E-cigarettes: The lingering questions

Christophe Ena/AP Photo

E-cigarettes are touted as a safe alternative to tobacco, but research has been inconclusive.

In many respects, the modern electronic cigarette is not so different from its leaf-and-paper predecessor. Take a drag from the mouthpiece and you get a genuine nicotine fix — albeit from a fluid wicked into the chamber of a battery-powered atomizer and vaporized by a heating element. Users exhale a half-convincing cloud of 'smoke', and many e-cigarettes even sport an LED at the tip that glows blue, green or classic red to better simulate the experience romanticized by countless writers and film-makers. The only things missing are the dozens of cancer-causing chemicals found in this digital wonder's analogue forebears.

E-cigarettes — also known as personal vaporizers or electronic nicotine-delivery systems among other names — are perhaps the most disruptive devices that public-health researchers working on tobacco control have ever faced. To some, they promise to snuff out a behaviour responsible for around 100 million deaths in the twentieth century. Others fear that they could perpetuate the habit, and undo decades of work.

Now, a group once united against a common enemy is divided. "These devices have really polarized the tobacco-control community," says Michael Siegel, a physician and tobacco researcher at Boston University School of Public Health in Massachusetts. "You now have two completely opposite extremes

with almost no common ground between them."

Evidence is in short supply on both sides. Even when studies do appear, they are often furiously debated. And it is not just researchers who are attempting to catch up with the products now pouring out of Chinese factories: conventional tobacco companies are pushing into the nascent industry, and regulators are scrambling to work out what to do.

Some countries, such as Singapore and Brazil, have banned the products entirely. The US Food and Drug Administration has proposed to bring them under its control alongside tobacco — but the path to regulation has been beset by lawsuits and delays. In May, the European Union finalized a major revision to the rules governing tobacco products in its member states. These include standards for e-cigarette products and restrictions on advertising, but the updated rules will take years to come into effect. On 26 August, the World Health Organization (WHO) released a report that recommended, among other things, to restrict the indoor use of e-cigarettes, to ban certain flavours and to confine sales to those who are 18 years and older. The report will be debated at a meeting in October to decide how the products are treated under the international Framework Convention on Tobacco Control, which commits governments to regulating tobacco and trying to reduce its impact on health.

The open questions include exactly what is in many commercially available products and what health effects they might have. But researchers are also concerned with whether e-cigarette users will give up conventional smoking, or simply become 'dual users'. Could e-cigarettes even act as a gateway, increasing tobacco use?

Siegel says that it is obvious what data and experiments are needed, but it is not guaranteed that anyone will agree about the results. "It's not clear to me that science is going to end this," he says.

Market conflagration

Devices for taking the smoke out of smoking have been around for years, but most have failed to gain traction or, like prescription nicotine inhalers, are restricted in their use. A Chinese inventor named Hon Lik is widely credited for developing the modern e-cigarette, about a decade ago. The Shenzhen-based company he worked for, now called Ruyan, commercialized the invention and has been joined by scores of competitors.

According to a study from the University of California, San Diego, there were 288 brands of e-cigarette available online in 2012, many with multiple products. By January 2014, there were 466, meaning that an average of more than 10 brands had been launched every month. Buyers have clearly been snapping them up: from a standing start a few years ago, the United Kingdom alone is now estimated to have more than 2 million users.

This explosive growth has blind-sided scientists and regulators alike. "I'm personally astounded by how quickly the market has grown," says Wilson Compton, deputy director of the US National Institute

on Drug Addiction in Bethesda, Maryland.

Further complicating the picture is the remarkably fast evolution of the devices themselves. Early models that resemble cigarettes — 'cigalikes' — have been joined by customizable vaporizers costing hundreds of dollars and sporting everything from gold plating to software that lets users tweak how the devices operate.

In response, researchers have radically scaled up their efforts to provide regulators with guidance. E-cigarettes promise to drastically reduce the death toll from smoking — without depriving users of the nicotine they crave. (A phrase often quoted in tobacco-control circles is that people 'smoke for the nicotine but die from the smoke'.)

But on the central question — are e-cigarettes safe? — there are many uncertainties. Long-term consumption of nicotine divorced from tobacco is thought to be relatively safe for most people, barring pregnancy or certain rare conditions. But nicotine is not danger-free. There have already been overdoses from people drinking the liquid from e-cigarettes, or spilling it on their skin, where it is absorbed.

Also unknown are the long-term effects of regularly inhaling propylene glycol, the chemical that makes up most of the liquid vaporized in e-cigarettes. This organic molecule is used in scores of commercial applications ranging from food to plastics, and it has been shown to be safe to consume except at very high levels. Some evidence from the theatre — where it is used to create fogs and mists — suggests that it may irritate the respiratory system, but there are no long-term data about the effects of inhalation.

Many e-cigarettes contain other chemicals added for flavouring, and little is known about these. There are also legitimate fears about quality standards for the products: toxic contaminants have been found, and in a very few cases batteries have exploded, leading to injury.

Tyrone Siu/Reuters/Corbis

Manufacture of e-cigarettes is booming in China.

Around the world, researchers are now subjecting e-cigarettes to the same kinds of tests used to shed light on how conventional cigarettes damage human health. Some have found genetic changes to human bronchial cells grown *in vitro* in a medium exposed to e-cigarette vapour (see *Nature* **508,** 159; 2014). These looked similar to changes induced by conventional tobacco smoke. Another study found that e-cigarette use, like normal cigarette smoking, led to a reduction in exhaled nitric oxide, which could be a sign that e-cigarettes alter lung function. But this work is early and still inconclusive.

Those who are positive about the potential benefits of e-cigarettes say that although their safety clearly needs to be monitored and further investigated, there is simply no way they can be as dangerous as conventional cigarettes.

“The key comparison here is to smoking,” says Lynne Dawkins, head of the drugs and addictive behaviours research group at the University of East London, UK. Dawkins says that the lower risks of e-cigarettes and the fact that many users believe they are an acceptable substitute for tobacco makes them generally a good thing. (Some of Dawkins’s research has been funded by e-cigarette companies.)

Snuff it out

Dawkins and others are optimistic that beyond being a safer substitute, e-cigarettes could help people to stop smoking. But in many of the jurisdictions where they are taking off, e-cigarettes cannot be sold as smoking-cessation aids. In the United Kingdom, for example, that would require them to be licensed as medicine. The United States also bans direct claims about helping people to quit, but some brands circumvent this with testimonials from users or other implied messages about the devices' benefits.

So far there is a lot of anecdote but only a little hard evidence. One of the few randomized controlled trials on e-cigarettes comes from Christopher Bullen, who studies tobacco control at the University of Auckland in New Zealand. His study, published last year, found that an early e-cigarette model was roughly as effective as nicotine patches at helping smokers to quit. But critics have cited weaknesses such as problems monitoring the actual use of devices and differences in how study participants obtained them. Participants may have had to go to more effort, for example, to obtain patches than to get e-cigarettes.

In the absence of further controlled trials, researchers have scoured the Internet for data and conducted surveys of smokers. Dawkins and her team have found that many people report using e-cigarettes for smoking cessation, and that these users had a longer 'time to first vape' in the morning than smokers had to their first cigarette, possibly suggesting reduced dependence on nicotine.

But opponents of e-cigarettes have their own ammunition. One study published this year followed 949 smokers reporting their habits online, and found that the e-cigarette users were no more likely to quit tobacco than other smokers. Dawkins and other e-cigarette defenders counter that because the devices may appeal to the smokers who are most heavily dependent on tobacco, results such as this do not actually shed light on the question (see *Nature* http://doi.org/t3f; 2014).

One problem with using e-cigarettes for smoking cessation may be that at the moment most are probably less effective at delivering nicotine than conventional smoked tobacco, says Peter Hajek, a tobacco researcher at Queen Mary University of London. "I think they need about five years, if the regulators don't kill them, to become as good as cigarettes in providing smokers with what they want." This, he says, could ultimately render normal cigarettes obsolete.

But in many ways, those in favour of stricter controls on the devices are worried about giving up any ground in the fight against tobacco. As smoking becomes more difficult — for example, through restrictions on where smokers can light up — e-cigarettes may be used alongside conventional tobacco to maintain nicotine levels. Such dual use could undermine efforts to stop smoking entirely. And although dual users may consume fewer cigarettes than heavy smokers, which would reduce their risk of cancer to some extent, even very low levels of smoking seem to elevate risks of cardiovascular problems.

> **"It's not clear to me that science is going to end this."**

Those who worry that e-cigarettes will do more harm than good also fret that they could make tobacco socially acceptable again. With many developed nations implementing heavy restrictions on advertising, as well as high taxes and medical warnings, tobacco consumption has been massively stigmatized. Now e-cigarettes — which are in many cases unregulated — threaten to disturb this status quo.

One of the opponents' greatest fears is that e-cigarettes will help to attract young people to tobacco. The US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, has found that in 2012, around 1.78 million adolescents in the United States had used e-cigarettes, and that a little less than 10% of those had never previously tried conventional cigarettes.

When those figures were released last year, CDC director Tom Frieden — who headed several anti-smoking initiatives in a previous role as New York City's health commissioner — said that "the increased use of e-cigarettes by teens is deeply troubling". And he warned: "Many teens who start with e-cigarettes may be condemned to struggling with a lifelong addiction to nicotine and conventional cigarettes."

But teenagers often experiment, and it may be that this is all that these data show. Advocates of the devices say that if they were going to cause increases in smoking, then smoking rates would already be going up, given the number of people using e-cigarettes. This does not seem to have happened yet — in developed nations, smoking rates are generally decreasing.

Young and vulnerable

A contentious paper on this subject, and one that exemplifies the debate, comes from Stanton Glantz, director of the Center for Tobacco Control Research and Education at the University of California, San Francisco, who has spent years fighting tobacco and the industry that produces it.

In March, Glantz and his colleague Lauren Dutra analysed a survey of US adolescents and found that those who used e-cigarettes were more likely than others to smoke conventional cigarettes. They wrote that "in combination with the observations that e-cigarette users are heavier smokers and less likely to have stopped smoking cigarettes, these results suggest that e-cigarette use is aggravating rather than ameliorating the tobacco epidemic among youths".

The paper drew strong criticisms for conflating correlation and causation. "These researchers are drawing conclusions that aren't justified by the data," says Siegel. Although there is clearly a correlation between heavy smoking and e-cigarettes, he says, it is not clear whether e-cigarettes are leading to smoking, or the other way around.

Glantz says that much of the ire directed at the paper is the result of the word 'gateway' being used in a press release, which he was unhappy with. He maintains that the data in the paper back the conclusion.

Overall, Glantz says, “properly regulated and available on prescription”, e-cigarettes might be a good thing, but they are currently increasing the number of children using nicotine, and promoting cigarette-smoking among children.

Parties on both sides of the debate had been petitioning the WHO even before it took its firm stance against the devices in August. In a 26 May letter to WHO head Margaret Chan, leading researchers including Dawkins, Bullen and Hajek argued that tough regulation would be counterproductive and would serve only to protect the conventional cigarette market. Harm-reduction approaches, they say, seem to have been “overlooked or even purposefully marginalized”.

Another group of equally eminent scientists — including Glantz — fired back in June, saying that there is insufficient evidence to show that e-cigarettes are useful for smoking cessation, that there is good evidence that they release toxic compounds, and that letting e-cigarettes go largely unregulated could once again allow tobacco companies the opportunity to influence policy.

Big tobacco is moving into the market with gusto. Leading US brand Blu — which Reynolds American, maker of Camel cigarettes, agreed to sell to rival Imperial Tobacco in July — has cornered about half of the US market by some estimates. Reynolds has kept hold of the popular VUSE brand. Altria, which is famous for the Marlboro cigarette brand, has its own MarkTen e-cigarette.

Jason Hughes, a tobacco researcher and head of the department of sociology at the University of Leicester, UK, notes that although e-cigarettes are often seen as something totally new, they may actually be just one more in a long line of attempts to make tobacco consumption more ‘civilized’, from chewing tobacco to cigarettes to cigarettes with filters. But they also represent a break point: although the nicotine in them is derived from plants, the users are now divorced from tobacco leaves completely.

Determining whether this break is truly a good thing becomes crucial when — despite continuous and graphic warnings of the risks of smoking — millions still put their lives at risk for a nicotine hit. Population studies to work out the true effects of this new technology are crucial, says Compton.

There is one thing that all researchers agree on: while they debate, e-cigarette use grows and grows. Whatever researchers think, says Compton, “The public is clearly voting with their feet.”