TOXICOLOGY

Cause of mystery vaping lung illnesses remains elusive

Little is known about the contents and toxicology of e-cigarette or THC products or their delivery devices

No one knows for sure why more than 1,200 previously healthy people in the US, more than half of them under the age of 25, have developed serious lung injuries that require hospitalization and, in many cases, mechanical ventilation and intensive care. Twenty-six people had died from the mystery illness as of Oct. 8, according to the US Centers for Disease Control and Prevention. Health officials have ruled out an infectious agent. The only common link is that all the victims have admitted to vaping nicotine or tetrahydrocannabinol (THC)—the psychoactive component in cannabis that produces a high—or both.

Federal, state, and local governments are scrambling to find answers to this emerging public health crisis. But after several months of investigation, "no one compound or ingredient has emerged as a singular culprit," Norman "Ned" Sharpless, acting commissioner of the US Food and Drug Administration, says in an Oct. 4 statement. "We do know that THC is present in most of the samples being tested," he says.

As the number of serious lung injuries attributed to vaping grows, so do the number of possible explanations. Over the past few weeks, fingers have pointed at vitamin E acetate and pesticides in vaping liquids, as well as cadmium-containing solder used in vape pens.

The ongoing investigation is particularly challenging because it involves nearly all US states, CDC principal deputy director Anne Schuchat told members of Congress at a hearing on Sept. 25. She added that "the investigation is complicated by the diversity of the e-cigarette or vaping product marketplace, with a multitude of products, a wide array of ingredients, and the intersection with potentially illicit substances such as marijuana." The bottom line is that "users do not know what is in their e-cigarette or vape solutions," Schuchat said. Even if they did know, little information is available on inhalation toxicity.

Although the lung injuries may seem similar, "it is not clear if they have a common cause or if they involve different diseases with similar presentations," Sharpless testified at the Sept. 25 hearing, held by the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce.

More than 1,200 people, mostly under 35, have developed serious lung injuries associated with vaping, but the cause is still unknown.

The latest evidence points to more than one type of illness. A group from WakeMed Hospital in North Carolina reported in early September that lung injuries in five people resembled lipoid pneumonia, a condition in which fats or oils deposit in the lungs (*Morb. Mortal. Wkly. Rep.* 2019, DOI: 10.15585/mmwr.mm6836e1). However, in a letter to the editor of the *New England Journal of Medicine* published on Oct. 2, Mayo Clinic and UnityPoint Health staff in Arizona, Florida, Illinois, and Minnesota report finding no evidence of lipoid pneumonia in lung tissue samples from 17 people with suspected vaping illness. The physicians instead point to lung inflammation "from one or more inhaled toxic substances" (DOI: 10.1056/NEJMc1913069).

Searching liquids for a culprit

While clinicians work on identifying and treating the lung injuries, others are actively looking for the cause. The FDA is analyzing samples of vaping products consumed by those who have developed lung injuries. The agency has received about 440 samples from 18 states, Sharpless says in the Oct. 4 statement. "More than half of the vaping liquid products have undergone some form of evaluation, with additional testing on these and other samples continuing daily," he says.

Scientists at the FDA's Forensic Chemistry Center are analyzing the samples "using state-of-the-art methods to assess the presence of a broad range of chemicals, including nicotine, THC and other cannabinoids, opioids, cutting agents and other additives, pesticides, and toxins," Sharpless testified at the Sept. 25 hearing. But such testing is limited, he noted, because many of the samples contain little to no liquid.

Of the samples analyzed by the FDA, about 70% contain THC, Sharpless said at the hearing. About half of the samples that contain THC also contain vitamin E acetate, he noted. On Sept. 5, the New York State Department of Health pointed to vitamin E acetate, an oil used as a nutritional supplement and as a diluent or thickening agent in THC vaping cartridges, as a possible cause of the lung problems. It is unclear whether vitamin E acetate is the cause of the lung injuries or a marker of an adulterated product, Sharpless said at the hearing.

Nonetheless, cannabis-testing labs are now starting to offer tests for vitamin E and

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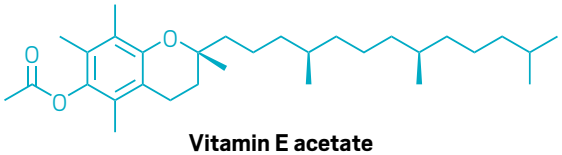
vitamin E acetate in THC vaping cartridges. "It is not a standard test" in the cannabis industry, says Amber Wise, science director at Medicine Creek Analytics, a Seattle-based cannabis-testing lab. But vitamin E is used in many other products, such as lotions and nutraceuticals, "so analytical labs already have protocols," she says.

Thickening agents are common in illicit THC cartridges but are rarely added to legal products where testing for potency is required, says Jeffrey Raber, cofounder and CEO of the Werc Shop, a California-based cannabis contract manufacturing and testing firm.

"THC concentrates are known to be thick and viscous when they are high potency," Raber says. So when street dealers dilute illicit products with various agents to maximize profits, those products are typically less viscous. Consumers can visually detect the viscosity of the product by turning the cartridge upside down. If a bubble goes from the top to the bottom quickly, it usually means that the product has been cut with something, Raber says. Dealers mask that visual test by adding a thickening agent, so the bubble doesn't move from the top to bottom as fast, and consumers think they are getting a high-potency product.

The illicit cannabis market "is out of control and concerning," even in states like California where recreational cannabis is legal, Raber says. In California, the cannabis black market is estimated to be three to four times the size of the legal cannabis industry, he notes.

One source of the black market problem is that California requires testing of final finished cannabis products, Wise says. If a product fails the test, more often than not it doesn't get thrown away. Instead, it enters California's black market and is distributed to states where cannabis is illegal, she says.



Vitamin E acetate

More recent reports suggest that pesticides in illicit THC products may be playing a role in the outbreak of vaping lung injuries. Last month, NBC News purchased THC vaping cartridges from both legal dispensaries and illicit dealers in California and sent the products to cannabis testing lab CannaSafe for analysis. The lab found no pesticides or other contaminants in the legally purchased products, but it found the fungicide myclobutanil in 10 of 10 illicit products tested for pesticides. When heated, myclobutanil produces hydrogen cyanide. Inhalation of hydrogen cyanide is fatal at high doses.

What is in the aerosols?

Determining what's in vaping products is a key part of understanding what's causing the lung injuries. However, knowing what's in vaping cartridges is not the same as knowing what's going into people's lungs. "You can test the oil all you want, but at the end of the day, what are you inhaling?" Medicine Creek Analytics' Wise asks. "That is the most important part to test in my opinion."

Scientists at the CDC are analyzing the aerosols produced by some of the products consumed by patients with vaping illnesses, the CDC's Schuchat testified at the September hearing. The analysis is complex because "users can modify the products, and the heating process can also influence the types and amounts of chemicals a user is exposed to," she said.

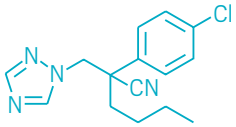
Cannabis testing labs are also investi-

gating aerosols generated by various vaping products. Before the outbreak of lung illnesses hit the news, Medicine Creek Analytics ordered a vapor collection machine to test a filter device for a client to determine whether it removes pesticides, cannabinoids, and terpenes from cannabis vaping products, Wise says. The machine will be useful for understanding what is in the aerosol that people are vaping, she says.

And then there's the question of which of the chemicals in aerosols might harm lung tissues. Little is known about the toxicity even of branded e-cigarettes, let alone THC products.

Scientists at the Institute for In Vitro Sciences (IIVS) are working with tobacco companies to evaluate the inhalation toxicology of products in development or on the market. They are using nonanimal, human cell–based testing platforms. The team is optimizing such tests for evaluating potential hazards associated with inhalable materials, including those from vaping devices, says Holger Behrsing, a principal scientist at IIVS.

"As part of our expansion of respiratory toxicology testing, we do utilize long-term pulmonary models and conduct repeat exposure studies to better recapitulate potential human exposures," Behrsing says. "We believe such an approach using human, multicellular, three-dimensional respiratory test systems will better allow us to detect key events that may lead to more severe, adverse pulmonary conditions."



Myclobutanil

As for the cause of the current lung injury crisis, the problem could be related to the battery, the heating element, or the cartridge itself, Wise says, pointing out that many devices are cheap and not very reproducible.

In an Oct. 5 blog post, owners of Colorado Green Lab, a company that sells nonpsychoactive cannabidiol (CBD) and CBD delivery systems, suggest that cadmium solder used in cheap vape pens may be the cause of some vaping lung injuries. "Cadmium-containing silver solder is less expensive than cadmium-free alternatives, and has improved flow properties which facilitate the joining of dissimilar metals found in vape pen electrical components," the company says. However, it adds, a "serious form of metal fume fever occurs after inhalation of cadmium oxide fumes."

Metal fume fever "is a condition in which the sufferer has influenza type symptoms—a raised temperature, chills, aches and pains, nausea, and dizziness," says the Welding Institute, a research and technology organization specializing in welding. The institute adds that exposure to some metal fumes, such as cadmium, "can cause more serious illness or even death."

The cause of the outbreak is likely to be a combination of many factors, Wise says. "This situation really points to the need for oversight, regulation, and product safety testing."

The broader cannabis industry echoes that position. "If it is confirmed that Americans are being hurt because of unregulated, illicit market cannabis vape products, it is yet another reason for real, comprehensive federal cannabis reform that will allow the regulated, tested cannabis industry to displace illicit market actors," says an Oct. 3 letter from the National Cannabis Industry Association to congressional leaders.—BRITT ERICKSON