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Potential of Ethenone (Ketene) to Contribute to Electronic Cigarette, or Vaping, Product Use–associated Lung Injury

To the Editor:

In 2019, the United States experienced an unprecedented outbreak of electronic cigarette (e-cigarette), or vaping, product use–associated lung injury (EVALI) (1–4). Although reports of lipid-laden macrophages in BAL fluid raised the possibility that EVALI represented exogenous lipoid pneumonia (5, 6), case series that focused on histopathology found patterns of acute lung injury, including diffuse alveolar damage and organizing pneumonia, often with bronchiolitis (7, 8). Thus, the available evidence to date suggests the outbreak is characterized by an airway-centered chemical pneumonitis rather than acute exogenous lipoid pneumonia.

Vitamin E acetate (VEA) has been strongly linked to the outbreak, as demonstrated by *1*) the presence and high concentrations of VEA in vaping product samples recovered from patients with EVALI; *2*) the detection of VEA in tetrahydrocannabinoid-containing vaping products seized by law enforcement in 2019 but not 2018, indicating temporality; and *3*) the identification of VEA in 94% of BAL fluid samples from patients with EVALI but not in samples from healthy controls (9).

The mechanism by which VEA might cause a chemical pneumonitis is still not understood. Vitamin E is a natural component of lung surfactant, and experimental models of phospholipid bilayers suggest that increasing concentrations of vitamin E or VEA could affect the physical structure and phase behavior of surfactant (9). Whether such effects alone sufficiently impact surfactant function *in vivo* to cause a cascade of increased surface tension, alveolar collapse, and acute lung injury is currently unclear.

Another potential mechanism involves a toxic agent, ethenone (C_2H_2O), the simplest of the ketene class of compounds. Ketenes, including ethenone, are highly reactive compounds used as intermediates in industrial chemical synthesis reactions. Wu and O'Shea recently demonstrated both the theoretical basis and experimental formation of ethenone from VEA under heated conditions through the pyrolytic cleavage of the acetate group (Figure 1) (10).

Early literature on ethenone creation reported its formation from acetone at 700°C in the presence of a tungsten catalyst (11). Several subsequent patents describe the use of other catalysts to assist the formation of ketenes of various sizes from acetate and other carboxylic acids, including fatty acids, at temperatures as low as 326°C, which are reachable with electronic vaping devices that

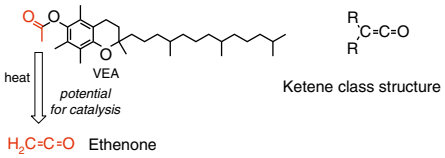

Figure 1. Formation of ethenone from vitamin E acetate and ketene class structure. VEA = vitamin E acetate.

allow variable user settings (12–15). These patents employed metal catalysts, including nickel, titanium, magnesium, iron, copper, and the metalloid silica. Though Wu and O'Shea formed ethenone from VEA without a catalyst (10), the presence of metals and silica in the vaping devices of patients with EVALI could theoretically amplify the creation of ethenone.

Though nicotine-based e-cigarette liquids and aerosols were already known to contain various metals, some of which overlap with the catalytic metals in ketene patents (16), whether EVALI-associated tetrahydrocannabinoid vape cartridges contain potential reaction catalysts was uncertain. Thus, we have been disassembling these devices under a reflected light microscope and analyzing the metal composition of the individual components using a portable X-ray fluorescence unit and scanning electron microscopy with energy dispersive X-ray spectroscopy. Our preliminary analyses suggest conditions favorable to ethenone formation, including evidence of high temperatures, thermal insulation, and nickel and chromium filaments encased in charred, oil-soaked, silica ceramic (Figure 2). Additional studies will build on the results of Wu and O'Shea (10) to evaluate the wide-ranging conditions that could influence ethenone formation, such as temperature, power, and vaping device type and components.

Ethenone toxicological literature is scant and historic but still alarming. Acute (10-minute) inhalation exposures were observed to lead to mortality in 0.8–16 hours in small studies of multiple species across a range of concentrations (50–1,000 ppm) (11). The only study to use high-purity ethenone (98–99%) observed acute pulmonary congestion and alveolar edema in monkeys exposed to concentrations of 12 ppm and higher (11). Mice in this same study exposed at 1 ppm for 14 days, 7 hours/day, had a 10% mortality rate (11).

Human data on ethenone toxicity are even sparser. One case report described a chemical industry worker who developed hypoxic

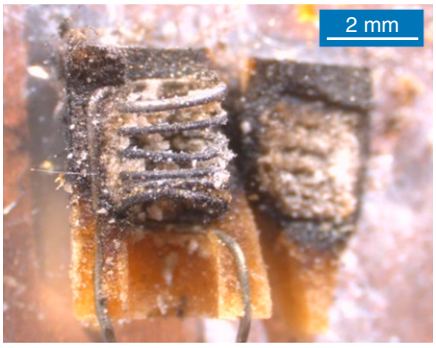

Figure 2. Stereozoom microscope image of dissected, cylindrical ceramic heating element from the vaping cartridge of a patient with electronic cigarette, or vaping, product use–associated lung injury, showing charring from high temperatures. Scale bar, 2 mm.

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respiratory failure and diffuse ground glass opacities on chest computed tomographic imaging, consistent with acute respiratory distress syndrome, 12 hours after a 5-minute exposure to a reportedly highly concentrated mixture of ethenone and crotonaldehyde (17). Notably, the reported delay between exposure and presentation, need for respiratory support, and relatively rapid improvement in this case are consistent with the natural history of EVALI (3, 4).

Ethenone's mode of action is thought to be similar to that of the chemical warfare agent phosgene, namely, acylation of proteins and other macromolecules leading to disruption of the blood–air barrier, edema, and inflammation (11, 18). These animal and human findings, along with ethenone's poor warning properties, align well with the clinical presentations seen in the EVALI outbreak. Estimating dosage in EVALI cases, however, is so far complicated by the complex user patterns of the cases and will require a better quantitative understanding of the efficiency with which ethenone can be formed under a range of vaping devices, e-liquid types, and use conditions.

Understanding the mechanism by which VEA might cause EVALI has preventive and prognostic implications (19). Acetate moieties capable of generating ethenone may be present in other compounds within nicotine- or cannabis-based e-liquids, especially in the unregulated market, such as other diluents and solvents or novel additives, including flavorings, herbal extracts, essential oils, homeopathic remedies, and probiotics. Testing of newer vaping devices may also help shed light on the poorly characterized additional impacts of heat, hydrophobic conditions, and catalytic materials on known or newly identified starting ingredients. Furthermore, mechanistic insights could inform the understanding of long-term health effects to patients with EVALI, including potential DNA damage and carcinogenicity from exposures to low concentrations of an acylating agent. Animal models, such as one that was recently reported (20), have the potential to address these issues and may benefit from delivery methods that allow reactive compounds to reach deep lung tissue, such as intratracheal or direct, nose-only delivery. We hope that this discussion will stimulate further scientific inquiry into the mechanism of lung damage in EVALI and, ultimately, preventive measures to address potential harm from vaping and e-cigarette use. ■

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In Patients with ARDS, Optimal PEEP Should Not Be Determined Using the Intersection of Relative Collapse and Relative Overdistention

To the Editor:

With great interest, we read the article by van der Zee and colleagues suggesting an individualized approach for setting the correct amount of positive end-expiratory pressure (PEEP) in ventilated patients with coronavirus disease (COVID-19) (1). In their cohort of 15 mechanically ventilated patients with COVID-19, they used electrical impedance tomography to study the relative overdistention and relative collapse curves. The authors state that optimal PEEP for these patients is at the intersection of these curves and close to the values suggested in the high PEEP/$F_{I_{O_2}}$ table. This intersection has indeed been used to set optimal PEEP but only for mechanical ventilation during surgery (2).

Using the intersection of relative collapse and relative overdistention suggests that both phenomena are equally harmful for patients with acute respiratory distress syndrome. Unfortunately, there is no evidence in the literature that supports this assumption. In fact, several studies and reviews suggest the opposite: overdistention may be more harmful (3–5).

We fully agree with the authors that an individualized approach for mechanical ventilation for patients with COVID-19 (or any form of acute respiratory distress syndrome for that matter) is very important. But instead of recruitment of the lung with high PEEP, prone positioning with lower PEEP levels could be considered to improve oxygenation and to recruit parts of the lung. In 14 patients admitted to our ICU, we have shown that using more PEEP often leads to reduction in lung compliance and increase in dead space ventilation, which suggests overdistention of alveoli (6).

In conclusion, although atelectrauma decreases with higher levels of PEEP, hyperinflation increases, which is potentially even more harmful. Therefore, using the intersection of the relative overdistention and relative collapse with electrical impedance tomography in patients with COVID-19 is not the technique to determine optimal PEEP for the individual patient. What van der Zee and colleagues do very elegantly show us with their research, however, is that there is always a tradeoff with higher levels of PEEP. ■

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Reply to van den Berg and van der Hoeven

From the Authors:

We thank van den Berg and van der Hoeven for the opportunity to further discuss our research letter in which positive end-expiratory pressure (PEEP) was titrated at the level of lowest relative alveolar overdistention and collapse based on electrical impedance tomography (EIT) (1). In their comment, the authors argue that PEEP should not be set at the minimum level of both alveolar overdistention and collapse, as alveolar overdistention is potentially more harmful.

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