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Electronic Cigarettes in the Indoor Environment

White Paper

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Executive Summary

The use of electronic cigarettes (e-cigarettes or "vaping") has seen an unprecedented increase worldwide. Vaping has been promoted as a beneficial smoking cessation tool and an alternative nicotine delivery device that contains no combustion byproducts. However, nicotine is highly addictive, and the increased use of nicotine-containing e-cigarettes among teens and individuals who are not in need of smoking cessation may lead to overall greater nicotine dependence in the population. 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 materials could present undefined potential health hazards to both e-cigarette users and bystanders, the full extent of which is not well-understood at this time. Whereas e-cigarette usage and exposures may lower some or most of the risks associated with conventional cigarette use, the health effects of nicotine and aerosol exposures from e-cigarettes are not fully characterized. Research indicates that vaping aerosols are not benign, especially for nearby people in areas with limited ventilation and people with compromised health conditions. In addition, e-juice liquids have already been responsible for an increase in accidental poisonings in children.

Because the magnitude of health and safety hazards that vaping may present to nonusers remains unclear, it is prudent to manage and control vaping in indoor locations where smoking is currently restricted.

Based on a review of current scientific information, the following actions should be taken to better understand and protect the public from potential health and safety risks associated with vaping in indoor environments:

1. E-cigarettes should be considered a source of aerosols, volatile organic compounds (VOCs), and particulates in the indoor environment that have not been thoroughly characterized or evaluated for health risk or safety.
2. Research on e-cigarettes should be conducted in at least the following areas:
    a. health effects from inhaling e-cigarette flavorings and other ingredients that are reported to be generally recognized as safe (GRAS) via ingestion but that have not yet been evaluated for inhalation toxicity, as well as their thermal degradation products;
    b. effects of secondhand emissions, thirdhand exposures, and nicotine addiction from e-cigarettes;
    c. the dynamics of pre- and post-respiration aerosols and their fate in the environment; and
    d. life cycle and end-of-use issues associated with e-cigarette manufacturing, use, and disposal.
3. Due to concerns about primary and secondary exposures to vapors and fluids (e-juices) used in e-cigarettes, risk-based regulations on e-cigarettes should be adopted using reliable safety, health, and emissions data. Four areas of regulation, relating to the safety of both primary users and people exposed to secondhand vapors or e-juice products, should be considered:
    a. All e-cigarette devices, whether they are used for therapeutic or recreational purposes, should be evaluated for potential physical and/or electrical hazards by a regulatory agency.
    b. The health risks and economic consequences of accidental exposure to e-juices by children, adults, and pets should be addressed, including proper labeling and child-resistant packaging requirements.

c. All future e-juice components that may be used by consumers should be fully evaluated for any potential health or safety hazards (e.g., toxicity, flammability, secondary exposures) prior to introduction into the marketplace.
d. As e-cigarettes are a potential source of pollutants (such as airborne nicotine, flavorings, and thermal degradation products), it is prudent to manage and control vaping in indoor environments consistent with current smoking policies, until and unless research demonstrates that these devices will not significantly increase the risk of adverse health effects to 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 to consume. 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-cigs, electronic vaping devices, personal vaporizers (PV), electronic hookahs, and e-hookahs. 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 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, a 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 with regular cigarettes.[2,3] On the other hand, several scientific studies suggest that e-cigarettes may cause a variety of short- or long-term health effects, such as increased airway resistance in the lungs[4-6] and DNA damage.[7] 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.[8] 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.[9] The American Lung Association has also issued a statement expressing its concern about the potential health and safety consequences of e-cigarettes.[10]

Poison control centers have warned of an increased rate of poisonings, especially in children, from the nicotine-containing multiflavored e-liquids (also called "e-juices") that are used to refill e-cigarettes.[11] 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.[12] 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.

Most of the literature reviewed for this report indicates that e-cigarettes are likely to pose a lower health risk than conventional tobacco smoking. Many questions, however, remain regarding the potential human health risks posed by the use of e-cigarettes indoors, especially to 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. This review updates a prior AIHA white paper published in June 2014.

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 bystanders, in the indoor environment. The methodology used by AIHA in conducting this updated literature review included a search of both current and recent past scientific literature using various publication search engines (e.g., PubMed). Additionally, to capture the rapidly changing landscape of information on e-cigarettes, AIHA has incorporated internet searches 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 updated white paper presents what is known and not known at the time of publication.

How E-cigarettes Work

Early e-cigarettes (first-generation) (Figure 1) 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, battery-operated heat source that converts liquid nicotine, flavorings, and diluents into a mist or vapor that the user inhales. The inhalation of aerosols from e-cigarettes is commonly called “vaping” instead of “smoking.”

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Figure 1: Early-generation disposable electronic cigarette resembling a traditional cigarette.

While some e-cigarettes are designed to be totally disposable, most other e-cigarettes contain a rechargeable lithium battery and disposable vaporization chamber, wicking system, and nicotine/flavoring cartridge. The cartridge containing e-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 simulate a flame and indicate that there is still charge on the attached battery. Second- and third-generation devices moved away from looking like tobacco cigarettes (Figures 2 and 3). These devices have larger batteries and larger

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Figure 2: Second-generation e-cigarettes.

royaltystockphoto/Getty Images

Figure 3: Examples of other kinds of e-cigarettes.

e-juice 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 airflow can greatly affect the amount of vapor generated with each puff. After inhalation, the user exhales a portion of the vapor.

In contrast to the larger and more powerful third-generation devices, smaller and "stealthier" devices have been developed that are easily concealed and produce little telltale plume.[13] Some look like flash drives or pens,[13] are charged through USB ports, and use nicotine "pods" that come in a variety of flavors.[14] In fact, one such product, JUUL, represented nearly 50% of the dollar share of the U.S. ENDS market in February 2018.[14] Manufacturers are also producing and selling lines of hoodies and other clothing specifically designed to conceal vaping by the wearer.[13]

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.[15] Nicotine levels within these cartridges, however, have been found to be inconsistent due to poor quality control.[15] 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).[16] Propylene glycol (PG) and vegetable glycerin (VG) 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.[16-18]

In regular tobacco smoke, many of the toxic and carcinogenic agents 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.[17,19] While the primary components of electronic cigarette cartridges are PG, VG, and nicotine,[19] e-cigarettes also contain flavoring agents and other compounds, and the use of e-cigarettes has been shown to emit aerosols, particulates, and VOCs, including nicotine, diethylene glycol, nitrosamines, 1,2-propanediol, acetic acid, acetone, isoprene, formaldehyde, acetaldehyde, propaldehyde, and flavoring compounds into indoor air.[8,18,20,21] Additionally, aerosols generated from e-cigarette consumption may contain various metals and silica particles from wick and heating coil constituents.[22] 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 many electronic cigarette cartridges that were labeled as containing no nicotine did, in fact, contain detectable levels of nicotine.[23] Three different cigarette cartridges that displayed the same label produced varying amounts of nicotine with each puff.[24] A French study evaluated the nicotine content and labeling of e-cigarettes and found incomplete or unusable information, as well as unreliable labeling.[25] The amounts of nicotine measured in 20 prepackaged cartridge samples were generally higher than that stated on the package, and, in some cases, the nicotine content was found to be two to five times greater.[25]

A review of a number of products purchased online revealed a lack of consistent labeling format and unclear information regarding nicotine content.[26] In one study, nico¬tine amounts in nine out of 20 analyzed cartridges differed by more than 20% from the values declared by their manufacturers.[27] 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.[11,18,27]

Two studies discovered that, in many cases, nicotine degradation products and other impurities, such as nicotine-cis-N-oxide, nicotine-trans-N-oxide, myosmine, anabasine, and anatabine, were present in refill liquids. The authors speculated the impurities were 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,[11,28] although the impurities were reported to be "below the level where they would be likely to cause harm."[28] Goniewicz found that, in addition to the lack of quality control in content and concentration, some products are inconsistent in delivering nicotine.[27] 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.[27] 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. Consequently, 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,[29] respiratory rate,[29] myocardial contractility,[30] blood pressure,[29] and level of alertness.[29] Ocular exposure can cause irritation and redness of the eyes.[29] 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.[29] Nicotine is a teratogen,[29] can promote tumor growth,[31,32] and has caused abnormalities in the offspring of laboratory animals.[33] In addition, the National Institute on Drug Abuse states that nicotine is highly addictive.[34] Addiction to nicotine can occur within days of inhaling one's first conventional cigarette.[35]

In addition to nicotine being a teratogen,[29] prenatal exposure to nicotine in animal studies with doses as low as 0.5 milligram/kilogram/day (mg/kg/day) have shown learning and attention deficits in both young and adult rats.[36] Nicotine has also been demonstrated to produce fetal brain cell damage.[36] A U.S. Environmental Protection Agency (EPA) 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.[37] 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.[38]

According to research by Slotkin, the effects of nicotine on brain development are very similar to those of cocaine.[38]

Study results have confirmed that some e-juices contain amounts of nicotine that are potentially lethal to both children and adults.[39] Because nicotine can readily pass into the bloodstream following dermal contact, there could be a considerable health risk to young children who accidently touch or swallow nicotine solutions.[39] One study reported that, in addition to nicotine, 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.[39]

Because nicotine can be absorbed into the body via inhalation, ingestion, skin contact and through the mucous membranes,[33] 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, Hopke, Zhao, and Babaian compared airborne concentrations of several components of both cigarette smoke and e-cigarettes.[21] The authors reported airborne nicotine concentrations from e-cigarettes ranged from 725 to 8,770 nanograms (ng) per liter (equivalent to 725 to 8,770 micrograms per cubic meter [$\mu g/m^3$]), which were lower than those from regular cigarettes, which ranged from 5,039 $\mu g/m^3$ to 48,050 $\mu g/m^3$.[21] 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.[24] 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 $\mu g/m^3$; the average concentration of nicotine from tobacco cigarettes was 10 times higher.[24] Schober et al. reported airborne concentrations of nicotine during a two-hour vaping session ranging from 0.6 to 4.6 $\mu g/m^3$.[39]

The Occupational Safety and Health Administration (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 (ACGIH) publishes a Threshold Limit Value for nicotine at the same level for an eight-hour time-weighted average (TWA).[40] However, ANSI/ASHRAE Standard 62.1-2016 – *Ventilation for Acceptable Indoor Air Quality*, 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.[41] These standards and guidelines do not attempt to eliminate all effects, such as unpleasant smells or mild irritation.[41] Therefore, the target population and use of these standards and guidelines differ from those for the populations of many public and commercial buildings.[41] Consequently, while the reported airborne levels measured for nicotine from e-cigarettes in the chamber study by Czogala et al.[24] and vaping session by Schober et al.[39] were at a fraction of the OSHA regulatory level, other factors 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.

Glycols and Glycerin

Propylene glycol (PG), a chemical found in theatrical smoke, and vegetable glycerin (VG) are both used in e-cigarettes as vehicles for the nicotine and the flavorings, and to create the "vapor" that is emitted.[16-18] Analysis of various vaping solutions has revealed concentrations of propylene glycol ranging from 60% to 90%, and up to 15% glycerin,[16-18] although some vendors have reported mixtures of equal parts and others substitute VG and water for PG completely.[42] Many websites now supply custom e-liquids formulated the way the user requests them, 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[43] with the help of numerous online concentration calculators[44] or calculation applications available for mobile phones. While PG 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.[19]

Concentrations of 1,2-propanediol (propylene glycol) in the range of 110 µg/m^3 to 215 µg/m^3 and glycerin in the range of 59 µg/m^3 to 81 µg/m^3 were found in the gas phase of emissions during one e-cigarette vaping study.[39] In a different study, PG concentrations of 1,600 to 1,650 mg/m^3 and 580 to 610 mg/m^3 of VG were measured in the vapor emitted from e-cigarettes.[45]

Another study reported airborne concentrations of PG ranging from 2.25 mg/m^3 to 120 mg/m^3.[21]

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.[46] However, in a study of the health effects of theatrical fogs, it was determined that exposure to these fogs at concentrations as low as from 0.02 to 4.11 mg/m^3 may contribute to both acute and chronic health issues, such as asthma, wheezing, chest tightness, decreased lung function, respiratory irritation, and airway obstruction.[47] Particularly, irritated mucous membrane symptoms as well as acute headache, dizziness, and drowsiness were associated with exposures to glycol-based fogs.[47]

Information shared among many vaping websites includes the following:

> 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.[48]

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.[49]

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.[50-52]

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. Studies have shown that the mass of aerosol produced during vaping increases dramatically with the power of the device, which increases as the square of voltage (power in watts = potential in volts2/resistance in ohms).[(53)] 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 6V.[(53)] 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.[(52,54)] This suggests a geometrically increasing risk of toxic effects as the devices gain power via stronger batteries, lower resistances, and adjustable voltages.

Formaldehyde, a recognized human carcinogen, is a known degradation product of propylene glycol and glycerol, and is found in higher airborne concentrations in e-cigarettes that operate at high voltage or feature a variable voltage battery.[(55)] This may be of particular concern in newer-generation e-cigarettes with adjustable voltages, which allow users to generate a thicker vapor.

Diethylene glycol, an impurity of PG, is also an organic compound of concern because it was found 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.[(8,18,19,39,42)] Toxicity studies with diethylene glycol indicate that chronic inhalation of vapor, fog, or mist should be avoided, especially when it is heated or used at elevated temperatures.[(56)] Because of its adverse effects on humans, diethylene glycol is not allowed in food and drugs.[(18)] A review of 15 additional studies of compounds associated with electronic cigarettes, however, did not find diethylene glycol to be present.[(19,42)]

Flavorings

A review of several online manufacturers and suppliers of e-cigarette liquids revealed that an extensive assortment of flavors is available. In January 2014, it was reported that over 7,700 unique e-cigarette flavors were on the market.[(57)] Flavor additives are often referred to as being "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.[(58)] The primary mechanism by which regulatory authority is granted 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 in grape flavoring, and 1-hexanol was in apple flavoring.[(12)] Cinnamaldehyde, a highly cytotoxic agent, was found in one study to be present in 51% of 39 different refill liquids tested.[(59)] Vanillin, cinnamaldehyde, eugenol (clove), acetylpyridine (corn or burnt flavoring), and menthol flavors have been noted to induce endothelial cell dysfunction.[(60)]

According to FEMA,

> 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 United States.[61]

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 temperatures. Therefore, a compound that may be GRAS when ingested is no longer automatically safe when inhaled.

A clear example of this problem is the use of diacetyl (aka butanedione or butane-2,3-dione) as a buttery flavoring for popcorn, baked goods, and liquor. Although it is considered safe for use when ingested in foods, over the past decade, numerous research papers have been published, and personal injury lawsuits filed, regarding employees in factories that manufacture or use artificial butter flavoring who have been diagnosed with bronchiolitis obliterans, a rare and very serious disease of the lungs caused by inhalation of this chemical.[62]

Diacetyl is just one example of a flavoring that is approved for ingestion, but that has potential significant adverse health effects when volatilized and inhaled. Acetyl propionyl (aka 2,3-pentandione) is another component that is considered GRAS, but the risks associated with inhalation of acetyl propionyl may be as high as from diacetyl, based on inhalation studies with rats.[63] Rats that inhaled acetyl propionyl developed necrotizing rhinitis, tracheitis, and bronchitis comparable to diacetyl-induced injury, and 2,3-pentanedione was found to alter gene expression in the rats' brain.[64] A study of 159 samples purchased from 36 manufacturers and retailers in seven countries found diacetyl and acetyl propionyl in 74.2% of the samples, even in samples from manufacturers that clearly stated that these chemicals were not present.[63] In a different study, diacetyl was found in the vapor, but not in the liquid, of 39 of 51 different e-liquid flavors that were tested, and acetyl propionyl and acetoin (another substitute for diacetyl) were detected in 23 and 46, respectively, of the 51 flavors tested.[65]

Due to a lack of strong quality control or labeling requirements, and the lack of research on domestic and imported e-liquids, it is currently unknown 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 and emissions. One German study compared secondhand emissions, including VOCs, of e-cigarettes and conventional cigarettes.[20] Researchers tested three different brands of e-cigarettes loaded with three different liquids — two containing nicotine and one that was nicotine-free. The authors stated that continuous monitoring of the e-cigarette vapor showed only a slight increase in formaldehyde concentrations, which they theorized may have actually been caused by the test subject, rather than the e-cigarettes.[20] Other contaminants 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 e-cigarette, with a 60-second delay between puffs, which may not be representative of normal vaping behavior.[20]

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.[39] Indoor concentrations of vanillin and benzylalcohol were only slightly increased compared with control values. However, PAH concentrations increased on average by 20% over background levels.[39]

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.[24] 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.[24]

Another Polish study examined the vapor generated by 12 brands of e-cigarettes filled with nicotine-containing liquid. The vapor was 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, and these two contaminants were found in almost all the e-cigarettes tested.[50] 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 that were reviewed, formaldehyde, acetaldehyde, o-methylbenzaldehyde, and acrolein were observed in nearly all e-cigarettes tested.[50]

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 benzene, toluene, ethylbenzene, and m,p-xylenes in the vapor.[49] However, the levels of these compounds found 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).[52]

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.[52]

Metal and Silica Particles

E-cigarettes are designed with metal components that have also been found in the vaping aerosol. Resistive wire filaments (nickel-chromium or other metals) are used to heat the wick and evaporate the e-liquid.(22) Often these resistive wires are coupled to non-resistive extensions of copper wire (sometimes coated with silver), and tin solder joints connect the wires to each other, as well as to the air tube and mouthpiece.(22) Fibers found in some cartomizers (atomizers, heating coils) had copper deposits, and both tin particles and tin whiskers were found in some cartridge fluid.(22) 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.(22) The silicates appear to come from fiberglass wicks used in the product and are not expected to be crystalline silica.(22) Goniewicz et al. also found cadmium to be present in the aerosol generated from some, but not all, e-cigarette products.(50)

One study found lead and chromium concentrations in e-cigarette aerosols within the same range as those found in emissions from conventional cigarettes (0.017 μg/10 puffs for lead and 0.007 μg/10 puffs for chromium).(22) 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).(22) 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. Another study found airborne aluminum concentrations increased from the approximately 0.20 μg/m^3 (background concentration) to approximately 0.48 μg/m^3 during e-cigarette vaping sessions.(39) These findings were supported by a subsequent study, which found emissions of chromium and nickel in e-cigarette aerosol being higher than those found in traditional cigarettes, emissions of cadmium lower than those found in traditional cigarettes, and for lead and zinc, similar concentrations to those found in cigarette smoke.(66) Williams, Bozhilov, Ghai, and Talbot found concentrations greater than 0.01 μg/10 puffs for copper, sodium, potassium, zinc, boron, iron, lead, and aluminum.(67) While the use of lead in solder has been banned in most countries, including China where most e-cigarette components and liquids are manufactured, the ban on using lead in solder is not strictly enforced in many countries. As such, users cannot assume that these products are lead-free.(67) Overall, Williams et al. found that aerosols from popular disposable e-cigarettes contained at least 35 elements/metals, 21 of which were not found in cigarette smoke.(67)

While the airborne exposure for all metals during vaping has not been well-defined in terms of either dose or concentration (e.g., 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 either carcinogens or "reasonably anticipated to be human carcinogens" (e.g., nickel and lead).(5,22,68) Lead, nickel, and chromium are also on FDA's "harmful and potentially harmful chemicals" list.(22) Olmedo et al.(66) estimated that 57% of e-cigarette aerosol samples evaluated exceeded the Agency for Toxic Substances Disease Registry (ATSDR) daily chronic minimum risk level (MRL) for nickel, 14% exceeded the daily MRL for manganese, 75% exceeded the U.S. EPA daily cancer reference concentration (RfC) for manganese, and 48% exceeded the U.S. EPA National Ambient Air Quality Standard (NAAQS) for lead. Williams, Villarreal, Bozhilov, Lin, and Talbot evaluated the cytotoxicity of electronic cigarette fluids, with and without tin particles, and found that the fluids with tin particles were cytotoxic in assays using human pulmonary fibroblasts, but the fluids without tin particles were not.(22) 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.[22]

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.[69] In this study, significant associations were found between mortality and ultrafine particle number concentration, ultrafine particle mass concentration, and fine-particle mass concentration.[69]

The particulate size distribution and composition of tobacco smoke is well-documented and is reviewed here only as a comparison with e-cigarettes. Schripp, Markewitz, Uhde, and Salthammer conducted studies in an 8 cubic meter (8 m^3) chamber to evaluate the size distribution of submicron particulates from both tobacco smoke and e-cigarettes.[20] 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 per cubic centimeter (particles/cm^3), while the e-cigarette produced a size distribution around a mean of 35 nm in diameter with a concentration 2.0×10^3 particles/cm^3.[20] Although the concentration of particulates from the tobacco smoke was found to be an order of magnitude greater than that of the e-cigarettes (when generated under the same conditions), these findings are significant because both the particulate size and concentration levels are a concern.

Schripp et al. 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 as 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).[20]

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 particles introduced bytobacco cigarettes.[20]

In another study of e-cigarette emissions, Ingebrethsen, Cole, and Alderman 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 106 particles/cm^3 range, were reported for aerosols from e-cigarettes measured with an electrical mobility analyzer.[70] These measurements were reported to be similar to those observed from tobacco cigarettes. Yet another study by Zhang, Summer, and Chen reported e-cigarette particle size between 10 and 1,000 nm, with an average of 400 nm.[71] Based on particle size, the authors expect deposition in the human lung similar to that of tobacco cigarette smoke.[71]

Research shows that ultrafine particles form from supersaturated 1,2-propanediol vapor, which can be deposited in the lung.[39] Schober et al. found that airborne $PM_{2.5}$ concentrations 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.[39] 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.(5) People who have frequently been exposed to theatrical fogs containing ultrafine particles of PG are more likely to suffer from respiratory, throat, and nose irritations than unexposed people, suggesting that e-cigarettes may foster similar health effects.(61) 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 Buanno, Stabile, and Ficco examined the acute effects of electronic and tobacco cigarettes on exhaled nitric oxide (eNO).(72) Exhaled nitric oxide has been used as a noninvasive method to measure inflammation of the lung after exposure to pollutants. Marini et al. applied eNO tests to a group of 25 volunteers who use tobacco, e-cigarettes with nicotine, and nicotine-free e-cigarettes.(72) The eNO tests were applied before and after smoking/vaping to allow for the comparison in the changes in eNO for individuals.(72) The average total particle number concentration peak was found to range from 3.1 × 109/cm3 for conventional cigarettes to 5.1 × 10^9/cm^3 for e-cigarettes with nicotine.(72) 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.(72) However, the main focus of this study 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 e-cigarettes without nicotine, with nicotine, and for conventional cigarettes, respectively,(72) while the control sessions were found to have negligible change in eNO.(72) Therefore, consumption of both e-cigarettes and traditional tobacco cigarettes led to immediate reduction in eNO, suggesting similar inflammation of the airways for all three products.

Floyd et al.(73) compared vaping aerosols from a second-generation adjustable voltage tank-style e-cigarette with tobacco cigarette smoke. These researchers simulated a puff using a glass syringe, then measured particle size distributions over a broad range, from 16 nm to 20 μm, and found that less than 40% of both the e-cigarette aerosol and tobacco-smoke aerosol particle mass was comprised of particles less than 1 μm in diameter.(73) The key finding of this work was a trimodal particle size distribution with modes at approximately 50, 300, and 1000 nm.(73) These researchers propose the short aging in the syringe during the puff was responsible for the third-largest mode due to coagulation of the high-concentration particles, which is similar to a mouth puff.(73)

Mikheev et al.(74) conducted real-time e-cigarette aerosol size measurement at the mouthpiece as aerosol was being generated and found a bimodal particle size distribution with modes around 10 and 150 nm. These researchers showed that the puff begins with a single mode of around 10 nm, and then forms the second mode after 1.5 to 2 seconds.(74) Mikheev et al. also performed dry puffs and showed nanoparticle metals were produced by the heating wire.(74) This, however, is not representative of real vaping conditions. Metals were also found in the e-cigarette aerosol and accounted for up to 10% of the particle mass.(74)

Considering the results of both Floyd et al. and Mikheev et al., e-cigarette primary aerosol appears to begin very small, but rapidly grow while in the mouthpiece and oral cavity during puffing. For that matter, particle size is expected to grow hygroscopically as it travels down the warm and humid respiratory tract; however, the semivolatile components of the particles will partition into the vapor phase and be absorbed by the respiratory tract, causing the particles to shrink. Further studies that carefully model these competing effects are needed to understand the behavior of e-cigarette aerosol in the lungs and its risk for exhalation causing secondhand exposures.

This research, then, suggests that e-cigarettes present a new source of aerosols in indoor environments. Because of the relatively new, widespread use of e-cigarettes, the relationship between exposure and health effects is still evolving. However, the evidence of health effects from studies linking ultrafine particles to respiratory and cardiovascular disease[(75)] 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 at concentrations well below TSNA levels found in regular cigarettes.[(19,50)] 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.[(76)] Some TSNAs are known human carcinogens and are suspected to contribute to the cancer burden of smokers.[(77)] There is little evidence that e-cigarettes are a significant source for TSNA exposure. E-juices that have shown substantial TSNA levels were steeped in cured tobacco, which seems to have extracted the TSNAs in addition to the flavor.

Nut Allergens

An understudied area is the presence of nut allergens that may be found in e-cigarette liquids. On the 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.[(78)]

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)[16] and that this technology may prove beneficial for specific prescription drug mobilization. With both the increase in the use of e-cigarettes, and the increase in legalization of medical and recreational marijuana, vaping of cannabis and other recreational drugs is becoming increasingly popular.[79] In short, one may now deliver liquid extracts of marijuana, hashish, and crack cocaine[80,81] into the vaping system with allegedly no odor detection by other room occupants.

Overall Health Effects Associated with E-cigarettes

To date, few published studies have evaluated the potential hazardous effects of the natural and/or synthetic chemicals used in e-cigarettes. However, some health effects have been 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.[82] 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% of e-cigarette users.[82] 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.[83]

Bahl et al. studied the cytotoxicity of 35 samples of e-cigarette refill fluids using human embryonic and adult cells.[84] Twenty-seven of the 35 refill samples were moderately to highly toxic to the embryonic cells, with less severe effects on the adult cells.[84] The observed cytotoxicity was not attributable to the nicotine present in the fluids, but rather was correlated with the number and concentration of chemicals used to flavor the fluids.[84] Their research indicated that the observed cytotoxic effects could potentially translate into embryonic loss or developmental defects during pregnancy.[84] Additional preliminary information presented by Cressey[85] 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. These researchers state that, while e-cigarettes may be safer than tobacco, “preliminary studies suggest that they may not be benign.”[85]

Overall airway resistance and lung function associated with e-cigarette use has been studied with varying results. Flouris et al.[17] 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% of FVC (FEF_{25-75}). However, a different study that evaluated FEV_1, FVC, FEV_1%, PEF, maximal expiratory flow (MEF), 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 eNO concentrations, which is a marker for oxidative stress in the lung.[5] 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] 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 conventional tobacco cigarettes.[17]

One study reported that e-cigarette users have, in general, approximately 10% of the nicotine concentration in their blood plasma as compared with tobacco cigarette users,[82] while other studies have shown no significant changes in plasma nicotine as a result of the use of some prepackaged products.[83] These values may change with the increased use of personal mixes of liquids in which 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.(86) Farsalinos et al.[87] reported that there were no acute adverse effects on cardiac function reported in smokers or nonsmokers using e-cigarettes. This is consistent with reports that cardiovascular disease from tobacco use is likely related to the combustion by-products of tobacco smoke.[84]

It has long been established that exposure to traditional tobacco cigarette smoke inhibits mucociliary function in the lung. Individually, hazardous contaminants found in both traditional cigarette smoke and e-cigarette emissions have been shown to impact mucociliary clearance. Acrolein causes an increase in mucous viscosity,[88] which reduces the mucociliary clearance process.[89] In addition, relatively low concentrations of formaldehyde are sufficient to cause mucociliary impairment.[90]

Acetaldehyde has been demonstrated to directly impair bronchial cilia function, causing slowing of cilia beating and impairment of mucociliary clearance of the lung.[91] Recent studies have also shown that mucociliary clearance can be impacted by e-cigarette vapor. Laube et al.[92] exposed mice to e-cigarette aerosol, generated from e-liquids containing either 0% or 2.4% nicotine in a propylene glycol carrier, 20 mininutes/day for either one week or three weeks followed by measurement of mucociliary clearance. While chronic exposure to propylene glycol alone stimulated mucociliary clearance, a chronic, daily 20-minute exposure to the nicotine/propylene glycol mixture slowed mucociliary clearance.[92] Moses et al.[93] showed that both traditional cigarette and e-cigarette exposure decreased the expression of genes involved in cilia assembly and movement. The changes from e-cigarette aerosols were generally less pronounced than the effects of traditional cigarette exposure and were more pronounced in e-cigarette products containing nicotine than in those without nicotine.[93]

E-cigarette exposure has also been shown to reduce bacterial and viral clearance. Sussan et al.[94] exposed mice to e-cigarette vapor containing menthol and 1.8% nicotine via a whole-body exposure system for 1.5 hours, twice a day for two weeks and then infected those mice with *S. pneumoniae* or mouse-adapted influenza A/California/4/2009 H1N1. Sussan et al.[94] determined that e-cigarette exposure reduces pulmonary bacterial clearance, impairs viral clearance, and causes significant morbidity and mortality in mice following influenza virus infection.

Second- and Thirdhand Exposures

Given that such a wide variety of e-cigarette devices are in use, and given that users' vaping styles can range from "stealth vaping," where nearly all emissions are intentionally limited, to "cloud chasing," where the intent of the practice is to generate as large and long of a "cloud" of vapor as possible, it is difficult to predict actual secondhand exposures to bystanders. Czogala et al.[24] reported that secondhand exposures of nicotine from e-cigarettes were found to be present in concentrations approximately 10 times lower than those of traditional cigarettes, but these studies were performed in chambers and assumed that no nicotine was absorbed by the user. McAuley et al.[21] used similar assumptions and reported secondhand emissions generated with a smoking machine. However, St. Helen et al.[95] studied retention of nicotine, propylene glycol, and vegetable glycerin in users of first- and second-generation e-cigarette devices, and found that, on average, 93.8% of the nicotine emitted from the devices was retained by the user, resulting in only 6.2% of the nicotine available to become a source of secondhand exposure.[95] For vegetable glycerin, on average, 84.4% of the dose was retained, while for propylene glycol, 91.7% was retained.[95] Actual users' secondhand exposure measurement data have been difficult to identify in the scholarly literature.

The amount of literature for information on potential surface deposition of nicotine from e-cigarette use (potentially resulting in tertiary, or thirdhand, exposure) has been increasing over the past few years. Nicotine deposition on surfaces has been identified to be present immediately after vaping[96] and identified in some homes where occupants are puffing electronic cigarettes 50 to 500 times daily.[97] Marcham and Floyd[98] determined that nicotine can remain on cloth and nonporous surfaces for at least 72 hours after vaping has occurred, and Floyd[99] has shown that e-cigarette aerosols can spread through HVAC systems to adjacent parts of a building, where it can deposit on surfaces. Nicotine contamination was found to be elevated on surfaces in shops adjacent to small vape shops. Cleaning regimens in the vape shops were very aggressive (daily or twice daily), and this seemed to control surface contamination adequately within the shops, but adjacent shops did not clean display cabinets as frequently, resulting in elevated nicotine contamination.[99]

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.[100] Some research shows that for smokers, the observation of others smoking increases the craving and potential for ultimate consumption of cigarettes.[101] 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, media attention has brought additional safety issues to light, 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 noted 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.[11] 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 power e-cigarettes. The most common causes of fires have been from either using incorrect chargers or overtightening the screwed connection to the charger, which can damage the battery cells and lead to overheating.[102] 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.[102]

It has been demonstrated online that it is possible to set off a smoke alarm using an e-cigarette,[103] and there is at least one anecdotal report of a "stealth" vaper setting off an airplane lavatory smoke alarm.[104] 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

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.[9] WHO noted that the safety of the devices has not been scientifically demonstrated.[9] 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.[105] 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.[105] Recommendations on regulatory options were provided in a 2016 report by WHO[106]; however, as of the publication date of this white paper, WHO has not established any official regulations.

The regulatory status of e-cigarettes is constantly changing. Although these products often use some ingredients derived from tobacco, such as nicotine, other ingredients are clearly not related in any way to tobacco products. The FDA has previously taken action against manufacturers of e-cigarettes, claiming that they violated good manufacturing practices and made unsubstantiated drug claims.[107] Effective August 8, 2016, the FDA extended its authority to regulate e-cigarettes, vape pens, and hookah tobacco, requiring manufacturers, importers, and retailers to report ingredients, place health warnings on products and advertisements, and limit sales to people under the age of 18[108] In the European Union (EU), the EU Tobacco Products Directive (TPD) came into effect in May 2016.[109] The United Kingdom (UK), in turn, established the Tobacco and Related Products Regulations in 2016, which includes a requirement for child-resistant and tamper-evident packaging, a requirement that devices deliver a consistent dose of nicotine under normal conditions, and a limitation of tanks and cartridge sizes to no more than 2 ml in volume and nicotine content of 20 mg/ml.[109] In addition, health warnings about the presence of nicotine are required.[109] Outside of the TPD, domestic legislation has been enacted across the UK to ban the sale of e-cigarettes to people under the age of 18.[109] Other countries, such as Brazil, Norway, and Singapore, have banned their use.[110]

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 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[111] and the cities of Los Angeles; New York; Washington, D.C.; Chicago;[112] and Duluth, Minn.,[113] have included e-cigarettes in indoor smoking regulations. Mississippi's DeSoto County has added e-cigarettes to the local smoking ban in government buildings,[111] 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.[114] Many other states and municipalities are discussing, or have enacted, 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 an encouragement for their use.

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.[107] 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.[107] Restrictions on advertising to minors and bans on internet sales or sales to minors have either been enacted, or are being planned, by all 50 states, the District of Columbia, the U.S. Virgin Islands,[115] and the FDA.[116]

In 2016, the U.S. Department of Transportation amended 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 and on charter flights where a flight attendant is required.[117] Also, because of the safety hazards associated with the lithium batteries in e-cigarettes, e-cigarettes must be carried onboard aircraft instead of being placed in checked luggage.[118]

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.[119,120] Some have even suggested that it be called a "nicotine inhaler" and insist that the use of the device is not covered by smoking bans on airplanes.[120]

Other transit systems, such as commuter rail lines, subway systems, and bus services, have also faced issues with ambiguity over e-cigarette usage by referencing only 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.[121] 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.[122] The Los Angeles County Metropolitan Transportation Authority amended its policy in March 2014 to prohibit vaping.[123]

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.[124] 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"[125]; however, the BoltBus policy simply states, "Smoking is prohibited aboard the bus in accordance with Federal law"[126] and the policy for Greyhound states, "There's no smoking allowed on the bus (it's against federal law)."[127]

The Centers for Disease Control and Prevention (CDC) National Institute for Occupational Safety and Health (NIOSH) *Current Intelligence Bulletin 67: Promoting Health and Preventing Disease and Injury Through Workplace Tobacco Policies* recommends that employers "establish and maintain smoke-free workplaces that protect those in workplaces from involuntary, secondhand exposures to tobacco smoke and airborne emissions from e-cigarettes and other electronic nicotine delivery systems."[128]

ASHRAE Standard 62.1 contains requirements for ventilation of spaces that are free of environmental tobacco smoke (ETS), and provides requirements for separation of ETS-free areas from any areas containing ETS.[41] Addendum c to ANSI/ASHRAE Standard 62.1-2013, published in 2015, clarifies that the definition of ETS "includes smoke produced from the combustion of cannabis and controlled substances and the emissions produced by electronic smoking devices" and recommends that "provision of acceptable indoor air quality is incompatible with the presence of ETS, including cannabis smoke and e-cigarette emissions."[129] Guidelines include designing ETS-free areas at positive pressure to ETS areas with solid walls, floors, and ceiling materials as well as doors with automatic closing mechanisms to separate ETS areas from ETS-free areas.[129] There should be no recirculation or transfer of air from ETS areas to ETS-free areas, and areas where ETS is allowed should have signage indicating the presence of ETS.[129]

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 their own 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 currently several key data gaps and areas of uncertainty that hinder a more quantitative assessment of health risks related to e-cigarettes. These include the following:

- Quality control is lacking with regard to e-cigarette product constituents. In addition, manufacturers may not disclose all of the chemical ingredients used in their products or, other than nicotine, their amounts.
- Because many e-cigarette users mix their own blends, and there are so many different types of devices, studies performed within a laboratory setting may not reflect actual exposures during use.
- There are limited data on chemical emissions/exposures, especially among bystanders and within 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 exposure levels (i.e., occupational vs. environmental) are lacking.
- 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.[130] 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, young 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 certainly 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. Unfortunately, the CDC reports that in 2016, more than 2 million middle and high school students had used electronic cigarettes.[131] Among current e-cigarette users aged 18 to 24, 40% had never been a regular cigarette smoker,[131] so these youth are not using these devices for smoking cessation. In fact, there is some evidence that e-cigarette use is prospectively associated with increased risk of combustible tobacco use initiation during early adolescence, meaning that it can lead users toward smoking traditional cigarettes. One study reports that among high school students that were ENDS users, 25% to 30% went on to be conventional tobacco product users.[132] Another study performed over a 12-month period evaluating e-cigarette use in 13- to 14-year-olds in the UK confirmed a sizable relationship between ever using e-cigarettes and subsequent initiation of cigarette use, but this study also acknowledged that whether friends smoke traditional cigarettes was a more accurate predictor of initiating cigarette use than e-cigarette use.[133] Many teens refer to the use of the JUUL device as "JUULing," indicating they may not consider it to be using an e-cigarette, and only 25% of individuals who recognized the product and 37% of users reported that JUUL always contains nicotine, meaning that a majority of users do not recognize the hazard and presence of nicotine in the JUUL.[14] In any case, for adolescents and 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. 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 and thirdhand smoke, the ingredients exhaled by the vaper include nicotine, metals, flavorings, and glycol which accumulate in the ambient air and can deposit on surfaces. Recipients of secondhand and thirdhand exposure have not chosen to — many, in fact, have explicitly chosen not to — use e-cigarettes. The exposure to secondhand and thirdhand vapor, just like secondhand and thirdhand 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 and thirdhand exposure, including children, pregnant women, and people with already compromised health, some of whom may have limited ability to leave the spaces where vaping occurs or has occurred.

Finally, 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[133] 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 other 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 in time, most people do not want to fly on an airplane or 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.[130] 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 known 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. 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 addressed. It should be noted that the EPA regulates the disposal of nicotine-containing products and e-liquids as a p-listed acute hazardous waste when discarded.[134] Considerations should also 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 are inhaled by the user and, possibly, by 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 or thirdhand. Therefore, e-cigarettes should be considered a source of aerosols, 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 is already known. Clearly, e-cigarettes lack the combustion by-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 GRAS 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 associated with e-cigarette manufacturing, use, and disposal.

Because of concerns about primary and secondary exposure to vapors and e-juice fluids, risk-based regulation of e-cigarettes using reliable safety, health, and emissions data should be implemented. 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 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.[108] Others include reviews by the Consumer Product Safety Commission and OSHA. Four areas of regulation related 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 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 health or hazards (e.g., toxicity, flammability, 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 should be managed and controlled in the indoor environment consistent with current smoking policies, until and unless research demonstrates that they will not significantly increase the risk of adverse health effects to occupants.

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