E-cigarettes, vaping-related pulmonary illnesses, and asthma: A perspective from inhalation toxicologists

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The recent outbreak of e-cigarette or vaping-product use–associated lung injury (EVALI) is alarming. As of October 18, 2019, 33 deaths and nearly 1500 hospitalizations associated with e-cigarette use have been reported in 49 states and the US Virgin Islands. Initial epidemiologic investigations of EVALI cases in Illinois and Wisconsin identified that more than 80% of the reported cases occurred in young white male subjects who presented with respiratory, gastrointestinal, and constitutional symptoms that rapidly progressed to severe acute lung injury.[1] Interestingly, underlying asthma was reported in 30% of these cases, which is much higher than the 8% to 10% of asthmatic patients seen in the general population. Although many questions regarding the safety of e-cigarettes have come to the forefront with the emergence of EVALI, health care providers and concerned parents are also asking what might be causing this outbreak and who might be susceptible to EVALI.

HISTORICAL CONTEXT

E-cigarettes were first marketed in the United States as harm-reduction products and tools to help smoking cessation. However, neither the safety nor the efficacy of these products as cessation aids had been evaluated.

In 2015, Public Health England, an executive agency of the Department of Health and Social Care in the United Kingdom, declared e-cigarettes to be 95% safer than traditional cigarettes, stating that, "While vaping may not be 100% safe, most of the chemicals causing smoking-related disease are absent and the chemicals that are present pose limited danger." Although Public Health England's statement was largely based on the presence and level of known cancer-causing chemicals in cigarette smoke, the toxicity of inhaling flavoring agents and chemicals unique to e-cigarettes was unclear. Indeed, some e-cigarette flavoring agents have been associated with greater toxicity in experimental models, and thermal decomposition of flavoring agents during vaporization at high-power settings can produce chemicals with known toxicities.[2] Furthermore, limited regulation of the e-cigarette industry has allowed new devices and e-liquids to enter the e-cigarette market at such a rapid pace that adequate toxicity and safety testing for emerging products is not possible. Hence early statements about their safety were made without sufficient supporting data.

Data from randomized controlled trials evaluating the effectiveness of e-cigarettes as cessation aids are currently being collected. A study recently published in the *New England Journal of Medicine* identified that e-cigarette use, in conjunction with behavioral support, improved smoking cessation in adults attempting to quit when compared with nicotine replacement therapy with behavioral support (18% vs 9.9%, respectively).[3] However, 80% of e-cigarette users in this study continued vaping after 1 year, whereas only 9% of nicotine replacement product users continued product use after 1 year. This is concerning because additional work indicates that vaping more than 1 year after quitting smoking is associated with smoking relapse.[4] Ultimately, evidence supporting the effectiveness of e-cigarettes as cessation tools must be balanced against the short- and long-term safety of these products.

Despite the ongoing debate regarding the efficacy of e-cigarettes as effective smoking cessation tools, asthmatic patients who currently smoke are often advised by their health care providers to switch to e-cigarettes as a safer alternative.[5] More alarming are surveys demonstrating that e-cigarette use is more popular among asthmatic teenagers compared with their nonasthmatic peers.[6] A recent study of 6089 US high school students found that e-cigarette use was independently associated with asthma.[6] Similarly, a cross-sectional study of 35,904 South Korean high school students found that e-cigarette use had an increased association with asthma and that asthmatic vapers missed school more frequently because of severe asthma symptoms.[2] Data from the Florida Youth Tobacco Survey indicate that 33% of 11- to 17-year-olds with asthma had secondhand e-cigarette aerosol exposure, which was associated with an increased risk of having an asthma attack.[7] Furthermore, emerging data from the vaping-related pulmonary illness cases in Illinois and Wisconsin indicate a higher-than-expected occurrence in asthmatic patients.[1] At the University of North Carolina, we recently described 2 case reports of adolescent asthmatic e-cigarette users who presented with life-threatening status asthmaticus necessitating veno-venous extracorporeal membrane oxygenation.[8] The available data clearly show that vaping among adolescent asthmatic patients is common and that these users might present a uniquely susceptible population for the adverse effects of vaping.

THE ROUTE OF EXPOSURE MATTERS

No specific single additive or substance has been determined to be responsible for EVALI. However, multiple cases have involved

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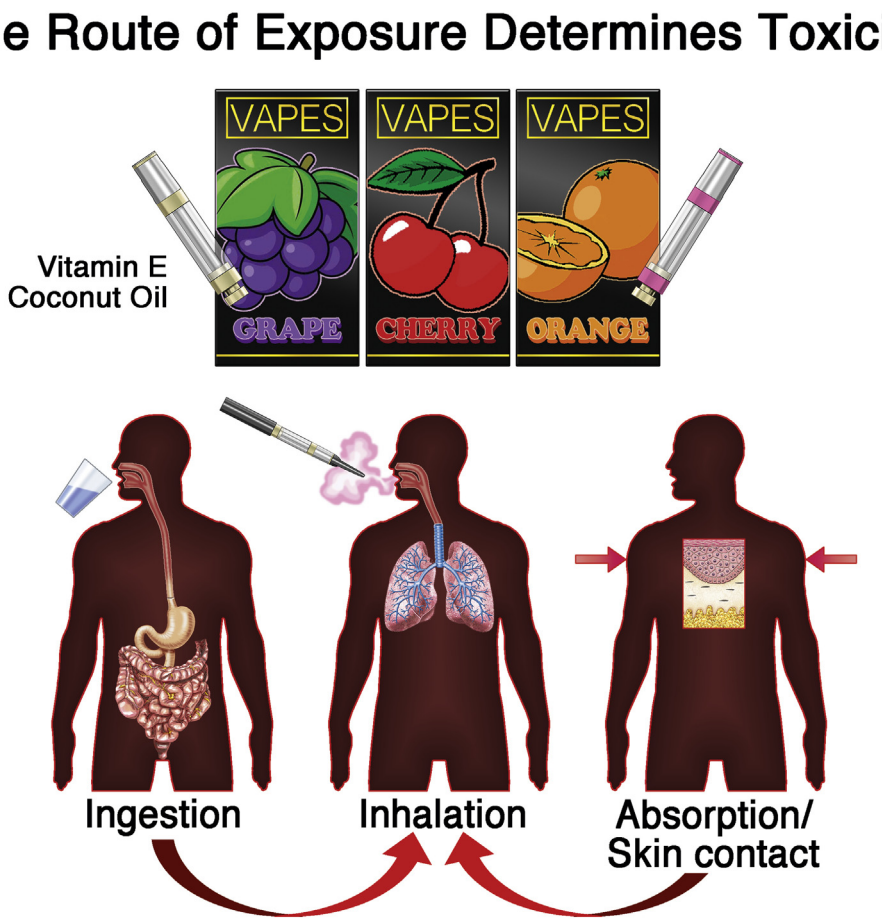

FIG 1. Route of exposure determines toxicity. Components contained in e-cigarettes and vaping products, such as flavoring agents, are safe for ingestion but cause toxicity in the lung on inhalation. Similarly, compounds, such as vitamin E and coconut oil, which have been identified in many vaping products associated with EVALI, are safe for ingestion or absorption through the skin. However, thermal oxidation, occurring as part of the vaporization process, and changing their route of exposure to inhalation likely modifies their toxic potential.

user modification of e-liquids to include cannabinoids, such as cannabidiol and tetrahydrocannabinol (THC), and solvents, such as medium-chain triglycerides and vitamin E acetate.[1] It remains unclear whether substances added by the user, substances added by manufacturers, or a combination of both are responsible for the current cases of lung injury.

Most substances used in e-liquid formulations are recognized as food safe; however, the vast majority of food-grade chemicals have not been tested for inhalation safety.[2] Vapers might believe that all substances that are safe to eat are broadly safe regardless of how they are consumed. A common example of a food-safe flavoring agent with recognized inhalation toxicity is diacetyl. Inhalation of diacetyl (2,3-butanedione), a common flavoring agent used to provide a buttery or creamy flavor, caused acute-onset bronchiolitis obliterans, an irreversible obstructive lung disease, in workers at a microwave popcorn production facility who were exposed to aerosolized flavoring agents.[2]

As illustrated in Fig 1, exposures that are benign for the skin or gastrointestinal track might pose a serious threat to the lungs because of variability in epithelial defenses and expression of detoxifying enzymes. For example, keratin provides the skin and underlying tissues with a physical barrier against dermal exposures, and the gastrointestinal tract and liver have robust expression of phase I and phase II drug-metabolizing enzymes, such as cytochrome P450 oxidases, which catalyze the metabolic breakdown and detoxification process of xenobiotics. The lungs have evolved other effective defense mechanisms, including a protective airway surface liquid milieu, mucociliary clearance, epithelial tight junctions, and resident lymphocyte populations, to protect the body against common environmental toxicants. However, it is entirely unclear how well these defenses will withstand new and emerging insults, such as those produced when vaping. Paracelsus termed the guiding principle of toxicology "the dose makes the poison," but in the context of flavored e-cigarettes, this statement should be amended the include that "the route of exposure makes the poison."

The US Centers for Disease Control and Prevention is continuing to collect data on potential components common to e-liquids used by patients with EVALI. The clinical manifestations of EVALI can include lipoid pneumonia, which is characterized by lipid-laden macrophages in the lung.[1] Inhalation of lipid aerosols, such as through inadvertent aspiration of lipid substances, can cause lipoid pneumonia. Vitamin E acetate, a lipid commonly added to facial moisturizers and skin creams, has been identified in some but not all of the

e-cigarette products associated with EVALI. Numerous vaping blogs describe the frequent use of vitamin E acetate to dilute concentrated cannabinoids. Additionally, these substances have been used to adulterate bootleg THC cartridges to make them appear thicker and more similar to commercial THC cartridges. Vaping blogs and vape shops warn against adding lipids to any e-liquid because the aerosolization and inhalation of lipid aerosols will cause lipoid pneumonia. However, the etiology of lipoid pneumonia can also be endogenous. A recent study reports that lipid-laden macrophages can be caused by disruption of lung lipid homeostasis after chronic exposure to inhaled base e-liquid components (eg, propylene glycol and glycerol) and not exogenous lipid inhalation.[9] Moreover, chemical reactions between e-liquid components can result in formation of secondary acetals and possibly tertiary reaction products with completely unknown or enhanced toxicity.[10] This further illustrates that, in the absence of regulations for the manufacture and distribution of vaping products, we simply do not know what chemicals e-liquid manufacturers are using or what will be the biological consequences of inhalation.

WHAT NOW?

Based on data from the 2019 Youth Tobacco Survey, there are now 5 million teenagers (>27%) who are using e-cigarettes. Although this survey shows that cigarette smoking rates are down to 5.8%, the sharp increase in e-cigarette use among teenagers represents a new generation of potentially nicotine-addicted persons. Given the newly appreciated harms associated with vaping, urgent action to minimize this use is essential. Education of adolescents and young adults about vaping-associated pulmonary illness by clinicians is an important first step. Appropriate and effective regulatory actions by the US Food and Drug Administration to reduce the availability and appeal of e-cigarettes to adolescents is also crucial. Specifically, regulations directed toward banning e-liquids with "kid-friendly" flavorings, images, and packaging should be prioritized.

The increased risk to patients with asthma makes this an especially important issue for the allergy and immunology community. Public health policies have effectively reduced tobacco use among children. Similar action is urgently needed for e-cigarette use, particularly among teenagers and young adults with asthma.

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