E-Cigarette or Vaping Product Use–associated Lung Injury: Developing a Research Agenda

An NIH Workshop Report

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Abstract

The NHLBI convened a working group on October 23, 2019, to identify the most relevant and urgent research priorities and prevailing challenges in e-cigarette or vaping product use–associated lung injury (EVALI). Experts across multiple disciplines discussed the complexities of the EVALI outbreak, identified research priorities, and recommended strategies to address most effectively its causal factors and improve diagnosis, treatment, and prevention of this disease. Many research priorities were identified, including the need to create national and international registries of patients with EVALI, to track accurately those affected and assess outcomes. The group concluded that biospecimens from subjects with EVALI are urgently needed to help define EVALI pathogenesis and that vaping has disease risks that are disparate from smoking, with the occurrence of EVALI highlighting the importance of broadening e-cigarette research beyond comparators to smoking-related diseases.

Keywords: e-cigarette; vaping; THC; EVALI; research

Key Points of Agreement

1. E-cigarette or vaping devices have been used to generate aerosols containing numerous active substances for inhalation, including nicotine, tetrahydrocannabinol (THC), and cannabidiol (CBD).
2. The etiology of e-cigarette or vaping product use–associated lung injury (EVALI) remains unknown. Available data from the CDC point to an association with oil-based ingredients, such as vitamin E acetate (VEA), added to THC liquids before vaping or dabbing (inhaling potent vapors from concentrated marijuana oil), but a specific cause for EVALI has not been proven mechanistically.
3. Vaping devices have not been shown to be safe for chronic use. The acute and chronic toxicities of inhaling aerosols generated from liquids containing

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vegetable glycerin, propylene glycol, nicotine, and/or flavors are unknown. Inhaling aerosols generated from THC- or CBD-containing liquids, which often contain additional chemical components, also have unknown health effects. Thus, elucidating their long-term respiratory, cardiac, and cancer health effects is a public health priority.
4. Physicians and other healthcare providers need further guidance on how to take an accurate and detailed inhalant history. Acquisition of such data from across the country will help track EVALI cases as well as other vaping-related health effects.

Key Priorities for Future Research

1. National and international registries of all patients with EVALI should be created, which could be accessed by researchers and clinicians, to track those affected and assess outcomes accurately.
2. We suggest that three cohorts of subjects be identified and followed over time: *1*) healthy vapers/dabbers, *2*) patients with severe EVALI, and *3*) patients with nonsevere (mild, moderate, subacute, and chronic) EVALI. Groups would be powered to identify causal agents, short-term and long-term effects on lung function, overall health, and biomarkers of EVALI in both target organs (e.g., the lung) and accessible biofluids (e.g., blood, urine, etc.).
3. Acquisition and analysis of biospecimens from humans affected by EVALI (whole blood, tracheal aspirates and/or BAL, lung biopsy specimens, urine, and autopsy specimens) will help profile inflammatory and fibrotic changes, determine whether a heretofore unknown viral or bacterial pathogen may be a causal agent, and gain an overall understanding of EVALI pathogenesis.
4. Research on vaping effects to date may not have identified EVALI because of multiple limitations, including but not limited to: lack of access to and, hence, testing of THC liquids used in vaping and dabbing; rapid evolution of products on the market; inadequate dosing/exposure to e-cigarette aerosol in animal models; and an absence of studies in which multiple device types and liquids are applied to models to mimic use patterns in the affected demographic.
5. The occurrence of EVALI highlights the importance of broadening e-cigarette toxicity questions beyond comparators to smoking and smoking-related diseases, because vaping has disease risks different from smoking.
6. Systematic and comprehensive laboratory-based studies should be conducted examining the toxicology and health effects of THC-containing vaping products to provide insights into potential causes of EVALI.

Goals of This Workshop

To discuss the complexities of the e-cigarette or vaping product use–associated lung injury (EVALI) outbreak, to gain a better understanding of what the research priorities should be, to determine research strategies, and to uncover cause-and-effect relationships to diagnose, treat, and prevent this disease most effectively.

Description of the Workshop

The NHLBI convened a working group meeting on October 23, 2019 entitled "EVALI: Developing a Research Agenda" to identify the most pertinent and urgent research priorities and prevailing challenges in the field. Participants included experts from the e-cigarette research community, clinicians and clinical researchers, and federal employees from the NHLBI, National Institute on Drug Abuse, National Cancer Institute, NIH Office of Disease Prevention, CDC, and U.S. Food and Drug Administration (FDA). Participants discussed the complexities of the EVALI outbreak, identified areas of agreement and research priorities, and recommended strategies to address most effectively its causal factors and improve diagnosis, treatment, and prevention of this disease. Although NHLBI convenes workshops to garner input on research priorities from the community, the key priorities discussed do not necessarily reflect the official views of the NHLBI, NIH, or the U.S. federal government.

Electronic (e)-cigarettes have been on the international market since 2007, and multiple lung diseases have been tied to vaping over the years. However, these vaping-related lung diseases were either occurring or being recognized at a low frequency (1–5). In mid-2019, a new disease entity, EVALI, was recognized first in a few states (6, 7) and soon followed by rapid identification across all of the United States (8, 9). As of February 2020, more than 2,800 cases requiring hospitalization have been confirmed, and 68 deaths have been attributed to EVALI. The consistency across EVALI cases in terms of gastrointestinal (GI), systemic, and respiratory symptoms, and the large number of cases occurring in a short period of time, are most suggestive of one new acute disease process caused by a common inhalation injury. However, variability in the duration of symptoms before presentation and differences in radiographic and pathologic findings across cases also suggest that some cases that were labeled as EVALI may actually have been other vaping-related lung diseases, such as hypersensitivity pneumonitis, eosinophilic pneumonia, lipoid pneumonia, and organizing pneumonia, which have been identified in vapers over the last decade.

Here we present an expert consensus, based on current data, on what is known and unknown about EVALI. We begin with details of the clinical disease, including symptoms, findings, treatments, and outcomes, before discussing possible roles of vaping devices, e-liquid components—such as solvents, flavors, and active agents—and the prevalent use of combinations of devices and liquids as potential contributors or causes of this disease. We discuss the role of screening for EVALI, the need to differentiate it from other vaping diseases, and how the creation of a registry may help track these new diseases. We have included bulleted recommendations regarding potential future research directions within each section.

The Clinical Entity of EVALI

Symptoms

On the basis of CDC reports and published case series, there are three types of symptoms commonly present across EVALI cases, including prominent GI, general systemic (fever and fatigue), and respiratory symptoms (6, 7, 10, 11).

A patient presenting with symptoms across the three categories is more likely to be diagnosed with EVALI, whereas a patient presenting with GI symptoms alone could be easily missed. Duration of symptoms has not been consistent across cases, with both subacute presentations, with symptoms for weeks to months, and acute presentations, with symptoms for hours to days (Table 1) (10–12).

Clinical Findings

Data from the largest case series demonstrate that patients with EVALI commonly are hypoxemic, tachycardic, and tachypneic (Table 1) (10). Leukocytosis, elevated CRP (C-reactive protein) and/or erythrocyte sedimentation rate (ESR), and elevated transaminases are the most prevalent laboratory findings. Patients must have bilateral pulmonary opacities by chest radiograph or computed tomography imaging to meet criteria for EVALI, and radiographic patterns most commonly show ground-glass opacities in multiple lobes, with sparing of the subpleura (12, 13). Interestingly, multiple cases of pneumomediastinum and pneumothorax have been documented (10), which suggests that barotrauma may play a role—potentially secondary to puff topography, breath holding, or bearing down during vaping. Alternatively, vaping may cause mechanical disruption of the lung parenchyma, leading to open channels between airways and pleural and mediastinal spaces (12, 14–16).

Spectrum of Disease Severity

Patients with EVALI have presented with a broad range of disease severities (10, 12, 15). The CDC is primarily tracking and reporting hospitalized cases, which include moderate and severe cases. Severe cases often require invasive mechanical ventilation for acute respiratory distress syndrome (ARDS). It has been noted that patients with mild EVALI may have only one or two categories of symptoms, such as GI symptoms alone, which makes accurate diagnosis and tracking of these patients less likely (10). Data thus far suggest that mild and moderate cases of EVALI have significantly elevated markers of systemic inflammation (e.g., CRP, 21; ESR, 66; and white blood cell count, 14.6), although lower than those seen in severe EVALI (e.g., CRP, 31; ESR, 91) (oral communication by Sean Callahan and Nuala Meyer during the Workshop). Defining a grading scale for EVALI may help in understanding this disease process (Tables 2 and 3).

Treatment of EVALI

Beyond supportive care, there is no proven treatment in patients with EVALI, although steroids are often given based on biologic plausibility and expert recommendations (17–19). Documenting doses and courses of steroids that clinicians are using for patients with EVALI may help ascertain steroid responsiveness within subgroups. There have been documented cases of subjects with EVALI having relapse of disease associated with recurrent vaping, indicating that all patients should receive nicotine and/or marijuana addiction counseling (Table 3). However, relapse in the absence of recurrent vaping has also been documented (10, 12). A strong understanding of the biological mechanisms by which vaping is causing lung injury will provide the best guidance as to potentially beneficial therapies.

Outcomes

There was consensus that long-term outcomes in EVALI are unknown, as it is a newly described disease entity. There is concern regarding follow-up care, because the affected are primarily a young healthy population who do not commonly seek health care.

Potential Etiologic Factors in EVALI

Devices

Most patients report using multiple devices, and no single device has been identified as common to all cases of EVALI. Thus, there are no vaping devices that can be identified as less dangerous or as specifically associated with causing EVALI. The FDA and CDC are collecting and analyzing data from patients with EVALI across the United States to assess for any association of devices with the disease. To complicate matters, there is an entire set of devices and tools used for the practice of dabbing—rapid heating and aerosolization of highly concentrated tetrahydrocannabinol (THC) (called a dab, wax, honey, etc.) for inhalation—for which very few data are available.

Vaping devices, as a product class, are exceptionally heterogeneous, with differences in materials, configuration, and electrical heating power output (20–23). Each of these characteristics can influence nicotine (24) and nonnicotine toxicant emissions (25–27) and thus can affect cellular damage and induction of disease (28–30). Particularly, device power has been shown to be a key characteristic that affects emissions of respiratory toxicants (including carbonyl compounds like formaldehyde, acetaldehyde, and acrolein) that are generated by thermal degradation of solvents (25, 27, 31–33). In addition, wicks and coils are made of various metals, plastics, and organic substances and can produce toxic chemicals that are inhaled (34, 35). Given this heterogeneity in devices and liquids (*see* sections below), some vaping device plus liquid combinations may generate toxic chemical exposures leading to EVALI (Table 4).

Vaping Liquids and Chemicals

Patients with severe EVALI typically used multiple vaping devices, multiple liquids, and more than one active agent (i.e., both nicotine and THC). However, 82% of cases were in THC users, with 33% reporting exclusive use of THC (36). No single type or brand of vaping liquid has been linked to all cases. Patients' descriptions of their behavior suggest that many affected individuals began vaping nicotine before

Table 1. Areas of Consensus, the Clinical Entity of EVALI

Presentation	
Symptoms	Respiratory, gastrointestinal, and systemic
Duration	Days to months
Findings	
Clinical	Hypoxemia, tachycardia, and/or tachypnea
Laboratory	Leukocytosis, elevated CRP and ESR, and/or elevated LFTs
Radiologic	Bilateral pulmonary opacities, pneumothorax, and/or pneumomediastinum

Definition of abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EVALI = e-cigarette or vaping product use–associated lung injury; LFT = liver function test.

Table 2. Proposal for Grading Clinical Severity

	Severe	Moderate	Mild
O_2 requirement	⩾6 L, noninvasive or invasive ventilation	1–5 L	None
Nonpulmonary organ failure	Any	None	None
Shock	Any	None	None
Hospital admission	Yes, frequently ICU level of care	Yes	No

using THC and cannabidiol (CBD). There is a possibility that chronic inhalation of aerosol formed from heating basic liquid constituents, such as propylene glycol (PG) and vegetable glycerin (VG), may change fundamentally the inflammatory and immune state of the lung (37), such that a second hit by an as-yet-unidentified infectious agent, viral or bacterial, or a toxic chemical inhaled through vaping or dabbing, leads to an overwhelming inflammatory reaction causing ARDS. Moreover, given that most patients with EVALI use more than one type of product, the potentially synergistic contributions of multiple product types (e.g., nicotine-VG/PG combined with THC or CBD in lipophilic solvents) cannot be dismissed (Table 4).

Solvents

Nicotine-containing liquids usually contain hydrophilic solvents like PG and VG (also known as glycerol). Because nicotine and THC have different physicochemical properties, there are important differences between the solvents used. THC vaping products are created through extraction with butane or CO_2, a distillation/purification step, followed by the addition of PG/VG, terpenes, and lipophilic compounds (commonly referred to as "cutting agents"), including vitamin E acetate (VEA), coconut oil, and medium-chain triglycerides (38, 39). Inhalation of hydrophilic solvents may lead to different complications than inhalation of lipophilic substances that may not be absorbed easily from lungs. THC products used for dabbing are commonly called butter and shatter and are thicker in consistency. Also, some vapers mix CBD oils with nicotine-containing liquids (18, 40). Thermal stability of commonly used solvents is highly variable, and they may undergo thermal degradation when heated, leading to the generation of toxic byproducts. Thermal decomposition resulting in generation of toxicants could also happen to THC and VEA (41, 42). VEA recently has been identified by the CDC as present in 48 of 51 BAL samples received from EVALI cases (43). Exposure of mice to inhaled VEA for 2 weeks led to EVALI-like changes in the lungs (44). Thus, VEA is a front-runner as either a potential causal agent in EVALI or as a marker of vaping liquids that are potentially causally related to EVALI.

Flavors

Hundreds of chemicals, including numerous flavoring agents and terpenes, have been identified within the vaping liquids, and the FDA, CDC, and others are working to identify potential causal agents.

Vaping Behaviors

Puff topography and breath holding may contribute to the development of EVALI, because they can exert direct mechanical effects (e.g., barotrauma leading to high incidence of pneumomediastinum and pneumothorax), might change aerosol particle properties, and alter e-liquid exposure levels. Thus, further information about these inhalation patterns is needed (Table 4). Furthermore, vaping in combination with conventional cigarette and marijuana smoke is common across inhalant users, and these pulmonary exposures may interact with each other and cause pulmonary diseases.

Team Science

To accelerate research on and to ensure a thorough understanding of the etiology, pathogenesis, and treatment of EVALI, it will be necessary to bring together experts from the fields of aerosol physics, e-liquid chemistry, epidemiology, e-cigarette design and operation, pulmonary and critical care, pathology, puff topography, and toxicology.

Table 3. Research Recommendations: Clinical Features

1.	Evaluating puff topography, breath holding, or bearing down via questionnaires, interviews, and assessment of vaping techniques in the laboratory setting may clarify the role of vaping styles in disease pathogenesis.
2.	Generation of more specific criteria for the diagnosis of EVALI is needed to differentiate between EVALI and other lung diseases caused by vaping.
3.	A definition of disease severity may help guide clinical research studies of EVALI, such as an O_2 requirement of ⩾6 L/min for severe, 1–5 L/min for moderate, and no O_2 requirement in mild cases.
4.	Classification of both duration of symptoms and disease severity may help identify risk factors for different severities and uncover whether different disease presentations represent a continuum of one disease or represent variants of the disease.
5.	Conducting translational research studies on biospecimens obtained from subjects with EVALI, across different time points and severities of disease, to define the cell types, phenotypes, and molecular pathways involved may yield critical data regarding mechanisms of injury and inflammation.
6.	Developing an EVALI animal model would give insight into disease mechanisms and allow for rapid testing of potential therapeutic agents.
7.	Research is needed related to addiction relapse prevention.
8.	Longitudinal studies in confirmed cases to define the mortality and short- and long-term morbidity for these patients is an important research need.

Definition of abbreviation: EVALI = e-cigarette or vaping product use–associated lung injury.

Table 4. Research Recommendations: Etiology

1.	Define the devices, and combinations thereof, associated with EVALI.
2.	A complete list of chemicals used by patients with EVALI should be made available to researchers such that rapid testing of top candidates can be done via *in vitro* and *in vivo* studies using available models, to identify mechanisms by which they may be causing injury. These studies should include human airway epithelial cell cytotoxicity and response to inflammatory stimuli, airway macrophage cytotoxicity and functional assays, and cytokine release that is tied with neutrophil recruitment to the lung.
3.	Define use behaviors of different products, including the latest THC delivery devices (dabbing, crackle, and waxing), and frequency and length of product use.
4.	Define combined pulmonary exposures (THC vaping plus conventional tobacco, etc.) and study each for evidence of interactions and even synergistic effects.

Definition of abbreviations: EVALI = e-cigarette or vaping product use–associated lung injury; THC = tetrahydrocannabinol.

The addition of GI and hepatology experts will also help define why inhalation of chemicals via vaping causes severe GI symptoms and transaminitis (6, 7, 10, 11). Behavioral scientists and addiction specialists are needed to address the needs of patients with EVALI who are unlikely to quit without help because of nicotine and/or THC addiction and may be at risk for relapse of their disease. THC and CBD have disparate chemical properties and extraction processes relative to nicotine. Therefore, input from experts on CBD, marijuana, and THC will be critical to inform the design of studies of each inhalant and to define the epidemiology of users. Finally, studies that also include patients with EVALI and nonsymptomatic vapers would help clinicians and researchers better understand vaping and dabbing practices and the challenges faced by patients and e-cigarette users (Table 5).

Continued discussions among experts will lead to *1*) a better understanding of the complexity of EVALI, *2*) identification of the most promising potential avenues of research by which mechanisms underlying the disease can be identified, and *3*) creation of new collaborations across disciplines with sharing of resources (Table 5). Mechanisms that promote and incentivize cross-institutional collaboration, including sharing of biospecimens and collaboration with public health departments and/or the CDC, would be particularly useful. Real-time face-to-face discussions would be most productive, and the working group discussed possibilities, including meetings via platforms that allow for both webcam and screen sharing every 2 to 4 weeks.

Table 5. Research Recommendations: Multidisciplinary Teams

1.	Cross-institutional collaborations integrating the expertise from a variety of different fields are needed to uncover cause-and-effect relationships.
2.	Given the rapidly evolving product landscape, streamlined timelines are essential, with the potential for rapid turnaround and response to changing epidemiologic patterns of vaping-associated lung injury.
3.	Identifying and clarifying approaches that allow researchers to study THC-containing products will be critical to enabling further progress toward identifying EVALI pathogenesis. Because many cannabis-associated products are prohibited by federal law, it is daunting for researchers to access and study these materials. Given this challenge, strategies to promote research in this area, such as changing federal restrictions on marijuana, THC, and CBD research, are essential to make any meaningful progress on establishing cause-and-effect relationships.
4.	Define combined pulmonary exposures (THC vaping plus conventional tobacco, etc.) and conduct studies modeling each combination for evidence of interactions and synergistic effects.

Definition of abbreviations: CBD = cannabidiol; EVALI = e-cigarette or vaping product use–associated lung injury; THC = tetrahydrocannabinol.

EVALI Registries

Although the CDC, as well as state and local health departments, has accumulated information on EVALI cases, there have been limitations on collection and release of data because of the burden of data collection and privacy issues. Creating national and international registries of all patients with EVALI that can be accessed by researchers and clinicians would enable accurate tracking of those affected and assessment of outcomes (Table 6). Ideally, researchers would have the ability to obtain BAL, plasma, and urine from all participants to identify EVALI biomarkers of exposure and harm. In particular, acquisition and analysis of biospecimens from humans affected by both severe and nonsevere EVALI will help profile inflammatory and fibrotic changes, determine whether a heretofore unknown viral or bacterial pathogen may be a causal agent, and promote understanding of EVALI pathogenesis.

It will be important to develop and use detailed questionnaires that accurately quantify vaping, dabbing, and other inhalant use for all known and suspected pediatric and adult EVALI cases. Ideally, these should be easy to use, linked to electronic medical records, and adaptable to the changing market and use patterns of vaping devices and products used. Obtaining accurate profiles of THC, CBD, and conventional marijuana use may be challenging; some patients are resistant to reporting use of these products, as they are illegal in many states and at the federal level (45). Because of the rapidly evolving nature of the products and the terminology used to refer to them, the use of pictures and images of common device types and device characteristics for patients or proxies may be helpful. Separate International Classification of Diseases codes could be developed to reflect vaping of nicotine versus THC and CBD, similar to existing ones for tobacco use. Finally, use of puff topography recording devices is recommended to obtain detailed information on vaping behaviors (Table 6).

Table 6. Research Recommendations: EVALI Registries

1.	Three cohorts should be identified and followed over time: • Healthy vapers and dabbers • Patients with severe EVALI • Patients with nonsevere (mild, moderate, subacute, and chronic) EVALI Cohorts containing subgroups of nicotine-only vapers and those who vape THC and CBD, as well as cases where presentations were subacute or chronic, would provide robust data for examination.
2.	The working group agreed on two mechanisms by which epidemiologic data could be acquired for open sharing: • An open registry could be established such that patients and vapers/dabbers can register themselves and provide full details on their vaping. Registrants could use an online registry portal to grant access to their electronic medical records and therefore provide researchers invaluable access to information about disease onset, course, and resolution; • Individual public health departments could be contacted to request access to their datasets while managing privacy concerns, to combine all known cases into a larger, comprehensive database.

For definition of abbreviations, *see* Table 5.

Translational and Basic Science Research

Bioassays and Biobanking

Biomarker studies will be critical to understanding mechanisms underlying EVALI and identifying diagnostic markers for the disease. Useful biomarker studies and biobanked samples would come from both patients with EVALI enrolled in studies and appropriate comparator groups, including equally sick patients with respiratory failure for non-EVALI reasons and healthy control subjects (nonsmokers and healthy vapers). Studies of vapers, along with never-smokers and smokers, may highlight how nicotine inhalation is different from vaping/dabbing with THC/CBD oils and how it is similar. Although the current outbreak of EVALI focuses mostly on THC/CBD, there are patients with EVALI who deny the use of these drugs, and the long-term effects of vaping with PG/VG and other chemical constituents may cause other diseases/injuries, including those with shared features of EVALI.

BAL or tracheal aspirates in intubated patients that are acquired, processed, banked, and used for inflammatory profiling and metagenomic studies can be used in future studies to define the viral and bacterial populations present in the airways of patients with EVALI and to identify key pathways involved in host responses (Table 7). These can be compared with healthy subjects as well as patients with ARDS, to identify organisms and/or pathways specific to EVALI. Independent of EVALI, biomarkers sampled from the lung and other target organs of smokers, former smokers, e-cigarette users, THC vapers, and never-smokers can elucidate toxic effects that are shared with smoking and independent from smoking (46, 47). These same biospecimens could also undergo various analyses for epigenomics, gene expression, lipidomics, metabolomics, microbiome, and proteomics. In patients with less severe EVALI, bronchoscopy with BAL may be a mechanism by which to assess for biomarkers, organisms, and chemicals such as VEA associated with EVALI. In patients who die as a result of EVALI, autopsy specimens will guide understanding of cellular and molecular mechanisms underlying the disease (48, 49) (Table 7).

Table 7. Research Recommendations: Defining Mechanisms

1.	Samples should be collected from subjects with EVALI and other cohorts noninvasively (e.g., blood, urine, or sputum) and from the lung and gastrointestinal tract when symptoms are present (e.g., target organs) in a standardized fashion.
2.	Samples should be paired with preexisting medical information and vaping exposure information, ideally including vaping history, device use and modification, liquids used, etc., as well as detailed prior tobacco-use history.
3.	Chemical profiles of vaping liquids, power and temperature data of devices, and overall materials of tanks and cartridges used by subjects with EVALI should be documented and cross-analyzed with biospecimens acquired.
4.	Rodent models would be ideal for high-throughput testing of different compounds and for testing novel EVALI treatments.
5.	Nonhuman primate models of EVALI may be useful, as inflammation and immune responses are more similar to those seen in humans.

Definition of abbreviation: EVALI = e-cigarette or vaping product use–associated lung injury.

Animal Models

Animal models replicating EVALI have not yet been established and will be crucial to understanding disease mechanisms and testing possible treatments. However, there are existing animal models of the inflammatory and toxic effects of e-cigarettes on multiple organ systems, including the lungs. Published studies of experimental e-cigarette exposures in rodents have used acute, subacute, and chronic exposures (37, 50–52), and only one study has found evidence of acute lung injury after exposure to vitamin E acetate aerosols (44). However, there is lag time between studying the latest devices and e-liquids and publication, and the majority of published research studies to date were performed with e-liquids and vaping devices purchased in or before 2018. Chronic exposure to solvents used in conventional e-cigarettes (i.e., PG and VG) is known to cause lipid accumulation in macrophages (evidence in both humans and mice) (37, 53) and abnormal surfactant production (evidence in mice) (37). In contrast, there have been almost no studies on the biological effects of aerosols from vaping devices containing CBD, THC, and vitamin E, which also contain constituents that may be very different from those in nicotine-based systems. Moreover, because many cannabis-associated products are illegal federally in the United States, there are no data from animal models or other *in vitro* laboratory-based experimental systems from these products. However, it will be imperative to perform studies of the liquids, aerosol products, and devices being used by patients with EVALI, to

define the pathology of EVALI and to understand the mechanistic pathways at play. Using complex models such as rodent inhalant exposures is more likely to yield results quickly (to identify the chemicals causing lung injury), after which exposure of pulmonary cells *in vitro* or *ex vivo* to drill down on the specific mechanism of cellular injury and dysregulated inflammatory response will be needed. Because rodent models may be limited in terms of delivery and deposition of aerosols into the terminal airways and alveoli, alternative models such as ferrets, guinea pigs, sheep, or nonhuman primates may be required (Table 7).

Conclusions

The CDC report made a strong connection between VEA used in THC products and EVALI, but no factors have yet been proven to cause the disease. Many unanswered questions require careful studies of vapers, with and without symptoms, as well as research with experimental models that use the same compounds (Tables 3–7). Over the past several years, the NIH and FDA, through programs such as the Tobacco Regulatory Science Program, have funded research on the devices, constituents, behaviors, policies, and health effects that are relevant to the regulation of nicotine-containing e-cigarettes. However, the sudden appearance of EVALI indicates that much more research needs to be done, particularly in the areas of vaping-induced lung injury and, importantly, in the emissions, behaviors, and health effects associated with THC-based vaping. To address urgent outbreaks such as EVALI, research can be stimulated via rapid grant mechanisms, such as administrative supplements, and the NIH has recently indicated an interest in supplement applications to address these questions.

As a society, we value public health and must do everything feasible to determine what the long-term consequences of inhaling aerosols generated from vaping devices will be. The EVALI outbreak could dissipate, as suggested by the declining number of cases since October 2019, as users switch vaping devices and liquids because of continued evolution of the devices and changing patterns of use. However, there is a high likelihood that other diseases will emerge as humans continue to inhale chemicals contained in unregulated and untested vaping liquids and dabbing substances. Research to define the etiologic agent(s) in EVALI and to determine the overall consequences of vaping on health is still desperately needed (Table 7). Furthermore, a system that allows local public health departments, the CDC, and the FDA to share biological samples and data with researchers could allow for rapid analysis and rapid answers about novel disease processes affecting the population both here in the United States and worldwide. ■

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