10-19-2014

White Paper: Electronic Cigarettes in the Indoor Environment

Cheryl L. Marcham
University of Oklahoma Heal, march617@erau.edu

et al.

White Paper: Electronic Cigarettes in the Indoor Environment

American Industrial Hygiene Association®

Protecting Worker Health

October 19, 2014

Sponsored by the AIHA®
Indoor Environmental Quality Committee and
Risk Assessment Committee

American Industrial Hygiene Association 3141 Fairview Park Drive, Suite 777, Falls Church, VA 22042 USA
main +1 703-849-8888 *fax* +1 703-207-3561

TABLE OF CONTENTS PAGE

Executive Summary

Electronic-cigarettes (e-cigarettes) are battery-powered devices of many different configurations that deliver vaporized nicotine and other chemicals or flavorings to users, but that do not contain tobacco or require combustion. E-cigarettes have an internal, rechargeable, battery-operated heat source that converts liquid nicotine and/or flavorings into a mist or vapor that the user inhales. These devices are frequently promoted as a healthier or safer alternative to traditional cigarettes for users and bystanders. Consequently, there has been growing interest among manufacturers and others to allow e-cigarettes to be used indoors and in other settings where traditional cigarettes have previously been banned. There has, however, been conflicting and at times confusing information presented to the public regarding the public health risks and benefits associated with e-cigarettes. This white paper attempts to present the best available science on the subject today.

The use of e-cigarettes (or "vaping") has seen an unprecedented increase worldwide. Vaping has been promoted as a beneficial smoking cessation tool and/or an alternative nicotine delivery device that contains no combustion byproducts. However, nicotine is highly addictive. Furthermore, available research indicates that vaping solutions and their emissions may contain much more than just nicotine, including aerosolized flavorings, propylene glycol, and other intentional and unintentional contaminants. These ingredients could present an as-yet undefined health hazard to both users and bystanders.

Whereas e-cigarette use and exposure may lower some or most risks associated with conventional cigarette use, the health effects of nicotine and aerosol exposures from e-cigarettes are not well-understood at this time. Current research indicates that vaping aerosols are not without risk, especially for nearby persons in areas with limited ventilation and persons with compromised health conditions. Limited published studies that evaluated the potential hazardous effects of the natural and/or synthetic chemicals used in e-cigarettes indicate that there are potential health effects reported for both users and those exposed secondhand.

Multiple scientific reports express the need for more research. There are several key data gaps and areas of uncertainty that hinder a more quantitative assessment of health risks related to e-cigarettes at this time. These include:

- Quality control of these products is lacking for both product constituents and labeling.
- Laboratory studies may not reflect actual exposures during use because of the variability in types of devices, user vaping habits and duration, and because many users mix their own vaping solutions.
- There is limited data on chemical emissions/thermal degradation products/exposures (especially among bystanders and in confined indoor settings).
- There is little information on the dynamics of pre and post respiration aerosols and their fate in the environment.
- There is limited information on dose-response relationships for many constituents, such as short- or long-term health effects associated with low-level exposures, including those for vulnerable populations.
- There is little or no information about the health effects of flavorings that are inhaled rather than ingested.
- There is little information about the synergistic effects from e-cigarette contents and other environmental contaminants.

Note that these issues are related only to an assessment of human health risks. They do not incorporate other potentially important factors, such as public risk perceptions, risk management options/control measures (e.g., ventilation), and nicotine dependence. In addition, serious safety issues have been reported and need to be addressed, including child safety and poisonings, battery explosions, and the potential for the vapor to set off smoke alarms.

Given this review of available information, the existing research does not appear to warrant the conclusion that e-cigarettes are “safe” in absolute terms. Although they may provide a “safer” alternative to tobacco cigarettes for the user, these products emit airborne contaminants that may be inhaled by both the user and those in the vicinity of vaping. Many of the data sources reviewed confirm that e-cigarettes are not emission-free and that their pollutants could be of health concern for users and those who are exposed secondhand. Clearly, e-cigarettes lack the combustion products produced by smoking tobacco, many of which are associated with cancer development. Although nicotine may not cause cancer, it is associated with other adverse physiological effects. In addition, the other components in e-cigarettes may not be without risk, particularly when they are inhaled rather than ingested. Therefore, e-cigarettes should be considered a source of volatile organic compounds (VOCs) and particulates in the indoor environment that have not been thoroughly characterized or evaluated for safety.

The Food & Drug Administration (FDA) currently regulates only e-cigarettes that are marketed for therapeutic purposes. However, the FDA has proposed a rule extending its tobacco product authorities to include other products like e-cigarettes and the World Health Organization (WHO) has recommended that consumers be strongly advised not to use electronic nicotine delivery systems, including e-cigarettes, until they are deemed safe and effective and of acceptable quality by a competent national regulatory body. Although several agencies and organizations have adopted restrictions on the use of e-cigarettes in public places, there is currently no U.S. federal law or regulation that explicitly bans the use of e-cigarettes on airplanes, railroads, buses, or other modes of transportation.

Because of concerns about primary and secondary exposure to e-cigarette vapors and liquids (also called “e-juices”), AIHA supports risk-based regulation of e-cigarettes using reliable safety, health, and emissions data. Four areas of risk based regulation relating to the safety of primary users and people exposed to secondhand vapors or e-juices should be considered:

1. Physical/Electrical Hazards - All e-cigarette devices, whether they are being used for therapeutic or recreational purposes, should be evaluated for potential physical and/or electrical hazards by applicable regulatory agencies.
2. Accidental Exposure - The health risks and economic consequences of accidental exposure to e-juice liquids by children, adults, and pets should be addressed, including proper labeling and child-resistant packaging requirements.
3. New Product/New Chemical Use - All future e-juice components that may be used by consumers should be fully evaluated for any potential hazards (e.g., toxicity, flammability, safety hazards, and secondary exposures) prior to introduction into the marketplace.
4. Relationship to Current Smoking Bans - Because e-cigarettes are a potential source of pollutants (such as airborne nicotine, flavorings, and thermal degradation products), their use in the indoor environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants.

Introduction

E-cigarettes are battery-powered devices of many different configurations that deliver vaporized nicotine and other chemicals or flavorings to users but that do not contain tobacco or require combustion. E-cigarettes are the most common type of electronic nicotine delivery systems (ENDS). Originally patented in 1963 as a smokeless, nontobacco cigarette,[1] these devices may also be referred to as e-cig, electronic vaping device, personal vaporizer (PV), electronic hookah, and e-hookah. Because no smoke is generated, e-cigarettes are frequently promoted as a healthier or safer alternative to traditional cigarettes for users and bystanders.[2] Consequently, there has been growing interest among manufacturers and others to allow e-cigarettes to be used indoors and in other settings where traditional cigarettes have previously been banned.

There has, however, been conflicting and at times confusing information presented to the public regarding the public health risks and benefits associated with e-cigarettes. For example, the Consumer Advocates for Smoke-free Alternatives Association (CASAA), the leading consumer advocacy group promoting the availability and use of low-risk alternatives to smoking, has reported that e-cigarettes pose no health concerns and yield a significant risk reduction compared to regular cigarettes.[2,3] On the other hand, several studies suggest that e-cigarettes may cause a variety of short- or long-term health effects, such as increased airway resistance in the lungs.[4,5,6] The Food and Drug Administration (FDA), a federal agency responsible for protecting and promoting public health in the United States, has concluded that the safety and efficacy of e-cigarettes are largely unknown and have not been fully studied.[7] Similarly, the World Health Organization (WHO) has concluded that the safety and efficacy of these products has not been scientifically demonstrated and their potential health risks remain undetermined.[8] The American Lung Association has also issued a statement expressing its concern about the potential safety and health consequences of e-cigarettes.[9]

Poison control centers have recently warned of an increased rate of poisonings, especially in children, from the nicotine-containing multi-flavored e-liquids (also called “e-juices”) that are used to charge e-cigarettes.[10] The use of commercially available flavors of e-liquids that imitate common food, candy, and liquor flavorings parallels a trend reported in 2007 of the marketing and use of flavored tobacco products as a gateway for children and young adults to become regular cigarette smokers.[11] Due to the lack of regulations on vaping, there is currently no standard message or warning statement on e-cigarette supplies that indicates their potential danger to the public, especially children. Flavorings and other e-juice additives that may be acceptable for ingestion are now being inhaled without a clear toxicological understanding of the potential health effects from a different route of entry.

Although the literature reviewed for this report in most cases supports findings that e-cigarettes are likely to be much less harmful than tobacco smoking, many questions remain regarding the potential human health risks posed by the use of e-cigarettes indoors, especially among bystanders from secondhand and thirdhand exposures. The purpose of this white paper is to provide a critical and objective review of the available literature on what is currently known and not known with respect to public exposures and health risks from e-cigarettes. A key outcome of this review is the identification of key data gaps and areas of uncertainty that hinder a more quantitative assessment of health risk. Recommendations for additional research are also provided.

The aim of this white paper is to present a review of the available scientific evidence-based literature concerning potential exposures and risks from the use of e-cigarettes, particularly for persons (especially bystanders) in the indoor environment. As part of this effort, AIHA has undertaken a search of current and recent past literature using various publication sources (e.g., PubMed). Additionally, to capture the rapidly changing landscape of information on e-cigarettes, we have incorporated Internet sources in an attempt to find original research and newly published information regarding the health aspects and regulation of e-cigarettes and the chemical components used therein. Because of the rapidly changing nature of events and science with respect to e-cigarettes, this white paper presents what is known versus not known at the time of publication.

How E-cigarettes Work

Early e-cigarettes (first generation) were designed to look like conventional cigarettes. However, e-cigarettes do not contain tobacco or require a flame to extract the nicotine from the cigarette. Instead, e-cigarettes have an internal, rechargeable, battery-operated heat source that converts liquid nicotine and flavorings into a mist or vapor that the user inhales. The inhalation of vapors from e-cigarettes is commonly called “vaping” instead of “smoking.”

Figure 1: Disposable electronic cigarette resembling a traditional cigarette.

While some e-cigarettes are designed to be totally disposable (see Figure 1), most other e-cigarettes contain a rechargeable lithium battery, vaporization chamber, wicking system, and nicotine/flavoring cartridge. The cartridge containing nicotine liquid is first attached to the vaporization chamber, which contains an atomizer and/or heating coil. When the user inhales (from the mouthpiece at the tip of the cartridge), the atomizer is activated and the heating coil begins to vaporize the liquid. The liquid, in turn, wicks more liquid from the cartridge to the atomizer. The vaporized liquid cools and condenses into a fine aerosol (called vapor), which is inhaled, delivering nicotine, diluents, and flavoring(s) to the respiratory tract.

Some first-generation e-cigarettes have a light-up tip that glows when the user inhales to either simulate a flame and/or to indicate that there is still charge on the attached battery. Second- and third-generation devices have moved away from looking like tobacco cigarettes (see Figures 2 and 3). These devices have larger batteries and larger e-fluid reservoirs than first-generation e-cigarettes and often have variable voltage (vv) or variable wattage (vw) batteries that allow the user to increase or decrease power to the atomizer. Some devices have a variable airflow option as well: adjusting the battery voltage or the inhalation air flow can greatly affect the amount of vapor generated with each puff. After inhalation, the user exhales a portion of the vapor.

Figure 2: Second-generation e-cigarettes.

Figure 3: Examples of other kinds of e-cigarettes. By Izord (Own work) [CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia.

Constituents of E-cigarettes: Emissions, Exposures, and Health Risks

Manufactured prepackaged cartridges can be purchased with varying concentrations of nicotine ranging between 0 and 24 milligrams (mg) of nicotine per cartridge.[12] Nicotine levels, however, have been found to be inconsistent due to poor quality control.[12] Flavorings are also frequently added to the liquid, with a variety of flavors available (e.g., tobacco, menthol, mint, chocolate, coffee, apple, cherry, and caramel). Occasionally, e-cigarettes have been advertised as containing other drugs, such as tadalifil (a drug used for erectile dysfunction) and rimonabant (a weight-loss aid).[13] Propylene glycol (PG) and vegetable glycerin are the main components used in e-liquids as the delivery vehicle and diluent for the nicotine and flavorings, and to synthesize the tactile sense of smoke (i.e., “vapor”) when the user exhales.[13,14,15]

Many of the toxic and carcinogenic agents in tobacco cigarette smoke are combustion byproducts, including nitrosamines, VOCs, polycyclic aromatic hydrocarbons (PAHs), and carbon monoxide. Because e-cigarettes do not have a combustion source, the health risks of vaping are believed to be greatly reduced compared with traditional cigarette smoking. However, many potentially toxic compounds are still present in the liquid or vapor components of e-cigarettes.[14,16] The primary components of electronic cigarette cartridges are propylene glycol, glycerin, and nicotine.[16] E-cigarettes also contain flavoring agents and other compounds, and the use of e-cigarettes has been shown to emit aerosols and VOCs, including nicotine, diethylene glycol, nitrosamines, 1,2-propanediol, acetic acid, acetone, isoprene, formaldehyde, acetaldehyde, propaldehyde, and flavoring compounds into indoor air.[7,15,17,18] Additionally, aerosols generated from e-cigarette consumption may contain various metals and silica particles from wick and heating coil constituents.[19] The following sections summarize what is currently known and unknown about public exposures and health risks from the constituents in e-cigarettes.

Nicotine

Nicotine is present in most e-cigarettes and e-liquids. However, advertising and labels for these products can often be inaccurate regarding their nicotine content.[3] In fact, the FDA reported that the analysis of many electronic cigarette cartridges that were labeled as containing no nicotine did, in fact, contain detectable levels of nicotine.[20] Three different cigarette cartridges that displayed the same label produced varying amounts of nicotine with each puff.[21] A French study evaluated the nicotine content and labeling of e-cigarettes and found incomplete or unusable information as well as unreliable labeling.[22] The amounts of nicotine measured in 20 prepackaged cartridge samples were generally higher than was stated on the package and, in some cases, the nicotine content was found to be two to five times greater.[22]

A review of a number of products purchased online revealed a lack of consistent labeling format and unclear information regarding nicotine content.[23] In one study, nicotine amounts in 9 out of 20 analyzed cartridges differed by more than 20 percent from the values declared by their manufacturers.[24] Several studies found that cartridges labeled as containing nicotine did not contain any nicotine, while other cartridges labeled as non-nicotine-containing did, in fact, contain nicotine.[10,15,24] Two studies discovered that, in many cases, nicotine degradation products and other impurities can be found in refill liquids, such as nicotine-cis-N-oxide, nicotine-trans-N-oxide, myosmine, anabasine, and anatabine, speculated to be from oxidative degradation of nicotine occurring either during the manufacturing of the ingredient or during the manufacturing of the final liquids, or from an unstable formulation[10,25], although the impurities were reported to be “below the level where they would be likely to cause harm.”[25] Goniewicz et al. found that in addition to the lack of quality control in content and concentration, some products are inconsistent in delivering nicotine.[24] In other words, some products may deliver different levels of nicotine to their users each time they are used even if they use cartridges that contain the same nicotine content.[24] In addition, because of this inconsistency in nicotine delivery, or because of the perception that e-cigarettes are “safer” than traditional cigarettes, users may consume e-cigarettes at a greater rate than traditional cigarettes and, therefore, generate greater amounts of secondhand contaminants. Therefore, user behavior and overall quality control of the e-liquids and of the e-cigarette devices may be in question when attempting to evaluate dosing and user responses.

The health effects of exposure to nicotine are well-documented. The effects of short-term (less than eight hour) exposures to nicotine at low concentrations are reported to include tremors and an increase in heart rate, respiratory rate, blood pressure, and level of alertness. Ocular exposure can cause irritation and redness of the eyes.[26] Ingestion or inhalation of nicotine can cause nausea, vomiting, abdominal pain, headache, dizziness, confusion, agitation, restlessness, and possible burning sensation in the mouth, throat, and stomach.[26] Nicotine is a teratogen,[26] can promote tumor growth[27,28], and has caused abnormalities in the offspring of laboratory animals.[29] In addition, the National Institute on Drug Abuse states that nicotine is highly addictive.[30] Addiction to nicotine can occur within days of inhaling one's first conventional cigarette.[31] Nicotine increases heart rate, myocardial contractility, and blood pressure.[32]

Nicotine exposure during pregnancy can potentially cause effects to the unborn child. According to the Centers for Disease Control and Prevention, nicotine is a teratogen.[26] Prenatal exposure to nicotine in animal studies with doses as low as 0.5 mg/kg/day have shown learning and attention deficits in performance in both young and adult rats.[33] Nicotine has also been demonstrated to produce fetal brain cell damage.[33] An Environmental Protection Agency study shows that maternal nicotine exposure during fetal development, in doses similar to the dose of nicotine acquired with moderate smoking (0.5 to 1 pack/day), can result in central nervous system and neurologic deficits such as impairments in learning and memory performance.[34] Nicotine acts on specific neurotransmitter receptors in the brain and is a neuroteratogen, which suggests that some of the adverse perinatal outcomes resulting from cigarette smoking may in fact be due to nicotine.[35] According to research by Slotkin, the effects of nicotine on brain development are very similar to those of cocaine.[35]

Study results have confirmed that some e-juices contain amounts of nicotine that are potentially lethal to both children and adults.[36] Because nicotine can readily pass into the bloodstream following dermal contact, one study reports that spilling of five milliliters (ml) of e-cigarette liquid (equivalent to 110 mg of nicotine) onto the skin can cause severe intoxications or even death.[36] In addition, the tested e-cigarette solutions were found to contain several sensitizing chemicals, including benzylalcohol and l-limonene, which can cause allergic contact dermatitis and immediate contact reactions.[36]

Because nicotine can be absorbed into the body via inhalation, ingestion, skin contact and through the mucous membranes [29], it is possible that the vapor from electronic cigarettes can potentially cause secondary and tertiary environmental exposure to nicotine for those in the area around e-cigarette users. Airborne concentrations of nicotine have been studied for both regular and electronic cigarettes. Using a smoking machine connected directly to sampling devices and a sample bag, McAuley et al. compared airborne concentrations of several components of both nicotine cigarette smoke and e-cigarettes.[18] The authors reported airborne nicotine concentrations ranged from 725 to 8770 nanograms (ng) per liter (equivalent to 0.725 to 8.77 micrograms per cubic meter [$\mu g/m^3$]), which were lower than those from regular cigarettes, which ranged from 5.04 $\mu g/m^3$ to 48.05 $\mu g/m^3$.[18] Czogala et al. examined e-cigarette vapors from three different brands and compared the components to those from secondhand tobacco smoke through the use of an exposure chamber.[21] Though the level of nicotine exposure varied by brand of e-cigarette, the authors reported that e-cigarettes were observed to emit nicotine in concentrations ranging from 0.82 $\mu g/m^3$ to 6.23 $\mu g/m^3$ while the average concentration of nicotine from tobacco cigarettes was 10 times higher.[21] Schober et al. reported airborne concentrations of nicotine during a two-hour vaping session ranging from 0.6 to 4.6 $\mu g/m^3$.[36]

OSHA regulates exposure to nicotine in the workplace to less than 0.5 mg/m^3 (500 $\mu g/m^3$) for the industrial workplace, and the American Conference of Governmental Industrial Hygienists publishes a Threshold Limit Value for nicotine at the same level for an eight-hour time-weighted average (TWA).[37] However, ANSI/ASHRAE Standard 62.1-2013 – *Ventilation for Acceptable Indoor Air Quality (IAQ)*, applicable to office buildings, schools, larger multifamily housing, and many other spaces, cautions that the OSHA standards and ACGIH guidelines are intended to limit worker exposure to injurious substances at levels that do not interfere with the industrial work process and do not risk the workers' health and safety. These standards and guidelines do not attempt to eliminate all effects, such as unpleasant smells or mild irritation.[38] Therefore, the target population and use of these standards and guidelines are different from those for the populations of many public and commercial buildings.[38] Consequently, while the reported airborne levels measured for nicotine from e-cigarettes in the chamber study by Czogala et al.[21] and vaping session by Schober et al.[36] were at a fraction of the OSHA regulatory level, there are other factors that need to be considered. OSHA standards are based on working with nicotine occupationally, so they are not entirely applicable or appropriate for IAQ irritation, nuisance, and exposure purposes.

A literature review for information on potential surface deposition of nicotine from e-cigarette use (tertiary, or thirdhand, exposure) revealed that very little information is available. In February 2014, the Roswell Park Cancer Institute in Buffalo, N.Y., presented data from an unpublished research project to the Society for Research on Nicotine and Tobacco in Washington state. Researchers analyzed three brands of e-cigarettes filled with varying nicotine concentrations.[39] The e-cigarettes were smoked, or vaped, in an exposure chamber, and the resultant nicotine levels on five different surfaces of the smoking chamber were measured.[39]

The surfaces included glass, floors, walls, windows, wood, and metal. The researchers found that three out of four experiments showed significant, yet varying, increases in nicotine found on the five surfaces. The researchers concluded by stating that future research should "explore the risks of exposure to carcinogens posed by thirdhand exposure from e-cigarettes."[39] According to Bloomberg School of Public Health Professor Dr. Patrick Breysse, in a pilot study conducted by Johns Hopkins University, two of three surface samples collected in a vaping lounge had detectable levels of nicotine (P. Breysse, personal communication, May 14, 2014).

Glycols and Glycerin

Propylene glycol, a chemical found in theatrical smoke, and vegetable glycerin are both used in e-cigarettes as vehicles for the nicotine and the flavorings, and to create the "vapor" that is emitted.[13,14,15] Analysis of various vaping solutions has revealed concentrations of propylene glycol ranging from 60 percent to 90 percent, and up to 15 percent glycerin,[13,14,15] although some vendors have reported mixtures of equal parts [40] and others substitute glycerin and water for PG completely.[41] Many websites now supply custom e-liquids formulated the way the user requests it, including such variables as flavors, nicotine concentrations, and whether glycols or glycerin are used and in what concentrations. Users may purchase raw materials and compound e-liquids themselves[42] with the help of numerous online concentration calculators[43] or calculation applications available for mobile phones. While propylene glycol has been used in other legitimate drug delivery methods, such as inhalers and nebulizers, the frequency of use and exposure is expected to be much higher for electronic cigarette users than for recognized medical uses.[16]

Concentrations of 1,2-propanediol (propylene glycol) in the range of 110 $\mu g/m^3$ to 215 $\mu g/m^3$ and glycerine in the range of 59 $\mu g/m^3$ to 81 $\mu g/m^3$ were found in the gas phase of emissions during an e-cigarette vaping study.[36] Another study reported airborne concentrations of PG ranging from 2254 ng/l to 120,000 ng/l (2.25 mg/m^3 to 120 mg/m^3).[18]

A generally recognized occupational guideline for airborne exposures to propylene glycol mists and vapors is the AIHA® Workplace Environmental Exposure Level (WEEL), which recommends a maximum eight-hour TWA for total vapor and aerosol of 50 parts per million (ppm) (156 mg/m^3);for aerosol alone the TWA is 10 mg/m^3.[44] Exposures during theatrical fog use are not expected to be near those levels.[44] However, in a study of the health effects of theatrical fogs, it was determined that exposure to these fogs may contribute to both acute and chronic health issues, such as asthma, wheezing, chest tightness, decreased lung function, respiratory irritation, and airway obstruction.[45] Information shared among many vaping websites includes the following information:

> Some of the side effects experienced by people that use propylene glycol are muscle pain, sore throat, and stronger smelling urine. These symptoms can all result from using e-cigs that use propylene glycol-based e-liquid. Since PG is considered a humectant (it collects moisture), your throat can become dry after use and potentially sore. It can also result in an increase of lactic acid production by your body causing muscle aches that occur more often than normal.[40]

In one case, the suspected cause of a patient's development of exogenous lipoid pneumonia, which is a rare form of pneumonia caused by inhalation or aspiration of a fatty substance, was from recurrent exposure to glycerin-based oils in e-cigarette nicotine vapor.[46]

An unfortunate outcome of the presence of glycerin may be the presence of acrolein, formaldehyde, and acetaldehyde in the vapor, which has been shown to form as a result of heating or pyrolysis of glycerin.[47] This is a particular concern with second-generation (tank type) and third-generation (rebuildable atomizer type) e-cigarettes with adjustable voltages, and perhaps low-resistance coils as well. As-yet unpublished laboratory studies by Johnson and Floyd have shown that the mass of aerosol produced during vaping increases dramatically with the power of the device, which goes up as the square of voltage (power in watts = potential in volts^2/resistance in ohms). In experiments with a tank type (second generation) variable voltage e-cigarette with a 3-ohm resistance coil, these researchers measured a 33-fold increase in fluid mass vaporized with only a doubling of voltage from 3V to 6 V. (D. Johnson and E. Floyd, personal communication, May 29, 2014). This suggests a geometrically increasing risk of toxic effects as the devices gain power via stronger batteries, lower resistances, and adjustable voltages.

Diethylene glycol, an impurity of PG, is also an organic compound of concern because it was observed to be present in one of 18 refill cartridges evaluated by the FDA and has thus been cited as a contaminant of concern by the FDA.[7,15,16,36,41] Toxicity studies with diethylene glycol indicate that chronic inhalation of vapor, fog, or mist should be avoided, especially where it is heated or used at elevated temperatures.[48] Because of its adverse effects on humans, diethylene glycol is not allowed in food and drugs.[15] However, a review of 15 additional studies of compounds associated with electronic cigarettes did not identify diethylene glycol to be present.[16,41]

Flavorings

A review of several online suppliers and manufacturers of e-cigarette liquids revealed that an extensive assortment of flavors is available. Flavor additives are often referred to as natural, though further information is not provided about the composition or source of these additives.

The most widely and readily available source of flavorings is for food products, so it can likely be assumed that many manufacturers of flavored e-cigarette liquids are using flavoring products intended for food ingestion.

The Flavor and Extract Manufacturers Association (FEMA) maintains an independent program that evaluates the safety of substances for their intended use as flavor ingredients.[46] The primary route to regulatory authority to use flavor ingredients in the United States is the FEMA GRAS program. Some manufacturers of e-liquids use a wide variety of natural and artificial flavoring agents, with the most readily available sources being those whose origins were intended for inclusion as flavoring in food products. Research on some flavorings used in tobacco products has revealed that benzaldehyde has been detected in cherry flavoring, methyl anthranilate was detected in grape flavoring, and 1-hexanol was detected in apple flavoring.[50]

Some websites that sell premade e-liquid mixes are using manufacturing sources from outside of the United States. FEMA has stated: “None of the primary safety assessment programs for flavors, including the GRAS program sponsored by FEMA, evaluated flavor ingredients for use in products other than human food. FEMA GRAS status for a flavor ingredient does not provide regulatory authority to use the flavor ingredient in e-cigarettes in the U.S.”[49] Therefore, the safety of the use of these flavorings in e-cigarettes has not been tested or approved. In addition, the heating process and vaporization of these products in electronic cigarettes result in an inhalation of aerosol, rather than ingestion. Further, no research is known to have been conducted on the pyrolyzation products of any of the flavorings, which may be occurring at higher vaping powers. Therefore, a compound that may be GRAS when ingested is no longer automatically safe for inhalation.

A clear example of this problem is the use of diacetyl (butanedione or butane-2,3-dione) as a buttery flavoring for popcorn, baked goods, and liquor. Numerous research papers have been published and lawsuits have been filed in the past decade regarding employees in several factories that manufacture or use artificial butter flavoring who have been diagnosed with bronchiolitis obliterans, a rare and very serious disease of the lungs.[51]

Diacetyl is an example of a flavoring that is approved for ingestion but has potential health effects when volatilized and inhaled. In November 2010, the state of California passed legislation relating to employee exposure, physical examinations, and personal protective equipment when working with diacetyl in the workplace because of the potential health concerns associated with inhaling the aerosolized flavoring.[52] Due to a lack of strong quality control or labeling requirements, and the lack of research on domestic and imported e-liquids, it is unknown at this time how many other GRAS (or non-GRAS) flavoring agents may fall into this same ingestion vs. inhalation quandary.

Volatile Organic Compounds

A number of published studies have been conducted worldwide examining, among other things, the presence of various VOCs in e-cigarette vapors. One German study compared secondhand emissions, including VOCs, of e-cigarettes and conventional cigarettes.[17] Researchers tested three different brands of e-cigarettes loaded with three different liquids, two containing nicotine and one that is nicotine free. The authors stated that continuous monitoring of the e-cigarette vapor showed only a slight increase in formaldehyde concentrations, which the researchers theorized may have actually been caused by the test subject instead of the e-cigarettes.[17] Other indoor pollutants of special interest, such as benzene, were detected only during the tobacco smoking experiment. It should be noted, however, that the test subject took only six puffs from each cigarette, with a 60-second delay between puffs, which may not be representative of normal vaping behavior.[17]

Another German study, using commercially available e-cigarettes and three different liquids (both with and without nicotine), reported that formaldehyde, benzene, and the pyrolysis products acrolein and acetone did not exceed background concentrations.[36] Indoor concentrations of vanillin and benzylalcohol were only slightly increased compared with control values. However, PAH concentrations increased on average by 20 percent over background levels.[36]

A Polish study of three popular e-cigarette brands with nicotine containing liquid reported that only toluene was detected in the exposure chamber after e-cigarette usage, and that the levels were not statistically above background concentrations.[21] The authors also studied emissions from regular cigarettes and compared them to those from the e-cigarettes. They noted that smoking as few as two tobacco cigarettes significantly increased the airborne concentration of toluene, ethylbenzene, m,p-xylene, and o-xylene, and that for toluene, the average concentration after smoking tobacco cigarettes was 3.5-fold higher than after using e-cigarettes.[21]

Another Polish study examined the vapor generated by 12 brands of e-cigarettes filled with nicotine-containing liquid analyzed for 11 common VOCs and 15 carbonyl-containing VOCs. Of the 11 common VOCs, only toluene and m,p-xylene were identified in the vapor generated from the e-cigarettes, but they were found in almost all of the e-cigarettes tested.[47] However, the researchers also noted that the levels of m,p-xylene detected in the vapor were similar to those found in the blank samples. Of the 15 carbonyl-containing VOCs, formaldehyde, acetaldehyde, o-methylbenzaldehyde, and acrolein were observed in nearly all e-cigarettes tested. [47]

A U.S. study examining emissions from four different high-nicotine-content e-liquids vaporized by generic two-piece e-cigarettes, as well as from conventional cigarettes, found detectable levels of ethylbenzene, benzene, toluene, and m,p-xylenes in the vapor.[18] However, the levels in the tobacco smoke were orders of magnitude higher than those found in the e-cigarette vapor.

A Japanese study of 13 e-cigarette brands (363 e-cigarettes in total) found that nine of the brands generated detectable airborne levels of various carbonyl compounds, including formaldehyde (concentrations up to 61 mg/m^3), acetaldehyde (concentrations up to 48 mg/m^3), acrolein (concentrations up to 34 mg/m^3), and propanal (concentrations up to 27 mg/m^3).[53] The authors noted that there were very large variations in the carbonyl concentrations, not only among the different brands but also among individual e-cigarettes from the same brand. They theorized that the compounds were generated as a result of the e-liquids incidentally touching the heated wiring in the atomizers.[53]

<u>Metal and Silica Particles</u>

Electronic cigarettes are designed with metal components that have also been found in the aerosol. Resistive wire filaments (nickel-chromium or other metals) are used to heat the wick and evaporate the e-liquid.[19] Often these resistive wires are coupled to nonresistive extensions of copper wire (sometimes coated with silver), and often tin solder joints connect the wires to each other and to the air tube and mouthpiece.[19] Fibers found in some cartomizers (atomizers, heating coils) had copper deposits, and both tin particles and tin whiskers were found in some cartridge fluid.[19] Aerosols generated from electronic cigarettes have been found to contain tin, silver, iron, nickel, aluminum, sodium, copper, magnesium, lead, chromium, manganese, potassium, zinc, silicates, and nanoparticles of tin, chromium, and nickel.[19] The silicates appear to come from fiber glass wicks used in the product and are not expected to be crystalline silica.[19] Goniewicz et al. also found cadmium to be present in the aerosol generated from some, but not all, e-cigarette products.[47]

One study found lead and chromium concentrations in electronic cigarette aerosols within the same range as conventional cigarettes (0.017 µg/10 puffs for lead and 0.007 ug/10 puffs for chromium).[19] Airborne nickel was found to be in higher concentrations in e-cigarette vapor than in conventional cigarette smoke (0.005 µg/10 puffs vs. the highest concentration of 0.0014 µg/10 puffs for conventional cigarettes).[19] Overall, the researchers found concentrations of nine different metals to be higher than or equal to the range of concentrations found in conventional cigarette smoke.[19] Another study found airborne aluminum concentrations increased from the approximately 0.20 µg/m^3 background concentration to approximately 0.48µg/m^3 during e-cigarette vaping sessions.[36]

While the airborne exposure for all metals during vaping has not been well-defined in terms of dose or concentration (in mg/m^3 or ppm), all of the elements found in the aerosol have the potential to adversely affect the respiratory system; some can affect reproduction and development (e.g., lead); and some are considered carcinogens or “reasonably anticipated to be human carcinogens” (e.g., nickel and lead).[19,54,55] Lead, nickel, and chromium are also on FDA’s “harmful and potentially harmful chemicals” list.[19]

Williams et al. evaluated the cytotoxicity of electronic cigarette fluids, with and without tin particles, and found that the fluids with tin particles were observed to be cytotoxic in assays using human pulmonary fibroblasts, but the fluids without tin particles were not.[19] The presence of tin in the fluid appeared to be dependent on the quality of the wire soldering and the extent of presale use or testing performed on the units, as several of the “new” units evaluated showed signs of use prior to purchase.[19]

Ultrafine Particulates

Research over the last two decades has demonstrated that exposure to airborne fine and ultrafine particulate matter results in a variety of adverse health effects. Wichmann et al. found significant associations of elevated cardiovascular and respiratory disease mortality with various fine (and ultrafine) particle indices.[56] In his study, significant associations were found between mortality and ultrafine particle number concentration, ultrafine particle mass concentration, and fine-particle mass concentration.[56]

The particulate size distribution and composition of tobacco smoke is well-documented and will be reviewed here only as a comparison to e-cigarettes. Schripp conducted studies in an 8 m^3 chamber to evaluate the size distribution of submicron particulates from both tobacco smoke and e-cigarettes.[17] The traditional cigarette produced a log-normal distribution around a mean size of 100 nanometers (nm) in diameter, with a peak concentration of 4.0×10^4 particles/cm^3, while the e-cigarette were found to produce a size distribution around a mean of 35 nm in diameter with a concentration 2.0×10^3 particles/cm^3.[17] Although the concentration of particulates from the tobacco smoke was found to be an order of magnitude greater than the electronic cigarettes (when generated under the same conditions), these findings are significant because both the particulate size and concentration levels are a concern.

Schripp also examined the size distribution as the e-cigarette particles aged. The aging process at different temperatures suggests that exhaled e-cigarette vapor can result in passive exposure as well a shift in the particle size, where peak size shifted to smaller sizes, from about 180 nm at 23°C to 60 nm and 45 nm at elevated temperatures (37°C and 50°C respectively).[17] However, e-cigarettes release particles only during exhalation, whereas regular cigarettes emit particles continuously during combustion via side-stream smoke. The overall conclusions presented by Schripp et al. were that vaping will introduce particles into the indoor environment that are of concern from both a size and concentration standpoint but are substantially less than tobacco cigarettes.[17]

In another study of e-cigarette emissions, Ingebrethsen reported even higher particulate concentrations and larger average particle masses. Particle diameters of average mass in the 250 nm to 450 nm range, and a total particle count in the 10^6 particles/cm^3 range, were reported for aerosols from e-cigarettes measured with an electrical mobility analyzer.[57] These measurements were reported to be similar to those observed from tobacco cigarettes. Yet another study by Zhang et al. reported e-cigarette particle size between 10 and 1000 nm, with an average of 400 nm.[58] Based on particle size, the authors expect deposition in the human lung similar to that of tobacco cigarette smoke.[58]

Research shows that ultrafine particles form from supersaturated 1,2-propanediol vapor, which can be deposited in the lung.[36] Schober et al. found that airborne $PM_{2.5}$ concentration during vaping sessions with e-cigarette users were approximately 373 µg/m^3, with the highest levels (514 µg/m^3) found during vaping sessions with no nicotine in the vaping solution.[36] These results reflect airborne concentrations in a fairly large room due to exhaled vapor. Therefore, these results relate primarily to the potential for secondhand exposures.

Another study, using a device that simulated vaping during a three-minute session, reported $PM_{2.5}$ concentrations of 43 µg/m^3 after three minutes.[54] People who have frequently been exposed to theatrical fogs containing ultrafine particles of propylene glycol are more likely to suffer from respiratory, throat, and nose irritations than do unexposed people, suggesting that e-cigarettes may foster similar health effects.[59] Therefore, while these limited results vary, the generation of airborne ultrafine particles from e-cigarettes is a potential indoor air quality issue.

As a measure of impact from inhaling ultrafine particles from e-cigarettes, Marini et al. examined the acute effects of electronic and tobacco cigarettes on exhaled nitric oxide (eNO).[60] Exhaled nitric oxide has been used as a noninvasive method to measure inflammation of the lung after exposure to pollutants. Marini applied eNO tests to a group of 25 volunteers who use tobacco, e-cigarettes with nicotine, and nicotine-free e-cigarettes.[60] The eNO tests were applied before and after smoking/vaping to allow for the comparison in the changes in eNO for individuals.[60] The average total particle number concentration peak was found to range from $3.1 \times 10^9/cm^3$ for conventional cigarettes to $5.1 \times 10^9/cm^3$ for e-cigarettes with nicotine.[60]

Oddly, the e-cigarette particulate emissions were found to be 1.5 times higher than those from traditional cigarettes, a stark contrast to previous studies.[60] However, the main focus of this article was to understand changes in eNO levels from e-cigarettes with and without nicotine. The mean eNO changes measured after each vaping test were found to be 3.2 parts per billion (ppb), 2.7 ppb, and 2.8 ppb for electronic cigarettes without nicotine, with nicotine, and for conventional cigarettes, respectively.[60] The control sessions were found to have negligible change in eNO.[60] Hence, the short-term respiratory effect found in this study was that e-cigarettes, as well as traditional tobacco cigarettes, led to immediate reduction in eNO, suggesting inflammation of the airways.

Floyd et al. recently compared vaping aerosols from a second-generation adjustable voltage tank style e-cigarette to tobacco cigarette smoke aerosol (D. Johnson and E. Floyd, personal communication, June 12, 2014). They measured particle size distributions over a broad range, from 16 nm to 20 µm, and found that less than 40 percent of both the e-cigarette aerosol and tobacco-smoke aerosol particle mass was comprised of particles less than 1 µm in diameter. They also observed a 32-fold increase in vaporized e-fluid when voltage was increased from 3.15 V to 5.81 V, demonstrating the potential for newer generation, more powerful devices to produce much higher concentration aerosols. The higher heating coil temperatures associated with these high-power devices also pose the risk of chemical changes in the e-fluid, which is suspected to produce aldehydes and carbonyls.[61,62]

The work completed to date on aerosols generated from e-cigarettes suggests that they present a new source of aerosols in indoor environments. While the aerosol number concentration is smaller than that from traditional cigarettes, the smaller size distribution of e-cigarette aerosols may result in different deposition locations within the lung. Because of the relatively new widespread use of e-cigarettes, the relationship between exposure and any health effects is still evolving. However, the evidence of health effects from a number of authors linking ultrafine particles to respiratory and cardiovascular disease clearly indicates a potential health concern.

Tobacco-specific Nitrosamines

Tobacco-specific nitrosamines (TSNAs) have been reported to be found in trace levels in electronic cigarettes in at least two studies, but are found in concentrations well below TSNA levels in regular cigarettes.[16,47] However, residual nicotine from tobacco smoke has been shown to react with ambient nitrous acid to form TSNAs over time, therefore increasing the overall potential exposure.[63] Some TSNAs are known human carcinogens and are suspected to contribute to the cancer burden of smokers.[64]

Nut Allergens

An area about which knowledge is currently lacking is the presence of nut allergens that may be found in e-cigarette liquids. On the General Frequently Asked Questions (FAQ) page of e-liquid supplier Johnson Creek's website, a question was posted from a consumer worried about allergy to nuts and the use of e-liquids. The company's website response was:

> If you have an allergy to nuts, we recommend that you NOT use Johnson Creek Original Smoke Juice. It is possible that some of our flavors may have nut-based ingredients, or may be produced in a facility that processes nuts.[65]

The presence or potential presence of nut allergens within e-cigarette liquid obviously poses a concern for users with nut allergies. What is currently unknown is whether a nut allergen contained in a flavored e-liquid can become airborne during e-cigarette use and pose an airborne exposure risk for sensitive individuals nearby. This is an area where research is warranted, especially with the implication of risk for individuals with nut allergies exposed to secondhand e-cigarette vapor. This identifies another area needing research: If a nut allergen becomes airborne, could this allergen then deposit onto surfaces in the area of use and then pose a dermal risk for allergic individuals – a thirdhand exposure?

Other Constituents

As previously stated, there is evidence that the vaporization technology used in e-cigarettes has been employed to deliver other drugs such as tadalifil (a drug used for erectile dysfunction) and rimonabant (a weight-loss aid)[13] and that this technology may prove beneficial for specific prescription drug mobilization. However, as the e-cigarette technology has been described in detail in the public domain and numerous online special interest groups (SIGs), hobbyists and dedicated e-cigarette users and supporters are able to purchase individual components to manufacture their own e-cigarette hardware configurations.

As of May 2014, this subject review has identified numerous websites that sell components for the elution of plant material extracts into the cigarette delivery system.[66] In short, one may now deliver liquid extracts of medical marijuana, hashish, and crack cocaine[67,68] into the vaping system with allegedly no odor detection by other room occupants.

Overall Health Effects Associated with E-cigarettes

Currently, there are limited published studies that evaluate the potential hazardous effects of the natural and/or synthetic chemicals used in e-cigarettes. Overall, the literature to date indicates that there are potential health effects reported for both users and those exposed secondhand.

E-cigarette users in online forums self-reported a variety of health symptoms that they associate with using e-cigarettes, including mouth and throat irritation, cough, nausea, changes in heart rhythm, and dizziness.[69] Although studies have shown that consumption of e-cigarettes did not show changes in blood pressure for participants, a review of these forums revealed that blood pressure changes were reported by 3.5 percent of e-cigarette users.[69] Some users also reported experiencing increased heart rates, although some scientific studies have shown that heart rate did not increase during the use of prepackaged e-cigarettes.[70]

Bahl et al. studied the cytotoxicity of 35 samples of e-cigarette refill fluids using human embryonic and adult cells.[71] Twenty-seven of the 35 refill samples were moderately to highly toxic to the embryonic cells, with less severe effects on the adult cells.[71] The observed cytotoxicity was not attributable to the nicotine present in the fluids but was correlated with the number and concentration of chemicals used to flavor the fluids.[71] Their research indicated that the observed cytotoxic effects could potentially translate into embryonic loss or developmental defects during pregnancy.[71] Additional preliminary information presented by Cressey indicates that human bronchial cells exposed to high levels of e-cigarette vapor in vitro expressed gene patterns similar to human bronchial cells exposed to tobacco smoke in vitro.[72] These researchers state that, while e-cigarettes may be safer than tobacco, “preliminary studies suggest that they may not be benign.”[72]

Overall airway resistance and lung function associated with e-cigarette use has been studied with varying results. Flouris et al. reported that neither a brief session of active e-cigarette smoking, nor a one-hour duration of passive e-cigarette smoking, resulted in any significant interference with lung function measured using forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, peak expiratory flow (PEF), or forced expiratory flow in the middle 50 percent of FVC (FEF_{25-75}).[14] However, a different study that evaluated the fraction of exhaled nitric oxide (FeNO), a marker of bronchial inflammation, along with FEV_1, FVC, FEV_1%, PEF, maximal expiratory flow (MEF) at 25 percent, 50 percent, and 75 percent of vital capacity, and total respiratory resistance discovered that five minutes of e-cigarette use was sufficient to lead to an increase in lung flow resistance and a decrease of FeNO concentrations, which is a marker for oxidative stress in the lung.[5]

However, another study found a rise of FeNO in users of nicotine containing e-cigarettes, but not in users of non-nicotine-containing e-cigarettes.[36] A limited Greek study found that e-cigarette users experienced an instant increase in airway resistance that lasted for approximately 10 minutes, using a spirometry test and other diagnostic procedures.[4] Smokers experienced an airway resistance from 176 percent (mean average) to 220 percent, while nonsmokers experienced an airway resistance from 182 percent to 206 percent.[4] Long-term exposures were not evaluated in any of these studies.

Early research showed that, per puff, nicotine absorption is lower for e-cigarettes than for tobacco cigarettes.[14] One study reported that e-cigarette users have, in general, approximately 10 percent of the nicotine concentration in their blood plasma as compared to tobacco cigarette users,[69] while others have shown no significant changes in plasma nicotine as a result of the use of some prepackaged products.[20] These values may change with the increased use of personal mixes of liquids where the user can control the nicotine concentration.

Flouris et al. found that while active and passive tobacco smokers experience an increased white blood cell count, lymphocyte count, and granulocyte count, active and passive e-cigarette smokers do not.[73] Farsalinos et al. reported that there were no acute adverse effects on cardiac function reported in smokers or nonsmokers using e-cigarettes.[74] This is consistent with reports that cardiovascular disease from tobacco use is likely related to the combustion byproducts of tobacco smoke.[71]

Other Health and Safety Issues

Because some styles of e-cigarettes resemble regular cigarettes, allowing the use of e-cigarettes in smoke-free places may lead people to believe that no ban on smoking in that location exists and, as a result, to light up conventional cigarettes.[75] Some research shows that for smokers, the observation of others smoking increases the craving and potential for ultimate consumption of cigarettes.[76] Therefore, careful consideration should be given to allowing the use of e-cigarettes without restriction in the workplace, as it may induce others who are attempting abstinence to desire to smoke as well.

Moreover, recent media attention has brought additional safety issues, including child safety and poisonings, battery explosions, and the potential for the vapor to set off smoke alarms. The American Association of Poison Control Centers reported that poison control centers have reported an increase in emergency calls regarding exposures to e-cigarette devices and liquid nicotine, with more than half of the exposures occurring in children under the age of six. [77] Although many e-cigarette vials have safety caps, the caps are currently not required by law.

Several incidents of fires and explosions have been reported from the lithium-ion batteries used to charge e-cigarettes. The most common causes of fires have been using incorrect chargers or over-tightening of the screwed connection to the charger, which can damage the battery cells and lead to overheating.[78] Unfortunately, many lithium–ion batteries used in e-cigarettes do not have overcurrent or overcharge protection, so if they are left charging, the coil can overheat and cause the battery to explode.[78]

One vaper demonstrated online that it is possible to set off a smoke alarm using an e-cigarette.[79] However, whether the vapor can or will set off smoke detectors appears to be dependent on the situation and the type of smoke alarm.

Current Regulatory and Health Agency Statements

E-cigarettes are enjoying some support from those who back their use as a way to reduce harm from smoking traditional tobacco cigarettes. Dr. Richard Carmona, the U.S. Surgeon General during the George W. Bush presidency and who was responsible for a 2006 report on secondhand smoke that helped to ban smoking in restaurants and bars, joined the board of directors of an e-cigarette manufacturer in March 2012.[80]

Carmona advocates that e-cigarettes reduce the risk for smokers and recipients of secondhand smoke by eliminating combustion byproducts, many of which are carcinogenic.[80] However, he notes that he joined the board on four conditions: (1) that the company seek FDA regulation; (2) that the company conduct research and openly publish results regardless of real or potential financial impact; (3) that the company may not use his name or previous position to promote its e-cigarettes; and (4) that the company not market e-cigarettes to children.[80] His idea is that the company will research effects of secondhand vapor and how well e-cigarettes help people totally wean themselves from both tobacco products and e-cigarettes.[80]

WHO has recommended that consumers be strongly advised not to use electronic nicotine delivery systems, including e-cigarettes, until they are deemed safe and effective and of acceptable quality by a competent national regulatory body.[8] WHO noted that the safety of the devices has not been scientifically demonstrated.[8] While WHO discourages the use of e-cigarettes, it has not yet taken a position on whether they should be banned. It has been reported that WHO is planning on regulating e-cigarettes in the same way as traditional tobacco products.[81] E-cigarettes would be classified as tobacco under the Framework Convention on Tobacco Control, which is a WHO treaty that obliges governments to curtail smoking rates around the globe.[81] However, as of the publication date of this white paper, WHO has made no official statement or position on this matter.

The regulatory status of e-cigarettes is constantly changing. Although these products may use some ingredients derived from tobacco, such as nicotine, other ingredients are clearly not related in any way to tobacco products. The FDA currently regulates only e-cigarettes that are marketed for therapeutic purposes.[82] However, the FDA has proposed a rule extending its tobacco product authorities to include other products like e-cigarettes.[83] The FDA has previously taken action against manufacturers of e-cigarettes, claiming that they violated good manufacturing practices and made unsubstantiated drug claims.[84] However, manufacturers sued the FDA, claiming that e-cigarettes should be regulated as tobacco products, and not as drugs.[84] Beginning in 2016, Great Britain will start to regulate e-cigarettes as a nonprescription medicine.[85] Other countries, such as Brazil, Norway, and Singapore, have banned the use of e-cigarettes.[85]

Several agencies and organizations have adopted the approach that e-cigarettes are equivalent to traditional cigarettes, or that the hazards are unknown and, therefore, are subject to the current bans on cigarette advertising; restrictions on sales; and bans on use in public places, transportation facilities, and restaurants and bars. For example, the states of Arkansas, New Jersey, North Dakota, and Utah[86]; and the cities of Los Angeles, New York, Washington, DC, Chicago,[87] and Duluth, Minn.,[88] have included e-cigarettes in indoor smoking regulations. Mississippi's DeSoto County has added e-cigarettes to the local smoking ban in government buildings,[86] and the governor of Oklahoma has banned the use of any electronic cigarette or vaping device on any properties owned, leased, or contracted for use by the state.[89] Many other states and municipalities are discussing similar legislation or bans.

Although traditional cigarettes are currently taxed heavily in the United States, e-cigarettes are not uniformly subject to tobacco taxes if no tobacco-derived products are involved, which makes them relatively less expensive than traditional cigarettes. The nontaxed cost of e-cigarettes can be viewed as encouragement of the use of e-cigarettes.

Several states have included e-cigarettes under tobacco tax requirements, though they are currently not subject to federal tobacco taxes. For example, Minnesota has modified the definition of "tobacco products" to include terminology that allows e-cigarettes to be taxed as tobacco products.[84] However, careful review of the wording of each state's tobacco laws would be required to extend purchasing limitations of e-cigarettes as a tobacco product to minors.[84] Restrictions on advertising to minors and bans on Internet sales or sales to minors have either been enacted, or are being planned, by several organizations including 38 states[90] and the FDA.[91]

Regarding whether the use of e-cigarettes is allowed or banned on commercial aircraft in the United States, the regulatory status is not clear. During a hearing in 2010 before the Senate Committee on Commerce, Science and Transportation, Susan Kurland, Assistant Secretary for Aviation and International Affairs, U.S. Department of Transportation (DOT), when asked whether the agency planned to explicitly ban the use of electronic cigarettes on commercial airplanes, stated that the smoking of e-cigarettes was already banned.[92] However, some question that statement, noting that only "tobacco products" are banned on certain scheduled air carrier flights in Part 252 of Title 14 of the Code of Federal Regulations, "Smoking Aboard Aircraft." [93]

In 2011, DOT proposed amending its existing airline smoking rule to explicitly ban the use of e-cigarettes on all aircraft in scheduled passenger interstate, intrastate, and foreign air transportation.[94] In their proposal DOT cited its specific statutory authority to prohibit smoking, under Section 41706 of the Title 49 of the United States Code, on "Prohibitions against smoking on scheduled flights" which does not specifically mention tobacco or explicitly limits its scope to smoking of tobacco products. [95] DOT also based its proposal on its general duty statutory authority that, regarding "interstate air transportation, [a]n air carrier shall provide safe and adequate interstate air transportation."[96] A group of organizations, including the American Lung Association, the American Heart Association, and the Cancer Action Network, sent a letter of support for DOT's proposal to prohibit e-cigarettes on all commercial aircraft. The reasons provided included that health consequences were unknown and that allowing the use would create significant confusion for passengers, along with enforcement challenges for airline personnel.[97] However, to date a ban has not been issued. In addition, the Federal Aviation Administration has not promulgated a ban and has left it to the airlines to set their own policies in regard to whether e-cigarettes are allowed on flights.

Major U.S. airlines have amended their no-smoking policies to specifically include e-cigarettes. For example, United Airlines' smoking policy states: "Smoking (including use of electronic simulated smoking materials and smokeless cigarettes) is not permitted on any flights operated by UA."[98] However, not all airline smoking policies are completely clear about e-cigarettes. For example, JetBlue's Contract of Carriage's smoking policy simply states: "Smoking aboard the aircraft is prohibited in accordance with Federal Law"[99], but the help section of JetBlue's website states, "JetBlue does not allow the use of [e-cigarettes] on any of its flights. It is considered a nuisance item as small amounts of vapor are expelled from the cigarette."[100]

Even with clear prohibition of e-cigarettes by certain airlines, some e-cigarette proponents have posted recommended strategies for being allowed to use the device, suggesting that it be called a "nicotine inhaler" and insisting that the use of the device is not covered by smoking bans on airplanes.[101]

Other transit systems, such as commuter rail lines, subway systems, and bus services, have also created issues with ambiguity over e-cigarette usage by only referencing federal law that smoking (of tobacco) is banned. Amtrak has had a no-smoking policy since 2008 that specifically includes e-cigarettes both on trains and in stations.[102] Many transit entities have updated their policies to specifically include e-cigarettes, such as the New York City-area Metropolitan Transit Authority, operator of the Long Island Rail Road and Metro-North Railroad, which updated its policy in the 2013.[103] The Los Angeles County Metropolitan Transportation Authority amended its policy in March 2014 to prohibit vaping.[104]

A trade magazine reported that, as of April 2014, at least six additional transit-rail agencies – Caltrain, Chicago Transit Authority, Dallas Area Rapid Transit, Metropolitan Atlanta Rapid Transit Authority, Tri-County Metropolitan Transportation District of Oregon, and Virginia Railway Express – had adopted e-cigarette restrictions.[105] Regarding private-sector bus companies, the Megabus policy states: "Smoking, including the use of electronic simulated smoking materials, e-cigarettes, and smokeless cigarettes, is prohibited in our buses"[106]; however, the BoltBus policy simply states that "Smoking is prohibited aboard the bus in accordance with Federal law"[107] and the policy for Greyhound states only that "Smoking is prohibited."[108]

To summarize, there is currently no federal law or regulation that explicitly bans the use of e-cigarettes on U.S. airplanes, railroads, buses, or other modes of transportation. For organizations and businesses that have smoking bans, especially those required by law, it would be advisable for them to update their bans to specifically include e-cigarettes in order to eliminate potential confusion among patrons as well as employees charged with enforcing those bans.

Key Data Gaps and Uncertainties

There are several key data gaps and areas of uncertainty that hinder a more quantitative assessment of health risks related to e-cigarettes at this time. These include:

- Quality control is lacking with regard to product constituents. (Manufacturers may not disclose all of the chemical ingredients used in their products, nor, other than nicotine, their amounts.)
- Because many users mix their own blends and there are so many different types of devices, what may be studied in the lab may not reflect actual exposures during use.
- There is limited data on chemical emissions/exposures (especially among bystanders and in confined indoor settings).
- There is limited information on dose-response relationships for many constituents (such as short- or long-term health effects associated with low-level exposures).
- Established safety levels (occupational vs. environmental) are lacking.
- At this time, there is no clear understanding of how much liquid is vaped by a user or a population of users in a given day in comparison to how many cigarettes are smoked in a day.[106] Variations in vaping habits, variable liquid strength, and uncertain overall daily vaping duration make any scientific conclusions about the vaping population tenuous at best.

Note that these issues are related only to an assessment of human health risks. They do not incorporate other potentially important factors, such as public risk perceptions, risk management options/control measures (e.g., ventilation), and nicotine dependence.

As the scientific community attempts to determine the inhalation health effects of the primary components of e-cigarettes, current literature reveals little about the potential synergistic effects of the main chemical components and of the numerous flavoring additives used. Additionally, there is a dearth of information about the synergistic effects from e-cigarette contents and other environmental contaminants.

Health and Sustainability Considerations

Many groups are affected either directly or indirectly by e-cigarettes. The type and magnitude of the effects are dependent on which group is being evaluated. Groups of interest include current smokers, former smokers, adults who never smoked, middle and high school students, children, pregnant women, workers, the public, and individuals with compromised health (e.g., immunocompromised, heart disease, and lung disease). Discussions in the general literature, and even in the scientific literature, often evaluate these groups indiscriminately.

For smokers, vaping is less toxic than smoking because the particulates and harmful toxicants generated by the burning process are significantly reduced or eliminated. On its surface, this is the only group that clearly benefits from e-cigarettes. For adults who are not current smokers or who have never smoked, vaping clearly introduces toxicants including nicotine, flavorings, and vehicle compounds, and their thermal degradation products.

Although the health effects to vapers may not be as great as those associated with traditional smoking, they are greater than not vaping at all. Nicotine itself raises blood pressure, increases heart rate, and is highly addictive. The flavorings used are often considered GRAS as food additives, but these chemicals are inhaled during vaping, which obviously changes the route of exposure. There is little or no information about the health effects of various food additives that are inhaled rather than ingested. For example, diacetyl is safe when ingested on popcorn, but it potentially causes severe lung problems when inhaled during the manufacturing process.[51]

If the only individual affected by using e-cigarettes were the vaper, the discussion could end here. That is not, however, the case. Similar to secondhand smoke, the ingredients exhaled by the vaper include nicotine, metals, flavorings, and glycol that accumulate in the ambient air. Recipients of secondhand vapor have not chosen to – many, in fact, have explicitly chosen not to – use e-cigarettes. The exposure to secondhand vapor, just like secondhand smoke, raises issues of involuntary exposure and competing rights. This is even more critical for groups that may be, and probably are, more susceptible to adverse effects of secondhand vapor, including children, pregnant women, and people with already compromised health, some of whom may have limited ability to leave the spaces in which vaping occurs or has occurred.

The question of scale must also be considered. When secondhand vapor is evaluated, the scale of the vaping must be included. This would include the volume of the space (size of the room), number and type of e-cigarettes in use, the length of time in use, and the ventilation rate. For example, ASHRAE has developed standards for ventilation rates to maintain indoor air quality in general, and for smoking rooms in particular.[38]

Even with the ASHRAE standards, smoking rooms still have the potential for elevated levels of toxicants from traditional tobacco products. In addition, the implementation of these ASHRAE standards is not without cost. Measurements and evaluation cost time and money. The health effects to individuals exposed before adequate standards are developed and implemented are another cost.

Lastly, health effects that occur throughout the life cycle of an e-cigarette should be considered. The health effects incurred by workers during the extraction of metals; the manufacture of nicotine, flavorings, plastics, and batteries; and the health effects costs to package and distribute e-cigarettes should be evaluated.

Sustainability requires an evaluation of social and economic aspects as well as health and environmental effects. Advertising is a large component of the social acceptability of e-cigarettes. Advertising promoted a positive social image of traditional cigarettes during the mid-20th century. If e-cigarettes are perceived as being used by individuals whom society admires (e.g., movie stars and athletes), their social acceptance will likely be assured. Advertising aimed at high school students and young adults is particularly effective. Once e-cigarettes are socially acceptable, the addictiveness of nicotine will provide a continued user group.

No doubt some individuals and businesses will profit from the development of an e-cigarette industry, and a few might become quite wealthy. There are several economic costs, however, that must also be evaluated. If e-cigarettes are not regulated in public places, contaminants produced by them in the ambient air may keep customers away. At this point, most Americans would not want to be an airplane passenger or be eating in a restaurant where traditional cigarette smoking is freely permissible. If e-cigarettes are not regulated in workplaces, the real and/or perceived effects will likely result in lost productivity, comparable to the lost productivity associated with poor indoor environmental quality. Any increased health care costs associated with the use of e-cigarettes, especially when health care costs are already enormous, must be factored into overall national and global economies.

Quantitative health risk assessment and the setting of exposure limits are useful in some situations, such as occupational exposure control and environmental cleanup projects.[110] Other types of risk assessment may be more useful in evaluating e-cigarettes, such as a risk assessment methodology that looks at the costs and benefits of using a product and then compares them to the costs and benefits of not using the product. In the case of e-cigarettes, the only group that may benefit from their use consists of people who already smoke and who may want to reduce their exposure to combustion byproducts. For other groups, however, there are no benefits and there may be health risks. The health consequences of secondhand exposure to nicotine and other substances may be imposed involuntarily on vulnerable populations, such as children, pregnant women, and people with cardiovascular and/or lung conditions.

Health effects that occur throughout the life cycle of the e-cigarette should also be considered. Sustainability evaluations involve life cycle analyses that evaluate costs associated with extraction, manufacturing, delivery, use and disposal of e-cigarettes. The health effects incurred by workers during the extraction of metals, the manufacture of nicotine, flavorings, plastics, and batteries, as well as the health effects costs to package and distribute e-cigarettes, should be evaluated. Metals used in e-cigarettes and the batteries to run them are mined by workers exposed to dust and other hazards. Also, inhalation and musculoskeletal health effects are associated with the manufacture of plastics, nicotine, and flavorings used in e-cigarettes.

End-of-useful-life considerations for e-cigarettes should also be done before mass production begins. Considerations should include battery recycling and/or reuse, and how the plastic used in the cigarette itself will be recycled or reused, in order to reduce the environmental impact of disposing of these e-cigarette components.

Conclusions and Recommendations

Given this review of available information, the existing research does not appear to warrant the conclusion that e-cigarettes are “safe” in absolute terms. Although they may provide a “safer” alternative to tobacco cigarettes for the vaper, these products emit airborne contaminants that may be inhaled by both the user and those in the vicinity of vaping. Many of the data sources reviewed confirm that e-cigarettes are not emission-free and that their pollutants could be of health concern for users and those who are exposed secondhand. Therefore, e-cigarettes should be considered a source of VOCs and particulates in the indoor environment that have not been thoroughly characterized or evaluated for safety.

Multiple scientific reports express the need for more research. Much can be learned, however, from critically evaluating what we already know. Clearly, e-cigarettes lack the combustion products produced by smoking tobacco, many of which are associated with cancer development. Although nicotine may not cause cancer, it is associated with other adverse physiological effects. In addition, the other components in e-cigarettes may not be benign, particularly when they are inhaled rather than ingested.

Some areas that need further research include:

1. Health effects from inhaling e-cigarette flavorings and other ingredients that are reported to be generally recognized as safe via ingestion but which have not yet

been evaluated for inhalation toxicity, as well as their thermal degradation products;

2. Effects of secondhand emissions, thirdhand exposures, and nicotine addiction from e-cigarettes, especially on vulnerable populations;

3. The dynamics of pre- and post-respiration aerosols and their fate in the environment; and

4. Life cycle and end-of-use issues.

Because of concerns about primary and secondary exposure to e-cigarette vapors and e-juice fluids, AIHA supports risk-based regulation of e-cigarettes using reliable safety, health, and emissions data. Current regulations for devices that are advertised for “therapeutic purposes” do not address the multitude of e-cigarette devices and flavored e-juice formulas. However, until reliable data can be obtained on the vapor contents, using standardized test methods and procedures, regulatory efforts may either fall short or overreach.

E-cigarettes are likely to touch several regulatory frameworks but have, until recently, fallen through the lattice of existing laws and regulations. The April 24, 2014, decision by the FDA to pursue regulation of e-cigarettes as a tobacco product is the first of several possible regulatory reviews of this product family.[80] Others include the Consumer Product Safety Commission and OSHA. Four areas of regulation relating to the safety of primary users and people exposed to secondhand vapors or e-juices should be considered:

1. All e-cigarette devices, whether they are being used for therapeutic or recreational purposes, should be evaluated for potential physical and/or electrical hazards by applicable regulatory agencies.
2. The health risks and economic consequences of accidental exposure to e-juice liquids by children, adults, and pets should be addressed, including proper labeling and child-resistant packaging requirements.
3. All future e-juice components that may be used by consumers should be fully evaluated for any potential hazards (e.g., toxicity, flammability, safety hazards, and secondary exposures) prior to introduction into the marketplace.
4. Because e-cigarettes are a potential source of pollutants (such as airborne nicotine, flavorings, and thermal degradation products), their use in the indoor environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants.

Electronic Cigarettes in the Indoor Environment Project Team Members

Cheryl L. Marcham, PhD, CIH, CSP, CHMM
Project Team Leader
The University of Oklahoma Health Sciences Center

John P. Springston Jr., MS, CIH, CSP
White Paper Editor
TRC Environmental Corp.

Alan Rossner, PhD, CIH, CSP
Member
Clarkson University

Mitch Bergner, CIH
Member
Conestoga-Rovers & Associates

J. David Krause, PhD, MSPH, CIH
Member
Geosyntec

Timothy Froehlig, CIH
Member
Amtrak

Mary O'Reilly, PhD, CIH, CPE
Member
School of Public Health, SUNY at Albany

Ralph A. Froehlich, CIH, CSP, QEP
Member
Helix Environmental Inc.

Dora Gosen, CSP
Member
California Institute of Technology

Pamela Williams, MS, ScD
Member
E Risk Sciences, LLP
Colorado School of Public Health

Veronica Stanley
Member
Johns Hopkins University

Ellen Gunderson, CIH, CSP
Member
University of Washington

Patrick Breysse, PhD, CIH
Member
Bloomberg School of Public Health

Warren Friedman, PhD, CIH, FAIHA
Member
HUD Office of Lead Hazard Control and Healthy Homes

Electronic Cigarettes in the Indoor Environment External Reviewers

David L. Johnson, PhD, CIH
Department of Occupational and Environmental Health
The University of Oklahoma Health Sciences Center

Evan L. Floyd, PhD
Department of Occupational and Environmental Health
The University of Oklahoma Health Sciences Center

David O. Carpenter, MD
Institute for Health and the Environment
University at Albany

Gary Adamkiewicz, PhD, MPH
Department of Environmental Health
Harvard School of Public Health

References

1. "Smokeless non-tobacco cigarette." Available at www.google.com/patents/US3200819 (accessed March 14, 2014).

2. **PR Newswire**: "CASAA: New study confirms that chemicals in electronic cigarettes pose minimal health risk" (Aug. 8, 2013). Available at www.prnewswire.com/news-releases/casaa-new-study-confirms-that-chemicals-in-electronic-cigarettes-pose-minimal-health-risk-218843731.html (accessed Sept. 9, 2013).

3. **Burstyn, I.**: Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks? 2013. Available at http://publichealth.drexel.edu/SiteData/docs/ms08/f90349264250e603/ms08.pdf (accessed Sept. 9, 2013).

4. **Nordqvist, C.**: Electronic cigarettes harm the lungs. *Medical News Today* (June 10, 2013). Available at www.medicalnewstoday.com/articles/249784.php (accessed Sept. 9, 2013).

5. **Vardasvas, C.I., N. Anagnostopous, M. Kougas, V. Evangelopou, G.N. Connolly, and P.K. Behrakis:** Short-term pulmonary effects of using an electronic cigarette: Impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest 141(6)*:1400–1406 (2012).

6. **Chen, I.**: FDA summary of adverse events on electronic cigarettes. *Nicotine and Tobacco Research 15*(2):615–616 (2012). doi:10.1093/ntr/nts145.

7. **Food and Drug Administration**: "FDA news release: FDA and public health experts warn about electronic cigarettes." 2009. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm173222.htm (accessed Aug. 21, 2013).

8. **World Health Organization**: *Questions and Answers on Electronic Cigarettes or Electronic Nicotine Delivery Systems (ENDS)*. 2013. Available at www.who.int/tobacco/communications/statements/eletronic_cigarettes/en/ (accessed Dec. 20, 2013).

9. **American Lung Association**: "American Lung Association Statement on E-Cigarettes." Available at www.lung.org/stop-smoking/tobacco-control-advocacy/federal/e-cigarettes.html (accessed Dec. 20, 2013).

10. **American Association of Poison Control Centers:** "E-Cigarette Devices and Liquid Nicotine." Available at www.aapcc.org/alerts/e-cigarettes/ (accessed April 17, 2014).

11. **Brown, J.E., W. Luo, L.M. Isabelle, and J.F. Pankow**: Candy flavorings in tobacco (Letter to the Editor). *New England Journal of Medicine. 370(23)*:2250–2252 (2014).

12. **Trehy, M.L., W. Ye, M.E. Hadwiger, T.W. Moore, J.F. Allgire, J. T. Woodruff, S.S. Ahadi, J.C. Black, and B. J. Western**: Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. *Journal of Liquid Chromatography & Related Technologies 34*:1442–1458 (2011).

13. **Foulds, J.**: Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. *International Journal of Clinical Practice 65*(10):1037 (2011). doi:10.1111/j.1742-1241.2011.02751.x.

14. **Flouris, A.D., M.S. Chorti, K.P. Poulianiti, A.Z. Jamurtas, K. Kostikas, M.N. Tzatzarakis, A.W. Hayes, A. M. Tsatsakis, and Y. Koutedakis**: Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation Toxicology 25(2)*:91–101 (2013).

15. **Riker, C.A., K. Lee, A. Darville, and E. J. Hahn**: E-cigarettes: promise or peril? *The Nursing Clinics of North America 47(1)*:159 (2012). doi:10.1016/j.cnur.2011.10.002.

16. **Cahn, Z., and M. Siegel**: Electronic cigarettes as a harm reduction strategy for tobacco control: A step forward or a repeat of past mistakes? *Journal of Public Health Policy 32*:16–31 (2011).

17. **Schripp, T., D. Markewitz, E. Uhde, and T. Salthammer**: Does e-cigarette consumption cause passive vaping? *Indoor Air 23*:25–31 (2013). doi:10.1111/j.1600-0668.2012.00792.x.

18. **McAuley, T.R., P.K. Hopke, J. Zhao, and S. Babaian**: Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhalation Toxicology 24(12)*:850–857 (2012). doi:10.3109/08958378.2012.724728.

19. **Williams M., A. Villarreal, K. Bozhilov, S. Lin, and P. Talbot**: Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS ONE 8(3)*:e57987 (2013). doi:10.1371/journal.pone.0057987.

20. **Food and Drug Administration:** *Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted by FDA*. 2009. Available at www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm (accessed April 17, 2014).

21. **Czogala, J., M.L. Goniewicz, B. Fidelus, W. Zielinska-Danch, W. Travers, and A. Sobczak**: Secondhand exposure to vapors from electronic cigarettes. *Nicotine and Tobacco Research*. 2013. doi:10.1093/ntr/ntt203.

22. **Villa, A.F., P. Sauvic, V. Gazin, and R. Garnier**: Electronic cigarettes: Risk assessment. *Clinical Toxicology 50(4)*:309–310 (2012).

23. **Trtchounian, A., and P. Talbot**: Electronic nicotine delivery systems: Is there a need for regulation? *Tobacco Control 20*:47–52 (2011). doi:101136/tc.2010.037259.

24. **Goniewicz, M. L.**: Nicotine levels in electronic cigarettes. *Nicotine & Tobacco Research. 15(1)*:158 (2013). doi:10.1093/ntr/nts103.

25. **Etter, J., E. Zather, and S. Svensson**: Analysis of refill liquids for electronic cigarettes. *Addiction 108*:1671–1679 (2013). doi:10.1111/add.12235.

26. **Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health**: *Nicotine: Systemic Agent*. 2013. Available at www.cdc.gov/niosh/ershdb/EmergencyResponseCard_29750028.html (accessed June 24, 2013).

27. **Davis R., W. Rizwani, S. Banerjee, M. Kovacs, E. Haura, D. Coppola, and S. Chellappan**: Nicotine promotes tumor growth and metastasis in mouse models of lung cancer. *PLoS One 4(10)*:e7524 (2009). doi:10.1371/journal.pone.0007524.

28. **Heeschen, C., J.J. Jang, M. Weis, A. Pathak, S. Kaji, R.S. Hu, P.S. Taso, F.L. Johnson, and J.P. Cooke**: Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. *Nature Medicine 7*:833–839 (2001).

29. **Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health**: *Occupational Health Guideline for Nicotine.* 1978. Available at www.cdc.gov/niosh/docs/81-123/pdfs/0446.pdf (accessed June 24, 2013).

30. **National Institute on Drug Abuse**: *Tobacco Addiction (Nicotine).* Available at www.drugabuse.gov/drugs-abuse/tobacco-addiction-nicotine (accessed June 24, 2013).

31. **DiFranza J.R., J.A. Savageau, K. Fletcher, J. O'Laughlin, L. Pbert, J.K. Ockene, A.D. McNeill, J. Hazelton, K. Friedman K, G. Dussault, C. Wood, and R.J. Wellman:** Symptoms of tobacco dependence after brief intermittent use. *Archives of Pediatric & Adolescent Medicine 161(7)*:704–710 (2007).

32. **Haass, M., and W. Kübler**: Nicotine and sympathetic neurotransmission. *Cardiovascular Drugs Therapy 10(6)*:657–665 (1997).

33. **Wickstrom, P.**: Effects of nicotine during pregnancy: Human and experimental evidence. *Current Neuropharmacology 5(3)*:213–222 (2007). doi:10.2174/157015907781695955.

34. **Environmental Protection Agency**: *Final Report: Developmental Neurotoxicity in Offspring Induced by Combined Maternal Exposure of Rats to Nicotine and Chlorpyrifos*. Available at http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/1756/report/F (accessed June 24, 2013).

35. **Slotkin, T.A.:** Fetal nicotine or cocaine exposure: Which one is worse? *Journal of Pharmacology and Experimental Therapeutics. 285(3)*:931–945 (1998).

36. **Schober, W., K. Szendrei, W. Batzen, H. Osiander-Fuchs, D. Heitmann, D., T. Schettgen, R. Jorres, and H. Fromme**: Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *International Journal of Hygiene and Environmental Health* (2013). doi:10.1016/j.ijheh.2013.11.003.

37. **Occupational Safety and Health Administration**: *Nicotine*. Available at www.osha.gov/dts/chemicalsampling/data/CH_256500.html (accessed Dec. 5, 2013).

38. **American Society of Heating, Refrigerating and Air-Conditioning Engineers**: ANSI/ASHRAE Standard 62.1–2013 – *Ventilation for Acceptable Indoor Air Quality*. Atlanta, Ga.: ASHRAE, 2013, p. 28.

39. "Roswell Park Researchers Present Findings of Two E-Cigarette Studies at SRNT Meeting." (Feb. 7, 2014). Available at https://www.roswellpark.org/media/news/roswell-park-researchers-present-findings-2-e-cigarette-studies-srnt-meeting (accessed May 7, 2014).

40. "What Is Propylene Glycol?" Available at www.discountvapers.com/what-is-propylene-glycol/ (accessed Jan. 9, 2014).

41. **Wagener, T.L., M. Siegel, and B. Borreli**: Electronic cigarettes: Achieving a balanced perspective. *Addiction 107*:1545–1548 (2012). doi:10.1111/j.1360-0443.2012.03826.x.

42. "Custom E-liquid Blends and Mixture Ingredients for Custom Blending." Available at www.myfreedomsmokes.com/ (accessed March 1, 2014).

43. "E-juice Recipe Calculator." Available at www.todmuller.com/ejuice/ejuice.php (accessed March 1, 2014).

44. **American Chemistry Council**: "Propylene Glycol Information Update." Available at www.lyondellbasell.com/techlit/techlit/2280.pdf (accessed Jan. 9, 2014).

45. **Varughese, S., K. Teschke, M. Brauer, Y. Chow, C. van Netten, and S.M. Kennedy**: Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. *American Journal of Industrial Medicine 47*:411–418 (2005).

46. **McCauley, L., C. Markin, and D. Hosmer**: An unexpected consequence of electronic cigarette use. *Chest 141(4)*:1110–1113 (2012). doi:10.1378/chest.11-1334.

47. **Goniewicz, M.L., J. Knysak, M. Gawron, L. Kosmider, A. Sobczak, J. Kurek, A. Prokopowicz, M. Jablonska-Czapla, C. Rosik-Dulewska, C. Havel, P. Jacob, and N. Benowitz**: Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control. 0:*1–7 (2013). doi:10.1136/tobaccocontrol-2012-050859.

48. **Cavender, F.L., and E.J. Sowincki**: Glycols. In *Patty's Industrial Hygiene and Toxicology* (4th ed.), G.D. Clayton and F.E. Clayton (eds.). New York: John Wiley, 1982. pp. 4657–4662.

49. **Flavor and Extract Manufacturers Association:** "Safety Assessment and Regulatory Authority to Use Flavors: Focus on E-Cigarettes." Available at www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-e-cigarettes (accessed Jan. 7, 2014).

50. **Brown, J.E., W. Luo, L.M. Isabelle, and J.F. Pankow**: Candy flavorings in tobacco (Letter to the Editor). *New England Journal of Medicine. 370(23)*: 2250–2252 (2014).

51. **Centers for Disease Control and Prevention**: *Flavorings-Related Lung Disease*. 2011. Available at www.cdc.gov/niosh/topics/flavorings/ (accessed April 21, 2014).

52. **California Safety & Health Code:** Subchapter 7. General Industry Safety Orders. Group 16. Control of Hazardous Substances, Article 109. Hazardous Substances and Processes Sec. 5197. Occupational Exposure to Food Flavorings Containing Diacetyl. 2010. Available at https://www.dir.ca.gov/title8/5197.html (accessed April 21, 2014).

53. **Uchiyama, S., K. Ohta, Y. Inaba, and N. Kunugita**: Determination of carbonyl compounds generated from the e-cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, followed by high-performance liquid chromatography. *Analytical Sciences 29(12)*:1219–1222 (2013).

54. **Vardasvas, C.I., N. Anagnostopous, M. Kougas, V. Evangelopou, G.N. Connolly, and P.K. Behrakis:** Short-term pulmonary effects of using an electronic cigarette: Impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest 141(6)*:1400–1406 (2012).

55. **Agency for Toxic Substances & Disease Registry**: *Reasonably Anticipated to be a Human Carcinogen.* 2012. Available at www.atsdr.cdc.gov/substances/toxorganlisting.asp?sysid=24 (accessed Dec. 5, 2013).

56. **Wichmann, H.E., C. Spix, T. Tuch, G. Wolke, A. Peters, J. Heinrich, W.G. Kreyling, and J. Heyder**: Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany. Part I: Role of Particle Number and Particle Mass. *Research Report Health Effects Institute*. 2000. *(98)*:5–86.

57. **Ingebrethsen, B.J., S.K. Cole, and S.L. Alderman**: Electronic cigarette aerosol particle size distribution measurements. *Inhalation Toxicology*. *24(14)*: 976–984 (2012).

58. **Zhang, Y., W. Summer, and D.R. Chen**: In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. *Nicotine Tobacco Research 15*:501–508 (2013).

59. **Moline, J.M., A.L. Golden, J.H. Highland, K.R. Wilmarth, and A.S. Kao**: "Health Effects Evaluation of Theatrical Smoke, Haze and Pyrotechnics." Prepared for Actor's Equity Pension and Health Trust Funds. 2000. Available at www.actorsequity.org/docs/safesan/finalreport.pdf (accessed May 10, 2014).

60. **Marini, S., G. Buanno, L. Stabile, and G. Ficco**: Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. *Toxicology and Applied Pharmacology. 278(1):* 9–15. (2014).

61. **Ohta K., S. Uchiyama, Y. Inaba, H. Nakagome, and N. Kunugita**: Determination of carbonyl compounds generated from the electronic cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, *Bunseki Kagaku 60(10)*:791–797 (2011).

62. **Kosmider L., A. Sobczak, F.C. Fuoco, J. Knysak, M. Zaciera, J. Kurek, and M.J. Goniewicz:** Carbonyl compounds in electronic cigarette vapors ─ Effects of nicotine solvent and battery output voltage. *Nicotine & Tobacco Research* (2014). doi:10.1093/ntr/ntu078.

63. **Sleiman, M., L.A. Gundel, J.F. Pankow, P. Jacob, B.C. Singer, and H. Destaillats**: Formation of Carcinogens Indoors by Surface-Mediated Reactions of Nicotine with Nitrous Acid, Leading to Potential Thirdhand Smoke Hazards. In *Proceedings of the National Academy of Sciences of the United States of America.* 2010. doi:10.1073/pnas.0912820107. Available at www.pnas.org/content/early/2010/02/04/0912820107.full.pdf+html (accessed Jan. 9, 2014).

64. **Ashley, D.L., R.J. O'Connor, and J.T. Bernert**: Effect of differing levels of tobacco-specific nitrosamines in cigarette smoke on the levels of biomarkers in smokers. *Cancer Epidemiology, Biomarkers & Prevention 19*:1389–1398 (2010).

65. **Johnson Creek:** "Allergies Health & Ingredients." Available at www.johnsoncreeksmokejuice.co+m/learn/general-faqshtml (accessed March 14, 2014).

66. "How to Put Marijuana, Concentrates and THC Liquids in an Electronic Cigarette." Available at www.gentlemansvapes.com/blogs/news/6151022-how-to-put-marijuana-concentrates-and-thc-liquids-in-an-electronic-cigarette (accessed March 10, 2014).

67. **10TV:** "Police Warn of New Way to Use Drugs In Plain Sight." (Oct. 1, 2013). Available at www.10tv.com/content/stories/2013/10/01/Columbus_Electronic_Cigarettes.html (accessed March 17, 2014).

68. **Gray, E.:** "Smokers Are Using E-Cigarettes to Get High." *Time* (Oct. 11, 2013). Available at http://nation.time.com/2013/10/11/smokers-are-using-e-cigarettes-to-get-high/ (accessed March 17, 2014).

69. **Hua, M., M. Alfi, and P. Talbot**: Health-related effects reported by electronic cigarette users in online forums. *Journal of Medical Internet Research*. 2013. Available at www.jmir.org/2013/4/e59/ (accessed Sept. 9, 2013).

70. **Vansickel, A., C. Cobb, M. Weaver, and T. Eissenberg:** A Clinical Laboratory Model for Evaluating the Acute Effects of Electronic "Cigarettes": Nicotine Delivery Profile and

Cardiovascular and Subjective Effects. *American Association for Cancer Research*. 2010. doi:10.1158/1055-9965.EPI-10-0288.

71. **Bahl, V., S. Lin, N. Xu, B. Davis, Y. Wang, and P. Talbot**: Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reproductive Toxicology 34*:529-537 (2012).

72. **Cressey, D.:** E-cigarettes affect cells: Questions raised over health effects of devices. *Nature/News 508*:159 (2014).

73. **Flouris, A. D., K.P. Poulianiti, M.S. Chorti, A.Z. Jamurtas, D. Kouretas, O. Owolabi, M.N. Tzatzarakis, A.M. Tsatsakis, and Y. Koutedakis**: Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food and Chemical Toxicology (0278–6915)*, 50(10), 3600 (2012). doi:10.1016/j.fct.2012.07.025.

74. **Farsalinos, K., D. Tsiapras, S. Kyrzopoulos, M. Savvopoulou, E. Avramidou, D. Vasilopoulou, and V. Voudris**: Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: Comparison with the effects of regular cigarettes. ESC Congress, 2012.

75. **Benowitz, N.L.**: Smokeless tobacco as a nicotine delivery device: Harm or harm reduction? *Clinical Pharmacology & Therapeutics 90(4)*:491–493 (2011).

76. **Wagner, D.D., S.D. Cin, J.D. Sargent, W.M. Kelley, and T.F. Heatherton**: Spontaneous action representation in smokers when watching movie characters smoke. *Journal of Neuroscience 31(3)*:894–898 (2011).

77. **American Association of Poison Control Centers:** "E-Cigarette Devices and Liquid Nicotine." Available at www.aapcc.org/alerts/e-cigarettes/ (accessed April 17, 2014).

78. **West Yorkshire Fire and Rescue Service**: "Advice to E-cigarette Users This Christmas." Available at www.westyorksfire.gov.uk/news/advice-to-e-cigarette-users-this-christmas (accessed Feb. 6, 2014).

79. **Electronic Cigarette Consumer Reviews:** "Do E-cigarettes Set off Smoke Alarms or Smoke Detectors?" Available at www.electroniccigaretteconsumerreviews.com/do-e-cigarettes-set-off-smoke-alarms-or-smoke-detectors/ (accessed April 17, 2014).

80. **Schmidt, C.:** Newsmaker Interview: A Former Surgeon General Lends His Support to E-Cigarettes. *Science*. *343(6171)*: 589 (2014). doi:10.1126/science.343.6171.589.

81. **Robinson, D., and S. Bond**: WHO Plans to Regulate E-cigarettes in Same Way as Normal Tobacco. *Financial Times* (April 13, 2014). Available at www.ft.com/intl/cms/s/0/d822d056-c1c3-11e3-83af-00144feabdc0.html#axzz2zctUtLoI (accessed April 23, 2014).

82. **Food and Drug Administration:** *Electronic Cigarettes (e-Cigarettes)*. 2014. Available at www.fda.gov/newsevents/publichealthfocus/ucm172906.htm (accessed March 27, 2014).

83. **Food and Drug Administration:** *Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products: A Proposed Rule by the Food and Drug Administration.* 2014. Available at www.federalregister.gov/articles/2014/04/25/2014-09491/deeming-tobacco-products-to-

be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the (accessed April 25, 2014.)

84. **Freiberg, M.**: "Options for state and local governments to regulate non-cigarette tobacco products." *Annals of Health Law* 21(2), 407 (2012). Available at http://lawecommons.luc.edu/annals/vol21/iss2/6/ (accessed September 24, 2014).

85. **Hirschler, B.**: Britain to regulate e-cigarettes as medicine from 2016. *Reuters* (June 12, 2013). Available at www.reuters.com/assets/print?aid=USBRE95B0HL20130612 (accessed Sept. 30, 2013).

86. "DeSoto County Bans Use of E-Cigarettes." *The Dispatch* (March 21, 2014). Available at www.cdispatch.com/news/article.asp?aid=32019 (accessed March 27, 2014).

87. **O'Connor, L.:** "San Francisco is the Latest City to Restrict E-Cigarettes Under Anti-Smoking Laws." *Huffington Post* (March 21, 2014). Available at www.huffingtonpost.com/2014/03/19/e-cigarettes-ban-san-francisco_n_4995546.html (accessed March 27, 2014).

88. **Ross, J.**: Duluth says no to e-cigarettes; state says it will consider options. *Star Tribune* (Sept. 11, 2013). Available at www.startribune.com/local/223235121.html (accessed Sept. 9, 2013).

89. **Fallin, M.**: "Executive Order 2013–43." Available at www.sos.ok.gov/documents/Executive/923.pdf (accessed Jan. 9, 2014).

90. **National Council of State Legislatures:** "Alternate Nicotine Products: E-Cigarettes." (Aug. 1, 2014). Available at www.ncsl.org/research/health/alternative-nicotine-products-e-cigarettes.aspx (accessed Sept. 3, 2014).

91. **Drill, S.**: FDA discusses banning online sales of e-cigarettes. *Wall Street Journal* (Aug. 23, 2013). Available at http://online.wsj.com/article/SB10001424127887323980604579028872575240180.html (accessed Aug. 26, 2013).

92. **Department of Transportation**: DOT Policy on E-cigarettes. Available at www.dot.gov/sites/dot.gov/files/docs/PolicyOnECigarettes.pdf (accessed Dec.5, 2013).

93. "Smoking Aboard Aircraft," *Code of Federal Regulations Title 14,* Part 252. 2000. Available at www.gpo.gov/fdsys/pkg/CFR-2001-title14-vol4/pdf/CFR-2001-title14-vol4-part252.pdf (accessed Dec. 5, 2013).

94. **U.S. Department of Transportation**: *Smoking of Electronic Cigarettes on Aircraft*. 76 FR 57008–57012. Sept. 15, 2011. Available at www.dot.gov/sites/dot.dev/files/docs/E-cigarette%20NPRM.pdf (accessed June 30, 2014)

95. **Government Printing Office**: 49 USC Sec. 41706. Prohibitions Against Smoking on Scheduled Flights. 2000. Available at www.gpo.gov/fdsys/pkg/USCODE-2011-title49/pdf/USCODE-2011-title49-subtitleVII-partA-subpartii-chap417-subchapI-sec41706.pdf (accessed Dec. 5, 2013).

96. **Government Printing Office:** 49 USC Sec. 41702. Interstate Air Transportation. 1994. Available at www.gpo.gov/fdsys/pkg/USCODE-2011-title49/pdf/USCODE-2011-title49-subtitleVII-partA-subpartii-chap417-subchapI-sec41702.pdf (accessed June 17, 2014).

97. **American Cancer Society Cancer Action Network, American Heart Association, American Lung Association, Campaign for Tobacco Free Kids, Legacy:** Letter to

the U.S. Department of Transportation. Nov. 14, 2011. Available at www.lung.org/get-involved/advocate/advocacy-documents/dot-e-cigarettes.pdf (accessed Sept. 9, 2013).

98. **United Airlines**: "Contract of Carriage." Available at www.united.com/web/format/pdf/Contract_of_Carriage.pdf (accessed Dec. 5, 2013).

99. **JetBlue**: "Contract of Carriage." Available at www.jetblue.com/p/jetblue_coc.pdf (accessed Dec. 5, 2013).

100. **JetBlue**: "Help: Electronic/Smokeless Cigarettes." Available at http://help.jetblue.com/SRVS/CGI-BIN/webisapi.dll/,/?St=59,E=0000000000184029089,K=6287,Sxi=17,Case=obj(395995) (accessed Dec. 5, 2013).

101. **Electronic Cigarette Review**: "Electronic Cigarette Smoking on Planes." [Blog]. Available at www.electroniccigarettereview.com/smoking-on-planes/ (accessed Dec. 5, 2013).

102. **Amtrak**: **"**Smoking Policy." Available at www.amtrak.com/smoking-policy (accessed Dec. 5, 2013).

103. **Metropolitan Transportation Authority: "**Sorry, No Smoking (Including E-Cigs.) *Train Talk.* Available at http://web.mta.info/lirr/TrainTalk/2013/07-2013.htm (accessed June 30, 2014).

104. **Los Angeles County Metropolitan Transportation Authority.** Executive Management and Audit Committee. Customer Code of Conduct Amendments — Transit Court. March 20, 2014. Amended LACMTA Administrative Code Sec. 6–05–110 to add a prohibition against "vaping." Available at http://media.metro.net/board/Items/2014/03_march/20140327rbmitem36.pdf (accessed June 30, 2014).

105. **Sneider, J**: Transit-rail agencies adapt smoking policies to cover e-cigarettes. *Progressive Railroading*. 2014. Available at www.progressiverailroading.com/passenger_rail/article/Transitrail-agencies-adapt-smoking-policies-to-cover-ecigarettes--40172 (accessed April 25, 2014).

106. **Megabus**: "Terms & Conditions." Available at http://us.megabus.com/terms.aspx (accessed Dec. 5, 2013).

107. **Boltbus**: "Terms and Conditions." Available at https://www.boltbus.com/Terms.aspx (accessed Dec. 5, 2013).

108. **Greyhound**: "Terms and Conditions of Purchase & Carriage." Available at www.greyhound.com/en/ticketsandtravel/TermsAndConditions.aspx#SmokingisProhibited (accessed Dec. 5, 2013).

109. **U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality:** Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. Past Month Smokers of One or More Packs of Cigarettes per Day among Daily Smokers, by Age Group: 2002–2012. Figure 4.6 and accompanying text. Available at www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm#ch4 (accessed June 30, 2014).

110. **Boelter, F., M. Jayjock, F. Hearl, C. Laszcz-Davis, P. Logan, C. McLaughlin, M. O'Reilly, T. Radcliff, and M. Stenzel**: "Human Health Risk Assessment," in *Patty's Industrial Hygiene and Toxicology,* 6th ed. V. Rose (ed.). New York: John Wiley, 2010. pp. 695–826.