important consideration, since e-cig users might experience sustained intermittent exposure to acrolein, just as regular combustible cigarette users are exposed to this toxicant. Thus, the likely health effects from acrolein exposure deserve some additional focus. In industrial applications, acrolein is a pesticide and is employed in the treatment of irrigation canals and water supplies of some industrial plants to control underwater plant, algal and slime growth. During World War I, acrolein was used as tear gas, when it was given the name Papite.

Acrolein can exert its toxicological effects on inhalational, oral and dermal routes of exposure, and are mediated almost immediately on contact with the exposed tissues and organs. An inhalational exposure to acrolein can provoke intense irritation to the eyes, nose, throat and lungs very quickly following exposure (Weber-Tschopp *et al.* 1977, Buckley *et al.* 1984). Moreover, bronchitis and excess accumulation of fluid in the lung – a process referred to as pulmonary edema, lung hemorrhage, and even death is possible on exposure to high levels of acrolein. Higher airborne concentrations of acrolein might provoke increasingly severe outcomes due to irritation of the entire upper and lower airways system. Both the severity and diversity of observed effects and depth of the respiratory system to which effects extend increases as the exposure level increases.

Thus, for those that vape e-cigs for extended and sustained periods of time, potential exists for over-exposure to acrolein when glycerol is used as a humectant, and subsequent adverse health effects. Excessive levels of acrolein over-exposure provokes eye irritation, skin and mucus membrane irritation, high fever, dyspnea, coughing, a foamy expectoration, decreased pulmonary function, delayed pulmonary edema, chronic respiratory disease and possibly death. Fatal pulmonary edema might develop several hours following acute exposure to high levels of acrolein. Although signs of pulmonary edema develop slowly over a 24 h period, the manifestation of pulmonary edema in e-cig users might manifest as a more smoldering or indolent progression to edematous disease of the lung.

Additionally, acrolein oxidation by lung or liver microsomes forms the metabolite glycidaldehyde, which could promote skin tumors in mice on dermal contact (DHHS ATSDR 2007). Glycidaldehyde can be further metabolized to glyceraldehyde, which then enters the glycolytic pathways. In a proposed model (Patel *et al.* 1980), glycidaldehyde appears to be the only chemical that could represent a risk to human health, since it exhibited carcinogenic properties in mice and rats when applied dermally (Van Duuren *et al.* 1967a, 1967b, Shamberger *et al.* 1974). Although this metabolic system has been demonstrated in animal models, it has not been shown in human biological systems on inhalation exposure. However, one particular study (Lam *et al.* 1985), found a dose-related depletion of glutathione in the nasal respiratory mucosa in a rat model following inhalational exposure to 0.1–2.5 ppm of acrolein for three hours. This observation was interpreted as being consistent with a chemical reaction that yielded glutathione-acrolein adducts (Lam *et al.* 1985).

E-cigs and flavorants

Healthcare professionals and clinical scientists concerned about the health effects of e-cigs have mainly focused on nicotine exposure – more on this below. Furthermore, besides the growing concern with targeted nicotine levels, it is increasingly evident that the chemical composition of the e-liquid mixture, including levels of humectants, flavorants, and other chemical mixtures during e-cig vaping are notoriously variable (Cheng 2014). As recognized by others, e-cig manufacturers provide only a casual listing of the chemical constituents of the e-liquid or indeed in the manufacturing process – a list that is often incomplete and/or incorrect (Cheng 2014, Goniewicz *et al.* 2013a).

The heterogeneity in e-liquid constitution is compounded by the variety of e-cigs that are commercialized in a range of models and design features found in first, second, third and fourth generation devices as was discussed above. These myriad devices offer unique design characteristics that vary from one model to another and generate a variety of physical and chemical characteristics when activated. Thus, the e-cig as a commercialized and heavily marketed product is rapidly growing in both variety and type, and in popularity among youth culture in a currently unregulated marketplace.

A major concern with regard the safety of e-cigs is that an e-liquid preparation might contain undisclosed additives or contaminants – particularly in the absence of firm and comprehensive FDA regulation, and enforceable good manufacturing practices (GMP). In addition, new formulations are continuously being introduced onto the market, especially from online vendors and so-called ‘vape stores’ or ‘vape cafes.’ However, current U.S. regulation prohibits conventional tobacco cigarettes from possessing characterizing flavors (this excludes menthol, which is found in many conventional tobacco products) such as pineapple, chocolate, apple, and cherry (Goniewicz *et al.* 2014a). Younger smokers oftentimes display a preference for flavored cigarettes. When one considers the unique flavorants sold online (the predominant marketplace for e-cig flavors), there were more than 15,500

unique flavorants available online found in the years 2016–2017 (Hsu *et al.* 2018), which was a significant increase above the more than 7500 flavorant labels found from online merchants of e-cigs in the years 2013–2014 (Zhu *et al.* 2014, Allen *et al.* 2016). The concern with flavorants in e-liquid formulations is their deployment as an inducer of secondary addiction (with nicotine being the primary inducer) among minors, adolescents and young adults. The many flavorants found in 'off-the-shelf' e-liquid formulas or those added to e-cigs as a 'ready-to-go' device are thought to play an important role in making e-cigs more palatable and easier to use, suppressing a desire for withdrawal, and eliciting the so-called anticipatory reward perceptions (Farsalinos *et al.* 2013b).

With regard the toxicology of flavorants found in e-cigs or e-liquid refill pods and tanks, scant information is available on their potential toxicity or post-exposure health effects. However, it is clear that the ENDS industry (including big tobacco companies and the smaller independent businesses), and their marketing and advertising research activities, focus very intensively on sensory characteristics of the ENDS device, with the goal of strengthening product appeal and ease of use (e.g., the familiar cylindrical-shaped closed system designs that have pre-filled e-liquid cartridges) – features that are very important in influencing smoking and would assume vaping behavior as well, irrespective of the addictive nature of nicotine (Carpenter *et al.* 2007, Vardavas and Agaku 2015).

Many of the articles available have focused specifically on the flavoring chemicals that, although regulated for ingestion, are not regulated for inhalational exposures (Farsalinos *et al.* 2015, Hutzler *et al.* 2014, Behar *et al.* 2016, Allen *et al.* 2016). Food product flavorings gained alarming public attention in the early 2000s because workers in microwave popcorn production facilities were reported to develop a serious lung condition referred to as bronchiolitis obliterans, following their inhalation exposure to high levels of diacetyl (2,3-butanedione), a highly volatile flavoring that was added to produce a buttery flavor (CDC 2002, Kreiss *et al.* 2002, OSHA 2010, Halldin *et al.* 2013). Bronchiolitis obliterans is a rare, irreversible, and debilitating disease of the lung in which acute inflammation and tissue scarring collectively obstruct the small conducting airways, i.e., the bronchioles. This condition lacks any effective treatment, and lung transplantation remains the only and most effective option (Morgan *et al.* 2008). However, the transplant procedure itself can trigger onset of bronchiolitis obliterans due to an immunological reaction that rejects the transplanted organ, which results in subsequent poor outcomes and low overall survival rates for such transplant recipients (Kelly *et al.* 2012).

The flavoring chemicals used at the popcorn plant (and those used elsewhere in food products intended for ingestion) were on the U.S. FDA's GRAS list, which applies only to food flavorings intended for ingestion, and does not apply to inhalation exposure – these chemicals were never intended for that mode of exposure or consumption. Exposures at the popcorn plant occurred by respiratory routes; however, very little scientific data was available on the potential inhalational

hazards of these chemicals at the time of these documented exposures (DHHS 2003).

A National Institute for Occupational Safety and Health (NIOSH) investigation at the popcorn plant established that workers there had greater than two times the expected rates of chronic cough, shortness of breath, asthma, and chronic bronchitis, and nonsmokers among those workers had more than 10-fold the expected prevalence of airway obstruction (Kreiss 2002, DHHS 2003). The occurrence of bronchiolitis obliterans in the sentinel cluster of eight staff that had worked at the Missouri microwave popcorn processing plant was strongly associated with airborne exposures to butter-flavoring chemicals in the facility, of which, diacetyl was the most prominent chemical found among the detected chemicals on conducting air sampling of volatiles (Kullman *et al.* 2005, Pendergrass 2004).

In addition, although smokers and nonsmokers (of regular combustible cigarettes) presented with similarly excess airways obstruction at the Missouri microwave popcorn processing plant, the prevalence ratios for nonsmokers were remarkable and found to be almost 11-fold higher than the national rates (Kreiss *et al.* 2002, Kreiss 2007). In the case of the Missouri popcorn processing plant, characteristics that included age, gender, and duration of working at the plant showed no association with the appearance of airways obstruction (Kreiss 2007).

No enforceable workplace standard that is specific to diacetyl exists at this time. NIOSH has placed a recommended exposure limit (REL) of 5 parts per billion (ppb) as an eight hour time-weighted average (TWA) during a 40 h occupational work week (DHSS, CDC, NIOSH 2011, Barrington-Trimis 2014). Additionally, to further protect against short-term exposure to diacetyl, NIOSH has, in its draft document, recommended a short-term exposure limit (STEL) for diacetyl of 25 ppb for a 15-minute period of time (DHHS 2011). At the Missouri microwave popcorn plant, cross-sectional studies showed that the eight hour TWA for diacetyl varied significantly in the process areas that were associated with workers that presented with health effects from diacetyl exposure (Kullman *et al.* 2005, Kreiss 2007). It was found that the diacetyl mixers had a mean area exposure of approximately 38 ppm, with a range up to 98 ppm.

It should be noted that diacetyl is present in a variety of flavors in addition to butter-flavoring (OSHA 2010), and its use is not limited to microwave popcorn facilities or food flavoring production facilities. Both 2,3-pentanedione (a structurally related replacement for diacetyl) and acetoin are also used as flavorings (e.g., caramel, butterscotch, piña colada, and strawberry) in the manufacture of many other foods. Many of these same flavors are found in e-cig flavor cartridges and are often sold under names that would appeal to children, teenagers, and young adults; such names include Cupcake, Waikiki Watermelon, Cotton Candy, Tutti Frutti, Double Apple Hookah, Oatmeal Cookie, and Alien Blood. Moreover, diacetyl substitutes such as 2,3-pentane-dione and 2,3-hexanedione, both used in flavorings, were found to be just as potentially toxic as diacetyl (Poter 2012).

During e-cig vaping, the heating, aerosolization, and subsequent inhalation of the flavoring chemicals have an

exposure pathway that is remarkably similar to that of microwave popcorn facility workers. In both settings, the diacetyl is aerosolized and individuals are exposed to it predominantly by the inhalational pathway.

In a recent study by Allen *et al.* (2016), 51 types of flavored e-cigs were carefully selected from among those sold by leading e-cig brands and whose flavors were deemed appealing to youths and young adults. In this study, e-cig contents were fully discharged, and the air stream was captured and analyzed for the total mass of diacetyl (2,3-butanedione), acetyl propionyl (2,3-pentanedione), and acetoin (3-hydroxy-2-butanone), which is a precursor chemical of diacetyl formation in e-liquids (Vas *et al.* 2019). Acetyl propionyl is an α -dicarbonyl homolog of diacetyl, and has been used in the food and electronic cigarette industries as an alternative and possible supplement to diacetyl in e-liquid formulations (Allen *et al.* 2016).

Relevant to e-cigs is the concerning revelation that when present, the reactivity of the commonly used e-liquid flavorants acetoin, acetyl propionyl and diacetyl were pH-augmented when nicotine was also present in the e-liquid (Vas *et al.* 2019). This group discovered that diacetyl concentrations were proportional to acetoin content, and could increase over time. It was also discovered that when present in the e-liquid, nicotine could accelerate diacetyl formation from the precursor acetoin (Vas *et al.* 2019). Collectively, these latter two observations confirm that not only does acetoin continue to produce diacetyl during the regular shelf-life of e-cig liquids, but the levels of diacetyl might attain potentially toxic concentrations during normal storage and prolonged use (Vas *et al.* 2019).

In 39 of the 51 flavors tested, diacetyl was detected above the laboratory limit of detection (range < limit of qualification to 239 micrograms per e-cig (239 $\mu\text{g}/\text{e-cig}$). Additionally, 2,3-pentanedione and acetoin were detected in 23 and 46 of the 51 flavors tested at concentrations of up to 64 and 529 $\mu\text{g}/\text{e-cig}$, respectively (Allen *et al.* 2016). Of crucial importance, the authors recommended urgent action to further evaluate this potentially prevalent exposure via flavored e-cig devices against what is known about the association(s) among diacetyl, bronchiolitis obliterans and other severe respiratory diseases seen in workers.

The flavorings commonly found in e-cigs strongly suggest potentially important health risks to those individuals who regularly vape any of the flavored e-cigs in use today (Allen *et al.* 2016).

Others have employed gas chromatography/mass spectrometry to analyze the flavor chemicals in multiple flavors of e-cig fluids, as well as in samples from E-fluid refill bottles commonly obtained online or from local 'vape' stores (Tierney *et al.* 2016). This group found that a significant number of the flavor chemicals were aldehydes (including benzaldehyde), a class of compounds recognized as 'primary irritants' of the mucosal membranes of the respiratory tract. Benzaldehyde was found in e-liquids that were cherry flavored and in more than three quarters of 145 e-cig refill liquids (Behar *et al.* 2016). Similarly, over half of 39 e-liquid refill cartridges tested positive for the highly toxic chemical cinnamaldehyde, while methyl anthranilate was detected in

grape juice flavorants, and 1-hexanol was found in apple flavorants (Behar *et al.* 2016). Thus, a significant number and diversity of the flavor chemicals analyzed were of toxicological concern, and clearly deserve further study (Tierney *et al.* 2016).

E-cigs – particulate matter and metals

Primary and secondary exposures to e-cig aerosols have resulted in detrimental effects, so much so, that e-cig use is now prohibited in many multi-use public areas (Mello *et al.* 2015, Farrimond 2016). The rate of emerging e-cig use has been staggering, and although the delivery process of a typical e-cig device differs drastically from that of their conventional tobacco counterparts, many current policies restricting e-cig use are based upon the reported adverse effects following conventional tobacco product use.

To get at the issue of secondary exposure health effects, some studies have analyzed e-cig emissions under mostly controlled conditions using a mechanical smoking machine to evaluate the potential for secondhand exposure to nicotine and other toxicants from e-cig aerosols. It was found that fine and ultrafine particulate matter (PM) emissions were present in many of the e-cig varieties tested (Czogala *et al.* 2014, Ruprecht *et al.* 2014). Pellegrino *et al.* (2012) evaluated PM emissions from e-cigs and conventional cigarettes. PM emissions from e-cigs slightly exceeded the WHO air quality guidelines (i.e., PM_{10} 52 $\mu\text{g}/\text{m}^3$ and PM_{1-5} 14 $\mu\text{g}/\text{m}^3$); however, these levels were 15 times lower than emissions produced by smoking traditional cigarettes (Pellegrino *et al.* 2012). Others relied on chemical analyses like inductively coupled plasma mass spectrometry (ICP-MS) or other approaches to analyze the toxic metal content of e-liquids Goniewicz *et al.* 2014a, Williams *et al.* 2013, Hess *et al.* 2017).

These data showing lower emissions from e-cigs could indicate less of a danger from exposures to second- and third-hand smokes or aerosols; however, in the absence of a standardized testing method, data from such studies are inconclusive and contain a high degree of uncertainty. Concerns remain regarding the potential for passive exposure to the aerosols exhaled by e-cig and ENDS users because these devices have seen increased use in indoor environments, many of which are designated tobacco smoke-free zones (Fernandez *et al.* 2015).

There is also a growing concern and an appreciation of the risks posed by heavy and transition metal toxicity, particularly at the nanoparticle size (i.e., particulate matter of less than 0.1 μm in aerodynamic diameter), on vaping an e-cig or other ENDS device. Most of these metals are non-essential and some display adverse health effects, even at appreciably low concentrations (Tchounwou *et al.* 2012). We are also learning that despite heavy marketing and advertising of e-cigs as safer alternatives to conventional tobacco-burning cigarettes, alternative conclusions are being drawn following more detailed characterization, analysis, and quantification of e-cig emissions (Goniewicz *et al.* 2014a, Williams *et al.* 2013, Hess *et al.* 2017, Badea *et al.* 2018).

Heavy and transition metals that included cadmium, nickel, lead, chromium and arsenic have also been detected in both the aerosols and cartridges of e-cigs (Williams *et al.* 2013, Goniewicz *et al.* 2014a). It was found that while concentrations of lead and chromium found in the aerosols of e-cigs were comparable to those found in that of conventional cigarettes, the levels of nickel, by contrast, were up to 100-fold higher (Williams *et al.* 2013). That study also determined that one puff of a tested e-cig contained numerous nanoparticles of tin, silver, nickel and aluminum (Williams *et al.* 2013). The health impacts from inhalation of nanoparticulate metal exposure is discussed in more detail below.

In an analysis of ten e-liquid cartomizer refills by ICP-MS, all analyzed metals that included nickel, manganese, lead, chromium, and cadmium were present in all of the e-liquids (Hess *et al.* 2017). Further, this group found that the levels of nickel and chromium, manganese and lead were highly variable, which were thought to be derived from the heating elements (Hess *et al.* 2017). It is unclear whether e-cigs or other ENDS formally represent a relevant exposure pathway for toxic metals by the end-user. By contrast, in a comparative cross-section study by ICP-MS analysis of blood specimens, the presence of heavy metals and rare earth elements (REE) was studied in nonsmokers, smokers and users of e-cigs (Badea *et al.* 2018). In a comprehensive analysis, this group assayed for 43 elements, including trace elements and other REE and minor elements currently considered 'emerging pollutants' (Tansel 2017, Badea *et al.* 2018).

It was found that unlike traditional cigarette smokers, e-cig users were found to have the highest levels of vanadium, silver and selenium, and beryllium, europium, and lanthanides, which were detected more often in e-cig users than in conventional cigarette users (Badea *et al.* 2018). Also, the serum levels of cerium and erbium increased with prolonged use of an e-cig. Further, in contrast to the study by Hess *et al.* (2017), it was found that smoking of traditional tobacco cigarettes was a source of heavy metals, while use of e-cigs is a potential source of REE (Badea *et al.* 2018). It is likely that the use of third and fourth generation e-cigs/ENDS that share features of both a traditional e-cigarette and use leaf tobacco products, might expose the end-user to a complex metal rich aerosol of both heavy/transition metals and REE.

The risk of inhalational exposure to metal nanoparticles is of particular concern from an engineering design feature most commonly found in, and of particular concern with, first generation e-cigs and cig-a-likes, and the second generation open- and closed-tank designs. Several coil types are used in e-cigs and include those constructed from an alloy of iron, chromium and aluminum – referred to as Kanthal (Farsalinos *et al.* 2015), and Nichrome, which is composed of a nickel and chromium alloy (Farsalinos *et al.* 2015). Others have confirmed the presence of zinc, vanadium, silver, nickel, and chromium in both the e-fluids and aerosolized emissions of e-cigs (Aherrera *et al.* 2017, Saffari *et al.* 2014, Williams *et al.* 2013, Williams *et al.* 2015, Williams *et al.* 2017). In addition, the study by Badea *et al.* (2018) was concordant with previously published work, which supported the notion that e-cigs are a source of toxic metal inhalational exposure and deposition (Williams *et al.* 2017). In the context of first- and

second-generation e-cigs, heavy metal and transition element exposures appeared to be derived from heating the filament (i.e., nickel and chromium), the thick wire (i.e., copper coated with silver), the brass clamp (i.e., copper and zinc), solder joints (i.e., tin, silver, and/or lead), and the wick and sheath (i.e., silicon, calcium, magnesium and aluminum) (Williams *et al.* 2017).

The issue of whether metals can be transferred from the heated metal coil that heats the e-liquid to generate the aerosol has been studied (Olmedo *et al.* 2018). In this comprehensive work, 56 e-cig devices were analyzed with samples obtained for the rechargeable e-liquid dispenser, the aerosol, and the e-liquid that remained in the refillable pod or tank. By collecting samples from regular consumers of standard tank-style e-cigs in the state of Maryland, this study explored the potential contributions of the heating coil and select metal exposures in e-cig users. A pre-selected 15-metal array was used to quantify metals that could be present in the e-liquid from the topping-up dispenser, from the tank system after an e-cig user had vaped from the device, and the resultant aerosols (Olmedo *et al.* 2018). Study investigators found arsenic in about 11% of dispenser samples at a median concentration of 26.7 µg/kg, which was similar to the concentrations found in aerosol and tank samples.

A particularly concerning observation was that aerosol mass concentrations for the measured *metals* exceeded current health-based limits in almost half of the samples examined for chromium, manganese, nickel and lead (Olmedo *et al.* 2018). This study also highlighted that e-cigs are a potential source of toxic metal exposure when inhaled, and included manganese and zinc. Significantly higher concentrations of toxic metals (predominantly chromium, nickel and lead) were found in the aerosol and refillable tanks as compared the dispenser, which indicated that on contact with the heated coil, the e-liquid is contaminated by metals that are toxic by the inhalational route of exposure (Olmedo *et al.* 2018).

The above studies add to the accumulating body of evidence that highlight concern of suspected adverse health effects from metal exposure, particularly chromium, nickel and lead, and exposures to essential metals that have the potential for toxicity following inhalation such as manganese and zinc, following vaping of e-cigs. Serious health effects include neurotoxic outcomes from lead exposures (Garza *et al.* 2006, Bannon and Williams 2016), lead-mediated toxicity to the cardiovascular system (Navas-Acien *et al.* 2007), and inhalational health effects and respiratory diseases including the potential for lung cancer from exposures to trivalent and hexavalent chromium (chromium III and chromium VI, respectively) and nickel (IARC 2012a, 2012b, Jaishankar *et al.* 2014, Gaur and Agnihotri 2019). Of heightened concern is that when compared to conventional combustible cigarette smoke, the levels of both nickel and chromium in the e-cig aerosol were found to be very high due in part to their leaching from the e-cig core assembly of the cartomizer (Williams *et al.* 2013, 2017).

An interesting outcome from the study by Olmedo *et al.* (2018) was increased concentrations of metals in the same e-liquid from the original topping-up dispenser on adding

the e-liquid to the device and had contacted the heating coil. Metal concentrations were increased in both the generated aerosol and in the residual e-liquid that had remained in the tank (Olmedo *et al.* 2018). This evidence points to the transfer of toxic levels of metals from the device to the e-liquid, and then from the e-liquid to the vaped aerosols inhaled by the end-user. Long-term or chronic health effects of inhalation exposure to the potentially toxic effects of e-cigarette vaped metals are unknown at this time and warrant detailed study.

E-cigs and the health risks of second- and third-hand exposures

The e-cig aerosol comprises at least 10 chemicals that are listed on California's Prop 65 (formally titled 'The Safe Drinking Water and Toxic Enforcement Act of 1986') list of chemicals known to cause developmental birth defects or other reproductive harm to the unborn fetus or development of the neonate. The 10 listed chemicals are acetaldehyde; benzene; cadmium; formaldehyde; isoprene; lead; nickel; nicotine; N-nitrosornicotine and toluene. Thus, concern has grown on whether there is a risk from secondhand aerosol exposures following a user drawing on the e-cig and inhaling the chemical-rich aerosol.

Studies have recognized that exhaled aerosols of e-cigs decrease indoor air quality by releasing fine and ultrafine PM and other toxicants. Collectively, these pollutants are environmentally persistent on surfaces commonly found around the home, (e.g., including large furniture items like flat surfaced tables and sofas), where they can persist for days, thus serving as a depot for subsequent passive exposure. These characteristics are similar to those of the environmental tobacco smoke derived from conventional smoking, which represent the sum of second- and third-hand smoke (Saffari *et al.* 2014, Protano *et al.* 2015). Others have shown that the exhaled aerosols of e-cigs can increase the levels of ultrafine PM of indoor environments that somewhat exceed WHO air quality guidelines (Pellegrino *et al.* 2012, WHO 2006), and even under conditions where these levels resulted in a 15-fold lower level of emissions than were seen for traditional cigarettes (Protano *et al.* 2015). Moreover, several toxicants pertaining to vaping e-cigs (discussed in the previous sections), including nicotine, tobacco-specific nitrosamines and other compounds, have the potential to persist on household surfaces for many days (Bekki *et al.* 2014, Goniewicz *et al.* 2014a).

The use of e-cigs in the indoor environment is capable of unintentionally depositing particulates and other pollutants on the clothing and hair of individuals and on the work surfaces, furnishings and floors of the indoor environment. In this way, secondhand e-cig exposure is the inadvertent exposure of individuals in close proximity to the exhaled aerosols of those vaping an e-cig. By contrast, third-hand e-cig exposure is the inadvertent exposure to particulates and other toxicants that are found in indoor environments in the absence of concurrent e-cig vaping (Bekki *et al.* 2014, Goniewicz *et al.* 2014a). However, there is a paucity of data

that has accurately detailed the immediate and long-term health effects of environmental electronic cigarette pollutants (EECPs).

Nonetheless, there is an emerging concern that using e-cigs or other ENDS in workplaces and common public places in general, represents a significant public health issue. This concern is partly due to a growing recognition of unregulated e-liquid constituent safety and the potential for health effects from the user adding customized supplements to the e-liquids. The concern is also in part derived from the potential health impact of e-cigs in the primary user and in the bystander from secondhand (and possibly third-hand) exposure to the exhaled aerosols. It is also appreciated that public confusion with regard the boundaries of where smoking is permitted might lead to compliance issues with any applicable smoke-free legislation.

At the time of drafting this article, the concern from second- and third-hand e-cig aerosol exposures in the United States of America was so pervasive that 892 local municipalities, 19 states, and two territories have included ENDS and e-cigs as products that are prohibited from use in 100% of smoke-free environments, and are thus restricted (ANRF 2019).

E-cigs – a gateway to recreational drug use, user abuse and stealth vaping

A growing concern among advocates of e-cigarette safety and product regulation, is the realization that e-cigs are a potential gateway to conventional tobacco-leaf cigarettes or other tobacco product uses, and have the capacity to reset the declining social acceptance tobacco smoking in private and in public places (Goniewicz *et al.* 2013a, Long 2014, Coleman *et al.* 2015, McMillen *et al.* 2015). Indeed, as discussed above, the fourth-generation of e-cigs have taken away any doubt that e-cigs could serve as a 'gateway' to conventional tobacco cigarette use, and do so by modifying behavior of the end-user to switch or concurrently use conventional tobacco-burning cigarettes. Indeed, these fourth-generation ENDS are modified to explicitly permit the user to be exposed to the effects of leaf tobacco-delivered nicotine.

As reviewed in detail (Giroud *et al.* 2015), there is accumulating evidence that e-cigs have provided smokers a new means of deliberate inhalational exposure to cannabinoids. One of the key reasons for this deliberate exposure is the smoker's belief that aerosolizing recreational cannabis (or cannabinoids) at lower temperatures is safer because lower quantities of toxic substances are produced, as compared to the more usual high temperature combustion of a marijuana cigarette (Giroud *et al.* 2015). In addition, the technology of ENDS has evolved significantly over the last decade and has permitted users to modify the intended use of an e-cig. For example, as briefly mentioned in this review, users can modulate the voltage, the battery power, and the chemical or drug constituents and supplements of the e-liquid.

It is claimed that an e-cig aerosol contains fewer harmful chemicals than ordinary tobacco cigarettes, and possibly when compared with regular marijuana cigarettes (Flahault

and Etter 2014, Earleywine and Barnwell 2007). Additionally, cannabis users believe that cannabinoids and synthetic cannabinoids containing cannabidiol oil (CBD) can be 'vaped' discreetly because deodorized cannabis extracts prevent cannabis detection by non-vaping bystanders or the authorities.

However, as with currently-used 'traditional' e-cigs, there are several drawbacks to vaping cannabis/psychoactive drugs via an e-cig device, including lack of safety, lack of quality assurances, and non-regulated practices in producing commercial or homemade cannabinoid-enriched e-liquids (Giroud *et al.* 2015). The public health concern here is that there is neither an expiration date nor any 'good manufacturing' guarantees for these products, nor are their preservation conditions known. Crucially, there is no information with respect to any toxicological or clinical assessment (Giroud *et al.* 2015). In addition, simple ground cannabis flower heads or concentrated, oily THC extracts (such as butane honey oil concentrate (BHO)) can be vaped in specially designed, pen-sized marijuana aerosolizers that have the appearance of regular, pen-like e-cig devices. Other recipes found on the Internet suggest substituting synthetic cannabinoids (e.g., JWH-018, APINACA) for THC (Giroud *et al.* 2015) and there are many examples describing this process found freely on the internet. An additional concern is that this technological innovation could attract many young people to such practices and thwart cannabis use prevention efforts in areas where cannabis use remains illegal.

The health consequences specific to vaping the above described preparations are currently unknown. However, it is possible that adults, adolescents or young children participating in such activities could be influenced by the psychoactive effects of cannabinoid exposure with potential compromise in mental capacity, judgment and other neurocognitive functions, which, in the context of the civilian workforce that supports the Military, could negatively impact the mission and readiness of the Military. Given that four states in the U.S. have legalized the cultivation, distribution and recreational use of marijuana, and a further 23 states, as well as Washington D.C., have enacted legislation that legalizes marijuana in some form, the potential for stealth vaping of cannabis by those that want to conceal use of this hallucinogenic agent from the general public, or in public places, is growing (State Marijuana Laws Map 2016).

The progressive legalization of marijuana came at a time when e-cig vaping was increasing in popularity; it was, therefore, only a matter of time before e-cig manufacturers took advantage of marijuana extract development and introduced their products on the market. One such marijuana electronic cigarette formulation, manufactured under the brand name Liberty Reach, is freely available for purchase. These devices are not only available the Internet but can be found in so-called 'derivatives' or 'head' shops (Peace *et al.* 2016, Varlet *et al.* 2016). Thus, e-cigs provide young people with an alternative gateway to cannabis use and vaping cannabinoids – behavior that is supported by some relatively recent health statistic studies (Camenga *et al.* 2014, Cohn *et al.* 2015, Richter *et al.* 2015, Miech *et al.* 2016, Richter *et al.* 2016, 20167). It was found that high school students reporting current e-cig or traditional cigarette use were more likely to co-

report alcohol and marijuana use as compared those who never used these products (Richter *et al.* 2017).

It was also reported that current e-cig users were almost three times more likely to report binge drinking, concurrent use of marijuana, and prescription drug misuse as compared to those who did not report current e-cig use (Miech *et al.* 2016). Others found that use of alcohol and marijuana by young adults was associated with cigarette, hookah, and e-cigarette use (Cohn *et al.* 2015). In those individuals that had substance-use disorders, it was found that current nicotine users were almost twice as likely as non-users to also have a marijuana-use disorder (Richter *et al.* 2016). Moreover, in adolescents who reported binge or heavy binge drinking habits, an almost three-fold increase in the likelihood of their also having a nicotine dependency was seen, as compared to non-risky drinkers of alcoholic beverages (Richter *et al.* 2015).

Since Service Members are routinely screened for illegal drug use, the vaping of illicit drugs may not be a concern for the Military *per se* due to this aggressive screening approach; however, there have been documented incidents of adverse health effects from vaping CBD containing synthetic cannabinoids as well as reports of active seeking of psychoactive chemicals for vaping not detected on typical drug screening tests.

Prevalence of e-cigarettes in society

The broad availability of e-cigs is a global problem, with unrestricted and unregulated availability to almost anyone wanting to purchase those devices (Adkison *et al.* 2013). In 2014, an estimated 2.5 million middle and high school students had used e-cigs, and by 2015, the U.S. Centers for Disease Control and Prevention (CDC) estimated that nearly three million U.S. middle and high school students were current (past 30-day) users of e-cigs (CDC 2016, Wang *et al.* 2018), which exceeded the estimated 2.46 million in 2014, and included about 1 in 6 high-school age students (CDC 2016). In addition, from 2011 through 2017, past 30-day use of e-cigs increased almost 8-fold for high school students (from 1.5% to 11.7%), and increased by nearly 6-fold for middle school students (0.60% to 3.3%; Wang *et al.* 2018).

The above figures demonstrate an increase from the 2012 CDC data, which estimated that almost 1.8 million minors had tried e-cigs, with 160,000 minors reporting that they had not used traditional combustible tobacco cigarettes at all (Corey *et al.* 2013, WHO 2014). In addition, from 2011–2013, the number of middle and high school students that had ever used e-cigs but had not habitually smoked combustible tobacco cigarettes more than tripled to 263,000 (Corey *et al.* 2013). Also, in a 2014 study, 17% of twelfth-graders reported using e-cigs, a figure that was more than double the number of those who reported having used conventional tobacco cigarettes (University of Michigan 2014). A representative study conducted by the CDC showed that in 2013 alone, more than 250,000 never-smoking youths had used e-cigs, and use of these devices was associated with an increased intention to smoke conventional tobacco cigarettes – the so-called 'dual-use' phenomenon (Bunnell *et al.* 2015). Of equal

concern was that these youth were nearly twice as likely to take up smoking conventional tobacco cigarettes as compared youths that had never used e-cigs (Bunnell *et al.* 2015).

A consumer-based mail-in survey that was conducted in 2009 from a pool of 10,587 adults, and in 2010 from a pool of 10,328 adults revealed that awareness of e-cigs had doubled from 16.4% in 2009 to 32.2% in 2010. Observations made in other large surveys similarly confirmed the increased awareness and use of e-cigs (Regan *et al.* 2013, King *et al.* 2015, Pearson *et al.* 2012). Most adult e-cig users were dual users of conventional combustible cigarettes. In 2014 for example, 3.7% of adults were past 30-day e-cig users, including 20.3% of conventional combustible cigarette users (Schoenborn and Gindi 2015). In addition, among the population of adult past 30 day e-cig users, 58.8% of them were dual users, and current smokers of combustible conventional cigarettes (NHIS 2015).

Moreover, emerging evidence suggests that e-cig use is prospectively associated with an increased risk of initiating conventional combustible tobacco cigarette use during early adolescence (Leventhal *et al.* 2015, Rigotti 2015). It was found that an estimated 16% of U.S. tenth graders had tried e-cigs, and of this population, 43% had never previously smoked combustible tobacco cigarettes. In addition, among middle and high school students that were ENDS users, 25% progressed to using conventional tobacco products, as compared nine percent of this middle and high school student population that had never used an e-cig or ENDS device (Leventhal *et al.* 2015, Rigotti 2015).

Additionally, according to a 2013–2014 survey, 81% of e-cig users among current youth cited the availability of the wide variety of attractive flavors in the ENDS device or e-liquid vaping cartridges or vaping bottles as a primary reason for using these devices (Villanti *et al.* 2017). This study found that current flavored tobacco product use was highest in youth aged 12 to 17 years (80%) and young adult tobacco users aged 18 to 24 years (73 percent). The proportion of U.S. youths or young adults that purchase e-cigs online remains uncertain. However, strategies to lure individuals to online purchasing include access and awareness of an expanding range of flavorant names that would appeal to minors and adolescents as the above studies have shown (Villanti *et al.* 2017). Such names include ‘Cherry Crush,’ ‘Vanilla Dreams,’ ‘Snappin’ Apple,’ ‘Wild Cherry,’ and ‘Caught’n Pick’n Kid.’

The online internet purchase of e-cigs is also a major concern from a general consumer safety standpoint because the origins and quality of many e-cig ingredients and the e-fluids used to refill non-disposable e-cig devices are generally unknown. While many such fluids enter the U.S. market, or are available online as premixed ‘cocktails’ of chemicals from predominantly China-based suppliers marketing their products online, some are now manufactured by companies in the U.S., the U.K., and many other countries in Western Europe. For example, China is estimated to manufacture in excess of 90% of the global e-cigarette inventory, and about 91% of U.S. imports of these devices, with Chinese manufacturers exporting in excess of 300 million e-cigs to the U.S. and Europe in 2014 (Barboza 2014, GAO 2017). According to the 2016 GAO report, imports of ENDS devices, including e-

cigs, component parts, and the e-liquid total more than \$340 million U.S. dollars (GAO 2017). By 2014, e-cig sales reached approximately \$2.2 billion U.S. dollars and sales were anticipated to continue growing through 2018 by nearly 50%.

Compounding the growing prevalence of e-cigs in the U.S. is the fact that up until relatively recently, they were unregulated devices. The U.S. Food and Drug Administration (FDA), an agency with the authority to regulate certain tobacco- and nicotine-containing products, and devices under the Food, Drug and Cosmetic Act, proposed a rule (FDA 2014) that would include e-cigs under the Act. Due in part to an increased uptake and popularity of e-cigs, there was a growing realization that more detailed data was needed on recreational exposures, and the potential for human health effects from e-cig use, as was the interpretation of such data. In the meantime, the U.S. FDA finalized the Deeming Rule in August 2016 – a regulation that extended the regulatory authority of the FDA under the Family Smoking Prevention and Tobacco Control Act to manufacturer’s suppliers, retailers, marketing and advertising practices for e-cigs, other ENDS devices and their e-liquid cartridges and refills vials (FDA 2016).

Scope of the problem in the U.S. Military

Habitual smoking of conventional tobacco products (e.g., combustible cigarettes) to deliver nicotine to the cigarette smoker is widely regarded as the single most preventable instigator of many chronic non-communicable diseases. These include cancer, airways diseases such as asthma, emphysema and COPD, and cardiovascular disease – all of which have the potential to promote premature death (Benowitz 2010, WHO 2012). Although tobacco smoking has also been referred to as a chronic and relapsing mental disorder (Lasser *et al.* 2000, American Psychiatric Association 1994), smoking of tobacco products is often perceived as a casual recreational behavior undertaken to alleviate stress. For example, tobacco smoking by civilian populations affected by armed conflict and by populations affected by post-traumatic stress disorder (PTSD) and common mental disorders (e.g., depression, anxiety and chronic alcohol dependence) is thought to alleviate the stress and psychiatric impact with which these experiences burden select ‘at-risk’ individuals (Breslau *et al.* 1991, Farrell *et al.* 2001, de Leon *et al.* 2002, Kassel *et al.* 2003, Kessler *et al.* 2005, Fu *et al.* 2007, Ziedonis *et al.* 2008, Lawrence *et al.* 2009, McKenzie *et al.* 2010).

One of the key drivers that encourages U.S. Service personnel to use conventional cigarettes is the perceived relief from stress and anxiety that tobacco products and presumably other nicotine-delivery devices provide, particularly during combat operations (Stein *et al.* 2008, Smith and Malone 2014, Lo *et al.* 2015). In addition, Military personnel who use tobacco products have reported higher levels of stress and anxiety than their non-tobacco user counterparts (Stein *et al.* 2008). In a published interview of thirteen leaders of national civilian public health and tobacco control entities in the U.S., tobacco use was described by some as a ‘coping mechanism’

that was used to 'calm the nerves' (Smith and Malone 2014). Moreover, leaders of these public health organizations voiced concern about depriving Service members of the stress relief that tobacco is presumed to provide and that personnel also use nicotine to assist with remaining alert (Smith and Malone 2014).

Other respondents stated that cessation would be challenging due to the stresses associated with active deployment, and that prohibiting tobacco or nicotine use in active combat might 'degrade performance' (Smith and Malone 2013, 2014). It is also formally possible that similar levels of stress, and anxiety disorders, might be prevalent in Military personnel who habitually use e-cigs, since the key function of these devices is to deliver nicotine, and withdrawal from nicotine is a key driver of both anxiety and stress-related disorders in Service personnel who smoke regularly (Giannakoulas *et al.* 2003, Smith and Malone 2013, Smith and Malone 2014). For example, in the same published interview of 13 leaders of national civilian public health and tobacco control entities in the U.S. described above (Smith and Malone 2014), leaders endorsed the idea of tobacco as a 'stress reliever,' although it likely primarily relieves the stress of nicotine withdrawal as described in several prior studies (Tselebis *et al.* 2001, Stein *et al.* 2008, Perkins *et al.* 2010). Furthermore, few civilian leaders envisioned a tobacco-free Military due to their belief that tobacco use was a coping mechanism for the stresses associated with Military life (Smith and Malone 2014).

This behavior is indirectly assisted by subsidized tobacco sales that provide serving Military personnel with reduced-cost cigarettes, as compared to the prevailing cost to the civilian population from neighborhood retail outlets. However, in July 2014, the Senate Appropriations Defense Subcommittee approved a \$549.3 billion defense spending bill that would eliminate the 25-percent discount on tobacco products, including cigarettes and chewing tobacco, purchased by Armed Forces personnel at commissaries and certain other retail establishments on Military installations.

The public health impact of tobacco product subsidies might include an increased risk of Active Duty Military personnel developing chronic non-communicable diseases and conditions and their associated co-morbidities. Such diseases and conditions might include those of upper and lower airway and lung inflammation, the cardiovascular system, and development of cancers of the pancreas, lung, oral cavity, and head and neck. These conditions might even be seen in individuals participating in low-frequency cigarette smoking of three to five cigarettes per day (Arvey and Malone 2008, Stein *et al.* 2008, Lubin *et al.* 2010, Smith and Malone 2013, Haddock *et al.* 2014, Berthiller *et al.* 2016, Islami *et al.* 2015, Yeo *et al.* 2015).

In 2014, then Secretary of the Navy Ray Mabus, announced that he wished to end tobacco sales on U.S. Navy bases and installations. Additionally, former Secretary of Defense Chuck Hagel stated that Military tobacco policy in general should be reviewed, including discussions of ending tobacco sales and establishing tobacco smoking-free Military installations, due in part to the high financial costs to Service Members and the harmful effects of tobacco smoking on

Military readiness. These policy statements have yielded a DoD review of tobacco use by, and sales to, Armed Forces personnel on Military installations. These statements followed a call by the IOM for a tobacco-free Military (IOM 2009a).

Coincident with the shifting policies in favor of ending conventional tobacco sales to and conventional tobacco product use by Military personnel is the increased prevalence of non-conventional devices, such as e-cigs and hookah pipes, among U.S. Service Members and the civilian population at large, where e-cig use is growing rapidly (Little *et al.* 2015). As with conventional cigarette use, e-cig use by Military personnel is suspected of leading to reduced physical fitness, an increased risk of injury, retarded wound healing, higher rates of mental health conditions, and a greater financial strain for junior enlisted personnel, as indicated by the economic impacts of e-cig use (IOM 2009a, Smith *et al.* 2014).

A major concern regarding any objective assessment of the public health impact of e-cigs is that relative comparisons of their use with conventional cigarettes lack the fundamental behavioral data necessary for a non-confounded evaluation. E-cig advocates mainly focus on past or current conventional cigarette smokers with a tendency to compare e-cigs with conventional cigarettes. Underpinning this tendency is a misconception that e-cigs lack any negative or adverse long-term health effects. The key issue from this assessment is that those data are not yet available. Further, those assessments fail to take into account the growing use of e-cigs in never-smokers; particularly in high-school age children, adolescents and young adults. Definitive studies showing e-cig use as either leading to a reduction in conventional tobacco use or as a habit that does not lead to conventional tobacco use are unavailable. However, current evidence points to e-cig use serving as a gateway to conventional cigarette smoking, although there are some reports to the contrary (Fillon 2015).

In a relatively recent study (Tam and Warner 2018), the concern surrounding e-cig use as a gateway to combustible cigarette smoking use in youths was explored, with the additional concern that nicotine exposure during this critical time in their lives might adversely affect brain development. The aim of this study was to determine to what extent non-smoking youth perceive the issue of being exposed to nicotine on using e-cigs. This study analyzed data on smoking and vaping that was available from the 2016 Monitoring the Future survey of eighth, tenth, and twelfth grade students were analyzed in 2017. Observations showed a significant relationship between smoking behavior and reportedly vaping nicotine or vaping only flavors (both at $p < 0.01$). Investigator concluded that the majority of nonsmoking students perceived that they were being exposed to limited nicotine from vaping. An important weakness of this study was that data was largely derived from self-reported e-cig use. Future research studies will need to determine the accuracy of self-reported e-cig nicotine content and carefully monitor youths that are knowingly using nicotine-containing e-cig (Tam and Warner 2018). Additionally, many current smokers practice dual use of conventional and electronic cigarettes or return to smoking conventional cigarettes in the

absence of quitting any tobacco- or nicotine-containing product. Indeed, reports indicate that most users of ENDS devices like e-cigs also smoke conventional combustible tobacco cigarettes (DHHS 2014, NHIS 2015). Statistical analysis showed that in 2014, that 3.7% of adults were e-cig users in the past 30-days, which included 20.3% of conventional cigarette smokers (DHHS 2014). In addition, among the adult past 30 day e-cig users, it was found that 58.8% of them were also concurrent conventional cigarette smokers or dual users in 2015 (NHIS 2015).

Both conventional cigarette and e-cig manufacturers have an aggressive advertising and marketing track-record, and often advocate the use of their products to as wide an audience as possible. For many years, it was thought that e-cigs would be a promising approach with which individuals could cease or at least reduce their dependence on conventional cigarettes (Bero *et al.* 2005, Proctor 2012, Adkison *et al.* 2013, Goniewicz *et al.* 2013). Moreover, it was initially thought that e-cigs were a healthier alternative to conventional cigarette smoking. Some prospective studies were optimistic about the capacity of e-cigs to serve as a smoking reduction and cessation tool (Caponnetto *et al.* 2013). A recent study showed that e-cig use increased the rate at which individuals stopped smoking (Kotz *et al.* 2014). This study further showed that individuals did so more effectively than those who received no aid at all or those who had received over-the counter nicotine-reduction therapies (Kotz *et al.* 2014).

These studies are tempered by a larger meta-analysis of population-based studies that showed users of e-cigs were markedly less likely to have ceased smoking than non-e-cig users (Grana *et al.* 2014). In addition, a longitudinal study in cancer patients found e-cig users twice as likely to also be smoking conventional cigarettes at the time of follow-up as compared to non-e-cig users (Borderud *et al.* 2014). The only available randomized smoking cessation study found showed that e-cig use was not significantly more effective than nicotine patch therapy; this finding counters some of the earlier logic on the use of e-cigs as smoking-cessation tools (Bullen *et al.* 2013b). Further, a survey sponsored by e-cig manufacturers, and conspicuously not cited by harm-reduction advocates, found that only one percent of e-cig users achieved sustained abstinence from smoking by using e-cigs (Heavner *et al.* 2010).

Although general surveying of the literature supports the notion that e-cigs might play a role in smoking cessation (Hartmann-Boyce *et al.* 2016), high quality studies formally demonstrating it are lacking, and there is considerable uncertainty as to whether habitual use of e-cigs promotes any health benefit at all. The alleged efficacy of e-cigs in smoking cessation programs or attempts by the individual user, have also been challenged by more detailed meta-analyses (Kalkhoran and Glantz 2016). We also remind the reader that ENDS, including e-cigs are not an FDA-approved aid to quit smoking conventional tobacco cigarettes. Current evidence is lacking to draw firm conclusions in support of the effectiveness of ENDS for smoking cessation. However, seven therapeutic aids (nicotine replacement therapy or NRT) have been approved by the FDA to help individuals quit smoking, and include skin patches, chewing (nicotine) gum, and lozenges.

Unlike ENDS (including e-cigs), they are proven both safe and effective when used as directed (FDA 2017).

The U.S. Military, tobacco use, and department of defense policy

Tobacco use is recognized as the leading cause of preventable death in the U.S., which kills more than 480,000 Americans each year (HHS 2014). The DoD has long recognized that the use of tobacco products has a detrimental effect on Military capability. It is also recognized that the Military is considered a high risk environment for cigarette smoking. Indeed, historical tobacco use by the U.S. Military and its association with Service personnel can be traced back to World War I, during which time tobacco companies deliberately targeted Service personnel by distributing cigarettes and including them in C- and K-rations (Joseph *et al.* 2005). Nonetheless, there can be little to debate the fact that cigarette smoking contributes to significant adverse health outcomes, disrupts socio-economic well-being, and contributes to the worsening of indoor air quality and the environment in much broader terms (WHO 2017a).

In response, by 1986, then-Secretary of Defense Caspar Weinberger issued DoD Direction (DoDD) 1010.10 (later referred to as DoD Instruction 1010.10), Health Promotion and Disease/Injury Prevention, in an attempt to encourage an active anti-smoking campaign at all levels of Military service (DoD 2003, Arvey and Malone 2008). This Directive banned the use of tobacco during basic training, increased the number of assigned nonsmoking zones, and prohibited those providing healthcare from smoking tobacco while on duty (Arvey and Malone 2008). Clearly, throughout the 1980s, the beginnings of an active process of fostering a tobacco-free Military was gaining traction within the DoD, due in large part, to diverse negative health effects on active Military service personnel (DoD 2003).

By March 7, 1994, DoD Instruction (DoDI) 1010.15, 'Smoke-free DoD Workplace,' had been issued and supplemented the direction found in DoDI 1010.10 (DoD 2001). Further, DoDI 1010.15 (1994) was canceled and replaced by DoDI 1010.15 of January 2, 2001. This instruction designated outdoor smoking areas and sought to ban smoking in work places and to promote a health education program that would inform personnel of the potential adverse health effects from cigarette smoking and encourage smokers to quit (Arvey and Malone 2008, DoD 2001). Indeed, paragraph four defined the policy of DoDI 1010.15, which clearly stated that 'it is DoD policy, under references (b) through (d), that smoke-free DoD facilities be established to protect all DoD civilian and Military personnel and members of the public visiting or using DoD facilities from the health hazards caused by tobacco smoke exposure.' References (b) through (d) above were specifically referring to Executive Order 13058, 'Protecting Federal Employees and the Public from Exposure to Tobacco Smoke in the Federal Workplace,' August 9, 1997; Secretary of Defense Memorandum, 'Phase-in Period for Compliance with Executive Order 13058 at DoD Morale, Welfare, and Recreation (MWR) Facilities,' December 7, 1990; and DoD

Instruction 6055.1, 'DoD Safety and Occupational Health (SOH) Program,' August 19, 1998' respectively. The DoD also released rules to expand smoking cessation for Military personnel (DA 2007, U.S. Federal Register 2013), and did so in an effort to significantly reduce tobacco use in the U.S. Military within the next 15 to 20 years. Such efforts would also address increased recognition that habitual cigarette smoking can cause suffering from cardiovascular and respiratory diseases and multiple types of cancer; foremost among which, are COPD and cancers of the head, neck and lungs.

Increasingly, the DoD recognized that smoking might also impair combat effectiveness of Military personnel, including their physical fitness, visual and hearing acuity and the progress of wound healing (IOM 2009a, HHS 2014). Cigarette smoking adversely affects warfighter performance and endurance (HHS 2014, Institute of Medicine 2009); furthermore, passive exposure to secondhand smoke might also adversely affect the health of fellow warriors, DA civilians and their families (IOM 2009a, HHS 2014).

It is currently unknown whether sustained and habitual use of e-cigs similarly affects Service personnel performance, endurance and thus readiness. Nonetheless, the U.S. Air Force was the first to implement an e-cigarette use policy (Air Force Publishes Regulations on e-cigarette Use [Internet] 2014). According to Air Force Instruction 40-102, Tobacco Use, '... establishes tobacco policy in the Air Force and explicitly includes e-cigs under the definition of tobacco, subjecting the product to all the restrictions implemented for cigarettes, cigars, and smokeless tobacco' (Air Force Publishes Regulations on e-cigarette Use [Internet] 2014). Although the Military has attempted to implement tobacco control initiatives by means of these and other publications, the association of cigarette smoking and the Military has sustained itself to the present day, with smoking rates depressingly high as compared to the civilian population.

The relatively high rate of smoking, tobacco use and nicotine consumption in the U.S. Military significantly affects the general health, physical fitness, troop readiness and active duty training costs associated with U.S. Military personnel and can affect the general health and welfare of veterans since both of these populations have been shown to smoke at much higher rates than the rest of the U.S. population (Joseph 2005, Brandt 2007, Arvey and Malone 2008, Smith and Malone 2009). Tobacco use not only adversely affects Military readiness – it also imparts a significant financial burden on the U.S. DoD and Veterans Administration (VA) healthcare systems. Despite a desire by many in the Military to quit smoking, most have failed to do so because of their addiction to nicotine (Joseph 2005, Brandt 2007, Arvey and Malone 2008, Smith and Malone 2009). The 2009 Institute of Medicine (IOM) report determined that the DoD spent more than \$1.6 billion each year on tobacco-associated healthcare costs and lost days of work-related productivity (IOM 2009a). Moreover, in 2006, direct tobacco-related costs to the Military Health Service alone totaled \$564 million (IOM 2009a).

In response, the DoD has offered some smoking cessation benefits and initiatives over the past several years. However, options were limited, under-utilized, and unfamiliar to many Military personnel. For example, as early as 1975, the DoD

discontinued providing traditional cigarettes in K-rations and C-rations, and by 1978, it had implemented smoking regulations that included designated smoking and nonsmoking zones at the workplace (Joseph, *et al.* 2005).

In a landmark example of the effectiveness of initiatives aimed at curbing tobacco smoking in the U.S. Military, the USS Theodore Roosevelt (CVN-71), which is the fourth aircraft carrier of the Nimitz class, became the first smoke-free U.S. Navy ship in 1993 (Offen *et al.* 2011). However, in 2008, the USS George Washington (CVN-73), the sixth Nimitz class aircraft carrier, suffered major structural damage following unauthorized smoking in the vicinity of improperly stored flammable refrigerant compressor oil – this particular case highlighted the additional hazards that are associated with cigarette smoking in Military facilities (U.S. Navy Report 2008). In addition, DoD data showed that the prevalence of tobacco use among new Military recruits upon entering the Armed Services was aligned to the U.S. national average. However, following these recruits' entry-level training and first units of assignment, the prevalence rates of tobacco smoking climbed to levels that far exceeded the national average.

By 2013, as part of its efforts to reduce tobacco use in the Military, the DoD issued rules to expand smoking cessation coverage for Military personnel (U.S. Federal Register 2013). A major concern was that smoking would increase training costs since smokers were at increased risk of being discharged during basic training (Klesges *et al.* 2001). In 2001, it was reported that smoking was associated with \$18 million per year in excess training costs to the U.S. Air Force, and more than \$130 million per year for all branches comprising the DoD (Klesges *et al.* 2001).

Despite implementation of effective health programs and tobacco control measures, new electronic nicotine delivery systems (ENDS), including e-cigs and other devices such as electronic pipes (E-pipes), aerosolizers, hookah pens and vape pens are substituting for conventional nicotine products (i.e., cigarettes and cigars, etc.). This trend presents unique challenges to healthcare officials and others with vested interests in protecting human health. The public health impact of an e-cig is unknown, as is the impact to an individual's disease susceptibility and long-term health outcomes.

As was discussed above, current marketing, product placement, and advertising strategies specifically target minors, adolescents, and young adults. Furthermore, marketing and advertising strategies also target Active Duty Military personnel by means that include aggressive billboard advertising and online offers for bulk discounts and other incentives to those serving in the Military (Melikian and Hoffmann 2009, Cobb *et al.* 2010, Chen 2013, Corey *et al.* 2013, Dublin *et al.* 2014, VMR Press Room 2014). These incentives include a customer reward program (referred to as the 'Vape 4 Free'), which boasts an offer of 15-percent discounts on its 'V2' e-cigarette brand for Service personnel and first responders (VMR Press Room 2014). One example that stands out is the 'Vape-a-Vet Project, whose logo is 'Helping Veterans Conquer Smoking.' The products that this project makes available are based on the Mod-style of ENDS, and are designed to appeal to Active/Retired Military personnel since the basic Mod

ENDS is decorated with a number of camouflage-like designs on the casing of the ENDS. The website boasts two major products that includes marketing language that might appeal to Military personnel; for example, the 'Basic Care Package' and the 'Upgraded Bad-ass Care Package.'

Concerns regarding the potential health impacts of ENDS devices have prompted Army Installation and Garrison commanders to issue new installation-level regulations or policy memoranda on the use of aerosol-producing devices like e-cigs. This guidance clearly states that due to the nature, appearance, and safety concerns of electronic cigarettes, they are to be considered in the same category as tobacco products and may not be utilized in any public U.S. Government building on the installation. For example, Department of the Army (DA) Garrison Ft. George G. Meade Command Policy #63 (DA 2015) provides guidance regarding the use of all aerosol-producing devices including, but not limited to, e-cigs; see also DA Garrison-Hawaii Policy Memorandum USAG-HI-65 (2014); DA Garrison Policy 05 Fort Leonard Wood (DA 2014). Moreover, Army-wide guidance is prescribed or mandated in Army Regulation 600-63 (DA 2007). Finally, the Army 2020 Campaign Plan, Annex C-10, Program 3-3.1 entitled 'Promote Tobacco Free Living,' clearly states an over-arching objective, which is '...to substantially decrease tobacco use by changing the Army culture on tobacco (Army Campaign Plan 2013).

Policies described above, make clear mention that 'Service members who violate e-cig policy are subject to punishment under Article 92 of the Uniform Code of Military Justice or the UCMJ. All others may be punished by administrative actions, debarment from installations, and other prosecution' (DA 2007, DA 2014a,b, DA 2015).

President Obama's Executive Order (EO) 13544 (2010), established the National Prevention, Health Promotion, and Public Health Council; and the DHHS National Strategy, 'America's Plan for Better Health and Wellness,' which identified tobacco-free living as one of seven priorities. In direct reference to EO 13544, then Secretary of Defense, the Hon. Ashton B. Carter signed Policy Memorandum 16-001 - Department of Defense Tobacco Policy (DoD 2016). The intent of this memo was to serve as a reminder to the DoD community of the health effects of tobacco use in the U.S. Military, which recognized the high prevalence of tobacco use in the U.S. Military, wherein 38% of current Military smokers initiated their smoking habit after enlisting. The memo also reminded the community of the health and productivity impact of tobacco use in the U.S. Military population, which costs the DoD an estimated \$1.6 billion per year (DoD 2001, 2016), while other estimates have found that the DoD spends almost \$1.02 billion per year (Elenberg *et al.* 2016).

The U.S. Military represents a unique population of interest and, like nonmilitary civilian populations, is comprised of diverse racial/ethnic, gender, rural and other sub-populations among its Service Members. This population is of interest to public health professionals for a variety of reasons, many of which are firmly rooted in the underpinnings of preventive medicine, strengthening readiness, and building resilience in the U.S. Military. In the context of this review article, interests in the U.S. Military population has also focused on observed

differences in tobacco- and nicotine-containing product (TNCP) use by Military personnel that might differ among the U.S. Military population, and as discussed below (Smith and Malone 2009, DoD 2001, Little *et al.* 2016a,b), and concerns regarding particular health disparities and differential health outcomes seen in demographically unique sub-populations (IOM 2009b).

According to the 2014 Demographics Report of the U.S. Military (prepared for the DoD) and other available data, the U.S. Military is currently the nation's single largest employer (Segal and Segal 2004, DoD 2014). The total number of Military personnel stands at more than 3.5 million, including DoD Active Duty Military personnel (1,326,273), of which the U.S. Army has the largest number (504,330); and civilian personnel supported by DoD appropriated and non-appropriated funds (836,484). Women comprise 15.1% of the DoD Active Duty force (200,692), while men comprise 84.9% (1,125,581) (IOM 2009a, DoD 2014).

Less than one-third (31.2%), or 412,070, of Active Duty members identify themselves as a racial/ethnic minority (i.e., Black or African American; Asian; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Multi-racial; or Other/Unknown). The proportion of Active Duty members who identify themselves as a racial/ethnic minority was greater in 2014 (32.9% of enlisted members and 22.5% of officers) than it was in 1995 (28.2% of enlisted members and 10.5% of officers). Of particular note is that to conform to the latest Office of Management and Budget (OMB) directives, 'Hispanic' is analyzed separately as an ethnicity. Overall, 12.0% of the DoD Active Duty force is of Hispanic ethnicity (DoD 2014).

The DoD, and particularly the U.S. Air Force, in its studies of young adult recruits, has been at the forefront of strengthening our understanding of racial/ethnic and gender disparities in smoking and smoking cessation among U.S. Service personnel (Ward *et al.* 2002, Little *et al.* 2015, 2016a). Consistent with our knowledge of cigarette smoking by the civilian population, traditional cigarette smoking and/or use of e-cigs has the potential to affect a richly diverse racial/ethnic minority population and other sub-populations that constitute the modern U.S. Military. In one study, Ward *et al.* (2002) examined the results of a self-administered survey of demographics, tobacco use, and other health risk behaviors that was conducted at the start of an Air Force basic training class of young adult recruits at Lackland Air Force Base, Texas. The study found that 54% of the recruits had ever smoked a cigarette, 24.9% smoked daily at the start of their Military training, and smoking rates were highest among white and Native American recruits (Ward *et al.* 2002). The study also found that whites and American Indian/Alaska Natives were less likely to quit and were more nicotine-dependent than other racial/ethnic groups. Additionally, smoking by young adult, white female recruits exceeded the observed prevalence of all other gender and racial/ethnic groups, wherein 62% of white women had ever smoked a cigarette, and 32% currently smoked. At the time of the study, these figures exceeded the national estimates for women of a similar age and educational level (Ward *et al.* 2002).

Despite implementation of DoD Directives and other initiatives, including health education programs and tobacco control interventions, more than 30% of Active Duty Military personnel, and about 22% of Veterans use tobacco as compared to fewer than 20% of Americans as a whole (IOM 2009a). There is greater concern that the overall rate of tobacco use in the Military has increased since 1998, a circumstance that threatens to reverse gains made from the gradual decline in tobacco use over the past several decades (IOM 2009a). Data show that on average, 38% of current Military smokers initiated tobacco use following enlistment (DoD 2001, 2016). Today, use of TNCPs by Military personnel are among the highest rates in the U.S. (Smith and Malone 2009, DoD 2001, Little *et al.* 2016a). For example, in 2005, the tobacco smoking rate of Military personnel was 32.2% as compared to the civilian tobacco smoking rate of 21% (Smith and Malone 2009).

Further, repeated studies conducted by the U.S. Air Force found that e-cig vaping had rapidly increased from a reported 3 to 10.5% across cohorts enlisting in the Air Force (Little *et al.* 2016a). Of greater concern was the apparent association between e-cig use and the increasing likelihood of using all assessed TNCPs; and dual- or poly-tobacco use (Little *et al.* 2016a,c). Military personnel display increased rates of multiple tobacco-use risk factors that are in common with the general U.S. population (Little *et al.* 2016c). These personnel are usually young male adults, sensation-seeking, and single/never-married (Farley *et al.* 2014, Little *et al.* 2016c). Previous work has shown that among U.S. Airmen, individuals that reported using e-cigs prior to enlistment were likely to be dual and poly-tobacco users by more than four-fold as compared with individuals that did not use e-cigs (Little *et al.* 2016a). To develop and implement effective prevention and cessation interventions, understanding the health effects of combinations of these products is of critical importance, as recognized by previous studies. Dual and poly-tobacco users have an elevated risk of developing cancer, cardiovascular disease and other tobacco-associated diseases and conditions (Teo *et al.* 2006, Huh and Timberlake 2009, Little *et al.* 2016c).

As shown by others (Little *et al.* 2016c), more than 25% of U.S. Airmen in Technical Training had used at least one tobacco product, and more than 50% of Airmen that reported using tobacco products had used more than one type of product. This same study determined that the majority of tobacco-product users had used more than one tobacco product, an observation that complicates prevention and therapy programs (Little *et al.* 2016c). In particular, tobacco intervention programs tended to address only a single form of TNCP, predominantly conventional cigarettes. Moreover, observations from this study strongly suggest that intervention and treatment strategies that tended to target a single form of use might fail patterns of use in at-risk populations (Little *et al.* 2016c). The authors recognized that if most of the tobacco users were using more than one TNCP, intervention approaches would need to be adapted to account for the risk of escalating use of another product as reductions in the use of a targeted product began (Little *et al.* 2016c).

A 2015 study reported that the most common combination of TNCP use was conventional cigarettes and e-cigs, which was unsurprising given the escalating prevalence of e-cig use in the population (Little *et al.* 2015). The study suggested that a key driver for dual or poly-TNCP use in addition to smoking conventional cigarettes was a desire to maintain nicotine levels in the absence of convenient opportunities to smoke conventional cigarettes (Little *et al.* 2015).

It has also been noted that an estimated 15% of Military personnel would initiate use of TNCPs within the first 12 months of having enlisted (Bray *et al.* 2009, Klesges *et al.* 2006, Little *et al.* 2015). This observation is consistent with the continuing dramatic increase e-cig prevalence among U.S. Air Force recruits during their Initial Technical Training (Little *et al.* 2015, 2016a). A major challenge at this time is the overall generalizability of the observations described in the studied U.S. Air Force group and how well they might align to other branches of the U.S. Military and civilian sub-populations (Little *et al.* 2016b).

Federal guidance and issuance of regulatory authority

Tobacco control is highlighted specifically in the 2030 Agenda for Sustainable Development, which was adopted by participating countries at the U.N. in September 2015. The agenda recognizes the dramatic impact of tobacco use on the health, social, environmental and economic well-being of the individual and community, which represents a major barrier to sustainable development that impacts health, poverty, global hunger, education, economic growth, gender equality, the environment, finance, and governance. The agenda recognizes that each year, over 7 million people die from the use of tobacco and tobacco products (GBD 2015), with more than 80% of deaths being seen in low- or middle-income countries (Mathers and Loncar 2006). Further, tobacco use imposes a dramatic global economic burden, with the financial cost of smoking alone estimated to be \$1400 billion – this represents an approximate 1.8% of the global gross domestic product or GDP (WHO 2016).

Since the first commercially successful e-cig entered the market more than 15 years ago, there has been an extraordinary timeline of regulatory and legal pushback against both tobacco products and electronic cigarettes (Figure 3).

By August 2016, the FDA finalized a rule extending the Center for Tobacco Products (CTP) regulatory authority to cover all tobacco products, including ENDS that meet the definition of a tobacco product according to the Federal Food, Drug, and Cosmetic Act (the FD&C Act), and as amended by the Family Smoking Prevention and Tobacco Act (please see Chapter IX of the Tobacco Control Act; 21 U.S.C. 387 as published by the Federal Register 2016). The purpose of the rule was to immediately cover cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco by the FDA's tobacco product authorities in Chapter IX of the FD&C Act (21 U.S.C. 387; Figure 4).

The above rules were in part a response to growing concerns with regard surging use of e-cigs by youth and young

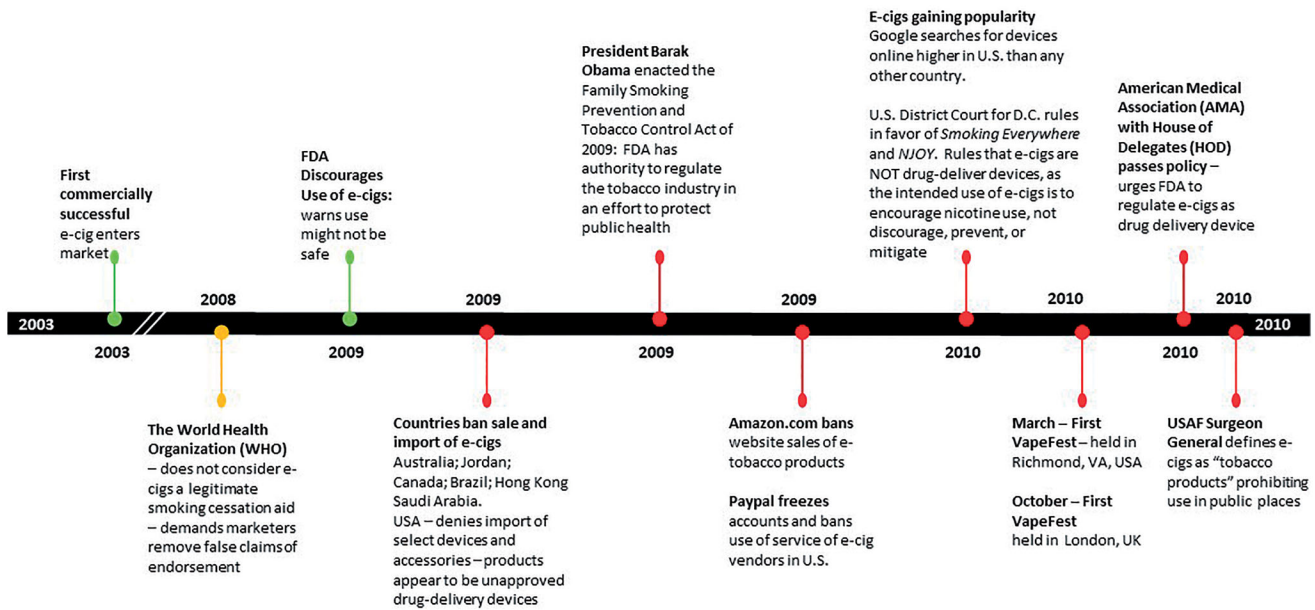


Figure 3. Timeline of electronic cigarettes entering the market, new tobacco product regulation and policies, and evolution of the electronic cigarette 2003–2010. A year after E-cigs were introduced to the U.S. market, the World Health Organization acted promptly to state that E-cigs were not legitimate smoking cessation aids due to a lack of any supporting evidence. Considerable push-back against these devices meant that the FDA discouraged their use, countries banned their sale and import, and commercial retailers like Amazon quickly banned website sales of electronic tobacco products. Nonetheless, E-cigs gained increasing popularity in the U.S., so much so, that the country’s first Vape Fest was held in March of 2010 and during that same year, the American Medical Association urged the FDA to regulate E-cigs as drug delivery devices, and the U.S. AF Surgeon General formally defined E-cigs as tobacco products, prohibiting their use in public places.

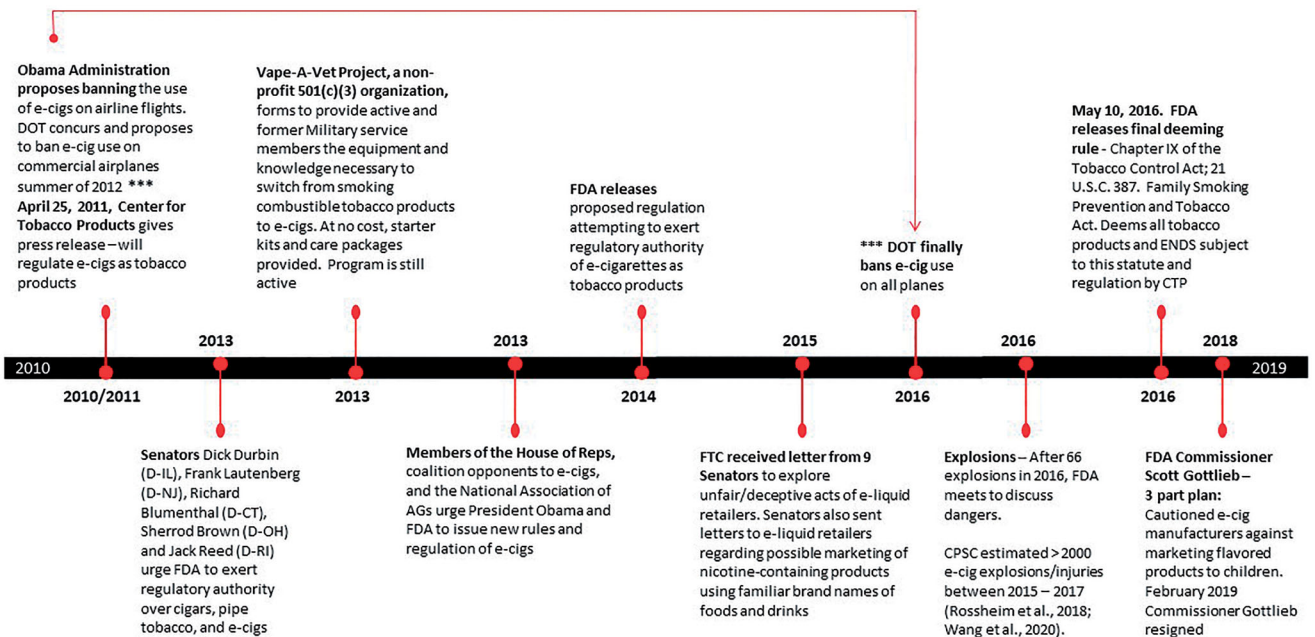


Figure 4. Timeline of electronic cigarettes facing regulatory agency regulation, policies, triggers and regulatory pushback 2011–2019. Continued guidance and legislation over the past 10 years, has seen the banning of E-cigarette use on commercial airlines, and the FDA to release proposed regulatory authority of E-cigarettes as tobacco products. Then, following reports of E-cig devices and/or their charging batteries exploding, catching fire and causing bodily injury, the FDA released its final deeming rule – Chapter XI of the Tobacco Control Act – which deemed all tobacco products and electronic nicotine delivery systems subject to statute and regulation, many components of which, have been enacted and enforced this past year or planned to be more rigorously enforced soon.

adults, and allegedly by the new and widely popular JUUL™ brand of e-cigs in particular (Schroeder 2018). The currently available data indicates that the JUUL™ product has captured almost 75% of the market partly because of its ability to deliver potent nicotine concentrations and its sleek design features. Many advocacy groups have continued to express concerns and have sought intervention by U.S. federal

authorities in what is considered a serious epidemic of vaping e-cigs or other ENDS by youth and young adults (Schroeder 2018). The concern is the recognition that e-liquids or JUUL™ pods have the capacity to deliver nicotine concentrations, and other potentially toxic ingredients when vaped and that inhalational exposure might adversely affect the developing brain or serve as a gateway to smoking

conventional combustible tobacco cigarettes (Barrington-Trimis and Leventhal 2018, Schroeder 2018). However, some argue that use of e-cigs use would serve as a gateway to combustible tobacco product use in young users has not materialized (Cummings *et al.* 2018, Wang *et al.* 2018, NCHS 2018, Mirbolouk *et al.* 2018).

Further, because ENDS and the involved technologies are so new, many countries are in the midst of debating regulation of these devices (Benowitz and Goniewicz 2013). As discussed in the preceding sections, the concern with e-cigs and ENDS is with the management and sale of nicotine. Since nicotine is considered a medicine in some countries, the status of e-cigs and how they are regulated is both controversial and heterogeneously administered. For example, in some European countries like Finland and Switzerland, it is illegal to sell e-cigs although import of e-cigs for personal use is permitted (Finland National Institute for Health and Welfare 2012, Baker 2013), while in others like Italy, Germany, Poland and France it is legal to both import these devices and sell them (Baker 2013, Cahn 2013, Capasso *et al.* 2014, Goniewicz *et al.* 2014b). Still, many other countries around the world have regulated e-cigs and determined that it is illegal to both import and sell e-cigs/ENDS including: Argentina, Brazil, Canada, Columbia, New Zealand, and Singapore, among several others (FIC Argentina 2015, Health Canada 2009, Ingebretsen *et al.* 2012, New Zealand Ministry of Health 2016).

Additionally, other countries like Denmark and the U.K., have passed legislation to regulate e-cigs as a medicine (Baker 2013). However, in the U.K., e-cigs can still be sold with government regulation for non-therapeutic uses, hence at this time, it remains legal to import and sell e-cigs in the U.K. (Baker 2013). By contrast, although both Finland and Denmark also regulate nicotine as a medicine, e-cigs cannot be sold without regulatory authorization (Danish Health and Medicines Authority 2012, Finland National Institute for Health and Welfare 2012). Additionally, in 2014, the European Union enacted legislation to prohibit the sale of e-cigs/ENDS that are not licensed as medicines (European Commission 2014).

For the many other varieties of tobacco products, (e.g., vapes, aerosolizers, vape pens, hookah pens, e-pipes and e-cigs, and any other noncombustible tobacco product identified as an ENDS device), the statute (see Chapter IX of the Tobacco Control Act; 21 U.S.C. 387 as published by the Federal Register 2016) gives the U.S. FDA the authority to issue regulations 'deeming' such disparate products as subject to such authorities as the Family Smoking Prevention and Tobacco Act (see Chapter IX of the Tobacco Control Act; 21 U.S.C. 387 as published by the Federal Register, 2016). Consistent with this statute, once a tobacco product is deemed as such, the U.S. FDA may put in place 'restrictions on the sale and distribution of a tobacco product,' including age-related access restrictions and advertising and promotion restrictions to also include the import, packaging, and labeling of ENDS products, if FDA determines the restrictions are appropriate for the protection of the public health (Federal Register 2017). With these new U.S. FDA rules now in effect, manufacturer's need to be aware that if they participate in

the making, modification, mixing, large-scale manufacture, fabrication, assembly, process, labeling, or importing of ENDS or any of their components, they need to comply with the requirements for manufacturers. A timeline for compliance according to a statutory phased approach from 2018 through 2022 for manufacturers is available on the U.S. FDA's website.

Beginning 2018, the compliance language states that all covered tobacco products must bear the required nicotine addiction warning statement on product packages and any advertisements. Similarly, there are rules that retailers of ENDS and e-liquids or any of their components must follow. In addition, vape shops that prepare liquid nicotine or mixes 'in-house' or customized nicotine-containing e-liquids, or modifies any type of ENDS product are cautioned that they are then considered a manufacturer and consequently, have to fulfill all of the legal responsibilities as both a manufacturer and retailer of a tobacco product.

On September 12, 2018, the Commissioner of the U.S. FDA Scott Gottlieb put forward a three-part action plan (see Figure 4). This plan was issued along with a warning to the five major e-cig manufacturers, including JUULTM, Nuse, blu, Logic and MarkTen that collectively control 97% of the current e-cig market (FDA 2018, Schroeder 2018). The three-part action plan essentially amounts to cautioning e-cig manufacturers from marketing flavored products specifically to children. The plan focuses on reducing youth access, significantly dampening any marketing to youths, and promoting education of the dangers of using any tobacco products, with adolescents as a key target audience (FDA 2018).

Further, in the warning sent to JUULTM, Nuse, blu, Logic and MarkTen, the U.S. FDA demanded that these manufacturers communicate plans on how they aim to curb the widespread use of their products by minors (FDA 2018). This U.S. FDA strategy seeks to accelerate regulation, which was originally deferred to an anticipated 2022 end-state, and includes a provision that requests systematic removal of flavored products from the market place (FDA 2018, Schroeder 2018). The proposed FDA delay to 2022, is the requirement that vaping devices and products go through a rigorous FDA approval process, which requires that pre-market tobacco applications remain on the market. However, health advocacy groups have legally challenged the U.S. FDA for delaying regulation by a period of four years to 2022. The concern is that new devices similar to the fruity and youth-appealing flavored JUULTM have been permitted to hit the market without rigorous review and approval.

Additionally, the 2017 National Youth Tobacco Survey that was released in June, 2018 determined that over two million middle school, high school and college teens are currently using e-cig devices including JUULTM. It was found that about 12% of high school students and three percent of middle school students have used an e-cig device in the last 30 days when the survey was conducted. It was recently reported that the increasing visibility through careful and strategically contrived product placement advertising, had strengthened the popularity of the JUULTM ENDS among youth and young adults in the U.S., thus presenting to society several potential public health concerns (Chu *et al.* 2018). In this very timely and interesting article, the extensive online/social media

presence of JUUL™ was studied. The study explored whether adolescents (age < 18 years) follow JUUL™'s official Twitter account and share any of JUUL™'s product advertising and news by re-tweeting JUUL™'s posts to their followers. It was determined that JUUL™'s official Twitter account is indeed being followed and its messages are being re-tweeted through Twitter by adolescents (Chu *et al.* 2018). This report cautioned of a need to implement tough policies and preventive programs to curb adolescent exposure to posted content by JUUL™ and online information exchanges of JUUL™'s products (Chu *et al.* 2018).

In similar studies (Allem *et al.* 2018), harvesting of social media data with the intent of capturing discussions and posts of e-cigarette end-users and their preferences was investigated. This study found that online posts or the topic area of 'Person Tagging' was the most prevalent topic at approximately 20.5%, closely followed at 14.7% by mentions of JUUL™'s refill cartridges or Pods that contain the nicotine and flavored e-liquid, and mentions of purchases of JUUL™'s products at 10.5% (Allem *et al.* 2018). It was noted that any mention of the topic area 'Quit Smoking' was scarce at only 0.29%.

Authors proposed that data from social media might be used to strengthen surveillance activities of emerging vaping products. Indeed, this group reported that public health scientists could study social media data to complement and extend surveillance of public health behaviors and to assist in the identification of newly emerging devices and products (Allem *et al.* 2017). Authors of the study revealed that a major concern was the thumb drive-appearing design of the JUUL™ device, which gives JUUL a discreetness that facilitates its stealthy use and concealment from public scrutiny of JUUL™ in locations that have prohibited public vaping (Allem *et al.* 2018). Since the device resembles a USB flash-drive, users place into a standard USB port of any laptop computer to charge the device or openly conceal it (Chu *et al.* 2018). Moreover, it was pointed out that although JUUL is branded as an alternative to conventional tobacco cigarettes or indeed other e-cigs, users of this device rarely if ever mentioned smoking cessation with JUUL on the social media website Twitter (Allem *et al.* 2018).

Others have also found that e-cigarette manufacturers have actively sought to exceed the initial misleading claims that e-cigs were safer alternatives to traditional combustible cigarettes (Basáñez *et al.* 2018). Manufacturers have done so by relating e-cigs with terms and phrases that one would associate with healthy foods; the net outcome of which, would be to mislead the public to assuming vaping is a healthy behavior (Basáñez *et al.* 2018). This research found that vaping is being marketed in a way that could persuade consumers in believing that e-cigs are health promoting. For example, the study found more tweets (from Twitter) referred to vaping as 'health-enhancing' (nine percent) than tweets that referred to it as a 'smoking-cessation device' (one percent). Moreover, the largest category of tweets referred to vaping as 'harmless' (28 percent), and thus compatible with a healthy lifestyle (Basáñez *et al.* 2018).

Clearly, e-cigarette marketers have practiced misleading advertising, which has set an unhealthy precedent. Since the

original publication of the above reports were published (Allem *et al.* 2018, Basáñez *et al.* 2018), U.S. FDA commissioner Gottlieb's September 2018 announcement (described above) made clear that it would investigate major e-cigarette manufacturers and review their sales and marketing practices. It has since been announced that JUUL™ plans to eliminate some (but by no means all of it) of its social media accounts, including the deletion of its Twitter, Instagram and Facebook accounts, and removal of inappropriate material from third-party social media accounts and thus targeted advertising to minors and adolescents. The key aim was to try and eliminate the discussion of JUUL™ and JUUL™ products on Twitter, and online elsewhere. Since all JUUL™ products contain nicotine, the concern is that minors and adolescents using JUUL™ products are unaware that these devices contain nicotine. JUUL™ has also agreed to cease most (but not all) retail sales of its flavor products as part of a plan to restrict access of the JUUL™ e-cig device to minors in high school and even middle school (Allem *et al.* 2018).

Electronic cigarettes and hazardous waste considerations

An emerging public health concern with regard to vaping and electronic cigarettes is the issue of the health implications of e-cigarette waste, and whether or not such devices should indeed be classified as hazardous waste (Krause and Townsend 2015, Hendlin 2018). A key issue is that new products tend to be introduced in the absence of relevant regulatory guidance and applicable laws. The issue with e-cigs is the challenge of determining an appropriate end-of-life regulatory status. The realization is that there has been a degree of ignorance and poor appreciation of the potentially adverse environmental effects that e-cigs pose (Krause and Townsend 2015, Hendlin 2018). In the case of regular electronic devices purchased for 'home use' by homeowners and tenants, there are manufactured components that are classified as regulated hazardous waste when discarded (Townsend 2011).

The recognized term for home use waste is 'Household Hazardous Waste or HHW', which is often referred to as 'domestic hazardous waste or DHW'. E-cigs that are of the single use disposable type, or even those devices that are discarded due to damage or other functional issues, tend to be discarded as an intact system; however, we are reminded that such devices have multiple components, including a lithium ion or rechargeable battery, an atomizer, other electronic components and an e-liquid chamber or pod containing nicotine (Franck *et al.* 2014, Grana *et al.* 2014, Krause and Townsend 2015). Essentially, others have proposed that e-cigs are similar to other electronic devices like electronic digital watches and medical devices that the European Union classifies as 'waste electrical and electronic equipment (WEEE)' (European Parliament 2012, Krause and Townsend 2015). Thus far, very little data is available in regard e-cigs and other ENDS devices, and concerns with their safe disposal and potential in contributing to the hazardous waste problem.

In one important study of e-cig impacts on waste management systems, the potential of e-cigs to exceed standard regulatory thresholds for hazardous waste when such devices are discarded, was explored (Krause and Townsend 2015). This study employed toxicity hazardous waste determinants, including the U.S. EPA's Toxicity Characteristic Leaching Procedure or TCLP (U.S. EPA 1992) and a separate leaching procedure developed by the state of California, which is referred to as the California Waste Extraction Test (WET; California Code of Regulations 1985) to complete the assessment. A pilot study was completed, wherein 23 disposable e-cigs brands (eight national and regional brands constituting 15 unique products) were investigated by TCLP to screen for heavy metal leaching. In subsequent studies, four e-cig devices were selected for replicate surveys using TCLP and WET analysis of the metal leachates (Krause and Townsend 2015). Lead was quantified at 50 mg/L by WET and 40 mg/L by TCLP, and regulatory thresholds were exceeded in two of the 15 products that were studied.

From this analysis, the study investigators concluded that while some e-cig products would be considered toxicity characteristic (TC) hazardous waste, other products would not. Furthermore, in the U.S. at least, e-cigs containing intact nicotine-supplemented e-liquid tanks or pods are considered commercial chemical products (CPP) and thus a listed hazardous waste (P075). The authors contend that manufacturers and retailers that have accumulated unused or expired e-cigs or other ENDS devices by inference, or even the nicotine-supplemented e-liquid would have to manage these products as hazardous waste at time of disposal. A key reason for this is that in the U.S., unused nicotine contained in discarded CPPs, and unused nicotine-supplemented e-liquid in disposable pods or cartridges as well as the discarded e-cig device itself are regulated as liquid waste (Krause and Townsend 2015). As the authors point out, disposable e-cigs and the disposable e-cig pods or cartridges, are consumed and discarded at a more frequent rate than regular electronic devices, which rapidly establishes these products as an emerging concern for waste managers (Krause and Townsend 2015).

It has been estimated that more than four trillion plastic cellulose acetate cigarette butts are littered annually by those consuming combustible tobacco products (WHO 2017b, Hendlin 2018). This environmental pollution has loaded and stressed sewer and storm water drain systems and polluted open green spaces, parks, and local communities. Further, it has been suggested (though by no means formally demonstrated) that because of their complex material composition of plastics, heavy metals and lithium ion battery, e-cig disposal might potentially pose an even greater environmental pollutant threat than conventional tobacco cigarettes (Hendlin 2018). Placed in context, others have estimated that in 2015, an approximate 58 million e-cigs and e-liquid vaping pods and refill cartridges were purchased in the U.S. This figure did not include sales from vape stores/vape cafes or online purchases over the internet. In addition, more than 19 million of these products and devices were designed as single use, and thus disposable products (Marynak *et al.* 2017).

In the commentary by Hendlin (2018), the case was made that electronic waste (e-waste) already presents to society an

overwhelming issue, with an estimated 99 billion pounds of e-waste disposed of each year and mostly transported to developing countries for reprocessing or incineration, according to global e-waste monitoring efforts (Balde *et al.* 2017). As was pointed out (Hendlin 2018), it is important to realize that a strategy of shipping significant quantities of waste from Western industrialized countries to developing countries, does not necessarily eliminate the challenge of e-waste by displacing the hazard and the associated pollutants and risk to the environment from incineration or reprocessing and reclaiming activities.

Although the disposal of e-cig and other ENDS devices is not formally tracked, anecdotal reports and available information suggest that disposed e-cig refill pods and capsules are often littered (Hendlin 2018). A major concern is the potential for heavy metals, battery acid and nicotine residues to leach or leak from carelessly discarded and damaged devices or refill cartridges, and thus pose an environmental health risk (biohazard) to human populations and wildlife (Krause and Townsend 2015, WHO 2017a,2017b, Hendlin 2018). In the context of wildlife species, there is growing concern that damaged e-cig components and e-liquid pods might be consumed by infants and present a choking hazard, or consumed by birds or small mammals exposing them to the hazards of e-cig waste including acidic components with a capacity to inflict burns, and puncture or explosion hazards (Krause and Townsend 2015).

Thus, e-cigarettes and other ENDS devices are an inherently complex mixture of chemicals, plastics and electronic hazards, and should be regarded as both e-waste and bio-hazardous waste. As yet, there is no clear guidance, written policy or product instructions on the appropriate and correct disposal of e-cigs and other ENDS devices (Hendlin 2018).

Knowledge gaps, data interpretation, conclusions and recommendations

Knowledge gaps and data interpretation

To date, evaluations of e-cig components have not found serious health effects, but findings must be interpreted with caution due to limited data and a lack of standardized testing methods. Furthermore, the research field on the toxicology and human health effects of e-cigs is challenging at best, and the literature is extensive and diffusely concentrated. Furthermore, no feasible laboratory animal model exists for assessing the adverse effects from subchronic or chronic inhalation exposure to vaping fumes, and aerosols. A major concern is that knowledge gaps remain in understanding or appreciating human health effects due to the relative infancy of both the research field and the e-cig devices. In addition, major flaws identified in the current literature both hamper data interpretation and raise additional questions.

First, the currently published studies apply only to the specific brand, model and batch of the e-cig device studied. There is uncertainty as to whether the findings from these studies will apply to future brands or to the growing realization that users can manually tune or customize the many supplementary and additive e-liquid ingredients. Further, e-

cig devices are continuously being modified; over 500 e-cig brands are now available and in excess of over 15,000 flavors. Second, the topography of e-cig use (i.e., the duration of the puff, the puff volume, and the average flow delivered by the e-cig device to the user) is markedly different between conventional cigarettes and e-cigs (Hua *et al.* 2013a, Behar *et al.* 2015). This means that when e-cig users vape, they puff or 'draw in' harder on the device; the puff duration is approximately twice that of a conventional cigarette, especially if the fluid or e-liquid content in the cartomizer (cart-ridge atomizer) or tank is low (Hua *et al.* 2013b). Third, most if not all of the human studies surveyed were based on very short-term puff exposures where vaping of the e-cig occurred for just a few minutes, a process that does not reflect real-world exposures to these devices.

Thus, it is likely that these studies have underestimated the actual uptake of harmful substances when e-cig-naïve users were tested. In addition, it was previously shown that 1) significant variation was found in puff topography among users of various e-cig devices (Farsalinos *et al.* 2013a), 2) both the battery voltage output (Kosmider *et al.* 2014), and low e-liquid levels in the cartomizer or tank (Hutzler *et al.* 2014) can influence the production of harmful substances that are subsequently inhaled by the e-cig user, and 3) the pH of the e-liquid might also influence the dose of nicotine delivered to users (Stepanov and Fujioka 2015). Such variables complicate research studies and warrant further investigation.

As discussed above, a marked concern is poor appreciation of the potential health effects of the components that are found in e-cigs but not in conventional cigarettes. For example, glycols (propylene glycol and glycerin) are major components of e-cigs. An internal technical report that was specifically commissioned by users and vendors of e-cigs concluded that the estimated exposure levels to glycols approached threshold-limit values. This conclusion raised concerns that the threshold limit values were derived from uncertainty rather than formal knowledge (Burstyn 2013, Pissinger and Dossing 2014). This issue is made more complex by a poor understanding of the consequences of e-cig users' switching among different e-cig brands and devices. This habit exposes the e-cig user to a myriad of more complex exposures, unlike those of conventional cigarette users, who tend to remain brand loyal. Furthermore, there are likely health effects from exposure to glycol and other contaminants or toxicants found in the various brands of e-cigs, as discussed above. Although many of these identified substances were detected at very low concentrations, e-cig use remains an intense and chronic process from a device that is highly efficient at delivering nicotine and other toxicants/contaminants to the lungs of the e-cig user.

Finally, there is an under-appreciated risk from carelessly disposing of electronic cigarettes, and the components that constitute an e-cig device. It is increasingly recognized that carelessly discarded e-cigs have the potential to impose an associated environmental burden on society (see Krause and Townsend 2015, Hendlin 2018). Efforts are underway to better understand the relative environmental impact of non-ideal e-cig disposal; some efforts have attempted to quantify the impact of littered replacement pods (Hendlin 2018). In addition,

the potential adverse effects of e-cigs on the environment is recognized as a major challenge by tobacco companies, in part due to an increasing appreciation that electronic components and batteries in e-cig devices pose a potential threat, including the risk of serious burn injuries (Hendlin 2018, Philip Morris International 2017, Wang *et al.* 2020).

Remaining research questions

Many methodological, population-specific and modulating factors influence the use and function of e-cigs and the approaches that could be adopted to advance understanding of their effects. In the literature, there is a paucity of data aligned to the comparative toxicology and health effects of the various designs and types of e-cigs. This is alarming given the clear availability of e-cigs over the Internet, at convenience and local stores, and elsewhere. The paucity of research data has as much to do with regulatory ignorance of the scope of the problem as it has to do with the relatively recent appearance (less than 10 years) of these devices in the marketplace.

Public and science policy issues are among the key areas that public health agencies, academics and regulatory agencies are exploring, including consensus agreement on what defines the class of devices currently available, as well as the appropriate terminology. For example, how should the various types of e-cigs be classified, and what terms should be used when surveying consumer use of devices that include the 'cig-a-like,' 'tank,' 'mods,' 'e-hookah' or 'hookah pen' and JUUL™ or T-vapor? Similarly, how should laboratory-based sciences adopt existing methods, develop new ones, and standardize them for determining the effects of e-cigs on health? More details are required of the chemical components and contaminants of the many available e-cig devices. Specific questions include how aerosols should be generated and standardized, and how machine-determined exposures should be designed so that they mimic human behavior. More detailed population-based studies are required, including clinical trial-based studies for smoking cessation applications, detailed outcome measures, and specific outcomes (e.g., cardiopulmonary function; acute versus chronic inflammation; and health effects studies).

Detailed consideration should also be given to how population-based and behavioral science issues impact e-cig use and dependency. Population studies should explore e-cig use and susceptibility to any observed health or behavioral effects. This should include studies aimed at exploring how age; gender; race and ethnicity; pregnancy; and vulnerable population factors, such as low socio-economic status, impact e-cig use and dependency and the presence of co-morbid mental stress disorders and illness. Also, we do not know how a history of e-cig use impacts smoking behavior among naïve/never-smokers, experienced e-cig users, and former tobacco smokers who use e-cigs. Clearly agreed-upon measurement standards are needed for both basic and behavioral/social science studies.

There is also a lack of consensus on the most appropriate basic research needs that would incorporate defining

measurement standards of e-cig emissions and establishing how best to measure the effects of e-cigs in relevant animal models. There is a lack of quality data regarding product design similarities and differences, constituents, and the capacity for abuse and modification of e-cigs by their user, all of which might impact subsequent health risks and outcomes, addiction risk, and sensory appeal.

The National Institutes of Health (NIH) recognizes that clinical studies with e-cigs are urgently needed but are severely restricted by the paucity of device standardization, the rapid evolution of e-cig design and its constituents, and the capacity for e-cig users to abuse the intended purpose of the device. Moreover, many clinical studies must be centrally registered and cannot be initiated without an investigational new drug (IND) application having been filed with the FDA for any particular e-cig device. This process is further complicated because IND approval requires detailed product data and manufacturing documentation that are not currently available. As mentioned, for clinical trials to be effective, investigators need a standardized and well-characterized e-cig that is not currently available. All of these issues and knowledge gaps are clear priorities that would facilitate new research on the health effects and risks of e-cig use, particularly in advancing understanding of the short- and long-term effects of e-cigs on human physiology and behavior (Walton *et al.* 2015).

Key recommendations

Given the brief history of e-cig use in the U.S. population in general, adverse health outcomes might not manifest for several more years to come. There is an opportunity for e-cig products to cause harm under conditions of sustained or chronic use. Thus, it is recommended that e-cig and other ENDS devices be considered unsafe using a precautionary approach, in the absence of as yet, formal regulation of the various electronic devices that continue to be made available to the public and U.S. Service personnel. Continued and sustained awareness of the potential health effects and hazards of e-cig use is strongly urged.

In the absence of a structured and evidence-based awareness of potential harm, health professionals, public health decision makers and federal regulatory agencies have a duty to exercise the highest level of precaution and responsibility to the public to pursue due diligence in protecting human health and to sustain combat readiness of the U.S. Army's Soldiers and Civilian personnel. Additionally, in the absence of established guidelines, policies, and regulations on the use of e-cigs, a high degree of uncertainty exists regarding subsequent health effects and possible chronic health outcomes from sustained, long-term e-cig use. Considerable uncertainty prevails regarding the safety of e-cigs and their intended use as devices designed to help individuals quit smoking.

Indeed, a relatively recent position statement of the forum of International Respiratory Societies (Schraufnagel *et al.* 2014) stated that 'the health and safety claims regarding electronic nicotine delivery devices (ENDS) should be subject to evidentiary review.' Moreover, the potential benefits of e-

cigs to an individual smoker have to be balanced against their potential for harm not only to the smoker but also to the individuals, particularly young children, in his or her vicinity. The position of this forum further stated that as a precaution, e-cigs should be restricted or even banned from public sale until reliable safety data are available, and that under conditions where e-cigs are permitted, they should be closely regulated as medicines or tobacco-related products (Schraufnagel *et al.* 2014).

Attempts should also be made to identify the most important constituents of e-cigs that impact human health (e.g., nicotine, pyrazines, monoamine oxidase inhibitors, propylene glycol, glycerol, heavy and transition and heavy metal particles), including flavorants and impurities in the liquids and aerosolized emissions. Similarly designed sub-chronic and chronic clinical toxicity studies of inhalation exposure to constituents of the e-cig aerosol and defined toxicological end-points are also lacking. The key driver to this concern is that many constituents of the aerosolized e-liquid aerosol in e-cig products are regulated only for ingestion (e.g., the flavorants that are regulated and approved as food additives), and are not regulated or toxicologically assessed for inhalational exposures.

Given the relative infancy of the habitual behavior of e-cig use among adults and adolescents, it is recommended that population-based epidemiological cohort studies be conducted to assess the relative risk of developing chronic non-communicable diseases (e.g., asthma, COPD, inflammatory airways disease, and certain cancers) associated with e-cig use in populations of interest (e.g., nonsmokers who currently vape e-cigs, former tobacco product smokers who currently vape e-cigs, and current smokers of both e-cigs and conventional cigarettes).

Awareness of the potential health effects from e-cig use must be increased. In the absence of characterizations of the chemical compounds formulated for e-cig use, increased awareness of the potential health effects and hazards of e-cig use is urged.

Considerable data gaps exist in controlled sub-chronic and chronic toxicity analyses of the various chemical formulations found in e-cigs or the types of e-cig products currently in use. It is recommended that detailed *In vitro* toxicological studies and *In vivo* animal exposure studies be pursued in an attempt to reveal biomarkers of pulmonary or cardiovascular conditions, cancer, and fetal toxicity to determine potential acute and chronic exposure effects of e-cigs. Similarly designed sub-chronic and chronic clinical toxicity studies of inhalation exposure to constituents of the e-cig aerosol and defined toxicological end-points are also lacking.

The socially acceptable phenomenon of e-cig 'vaping' might also degrade the device's intended benefit of satisfying a conventional tobacco smoker's nicotine cravings toward satisfying the e-cig user's need for psychoactive drugs (e.g., tetrahydrocannabinol or THC). This concern is highly relevant to young people, and is a critically important concern in sustaining operational readiness and performance of U.S. Service personnel. Given the relative infancy of the habitual behavior of e-cig use among adults and adolescents, it is recommended that population-based epidemiological studies be

conducted to assess the relative risk of developing chronic non-communicable diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), inflammatory airways disease, and certain cancers) from e-cig use in populations of interest.

Key research gaps exist in describing the thorough testing of the design and constituents of the many varieties of e-cig currently available, including indicators of health risk, addiction and sensory appeal when using e-cigs, and the behaviors of use by current, former and never-smokers. Limitations have been identified for existing toxicological animal model data that reveal relevant pulmonary, cardiac, cancer, and fetal toxicity biomarkers aimed at determining acute and chronic exposure effects of e-cigs. Limitations have also been found in identifying the most important constituents of e-cigs that could impact human health (e.g., nicotine, pyrazines, monoamine oxidase inhibitors, propylene glycol, glycerol, etc.), including flavorants and impurities in the liquids and aerosols. In addition, considerable data gaps exist in characterizing e-liquid formulations and aerosols. Although the hydrocarbon content of e-cigs is measurably and considerably lower than that of their conventional cigarette counterparts, the long-term health effects of e-cig use is unknown.

The liquid and aerosolized components of e-cigs or other ENDS have the potential to deliver a complex mixture of respirable organic, inorganic and particulate toxicants to habitual users of these devices. Among these toxicants are particulate matter, heavy and transition metals, flavorants that are neither regulated nor intended for respirable exposure, tobacco-specific nitrosamines, and carbonyl and volatile organic compounds including formaldehyde and benzaldehyde. However, the weight of an accumulating body of experimental and clinical evidence clearly indicates that e-cig use has not been shown to be either safe relative to conventional tobacco cigarette smoking or without unacceptable risks to human health. Moreover, recent research and observational evidence since 2013 suggests genuine concerns, and a need for immediate regulation, to include standardization and guidance on the appropriate use of potentially dangerous nicotine-delivering devices.

Conclusions

Electronic cigarettes, have gained significant global popularity and across all demographics or age groups as an alternative to smoking combustible tobacco. E-cigs are being marketed to be particularly appealing to minors, adolescents and young adults, in part through engaging advertising and carefully targeted marketing efforts. Although often marketed as a safe aid to smoking cessation, there is no evidence that e-cigs or other ENDS devices are an effective tool to quit smoking. The health consequences of conventional tobacco products are well known, including increased healthcare visits and higher likelihood of injury in Service Members; however, the health effects of ENDS are still emerging.

In a very short time, e-cigs and ENDS have established themselves as ever increasingly popular devices among teenagers and young adults, and as an alternative to conventional smoking of combustible tobacco products. Although

often marketed as an aid to smoking cessation, research evidence has not demonstrated a positive impact on decreased tobacco consumption or abstinence, or established e-cigs as safe – there is currently no data supporting or formally demonstrating the safety of e-cig use. Although e-cigs are oftentimes stated by advertisers, and indeed even in the peer-reviewed literature, as being relatively ‘safer’ (but certainly not safe) than combustible tobacco cigarettes, what does ‘safer’ actually mean in the context of human health, when the device and its contents are quite clearly unsafe?

While the health consequences of conventional tobacco products are well established, including increased health care visits and higher likelihood of injury in Service Members, the potential health effects of using ENDS are only beginning to emerge, and will likely remain largely unknown for several more years to come. Despite many peer-reviewed and published scientific papers, an effort aimed at defining an ‘evidence-based risk profile’ for e-cig use remains challenging at best. In addition, many of the studies summarized in this report were derived from authors and/or institutions/entities with clear conflicts of interest, some of which, were funded primarily by the big tobacco companies or e-cig device manufacturers. Moreover, the harm reduction strategy of e-cig use is fundamentally flawed. While there might be potential benefits to smokers reluctant to cease smoking conventional combustible tobacco cigarettes, it is concluded that ex- and never-smokers are susceptible populations that are at increased risk should they elect to use e-cigs, particularly minors, adolescents and young adults (Schraufnagel 2015) that are targeted by advertising and marketing strategies.

However, we are aware that hazardous chemicals are indeed found to be incidentally formed from e-cig device use. For example, formaldehyde is generated by the oxidation of the humectants glycerol/glycol when the e-liquid contacts the heated wire coils of the e-cig. Exposure studies are urgently warranted because many of the ENDS devices available on the market are heterogeneous in their design and capabilities, empowering the end-user with the ability to customize the applied battery voltage and thus heat generated, the puff rate and topography, and the type of e-liquid that is vaped. Such variables can impact exposure duration, concentration, and effective dose to toxicants like formaldehyde that the end-user is exposed to every time they are used. Thus, the long-term or chronic health effects from sustained and repetitive use of e-cigs is unknown.

The nicotine dose delivered by vaping e-cigs and ENDS, and a plethora of other chemical components and contaminants to which e-cig users will be exposed, varies markedly among the devices. Consequently, there is no typical or standard e-cig or ENDS. It is recognized that there are concerns with regard the general safety of e-cigs and their suspected effects on human health and well-being. Additionally, there have been increasing reports of accidental or intentional poisoning and attempts at suicide by ingestion of nicotine-containing liquid solutions intended for recharging non-disposable tank-style e-cigs.

It is remarkable that the manufacture and aggressive sales and marketing of a product with unknown chronic or long-term health effects is permitted in the absence of

standardized quality control, descriptive or informative labeling, and adequate public health regulation. However, in relatively recent developments, the FDA extended their definition of tobacco products to include ENDS, applying existing tobacco regulations to the sale, distribution, marketing, and advertising of these products. DOD Policy Memorandum 16–001, Tobacco Policy, 8 APR 2016; AR 600–63, Health Promotion and Wellness; and MEDCOM OPORD 15–48, Tobacco Free Living, have collectively established that ENDS will be treated as tobacco products and covered by tobacco-related policy.

Recent studies of the chemical components in e-cigs and other ENDS devices found combinations of carbonyl compounds, formaldehyde, heavy and transition metals, fine and ultrafine (or nanoparticulate) particulate matter, and volatile organic compounds (VOCs), among other chemical components or customized supplementation of the e-liquid. Although the major associated health concern is delivery of addictive and potentially toxic levels of nicotine, long-term adverse effects remain unknown.

There are also concerns about the potential health risks of second- and third-hand exposure to exhaled aerosols and settling of particles in the dust found on furniture, carpeting, flat surfaces and personal clothing and hair, potentially adversely impacting indoor air quality. Clear potential also exists for users to abuse vaping devices to consume cannabis and other psychoactive drugs, and to potentially do so undetected. Another growing concern is that current marketing strategies also specifically target Service Members, in addition to the known advertising and marketing strategies that make e-cig and ENDS devices appealing to minors and adolescents by virtue of the names and colors of the flavorant supplements present in the e-liquid formulations. Emergent evidence indicates the possibility that e-cig users could develop adverse pulmonary diseases following respiratory exposure to e-cig liquid flavorants.

In the context of the wider environmental concern with regard e-cig disposal and littering, there is an emerging appreciation that metals and other e-cig components could leach from these battery-operated and electronic devices. By doing so, ENDS devices could endanger the well-being of children that might choke on the debris or e-liquid pods derived from these devices. In addition, carelessly littered e-cigs and e-liquid refillable capsules might also present a risk to many wildlife species including birds and small mammals that forage through foliage and grassy areas of parks, open spaces and landscaped neighborhoods, and thus inadvertently consume components of these devices with undesirable consequences to their health.

Although it is generally recognized that e-cigs are touted as a smoking cessation aid, and are marketed as such in the absence of any systematic phased clinical trials of the efficacy and potential toxicity of new products, this prevailing situation is somewhat contrary to the conventional process applied to the clinical testing, marketing and sale of a therapeutic intervention designed for human intervention or treatment. Further, there are genuine public health concerns regarding the safety and validity of e-cigs as clinically-useful or recreationally acceptable devices. In addition, e-cig use is

often not employed to help smokers quit conventional tobacco cigarettes but is instead abused in a practice commonly referred to as ‘stealth vaping.’ The practice of stealth vaping is to avoid smoking bans associated with traditional cigarettes and to customize devices in such a way that vaping can occur without being easily detected.

It is concluded that given the complexity and user customizable options of e-cigs, the regulatory and scientific communities need to pursue detailed and rational studies to address three main concerns with regard to the current public health impacts of continued e-cig marketing and use: 1) in carefully controlled studies, determine the degree of toxicity and potential for harm of the chemicals and compounds found in the array of e-cig devices; 2) determine how widespread e-cig use actually is; and 3) identify the populations at risk of e-cig health effects once those health effects have been identified.

It is further concluded that clear potential exists for e-cig abuse to impact Military readiness and resilience. For example, liquid and aerosolized e-cig components deliver respirable toxicant mixtures to users, including organic, inorganic and particulate toxicants; flavorants that are clearly not regulated or intended for respirable exposure, and tobacco-specific nitrosamines and carbonyl and volatile organic compounds. In response, we suggest that U.S. Army policy must strive to continuously evolve and maintain a posture of continued surveillance of new devices and products with the intention of being ready and able to address known hazards of combustible tobacco use and new challenges that are presented by the use and misuse of e-cigs and other more complex and increasingly sophisticated and ‘stealthy’ ENDS.

Many opportunities exist to mitigate the impact on individual health and force readiness by extending current restrictions on combustible tobacco use, including expansion of tobacco-free campuses, applying current restrictions in Initial Military Training to Advanced Individual Training, and prohibiting the use of tobacco or ENDS products by all Soldiers while in uniform.

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