COMMENTARY

Toxic ketene gas forms on vaping vitamin E acetate prompting interest in its possible role in the EVALI outbreak

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Recent efforts by the Centers for Disease Control and Prevention (CDC), the US Food and Drug Administration (FDA), and state authorities have led to the determination that vitamin E acetate (VEA) is strongly associated with e-cigarette or vaping product use-associated lung injury (EVALI) (1). VEA has been found in nearly all patient lung fluid samples analyzed and not observed in lung fluid from healthy cohorts. Despite strong evidence linking VEA to EVALI, its putative role as a causative agent has yet to be determined. To address the key issue of whether VEA is a just marker or a significant mediator of EVALI, Wu and O'Shea (2) report in PNAS that VEA reacts when aerosolized with an e-cigarette to produce the highly toxic gas ketene. Confirmation that VEA-derived ketene is a causative agent of EVALI must await rigorous clinical investigation. However, Wu and O'Shea (2) have in the meantime uncovered a compelling lead.

One of the most concerning aspects of EVALI is its aggressive onset. In contrast to the devastating effects of traditional cigarettes that take decades to manifest, EVALI has afflicted young patients who developed life-threatening symptoms literally within hours after experiencing initial nausea and respiratory discomfort (3). This seems consistent with ketene toxicity, which has been reported to cause severe, acute lung damage in animal models at the alveolar level within 24 h after exposure. The Acute Exposure Guideline Level (lethal) 10-min exposure value for ketene is 0.24 ppm (4).

Importantly, the finding reported in PNAS that ketene can be produced from VEA using a commercial vaping device (2) highlights the need to investigate the chemical reactions that take place during vaping to enhance understanding of toxicological pathways. Some vaping proponents have been dismissive of the relevance of nonclinical chemical investigations of e-cigarette aerosol chemical toxins, positing that vapers can effectively self-regulate any elevated toxin intake simply by sensorial perception (5). Sadly, the EVALI outbreak has shown

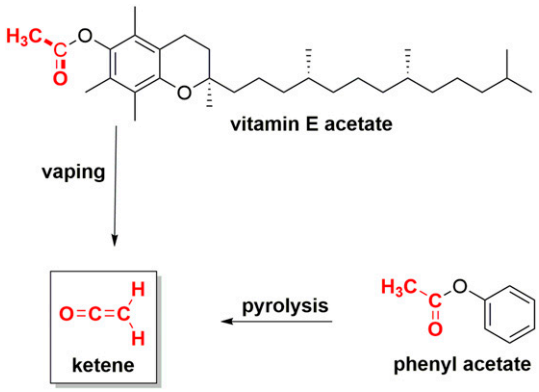

Fig. 1. The pyrolysis reaction of phenyl acetate to produce ketene reported in 1938 and the analogous transformation of vitamin E acetate to ketene recently shown to occur on heating and aerosolization in a commercial vaping device.

self-regulation by vapers to be unreliable at best and deadly at worst. Moreover, without a chemistry-focused study, such as reported by Wu and O'Shea (2), the potential relevance of ketene to EVALI would have gone unnoticed. This is largely because ketene's notorious instability renders its direct determination highly impractical in processed patient samples. Challenging indirect detection strategies may thus be required to link ketene to EVALI patients, such as the determination of biological footprints, including posttranslationally modified proteins (4) and characteristic reaction products.

The rationale for the formation of ketene from VEA has its roots in 1938 reports describing the pyrolysis of organic esters (6, 7). VEA possesses a phenyl acetate functional group known to convert smoothly to ketene and phenol (Fig. 1) (6). However, the thermal conversion of VEA to ketene has a relatively high activation energy (2), prompting the question as to whether significant levels of ketene can form under vaping temperatures and conditions that are realistic

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for users (8). Narimani and de Silva (8), for example, recently calculated that the formation of ketene from VEA is feasible only at temperatures above 500 °C or "dry puff" conditions. Under such conditions, they determined that ketene lung concentrations would attain severe (30-ppm) levels (8).

Dry puff is a colloquial term that is used by some vaping proponents as a panacea to reports describing dangerous toxin levels in e-cigarette aerosols (5). The term implies the condition whereby e-cigarette solvent levels are so low as to prevent effective wicking and cooling of the heating coils, resulting in overheating and the resultant formation of elevated levels of hazardous partial combustion products. However, it has been shown that e-cigarettes can emit hazardous levels of aerosol toxins under conditions that are not associated with dry puff (9). For example, Narimani and de Silva (8) speculate that, as an alternative to dry puff, surface catalysis could enable the formation of ketene under benign vaping conditions. Indeed, it has been conclusively demonstrated by Shihadeh and coworkers (10) that e-cigarette filament wires exhibit strong catalytic effects that modulate aerosol toxin formation at low temperatures.

While catalysis originating from metal device components could lead to ketene formation at relatively low temperatures, one issue not clearly noted in the recent reports focusing on ketene is that most EVALI patients vaped cannabis as opposed to tobacco products (1). VEA is used for tetrahydrocannabinol (THC) concentrate (cannabis oil) adulteration. Importantly, THC is highly viscous and will require more heat to aerosolize compared with tobacco e-cigarette solvents and ingredients. For example, the cotton wick materials used for tobacco product vaping have been known to catch fire when used for cannabis oil vaping (9). Another important consideration is that counterfeit THC vape cartridges were used by a large proportion of EVALI patients (1, 11). Such devices will exhibit overall poorer wicking and heat transfer efficiency compared with authentic licensed dispensary and medical use vaporizers. Thus, vaping highly viscous, adulterated materials with cheap, low-quality vaping devices will optimize toxic aerosol emissions.

In summary, the study by Wu and O'Shea (2) shows that vaping VEA can lead to exposure to the poisonous gas ketene. This is a significant finding that is already prompting further investigations to determine whether ketene produced from VEA plays a causative role in EVALI (1). Additionally, it demonstrates that an understanding of the reactions that can lead to toxic aerosol emissions is needed to augment the focus on screening chemical ingredients in unvaped samples. Currently, the CDC cannot rule out chemicals of concern other than VEA, including tobacco products, as playing a role in the development of EVALI (1). For instance, Rahman and coworkers (11) have shown that numerous hazardous and potentially hazardous compounds are present in the aerosols derived from vaping products recovered from EVALI patients. These include solvent-derived hydrocarbons, silicon-conjugated compounds, pesticides, plasticizers, polycaprolactones, and metals (11). Finally, the study by Wu and O'Shea (2) embodies a stark reminder that flavorings, vitamins, and other additive molecules deemed safe for ingestion should never be assumed safe for vaping without proof in the form of rigorous evidence-based data.

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