

Vaper, Beware: The Unique Toxicological Profile of Electronic Cigarettes

Silke Schmidt

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Many parents and pediatricians worry about the appeal of electronic cigarettes to teenagers. And they are not alone. Back in March 2017, for instance, Terry Gordon was contacted by a high school junior about ideas for a science fair project. At one point, the boy mentioned his concern about vaping in the school's restrooms.

"A light bulb went off pretty quickly," recalls Gordon, a professor of environmental medicine at New York University (NYU) Grossman School of Medicine. "We decided to take some air measurements to see if vaping was harmful for kids who do not do it themselves."

With support from administrators and teachers, the Board of Education, and the Parent Teacher Association, Gordon's team eventually installed air monitors in the restrooms at one high school and one middle school. The vaping-associated nicotine levels the researchers measured in these restrooms were similar to those in New York City public housing units where residents smoked heavily, says Gordon.¹

The jury is still out on whether e-cigarettes are as effective as, or superior to, nicotine replacement therapy to help quit smoking.² To date, no e-cigarette has been approved by the U.S. Food and Drug Administration (FDA) as a smoking cessation aid.³

Although e-cigarettes may not expose users to all of the toxicants produced by tobacco combustion, the health risks

associated with exposure to e-cigarette aerosols are not well characterized.⁴ This means harm reduction in smokers who switch to e-cigarettes should be weighed against the potential risk to non-smokers who find vaping much more appealing—and perceive it as safer—than cigarette smoking.

The 2019 outbreak of so-called "e-cigarette, or vaping, product use associated lung injury" (EVALI) in the United States also affected many young individuals; more than half were under age 25.⁵ Although likely caused by vitamin E acetate added mainly to THC-containing vapes,⁵ the event intensified public concern about a simultaneous youth vaping epidemic, supported by growing scientific evidence that e-cigarettes are far from safe.⁶

Combustible Cigarettes vs. E-Cigarettes

E-cigarettes contain a battery-powered heating element, usually a metal coil, that heats an "e-liquid" mixture of solvents, nicotine, and flavoring chemicals. Users inhale the resulting aerosols into their lungs. Manufacturers are not required to publicly disclose the ingredients in e-liquids (although they must report them to the FDA), and substantial discrepancies exist between the labeled and actual nicotine content of many brands.^{7,8,9,10}

E-cigarettes appeared on the U.S. market in 2006.¹¹ Their designs have changed substantially over time. The first-generation



The percentage of high schoolers reporting recent e-cigarette use increased from 1.5% in 2011 to 27.5% in 2019.²⁶ The rapid increase in youth vaping is one reason the FDA is cracking down on manufacturers targeting young consumers with kid-friendly marketing. Image: CC BY 4.0 (cropped original).

“cigalike” models resemble real cigarettes; pen-like second-generation devices have rechargeable batteries and refillable cartridges; third-generation “mods” have larger tanks with variable voltage settings and other adjustable features; and the smaller fourth-generation e-cigarettes, including JUUL[®], have disposable or refillable pods but few, if any, manually adjustable settings.¹¹

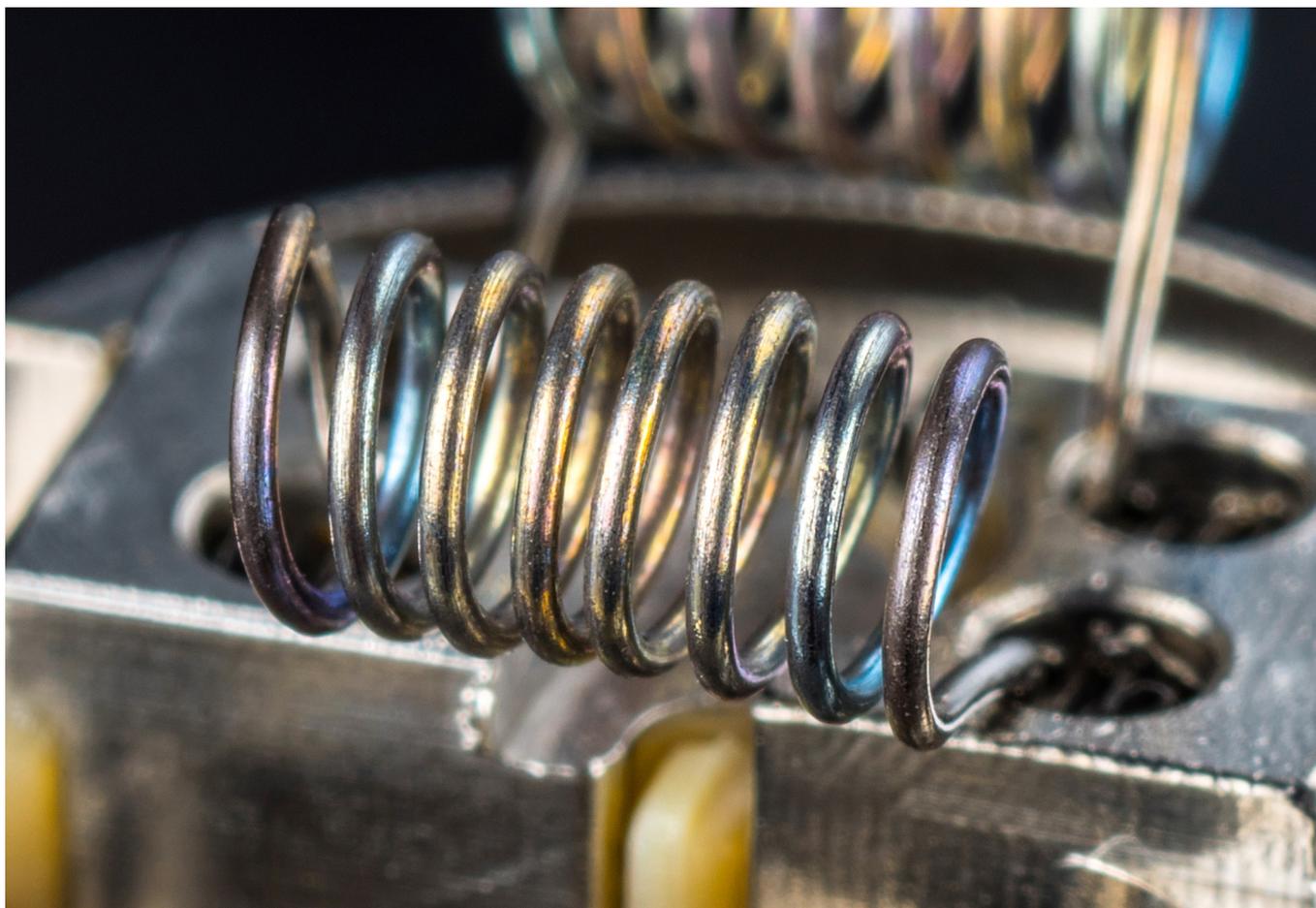
Yet, despite this complex and heterogeneous market, the bottom line is simple. “An e-cigarette is really nothing more than a chemical reactor,” says Thomas Eissenberg, a professor of health psychology at Virginia Commonwealth University. The device power, measured in watts, is a function of battery voltage and coil resistance. Many e-cigarettes operate between 5 and 10 W, up to 200 W.¹² And the power of the device, according to Eissenberg, may have the largest influence on a user’s exposure to nicotine and other toxicants. “The more energy you throw into the reactor, the more likely is the thermal degradation of e-liquid components into harmful chemicals,” he says.

Because high-power devices aerosolize much more liquid per puff,^{13,14,15} plasma nicotine levels can rise rapidly during vaping. Some studies have shown that one e-cigarette can deliver as much or, in some cases, even more nicotine than a combustible cigarette.^{16,17} In addition, some brands, most notably JUUL[®], use smooth-tasting protonated nicotine (“nicotine salt”) in their e-liquids.¹⁸ Conjugating nicotine with a weak acid produces nicotine salt, which creates a much more palatable aerosol than the harsh-tasting alkaline free-base (unprotonated) nicotine.¹⁰ There is also evidence that nicotine salt formulations are associated with increased nicotine yields or exposure^{19,20} and faster nicotine absorption.²¹

Much of the decline in U.S. smoking in the last few decades has been attributed to tobacco control measures such as cigarette taxes, smoking bans, and health educational campaigns.²² In the United State, more than 55% of men and 35% of women smoked in the 1960s, whereas only 13.7% of adults smoked in 2018.²³ Globally, the estimated global age-standardized prevalence of daily smoking in 2015 was 25.0% in men and 5.4% in women.²⁴ Most countries whose smoking prevalence in men significantly exceeded the global average are located in central and eastern Europe, China, and southeast Asia. For women, the smoking prevalence is higher than average in western and central Europe.²⁴

Among U.S. high school students, smoking prevalence has fallen since 2011.²⁵ Meanwhile, the percentage of high schoolers reporting recent e-cigarette use increased from 1.5% in 2011 to 27.5% in 2019.²⁶ In addition, 10.5% of middle school students reported current vaping, making e-cigarettes the most popular nicotine delivery device among U.S. youth.²⁶ Although only 3.2% of adults said they vaped occasionally or daily in 2018,²³ an upward trend for adults has also been reported.²⁷

JUUL[®] e-cigarettes, introduced in 2015, have experienced an especially dramatic rise in popularity. By 2019, 59% and 54% of U.S. high school and middle school e-cigarette users, respectively, named JUUL[®] as their usual brand.²⁶ Its sleek and easy-to-conceal design¹⁸ and the targeted marketing of its appealing flavors (which has recently come under regulatory scrutiny²⁸) have made the brand highly popular with teens.^{18,29}



Brand-new heating coils emit more metal particles than older ones. But that is just one characteristic of individual devices that can affect total metal emissions. Image: © iStockphoto/gawriloff.

Surveys have shown that the availability of different flavors is among the most attractive features of e-cigarettes in this age group.³⁰ Teenage vaping, in turn, has been shown to increase the likelihood of smoking, with or without concurrent e-cigarette use, later in life.^{31,32,33} A review study found that adolescents, males, and white people are more likely than other groups to consume e-cigarettes in the United States and several other countries.³⁴ Compared with cigarettes, e-cigarettes have unique toxicological profiles for metals, solvents, and flavoring chemicals.³⁵ Evidence of harm has been reported for all three of these categories.

Metals in E-Cigarettes

Ana María Rule, an assistant professor of environmental health and engineering at Johns Hopkins University, has been measuring metals in e-cigarettes since 2014. She started her studies in e-liquids, followed by aerosol and user specimens, including urine, saliva, and exhaled breath condensate.

Her studies and others have implicated nickel and chromium as metal exposures of particular concern to e-cigarette users.^{36,37,38,39,40,41,42,43} Nickel in urine and saliva samples of users and chromium in saliva samples have been strongly associated with concentrations of metals in e-cigarette aerosols.⁴⁴ Although human health effects of such exposures can only be identified in long-term studies, hexavalent chromium and some nickel compounds are known lung carcinogens.^{45,46}

Other metals have also been detected in e-cigarette aerosols, although at more variable levels than nickel and chromium. They include copper, zinc, manganese, arsenic, and others.³⁵ Possible metal sources are the coil, especially for nickel and chromium, the soldering and wiring, and the device body.^{42,47} Tobacco leaves also contain multiple heavy metals at varying concentrations.^{48,49} However, e-cigarette manufacturers claim to use highly purified pharmaceutical-grade nicotine for e-liquids,³⁵ and tobacco leaves may only be used for tobacco-flavored products.

The features of individual devices can influence how much metal users inhale.⁴² “We expected a greater release of metals from older coils but actually found the opposite,” says Rule. “Brand-new coils released the most.” She explains that the coil degrades a little every time it is heated. Over time, the heat breaks down the initially pristine metal alloy from which the coil is made. Rule also found that users tend to change their coils frequently because the accumulation of oxidized residues reduces the coil’s heating efficiency. That means more puffs are needed to deliver the same amount of nicotine.

Metal emissions also may be affected by the wattage of the device. One study showed that aerosol concentrations of several metals rose with increasing wattage but leveled off or even decreased after a certain point.⁴² Whether substantial variation in e-liquid pH levels affects metal emissions is currently being studied,^{50,51} says Rule.

She also notes other potential interactions. “The inhalation of common flavoring chemicals may help bring metals into brain and



Manufacturers and vapers mix the solvents propylene glycol and vegetable glycerol (also known as vegetable glycerin or glycerine) in different proportions to achieve desired effects from e-liquids. These include the intensity of the flavors, the strength of the “throat hit” (or sensation from inhaling nicotine), and the size of the resulting vapor cloud.¹¹² Image: CC0 Public Domain.

heart tissue cells,” she says. For example, maltol, a common flavoring chemical in e-cigarettes, avidly binds to iron.⁵² “I think this is an area where more research is urgently needed,” says Rule.

E-Liquid Solvents

The solvents in e-liquid are typically a mixture of propylene glycol (PG) and vegetable glycerol (VG) at variable ratios.¹⁰ Researchers have raised concern about the inhalation toxicity of these solvents alone, even without nicotine and flavoring chemicals.³⁵

When PG and VG are exposed to heat, breakdown products include three aldehydes: formaldehyde, acrolein, and acetaldehyde.^{53,54} Part of the larger class of carbonyls, these toxicants are also found in tobacco smoke. Some e-cigarette aerosols contain formaldehyde hemiacetals, a recently discovered form of formaldehyde that may deposit more deeply in the lungs than gaseous formaldehyde.^{53,55}

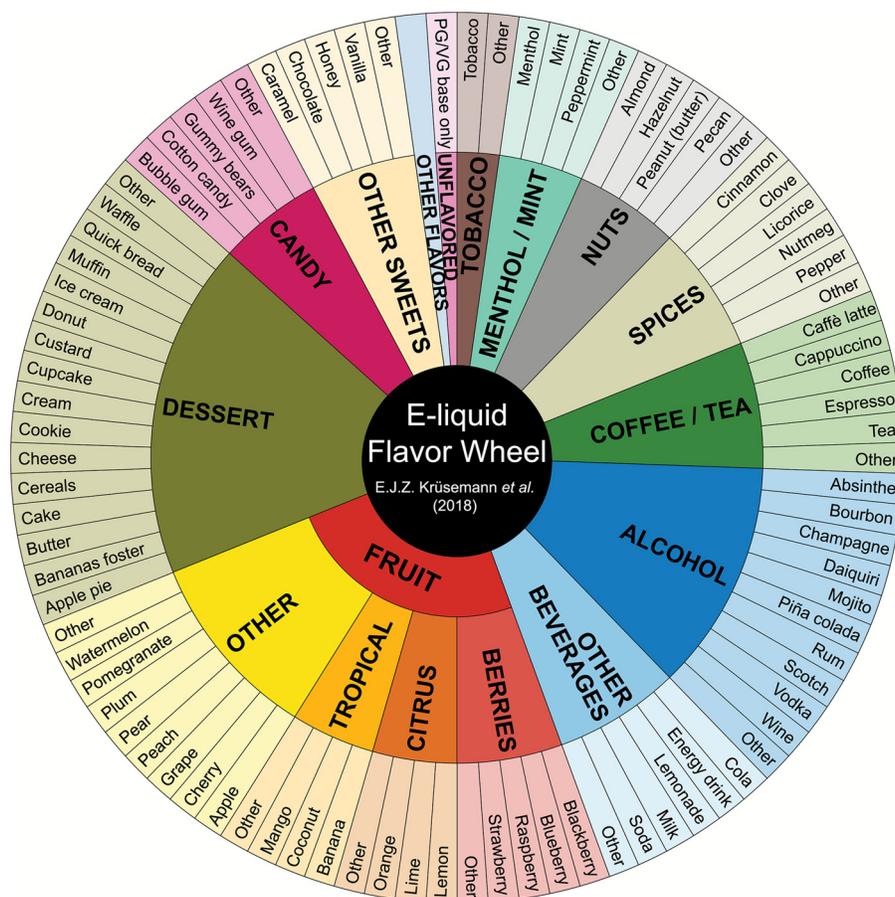
Solvent mixtures on the current market span the range from 100% PG, to 50/50, to 100% VG.¹⁰ Studies showed that e-liquids with a higher VG content produce more formaldehyde and acrolein than those with more PG, especially at high power settings. This might expose e-cigarette users to higher aldehyde levels than smokers^{10,56,57,58} and is a concern for “cloud chasers,” who prefer VG-heavy e-liquids for the large visible clouds they produce.¹⁰ A higher PG content, on the other hand, was shown to enhance nicotine delivery to the blood, potentially accelerating the development of addiction.⁵⁹

In a detailed analysis of solvents, researchers subjected groups of mice for four months to one of four exposure categories: aerosol from a 60 PG/40 VG mixture, with or without nicotine; cigarette smoke; or room air.⁶⁰ Unlike the smoke-exposed animals, the aerosol-exposed mice did not develop lung inflammation or emphysema. However, they did experience alterations of lung epithelial and resident immune cells that made them more susceptible to influenza infections than the mice breathing room air.

PG and VG additives are generally recognized as safe for use as emulsifiers in foods.^{61,62} They are also used in cosmetics. When inhaled, however, their emulsifying properties seemed to promote an accumulation of distinct lipids in pulmonary cells that was not observed in mice exposed to tobacco smoke.⁶⁰ The study’s findings were novel but consistent with previously reported changes in human lung tissue exposed to solvent aerosol alone.^{63,64} The authors concluded that their findings “raise alarm about the potential deleterious effects that [e-cigarettes] may have on the alveoli”⁶⁰ and called for additional toxicity studies of inhaled solvents.

Flavoring Chemicals and Interactions with Solvents

For Reinskje Talhout, a chemist and senior scientist at the National Institute for Public Health and the Environment in Bilthoven, the Netherlands, the most obvious problem with flavored e-cigarettes is that they conceal the taste of nicotine. “This makes the product more appealing to new users,” says Talhout.



Studies of vapers’ e-cigarette preferences and habits have revealed a lack of consistency in naming of flavors. In 2018, researchers developed a “flavor wheel” consisting of 13 main categories and 90 subcategories.¹¹³ A common vocabulary for classifying flavors makes it easier to compare findings across studies. Image: © The Authors 2018. Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco. Originally published in: Krüsemann EJZ, Boesveldt S, de Graaf K, Talhout R. 2019. An e-liquid flavor wheel: a shared vocabulary based on systematically reviewing e-liquid flavor classifications in literature. *Nicotine Tob Res* 21(10):1310–1319, DOI: 10.1093/ntr/nty101.

Another problem is the chemistry behind the flavors. The combination of a few hundred distinct chemicals generates thousands of flavors on the U.S.⁶⁵ and European⁶⁶ markets, says Talhout. Moreover, notes Ilona Jaspers, mixing these chemicals may generate secondary and tertiary reaction products in the complex e-liquid environment. Jaspers is a professor in the Department of Microbiology and Immunology at the University of North Carolina at Chapel Hill and the Department of Pediatrics at the UNC School of Medicine.

Similar to solvents, flavoring chemicals that may be generally recognized as safe for food and cosmetic products had not been tested for inhalation toxicity prior to early e-cigarette research studies.^{67,68,69} When Jaspers and other researchers^{67,68,69} became aware of the growing trend of youth vaping, they began to study flavoring chemicals in human cells.

For Jaspers, cinnamaldehyde was the first compound to stand out. It is a common ingredient in several popular flavors that showed strong cytotoxic effects on human pulmonary cells exposed directly to the e-liquids.⁷⁰ “We were surprised initially,” Jaspers recalls. “But as an aromatic α,β -unsaturated aldehyde, it makes perfect sense that this is a very, very reactive chemical with significant health effects.” Other known α,β -unsaturated aldehydes with significant chemical reactivity include acrolein, she says.

The cinnamaldehyde findings^{70,71,72} led to the *in vitro* testing of other chemicals in the same functional category of aromatic aldehydes. Similar effects were found for ethyl vanillin (vanilla flavors) and benzaldehyde (almond and cherry flavors).^{73,74} The highest flavoring chemical exposures for the human cells used in

the Jaspers lab were two orders of magnitude below the ranges reported for e-liquids and aerosols.⁷³ Several flavoring chemicals transfer from e-liquids into aerosols at high efficiency, with an average of 86% reported for some devices.⁷⁵ However, the levels of these chemicals in biological specimens of e-cigarette users are currently unknown.⁷³

Researchers also found that reactions between aromatic aldehydes and solvents occur at room temperature—potentially, for instance, as e-cigarettes sit on store shelves. In several *in vitro* assays, the reaction products were more harmful than the flavorants alone.^{76,77} For example, benzaldehyde PG acetal was more toxic to human cells than benzaldehyde,⁷⁴ and flavorants in JUUL[®]s Creme Brulee e-liquid formed potent acetals with both PG and VG.⁷⁸ Jaspers notes that acetals illustrate just one of many possible chemical interactions.

Other chemicals with cytotoxic properties include maltol and ethyl maltol; the latter was found in 80% of the products assessed.^{79,80} Of particular concern is the butter flavoring diacetyl, a member of the ketone family. Although safe when ingested, aerosolized diacetyl causes bronchiolitis obliterans (“popcorn lung”) and other severe respiratory diseases in certain industry employees.^{81,82} Investigators recently reported evidence that vaping may have contributed to a Canadian teenager’s bronchiolitis obliterans.⁸³

Following up on an earlier report,⁸⁴ researchers found diacetyl above the limit of detection in 39 of 51 e-liquid products, including those with names and flavors that researchers think may particularly appeal to youth.^{85,86} In addition, nicotine may accelerate the transformation of acetoin, another common flavoring chemical in the ketone family, into diacetyl over time.⁸⁷



Emerging evidence suggests that secondhand exposure to vaping aerosols may expose bystanders to potentially harmful chemicals. As of 2 January 2020, 22 U.S. states and territories had restricted the use of e-cigarettes in smoke-free environments.¹¹⁴ Image: © iStockphoto/mediaphotos.

Jaspers notes that metals are chemical catalysts that could further enhance the reactivity of e-liquid constituents. In addition, she says, some flavoring chemicals may interfere with the metabolism and detoxification of nicotine and enhance its stability.

Potential Health Effects for E-Cigarette Users and Bystanders

Cigarette smoke, which has been studied for more than a century, contains more than 7,000 chemicals, of which at least 250 are harmful and 69 are known carcinogens.⁸⁸ Tobacco smoking accounts for an estimated 85% of lung cancers and 50% of bladder cancers.⁸⁹

Given the recent market entry of e-cigarettes, their long-term health effects are much less certain. It is true that some of the chemicals in tobacco smoke, such as tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons, have been found in much lower levels in e-cigarette users, compared with smokers.⁹⁰ “Exclusive e-cigarette users will not die of [smoking-related] lung cancer,” says Eissenberg. “But whether they are likely to die, after decades of use, of other cancers or other diseases at higher rates than nonusers or smokers, we simply do not know yet.”

Epidemiological and experimental evidence for harmful effects of e-cigarette aerosols has been reported for the pulmonary, cardiovascular, and immune systems,^{4,35,91,92,93} the brain,^{94,95} and the oral cavity.⁹⁶ An increased risk of lung and bladder urothelial cancers has been found in mice.⁹⁷

Talhout and others have found evidence of secondhand exposure to harmful chemicals, such as metals and TSNAs, in studies of

limited sample size.^{98,99,100} “It is an important message that bystanders [may] experience harm from e-cigarettes,” Talhout says. “I think it justifies banning the use of these products in public places.”

NYU’s Gordon directs an ongoing panel study of households with at least one adult who smokes, vapes, or uses a hookah, and one adult or child who does not.¹⁰¹ “We’re measuring home air quality and cardiopulmonary outcomes with fairly quick, noninvasive methods and are seeing health effects from secondhand exposure to e-cigarette aerosols,” he says.

E-Cigarette Regulation

Several countries, including Brazil, India, and Uruguay, have banned the sale of all e-cigarettes or those that deliver nicotine.^{102,103,104} The European Union has set a regulatory limit of 20 mg/mL on nicotine in e-liquids to prevent e-cigarettes from delivering more than the standard cigarette dose.¹⁰⁵

In the United States, e-cigarettes and other so-called electronic nicotine delivery systems (ENDS) fall under the Tobacco Control Act. The FDA made this determination in a “deeming rule”—meaning ENDS were deemed subject to the act—that went into effect on 8 August 2016.¹⁰⁶ All e-cigarettes on the market at the time were required to have premarket authorization from the FDA to be marketed; however, none did. In other words, all ENDS products being sold at the time were considered illegally marketed.¹⁰⁷ (As of this writing, still no ENDS product on the market has actually been authorized by the FDA.)

At first, the FDA sent warning letters to manufacturers but deferred further action. That changed as rates of youth vaping



E-cigarettes have long been touted as a healthier alternative to smoking. And it is true that vapers may avoid many of the toxic exposures associated with smoking. However, e-cigarettes come with potentially hazardous exposures of their own. Image: © Philip Brookes/Alamy Stock Photo.

began skyrocketing. In January 2020, the agency announced it would begin enforcing the act.¹⁰⁷ With none of the e-liquids on the market in compliance, companies had a month to get their products off shelves. Manufacturers have until 12 May 2020 to submit a Premarket Tobacco Product Application to the FDA if they wish to resume sales.¹⁰⁶ These applications must provide “scientific data that demonstrates a product is appropriate for the protection of public health.”¹⁰⁸

In general, regulatory action for e-cigarettes is complicated by the need to strike a balance between *protection* from harm for nonsmokers and harm *reduction* for current smokers. “Smokers who switch completely [to e-cigarettes] are exposed to lower levels of [certain] carcinogens and other toxicants,”^{90,109} says Gideon St.Helen, an assistant professor of medicine at the University of California, San Francisco. “This lowers the risk of several tobacco-related diseases and may result in a public health benefit.”

Other experts agree with this assessment, although the net impact of vaping on public health over time depends on demographics and future population growth.⁴ For example, a population with growing birth rates may prioritize risk reduction in adolescents differently than a population with an increasing proportion of older adults who are lifelong smokers.

Other potential policies, such as prescription-only access for smokers wishing to quit, also have critics. “Some people argue that a prescription-based market is unfair to smokers because it places hurdles on obtaining a safer product,” says Joanna Cohen, a professor of disease prevention at Johns Hopkins University who has studied tobacco control from an international perspective. “The best example of an integrated smoking cessation system is England, whose public health experts have long felt that cigarettes are so bad for you that anything else is better and should be easily accessible.”

For St.Helen, that’s a valid argument. “We already know it is more difficult for minorities and underprivileged people to access nicotine replacement therapy in the U.S.,” he says. “We do not want to create the same problem with e-cigarettes. But making them available only to smoking adults, in some other way, would be good.”

Talhout and Jaspers call for policy guidelines for testing the inhalation toxicity of flavoring chemicals and solvents. Eissenberg suggests combining the EU nicotine cap with a mathematical model of nicotine flux that he codeveloped.^{110,111} “Since it is very difficult to address multiple design components that go into an e-cigarette, regulation should focus on what comes out,” he says. Eissenberg’s team showed that the model’s predicted nicotine flux (the rate at which a device delivers nicotine) was highly correlated with actual measurements and accounted for device power and e-liquid nicotine content.¹⁵

A nicotine flux policy would ensure that users cannot circumvent a nicotine cap for e-liquids with higher power settings. It would apply to formulations with nicotine salt or free-base nicotine. But it only works for “closed-system” devices whose components cannot be swapped out or refilled, says Eissenberg. The regulation of open-system devices on the current U.S. market is more challenging, he adds.

Other urgent action items go beyond regulation. “We need to help the kids whose nicotine addiction started with vaping,” says Jaspers. “That requires scientists, parents, and health care providers joining forces to develop new tools that get them off this dangerous habit. Teachers will be instrumental in adding to the education about the potential harm of vaping.”

Silke Schmidt, PhD, writes about science, health, and the environment from Madison, Wisconsin.

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