truth initiative®
INSPIRING TOBACCO-FREE LIVES

ACTION NEEDED: E-CIGARETTES

Since their introduction in 2008, **e-cigarettes** have become both **ubiquitous** and an increasing source of public policy concern and debate. This concern stems primarily from **drastic increases in youth e-cigarette use**. The most recent data show that **27.5%** of high schoolers are using these products — a rate of youth tobacco product use not seen in nearly two decades. The public health community, parents and educators are shocked and worried to find their children and students using these products at home and even in class. **Young people are reporting severe signs of dependence**, including using e-cigarettes when they first wake up, inability to concentrate in the classroom without using an e-cigarette, and even waking in the night to get a nicotine fix.

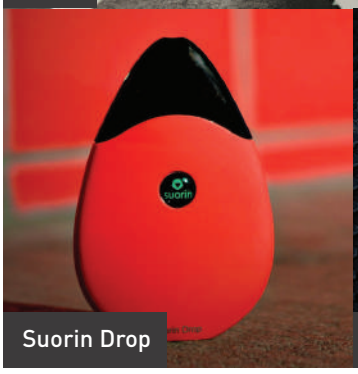
We have known for decades that **youth in particular should not be exposed to nicotine because it changes brain chemistry to create a stronger addiction**, can lead to memory and concentration problems, and can make youth who use it more susceptible to addiction to other substances. Research also suggests that young people who use e-cigarettes are four times more likely to go on to smoke combustible cigarettes.

E-cigarettes are now threatening to undo all the progress that the public health community and government have made over decades to reduce cigarette smoking. Indeed, the surgeon general raised the alarm by issuing an advisory declaring a youth e-cigarette **epidemic** in December 2018. Since then, data show that more and more youth continue to use e-cigarettes. And this isn't just experimental or occasional use — it's regular use likely driven by **addiction**. The most recent National Youth Tobacco Survey data show that **34.2%** of current **high school e-cigarette users** use them on 20 days or more per month.

E-cigarettes are now threatening to undo all the progress that the public health community and government have made over decades to reduce cigarette smoking

Current generation of e-cigarettes

JUUL



Suorin Drop

Photo: Suorin USA

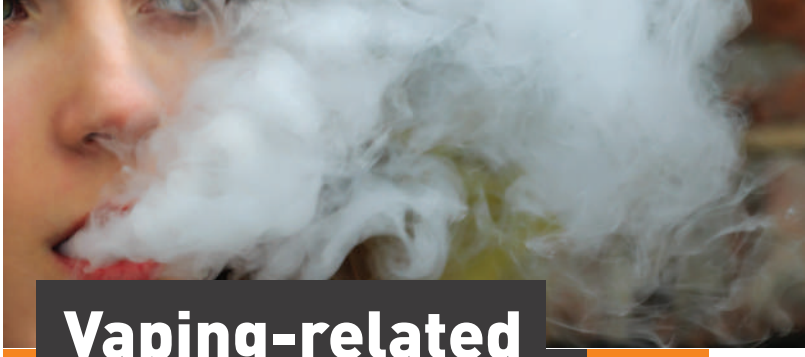
Vuse Alto

Photo: Vuse Vapor

Conversely, as the youth e-cigarette epidemic has continued unabated, we have seen adults, and especially older smokers, simply reject the product. In 2014, the first year that the National Health Interview Survey measured adult use of e-cigarettes, 3.7% of adults used the product in the last 30 days. In 2018, the adult usage remained low, at **3.2%**, and was largely driven by young adult users (7.6%), who have matured during the youth e-cigarette epidemic. While some adults have switched completely to e-cigarettes from combustible cigarettes, the **predominant pattern among adult users continues to be e-cigarette use in conjunction with smoking**. This "dual use," however, provides no reduction in the harms associated with smoking.

As youth use continues to rise, the science around the potential harms of e-cigarettes has grown. Studies show that e-cigarettes produce lower amounts, but are not free from the toxins found in cigarettes. At the same time, **flavoring compounds and other ingredients may be producing their own unique harms**. Recent studies demonstrate the harms e-cigarettes pose to the respiratory system. Similarly, new studies show e-cigarettes may present unique threats to cardiovascular health. It continues to be nearly impossible to make generalized statements about the potential harms and benefits of the overall category of e-cigarettes due to the incredible variation in hardware design and ingredients. Moreover, as industry executives themselves have acknowledged, **we simply do not know the long-term health impacts of e-cigarette use**. It took us many decades to understand the toxicity of cigarettes, and, even today, we are discovering new ways in which they harm health.

Simply put, the data show that **e-cigarettes** as they are currently sold and regulated in the United States are overwhelmingly a **vehicle for youth initiation**, not adult cessation. **E-cigarettes expose kids — who otherwise never would have been — to nicotine** and put them at risk for both long- and short-term health consequences.



Vaping-related illness outbreak

As of this writing (November 2019), the country is experiencing an outbreak of vaping related illnesses. More than 2,000 cases have been reported across 49 states with 39 deaths. Most of these cases were from users who reported use of THC, about 86% reported use of THC and 64% reported use of nicotine vaporizer products and 11% report exclusively using nicotine products. The Centers for Disease Control and Prevention continues to update this information on its **website**. On November 8, 2019, the CDC identified vitamin E acetate as a significant concern in the outbreak, finding the chemical in all 29 samples it had analyzed from victims. The CDC states, "it is possible that more than one compound or ingredient could be a cause of lung injury, and evidence is not yet sufficient to rule out contribution of other toxicants." It continues to advise non-smokers to avoid vaping of any variety and for everyone to avoid all vaping products purchased "off the street."

THE POSITION OF TRUTH INITIATIVE®

Truth Initiative has maintained that there may be some possible public health benefit from properly regulated e-cigarettes, provided manufacturers can demonstrate that the products can help adults quit smoking combustible cigarettes safely and completely. However, no e-cigarette has been approved for smoking cessation and no e-cigarette has gone through the rigorous scientific review necessary to determine whether it actually does help smokers to quit. Furthermore, **any public health benefit from e-cigarettes for smokers must be weighed against the incredibly high youth use of e-cigarettes** and the fact that there are currently no significant marketing restrictions on these products. **Without a significant change in regulatory approach, it is unlikely that e-cigarettes will contribute to the overall benefit of public health.**

Photo: Stanford Research into the Impact of Tobacco Advertising

While the industry was creating the e-cigarette problem, the federal government had the tools it needed to slow — if not prevent — this epidemic. Unfortunately, it failed to use them. The government must use those tools now to rein in and reverse this dangerous turn of events. It took the Food and Drug Administration until 2016 to assert authority over e-cigarettes, despite being given the ability to do so by Congress in 2009. Once they had the authority, the FDA could have ensured that products were reviewed to determine whether they provided any public health benefit, as required by the Tobacco Control Act, and that strong marketing restrictions were in place to protect youth. However, in 2017 the FDA chose to delay the due date for all e-cigarettes to submit their scientific public health review applications to 2022. This left products on the market about which the public (or the FDA for that matter) knew nothing — particularly in terms of their individual health effects, appeal to youth, and risks and benefits to smokers — unchecked for five additional years. It also **opened the door for the newest generation of high-nicotine content e-cigarette products, such as JUUL and Suorin Drop, to hit the market**.

These high tech "pod" or "pod mod" **products** are easily **concealable**, come in fruit and candy **flavors highly attractive to youth**, and some were introduced to the market with **advertising campaigns aimed directly at young people**. Although one of the manufacturers, market leader JUUL, has announced its plan to halt distribution of some flavors, it will continue to sell mint/menthol flavors, which nearly two-thirds of high school vapers use. In addition, other nicotine pod brands continue to sell a wide variety of fruit and candy flavors and market the products, featuring highly appealing advertising and social media campaigns directed at youth.

As we find ourselves in the midst of another tobacco epidemic, many e-cigarette companies try to claim that they are not part of the tobacco industry. That is simply not true. Tobacco companies either fully own or have significant vested interest in four of the top five e-cigarette companies. E-cigarette companies are emulating their Big Tobacco siblings in order to entice kids and increase their market share. Tactics

E-cigarette companies are emulating their Big Tobacco siblings in order to entice kids and increase their market share.

such as increasing their nicotine content; marketing their products with slick, colorful ads and using popular social media influencers; and claiming that their products are safer, despite no federal review of the products or these safety claims, come straight out of the **Big Tobacco playbook**.

As a result, we have a situation where **millions of youth are at risk of addiction to these products while no one, including the FDA or the e-cigarette companies themselves, knows the long-term or even all the potential short-term health effects**. Truth Initiative, along with several other public health organizations, has sued the FDA to force the agency to take action much sooner than 2022 in order to get this epidemic under control. The court ruled that e-cigarette manufacturers must submit their scientific information on the public health impact of their products by May 2020. Additionally, in September 2019, the administration stated that it would pull all flavored e-cigarettes off the market until the manufacturers could show that a flavored e-cigarette has a public health benefit. As of this writing, the **administration has not moved forward** with this plan.

In the meantime, the public health community and all levels of government must help the millions of youth and young adults who are now being exposed to nicotine and prevent this generation from falling into the next trap set by the tobacco industry. The FDA has many tools at its disposal to address the

situation but it has chosen not to use them. **The time is long past for the FDA to take action and use its authority to correct this massive regulatory failure.** In addition, states and some localities can take action to protect their youngest citizens.

We outline **key actions** all levels of government should take below.

FEDERAL ACTION NEEDED

- **FDA review:** First and foremost, the FDA must enforce its authority to require a **full scientific review of all e-cigarette products** to determine their impact on public health. The agency must **adhere to the court-ordered date** of May 2020 and take products that do not comply off the market immediately. If the FDA had done this in the first place, many of the problems we're seeing now, including skyrocketing youth use, would have been significantly reduced.

- **Extend marketing restrictions on cigarettes to e-cigarettes:** The FDA must restrict e-cigarette marketing so that it does not target or appeal to youth. Specifically, the agency must immediately **extend the marketing restrictions that apply to combustible cigarettes to e-cigarettes**.

The FDA must enforce its authority to require a full scientific review of all e-cigarette products to determine their impact on public health.

These include prohibitions on:

  - Sponsorships of sports and cultural events
  - Self-service access to the products (i.e., keeping the products behind the counter)
  - Free gifts with purchase, other than tobacco products (i.e., no branded t-shirts, hats, etc.)

- **Other marketing restrictions:** E-cigarette manufacturers have marketed their product as sleek and high tech using similarly high-tech marketing tactics in **digital and social media** as well as social media influencer campaigns. **The FDA must institute restrictions** on this type of marketing — particularly as it applies to **third parties who endorse products** on behalf of tobacco companies.

  - Other federal agencies have a role to play as well. For example, the Federal Trade Commission (FTC) must also ensure that all industry-funded influencer endorsements clearly indicate that they are paid advertisements and clearly indicate the risks associated with nicotine use.
  - The FTC must collect data from the e-cigarette industry on marketing spending just as they do for cigarettes and smokeless tobacco.

- **Internet sales:** The FDA should **prohibit all non-face-to-face sales, along with internet sales**, of all tobacco products, including e-cigarettes.

- **Product standards:** The FDA also has the ability to **institute product standards on e-cigarettes, preventing the sale and marketing of any product that does not adhere** to those standards. This is a powerful tool the agency needs to exercise in several areas:

  - **Flavor restrictions:** Truth Initiative has long supported the removal of flavors in cigarettes, cigars and smokeless tobacco products. We know that **flavors have overwhelmingly been used to attract**

those who have not previously used nicotine or tobacco products. Given the state of the youth e-cigarette epidemic, we strongly support **removing all flavored e-cigarettes from the market, including mint and menthol**, pending an FDA review. The burden should always have been on manufacturers to show that their products would not appeal to youth before going to market. Given what we now know about how dramatically flavors influence youth e-cigarette use, the burden should be high. We support a permanent ban on flavors unless a manufacturer can demonstrate three things to the FDA: 1) that a particular flavor helps current tobacco users to stop smoking, 2) it will not lead non-tobacco users, such as youth, to start, and 3) it does not increase the risk of harm from using the product.

- **Product packaging:** E-cigarettes and e-liquid in particular should come only in **child-resistant packaging** to prevent young people from ingesting these products, which causes sickness and, in some cases, can be **fatal**.
- **Restrictions on nicotine concentrations and delivery:** There are currently no restrictions on the concentrations of nicotine in e-cigarette products in the U.S. JUUL, the most popular e-cigarette in the U.S., contains 59mg/ml (or 5%) nicotine. Some of its competitors contain as much as 7% nicotine. This is in stark contrast to the European Union, where the highest nicotine concentration allowed is 20 mg/ml (2%). Truth Initiative supports **restricting not only the nicotine levels but also the mechanism by which nicotine is delivered** to reduce the level of nicotine actually delivered to the body in e-cigarettes. This will help reduce its addictiveness.

Flavors have overwhelmingly been used to attract those who have not previously used nicotine or tobacco products.

- **Good manufacturing standards:** The FDA must ensure that all e-cigarettes deliver nicotine at the level indicated on the package, **minimize hazardous constituents** and are manufactured at the highest quality standards.
- **Battery safety:** The FDA should ensure that battery and device quality are sufficient to **prevent explosions** and overheating.

- **Enforcement:** The FDA must use its considerable enforcement authority to ensure that all aspects of the **Tobacco Control Act, as well as all subsequent regulations, are enforced to the full extent of the law**. Without enforcement, these measures will not protect youth. Additionally, other federal agencies, such as the FTC, should work with the FDA to protect against misleading marketing.
- **Taxation:** Federal, state and local tax-writing authorities should set the **highest possible taxes on all tobacco products, including e-cigarettes, to discourage youth use**. Above that, combustible tobacco products should be taxed at the highest level, and the least harmful, well-regulated and FDA-reviewed noncombustible tobacco products should be taxed at lower levels.

- **Cessation:** Federal agencies such as the FDA and the National Institutes of Health must **redouble all efforts to develop nicotine cessation interventions for the millions of youth and young adults** who now find themselves addicted to nicotine from e-cigarette use. Additionally, the Centers for Medicaid and Medicare Services and insurance companies should make **quitting services** available for all those addicted to nicotine — whether from e-cigarettes or combustible tobacco products — with **no barriers to treatment, such as co-pays**.
- **Federal research:** The FDA and NIH should **fund research to better understand e-cigarette harms**, behavioral use patterns and impact on tobacco use cessation (separate from the research mentioned above).

States and local communities are often the incubators of strong tobacco control policies.

STATE AND LOCAL ACTION NEEDED

States and local communities are often the incubators of strong tobacco control policies. They have an important role to play when it comes to protecting youth from e-cigarettes as well. Some examples include:

- **Licensing:** **Requiring all e-cigarette vendors to be licensed and registered** with the state or local (where allowed) government. Licensing, besides being an important way to keep track of who is selling tobacco products, can also be a tool to limit the density and location (i.e., not near schools) of tobacco retailers.
- **Flavor restrictions:** Many local jurisdictions have taken action to **restrict or prohibit the sale of flavored tobacco products**. Truth Initiative supports such actions because they limit the availability of such highly appealing tobacco products to youth.
- **Clean indoor air:** State and local governments should **require e-cigarette use to be subject to clean indoor air laws** and requirements.
- **Tobacco 21:** State and local jurisdictions should **limit sales of all tobacco products, including e-cigarettes and their components, to those age 21 and older**, with the onus lying with the retailer. We note that the tobacco industry has recently supported Tobacco 21 policies, selling the idea that this policy will take care of the youth tobacco problem. While Tobacco 21 is an important tool in the tobacco control toolbox, by itself it is not sufficient to keep tobacco out of the hands of young people. Tobacco 21 policies must be accompanied by complementary and strong policies, including but not limited to those listed above, to protect youth from tobacco.

truth initiative
INSPIRING TOBACCO-FREE LIVES

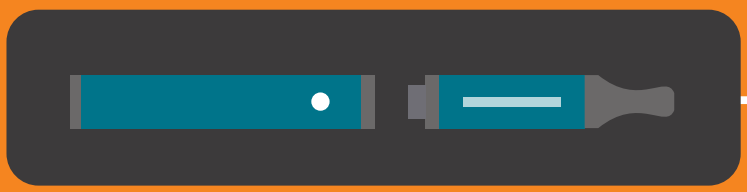
E-CIGARETTES

Among **youth who vape**, 97% used a **flavored e-cigarette** in the past month.

97%

E-liquids contain at least **60 chemical compounds**. E-cigarette aerosol contains even more.

60



Young people who use **e-cigarettes** are **4x times** more likely to start smoking tobacco **cigarettes** than their peers who don't vape.

4x

16x

15- to 17-year-olds have more than **16x greater odds** to be current **JUUL** users vs. adults.

27.5%

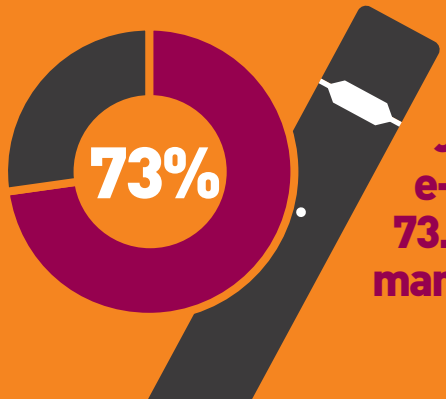
In 2019, **e-cigarette use** among high schoolers **rose to 27.5%**.

For high school seniors, the rate has **doubled since 2017**.

2017

2019

73%



JUUL remains the top e-cigarette brand and took **73.4%** of the **e-cigarette marketplace** by July 2019.

truth initiative®
INSPIRING TOBACCO-FREE LIVES

E-CIGARETTES

BACKGROUND

Electronic nicotine delivery systems (ENDS) go by many names. The most common name is "e-cigarette," but others such as e-cigs, vapes, vape pens, mods and tanks are common terms. Recently, the e-cigarette brand **JUUL has become so ubiquitous among youth that "JUULing" is also used as a common verb** for all e-cigarette use. For the purposes of this resource we refer to the entire category as "e-cigarettes."

WHAT IS AN E-CIGARETTE?

- E-cigarettes are devices that operate by heating a liquid solution to a high enough temperature so that it produces an aerosol that is inhaled.[1]
- Solutions, sometimes called **e-liquids**, almost always include **nicotine**, **flavoring** and a humectant, such as propylene glycol, to retain moisture and create the aerosol when heated.[1,2]
  - While many of the **flavorings** and humectants used in e-liquids have been approved by the Food and Drug Administration for oral consumption,[2] they **have not been approved for inhalation**. Thus, their health consequences are not well known when consumed in this manner.
  - There is an ongoing outbreak of **significant lung illness and death (2,051 reported cases and 39 deaths as of November 5, 2019)** due to vaping. Most of these cases (over 80%), but not all, were from users who reported use of THC vaporizer products. On November 8, 2019, the CDC identified vitamin E acetate as a significant concern in the outbreak finding the chemical in all 29 samples it had analyzed from victims. The CDC states, "it is possible that more than one compound or ingredient could be a cause of lung injury, and evidence is not yet sufficient to rule out contribution of other toxicants." It continues to advise non-smokers to avoid vaping of any variety and especially products purchased "off the street."

Nicotine salt formulas in the most recent generation of e-cigarettes allow for much higher levels and efficient delivery of nicotine.

- Older generations of e-cigarettes used a form of nicotine called free-base nicotine. The most recent generation of e-cigarettes on the market, which include pre-filled pod systems like JUUL and refillable systems like Suorin Drop and Kandypens, use nicotine salts in the e-liquids.
  - The **nicotine salt formulas allow for much higher levels and efficient delivery of nicotine** with less irritation compared to earlier generations of e-cigarettes — prompting questions about the use, purpose and safety of this novel form of nicotine.[3]

- **Higher nicotine e-cigarettes have driven the surge in e-cigarette sales** in recent years, with those containing at least 4% nicotine comprising nearly three-quarters of the e-cigarette market in 2018.[4] Unlike in Europe, where e-cigarette nicotine concentrations cannot exceed 2%, there are no nicotine concentration restrictions in the United States.[5]

While using an e-cigarette is often called "vaping," the devices produce an aerosol, not a vapor.

- **Unlike vapor, which is simply a substance in gas form, the aerosol from an e-cigarette contains tiny chemical particles from both the liquid solution and the device** (e.g., metals from the heating coil). There is evidence to suggest that these particles lead to **cardiovascular injury**, with links to negative effects on resting heart rate, blood pressure and the cells that line the blood vessels.[6,7]

WHAT ARE THE TYPES OF E-CIGARETTES?

When e-cigarettes first began entering the market around 2007, some devices were designed to resemble regular cigarettes, while others looked more like cigars, pipes, pens and even USB flash drives.[1,8]

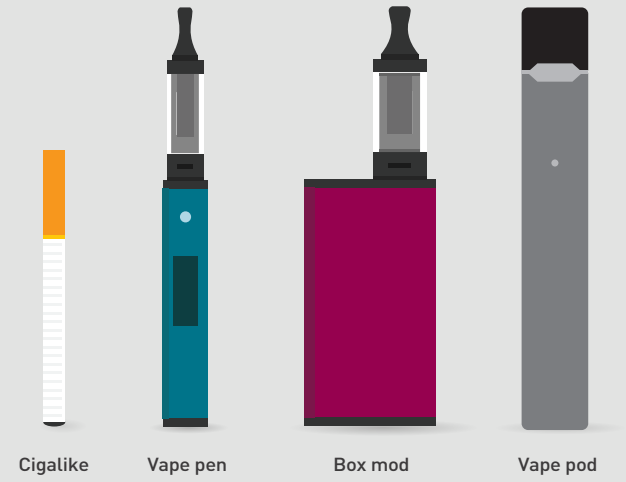
To account for the diversity in product design, some researchers have classified e-cigarettes as first, second or third generation devices.[2]

A **first generation** e-cigarette is one that closely resembles a **cigarette** and is **disposable**.[9]

A **second generation** e-cigarette is a larger, usually **pen-shaped** device, that can be **recharged**.[9]

A **third generation** e-cigarette refers to devices that do **not resemble a combustible cigarette** and often have very large and sometimes customizable batteries. Some parts may be **replaceable**, which is why they are sometimes called **"mods."** These devices are **refillable**.[2,9]

Evolution of the e-cigarette



Source: https://www.ruthlessvapor.com/blogs/ruthless-e-liquid/nicotine-salt-devices-vape-pods

More recently, e-cigarettes that have a **sleek, high-tech design** and easily rechargeable batteries have entered the market.

- The most popular, **JUUL**, emerged in 2015 and quickly established itself as a leading e-cigarette product, comprising nearly **three-quarters (73.4%) of the e-cigarette marketplace** by July 2019.[10]
- "Copycat" products, such as Suorin Drop, myblu and Vuse Alto, follow JUUL's blueprint of high-tech design and high nicotine delivery through the use of nicotine salt e-liquid formulations. These devices are all often referred to as "JUUL" due to the ubiquity of the brand, but they are also referred to as **"pod mods"** because the e-liquid is sold in self-contained disposable pods.
- The enormous popularity of JUUL has encouraged copycat devices that are specifically compatible with JUUL, including Eonsmoke and Vapor4Life, that deliver similarly high amounts of nicotine in sleek, discreet devices or in devices that either use JUUL pods or have pods that can be used in JUUL devices.[11]

Heated tobacco products

In addition to e-cigarette products, tobacco companies have begun introducing **tobacco heating systems** or, as the industry calls them, "heat-not-burn" tobacco products. These devices work by heating tobacco instead of burning it. Sometimes the tobacco is treated with a humectant like propylene glycol to produce an aerosol inhaled by the user. Manufacturers claim this delivery method is substantially less harmful than traditional cigarettes,[12] but **current data on health effects of these devices are sparse** and most of what has been published has been by tobacco industry scientists.

In 2019, the FDA allowed the first type of tobacco heating system to be marketed and sold in the U.S.[13] IQOS, produced by Philip Morris International (PMI), is now being sold in select test markets by Altria around the country.[14] Data in foreign markets submitted by PMI indicate that dual use of heated tobacco products along with cigarettes is, by far, the most dominant pattern of use, which raises substantial issues about what impact they might have on overall public health.[15] Notably, research has shown that **dual use is not associated with reduced cigarette use**, but rather increased exposure and poorer health outcomes than using cigarettes or e-cigarettes alone.[16] Read comments and potential concerns from Truth Initiative on the IQOS application. Truth Initiative will continue to monitor patterns of use as the product becomes more common in the U.S.

HOW MUCH NICOTINE IS IN AN E-CIGARETTE?

Nicotine levels in e-cigarettes are highly **variable**, with some reaching or **exceeding** levels found in combustible **cigarettes**.[2,17]

- **Labeling is not always a reliable indicator** of nicotine content, as studies have found mislabeling to be a common issue in the category.[2,17]
- The way an e-cigarette is used or **modified** also affects the delivery of nicotine to an individual user.[2,18]
- Some e-cigarette products deliver nicotine as efficiently as a cigarette. The use of nicotine salts also lowers the pH of e-liquids, which allows **higher concentrations of nicotine to be delivered with less irritation**.[19] For example, the maker of JUUL claims the product has a nicotine content like traditional cigarettes, and that it delivers the nicotine up to 2.7 times faster than other e-cigarettes.[20]
- In the U.S., JUUL devices were originally introduced with a 5% nicotine salt pod.[21] Following suit, **JUUL competitors began offering nicotine salt concentrations as high as 7%** in what has been called a "nicotine arms race."[21] However, in 2018, JUUL introduced a lower nicotine pod, with 3% nicotine strength.[4]
- In addition to the rate of nicotine delivery, the nicotine content of products like JUUL also raises concerns about the potential for addiction. A 2018 Truth Initiative study published in Tobacco Control found that **among current youth and young adult JUUL users, the majority — 63% — did not know that the product always contains nicotine**.[22] Anecdotally, youth are reporting signs of **severe dependence**, such as inability to concentrate in class, using an e-cigarette upon waking, and using e-cigarettes at night after waking with a craving.[23,24]

ARE E-CIGARETTES LESS HARMFUL THAN CIGARETTES?

It is generally accepted that e-cigarettes produce fewer of the toxins found in cigarette smoke.[2] However, it is becoming increasingly apparent that this frame is not adequate to tell the entire story regarding individual health impacts. The most recent evidence suggests that **e-cigarettes may pose their own unique health harms** and that comparison to cigarettes may not be the only relevant question for determining their impact on individual health.[25-27] Indeed, the growing evidence of potential health risks related to e-cigarette use has led some researchers to question whether e-cigarettes are safer than combustible cigarettes.[27] For more information see "Health Effects" on p. 17.

The recent outbreak of vaping related lung injuries also supports caution with respect to e-cigarettes. While a substantial number of cases in the recent outbreak of vaping related lung illness (see "Health Effects" on p. 18) appear to be related to THC vaping and the CDC recently identified vitamin E acetate as a chemical of significant concern, the agency has been cautious to say it has not found a single cause and continues to recommend caution with respect to all vaping as the investigation continues.[95] At minimum, this outbreak dramatically demonstrates the dangers of an unregulated market in inhaled substances with no premarket review for consumer safety.

We also note the frequently cited claim from **Public Health England** that e-cigarettes are definitively — 95% — safer than traditional cigarettes. First, this analysis was originally conducted in 2013, prior to recent research on health effects of vaping. Moreover, further analysis into the original research finds that the evidence for such a statistic remains unclear and not fully comprehensive, among other concerns about author and funding conflicts of interest.[28] The Public Health England claim also fails to acknowledge the reality of the potential for negative net public health impact among a population of users that have otherwise never used tobacco products or the lack of clinical and long-term evidence of these products' safety in humans, regardless of current smoking status.[28]

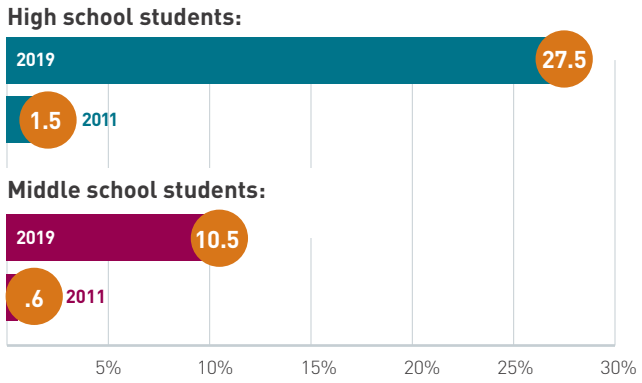
Recent reports of lung illnesses related to vaping have raised questions about both the long- and short-term effects of vaping.

While a 2018 National Academies of Sciences, Engineering, and Medicine report found substantial evidence that exposure to toxic substances from e-cigarettes is significantly lower compared to combustible cigarettes, recent studies are showing that is not the end of the story on health impact. It now appears that **e-cigarettes may present their own unique health risks, including to the respiratory and cardiovascular systems**. Given the products' relatively recent introduction to the marketplace, further research is needed to evaluate the short and long term health impacts of e-cigarettes.

The evidence for e-cigarettes' effectiveness as a cessation tool also remains inconclusive and, until an FDA review, the safest, most evidence-based cessation strategy should include a combination of counseling, nicotine replacement therapy, and/or cessation drugs like varenicline, approved by the FDA.[29] Moreover, while the basic technology behind e-cigarettes is consistent, there is enormous variability within the product category and there is no typical e-cigarette. The products include different ingredients, different hardware and deliver highly variable amounts of nicotine and potentially **toxic chemicals**, including heavy metals such as cadmium, lead, nickel, tin and copper.[30] This variation makes it difficult to issue overall public health recommendations about the category and demonstrates the huge and long-standing need for pre-market review of these products.

Consumers need to consistently know what they are getting and whether it is safe — particularly from a product designed to deliver chemicals by frequent inhalation. The growing evidence of potential health risks and lung injuries related to e-cigarette use has led researchers to question whether e-cigarettes are safer than combustible cigarettes.[27]

Current e-cigarette use among middle and high school students



Source: 2019 National Youth Tobacco Survey

PATTERNS OF USE

E-cigarette use has increased in recent years, especially among youth and young adults, who use e-cigarettes more than any other age group. **In 2018, the rapid rise of tobacco products led the U.S. surgeon general to issue an advisory about the youth e-cigarette "epidemic."** Since then, rates have only increased, and e-cigarettes are now by far the most commonly used tobacco product among youth.[31,32]

YOUTH

The last five years have seen enormous spikes in youth e-cigarette use rates.[33]

- In **2017**, **11% of high school students** had used an e-cigarette in the past 30 days.[34] By 2018, that number had risen to 21% and, by **2019**, **27.5%** of high school students had used e-cigarettes in the past month.[33,35]
- Compared with the very small amount of youth use in 2011 (1.5%), this represents an **increase of more than 1,800% in just eight years**, with a substantial increase occurring between 2013 and 2015, when use rose from 4.5% to 16%, coinciding with the emergence of **JUUL**.[36-38]
- The current use rate among middle schoolers rose from 0.6% in 2011 to 10.5% in 2019.[39]
- Using e-cigarettes has been shown to **increase the likelihood of smoking cigarettes among young people**, raising concerns that e-cigarettes are acting as **entry nicotine products** that may lead to use of more dangerous nicotine products.[32,40,41] According to a recent study, U.S. youths are 4 times more likely to try cigarettes and 3 times more likely to currently use cigarettes if they previously used e-cigarettes. The study also estimated that e-cigarettes are likely responsible for **22% of new ever cigarette use** (trying a cigarette) and 15.3% of current cigarette use for the same group — totaling nearly **200,000 new cigarette initiators**.[42]
- **Many young e-cigarette users do not know what is in the products they are using.** A recent study found that 99% of all e-cigarette products sold at convenience stores, supermarkets and similar outlets contain nicotine.[43] Yet, many young people **aren't aware that the products they use, like JUUL, contain nicotine**.[22] In fact, a Truth Initiative study showed that nearly two-thirds of JUUL users aged 15-21 were not aware the product always contains nicotine.
- As rates of use increase, we are also seeing the **frequency of use** (how many times a user vapes in a day) go up, indicating that users are not simply experimenting with e-cigarettes but are instead using them **habitually**. The 2019 National Youth Tobacco Survey data show that 34.2% of current high school e-cigarette users and 18.0% of current middle school e-cigarette users use e-cigarettes on 20 days or more per month and Monitoring the Future found that in 2019, 11.7% of high school seniors vape every day, suggesting that more users are becoming dependent on these products.[39,44]

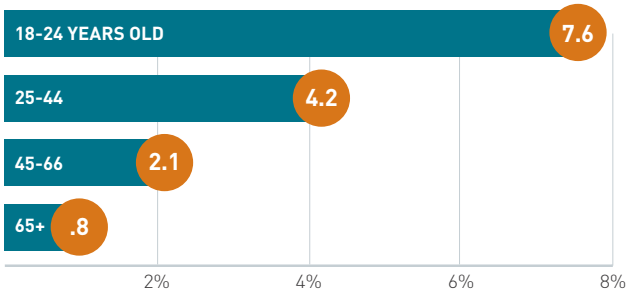
- **Youth e-cigarette users cite flavors as a top reason they began using e-cigarettes**, second only to use by a family member or friend.[46]
  - A study that included middle and high school students reported that **43%** of young people who ever used e-cigarettes **tried them because of appealing flavors**.[47]
  - The FDA has also reported that, among current youth users of e-cigarettes, **97%** used a **flavored e-cigarette** in the past month.[48]
  - As much as **98.7%** of **flavored e-cigarette products** sold in convenience, dollar, drug and grocery stores contain **nicotine**.[49]
  - Despite JUUL removing some flavors from retail stores in April 2019, they continued to hold a majority of the U.S. e-cigarette sales market share.[50] Research suggests that mint and menthol, which remain available for sale, have continued to increase in popularity. 2019 NYTS data show that **mint and menthol e-cigarette use rose to 57.3% from 51.2% in 2018 among high school current users**, suggesting a switch to these flavors once mango and fruit medley became harder to obtain.[35,39,51]

For more information, see "Flavors" on pg. 25.

YOUNG ADULTS

- **Like youth, young adults aged 18-24 are also using e-cigarettes at increasing rates.** Young adult use of e-cigarettes every day or some days increased from 2.4% in 2012 and 2013 to 5.2% in 2017, and increased again to **7.6% in 2018** based on a recent analysis.[32,52,53]
- A 2016 report from the Behavioral Risk Factor Surveillance System survey found that **44.3% of young adult current e-cigarette users were never smokers before trying e-cigarettes**.[54]
- Compared with adults aged 25 and older, **young adults are more likely to try e-cigarettes** and report having used e-cigarettes in the past 30 days.[32]
- A study in Mississippi suggests that using **JUUL leads to more sustained use than other e-cigarettes**. It concluded that the continued use of JUUL by Mississippi undergraduate students was more likely than the continued used of other e-cigarettes after an initial trial. The study found that 30-day use was **three times higher** among those who had tried JUUL than a different e-cigarette.[55]
- The growth in the popularity of e-cigarettes among young adults has caused concerns that use will lead to the **initiation of cigarettes** and other tobacco products.[56-62]

Adults who currently use e-cigarettes as of 2018



Source: 2018 National Health Interview Survey

ADULTS

- E-cigarette use has remained relatively low and stable among adult users since around 2012. Between 2012 and 2013, 2.4% of adults aged 25-44 and 2% of adults aged 45-64 used e-cigarettes. By 2016, the rates had increased to 4.2% and 2.8%, respectively. The most recent data for the year 2018 show current use of e-cigarettes remaining at 4.2% among adults 25-44 and 2.1% among adults aged 45-64.[52,63]
- The overall adult rate of e-cigarette use in 2018 was 3.2%, down from 3.7% in 2014.[52]
- Those aged **45 and older** are **significantly less likely** to have ever tried an **e-cigarette** compared to young adults.[64]

DUAL USE OF TOBACCO PRODUCTS

Among all age groups, e-cigarettes are most commonly used by **those who also use other tobacco products**, such as combustible **cigarettes**.[52,54,65] This pattern is commonly referred to as "dual use" or "poly tobacco use."

Among **adult** users, this is a **troubling pattern** because it suggests that some **e-cigarette use may be supplementing smoking instead of replacing it**. Because there is no safe level of smoking, there are concerns that this behavior suppresses efforts to completely quit smoking (i.e., people choosing to "cut down" instead of quitting smoking entirely). Some individuals using e-cigarettes to quit may experience a period of dual use as they transition between products, complicating the issue.

Among youth, the data tell a different narrative. A 2018 report from the NASEM concluded that there is **"substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults,"** suggesting that e-cigarette use itself is a risk factor, not just a correlation with smoking.[2,32] More recent studies have suggested that **young e-cigarette users are four times more likely to begin smoking cigarettes** compared to their peers who do not use e-cigarettes.[42,60,66]

DUAL USE PREVALENCE

- Among **adults** in 2016, **54.6%** of current e-cigarette users **also smoked cigarettes**.[54]
- Among adults who used more than one tobacco product in 2017, the most common combination was **cigarettes and e-cigarettes**.[52]
- **Dual use** of e-cigarettes and cigarettes is **highly common** among **youth** and **young adults**.[54,65,67,68]
- A nationally representative survey in 2016 found that among youth and young adult e-cigarette users aged **13-25**, more than half (**55.9%**) **used another tobacco product in addition to e-cigarettes**.[65]
- Among **young adults** aged **18-35**, **e-cigarette** use was associated with **more frequent cigarette smoking** and more intensive cigarette use.[69]
- Young adults (18-35) who used e-cigarettes the previous year increased their odds of daily cigarette use by 1.67 and increased their odds of being diagnosed with tobacco use disorder by 2.58.[69]

JUUL

Since 2016, the e-cigarette brand JUUL has surged in popularity among young people and, as of October 2019, holds 64.4% of the e-cigarette market share measured by Nielsen.[50] The traditional tobacco industry took notice of JUUL's rapid ascent. In 2018, Altria, the makers of Marlboro cigarettes, acquired a 35% stake in the company for $12.8 billion. In September 2019, an Altria executive replaced the former head of JUUL as CEO.[10,70,71]

A 2017 study by Truth Initiative found 25% of survey respondents, aged 15-24, recognized a JUUL e-cigarette device when shown a photo of the product. And among those who recognized JUUL, 25% reported that use of this product is called "JUULing," indicating that this product is so distinctive, it's perceived as its own category.[72] However, it's likely that recognition is higher now given that JUUL's sales market share continued to rise throughout 2018 and top out at 75% among U.S. e-cigarette sales in July 2019.[22,50]

The most recent data from the CDC's 2019 National Youth Tobacco Survey confirms JUUL's grip on America's kids. More than 59% of high school e-cigarette users reported that JUUL was their "usual brand." Among middle school e-cigarette users, the number was more than 54%.[39] This equates to more than 3 million children reporting regular use of JUUL. Investigative reporting by Reuters shows that even early in its operations, JUUL was aware that its products were attracting unprecedented youth use, yet, in the face of enormous revenue growth, the company failed to take effective action to stem that trends.

Flavors are a top reason why young people begin using e-cigarettes. A 2018 Truth Initiative survey found that mint was among the top three favorite flavors among young JUUL users aged 12-24, meaning they chose it last time they vaped. New research shows that mint and menthol e-cigarette use among high school users rose from 16% in 2016 to 57.3% in 2019.[39] Among high school JUUL users, 67.5% reported that their preferred flavor was mint or menthol. Another study, conducted before JUUL pulled its other flavors from the market, found that mint was one of the most popular flavors among high school student JUUL users, but that menthol was less so.[45] However, study authors themselves caution that leaving both mint and menthol on the market undermines the purpose of removing flavors — which is to prevent kids from using e-cigarettes at all.

Promoted as a "satisfying alternative to cigarettes," **JUUL is putting a new generation of youth at risk of nicotine dependence and future cigarette use**.

- JUUL has spent more than **$1 million to market its products on the internet** and has paid for campaigns on Twitter, Instagram and YouTube.[73] However, recently JUUL announced that it would "suspend all broadcast, print and digital advertising in the U.S." It was not clear from the announcement how long that suspension would last.[74]
- JUUL also **hired social media influencers** for product promotion.[75] The company had an entire department dedicated to influencer marketing and specifically looked for influencers under 30 and created a "VIP Portal" for celebrities.[76,77]

QUITTING SMOKING

There are substantial research gaps in proving the effectiveness of e-cigarettes as quit smoking aids. The 2018 NASEM report found limited evidence on the effectiveness of e-cigarettes to promote quitting.[2,78-82] Additionally, **e-cigarettes are not approved as quit aids** by the U.S. Preventative Service Task Force or the FDA.

While some evidence supports the use of e-cigarettes as quit devices, recent research suggests that their efficacy for quitting is overstated.[25]

- **A study published in 2016** reported that within two randomized control trials, **e-cigarettes with nicotine helped individuals quit better than non-nicotine e-cigarettes**.[1,2,83] The NASEM also reported that more frequent e-cigarette use may increase an individual's likelihood to quit smoking.[2]
- **A 2019 study by the U.K. National Health Service published in the New England Journal of Medicine found e-cigarettes may help adults quit.** A group assigned to e-cigarettes as a combustible tobacco replacement were more likely to remain abstinent at one year compared with a group using nicotine replacement products (18% versus 9.9%). However, a majority of e-cigarette users were still using e-cigarettes at the one-year follow-up. Researchers noted the **study was based on a middle-aged adult population (median age of 41) actively seeking to quit smoking** and receiving at least four weeks of behavioral support.[84] Notably, the U.K. also places severe restrictions on the marketing of e-cigarettes.[5] **No similar study has replicated these results in the U.S.**
- Another recent 2019 study exploring whether e-cigarettes' presence on the U.S. market has inspired more successful quit attempts found that users of e-cigarettes had 70% lower odds of quitting than non-users.[85]

While some e-cigarettes may be an effective resource for quitting smoking, the diversity of products as well as the variations in quality and the lack of regulation make determining the potential of any particular product as a quit aid difficult.[2,25,27] Some smokers have switched to e-cigarettes or used them to quit tobacco completely; however, e-cigarettes, unlike FDA-approved cessation therapies, lack an evidence base that demonstrates their safety and efficacy.[25] Truth Initiative supports regulation that encourages the development of consistently **less harmful nicotine delivery alternatives** that allow smokers to **quit tobacco** altogether or **switch** completely to a much **less harmful, well-regulated product**.

While some evidence supports the use of e-cigarettes as quit devices, recent research suggests that their efficacy for quitting is overstated.

One study shows that product appeal, including flavoring, is likely to encourage smokers to try to use e-cigarettes to quit or switch completely.[86] But, because the youth e-cigarette epidemic in the U.S. and the youth appeal of flavored e-cigarettes go hand in hand, **Truth Initiative strongly supports removing flavored e-cigarettes from the market**, pending an FDA review. Given what we now know about how dramatically flavors influence youth e-cigarette use, the burden should be high. We support a permanent ban on flavors unless a manufacturer can demonstrate three things to the FDA: 1) that a particular flavor helps current tobacco users to stop smoking, 2) it will not lead non-tobacco users (such as youth) to start, and 3) it does not increase the risk of harm from using the product. In addition to flavor restrictions, Truth Initiative supports strong regulations to keep all tobacco products, including e-cigarettes, away from youth. (See "Action Needed" on p. 1 for more information.)

Age differences: Reasons for e-cigarette use

Analyses from the Population Assessment for Tobacco and Health study show that the leading reason for **youth and young adult e-cigarette use** is **"they come in flavors I like"** — with **77.9%** and **90.3%** selecting this as a reason, respectively. In comparison, only 66.4% of adults aged 25 and over selected this as a reason.[87]

The FDA has also reported that, among current **youth** users of e-cigarettes, **97% used a flavored e-cigarette** in the past month.[48] Youth and young adults had more than three times the odds of using fruit-flavored e-cigarettes compared to older adults.[87]

The leading reason for e-cigarette use among adults (25 and older) was the belief that e-cigarettes may be less harmful than combustible cigarettes both to themselves and others, with 79% selecting this as a reason. Additionally, 7 in 10 (71.5%) adults indicated that they believed e-cigarettes could facilitate quitting.[87]

HEALTH EFFECTS

To date, no one knows the long-term effects of e-cigarette use, although **research continues to investigate some of the rapidly emerging evidence of adverse effects** on lung and cardiovascular health.

- A recent and **robust research literature review** of **e-cigarette** health effects found that use of these products has been associated with increased odds of chronic **cough, phlegm and bronchitis**, as well as **asthma** diagnoses.[27]
- Ongoing case studies and in vitro research that exposed human tissue to e-cigarette aerosol suggested that **e-cigarettes may be causing quantifiable injury to the small airways of the lungs** and were associated with a number of inflammatory diseases of the respiratory system, like pneumonia and interstitial lung disease.[27]
- **Human cells exposed to vaped e-liquid have also been found to have decreased viability, with certain flavor compounds posing particular cell toxicity risks.** Other studies also showcased impaired immune cell function in the lungs, raising questions about e-cigarette users' susceptibility to bacterial and viral infections of the respiratory system. There is uncertainty regarding the way these infections may manifest given the potential for other lung injury and inflammation in lung tissue from e-cigarette use.[27]
- The first study to link e-cigarette use to cancer was published in October 2019. Researchers found that **mice exposed to e-cigarette aerosol for 54 weeks developed carcinomas of the lungs and abnormal bladder cell growth**.[88]
- Research has also found that **some flavors are potentially more toxic** than others.
  - Researchers found that exposure to increased **cinnamon** flavoring caused significant **cell death** compared to other flavors.[89]

- Another concern related to flavoring stems from **pulegone** — a compound found in prepared oil extracts of certain **mint** plants. Pulegone is a **known carcinogen** and the tobacco industry has in the past reduced the amount of this compound in menthol tobacco products as a result of toxicity concerns. The **FDA banned pulegone as a food additive** in 2018, yet studies have identified that **substantial amounts of this additive are found in mint and menthol e-liquid** in the U.S. — raising concerns about the potential toxicity of these popular flavors.[90]
- Research also indicates that **mixing multiple flavors can be more toxic to cells** than exposure to just one flavor at a time.[91]

- Research regarding the impact of e-cigarettes on cardiovascular health has yielded mixed results. Some studies have shown that short-term exposure to e-cigarette aerosol has no measurable harm on cardiovascular health. However, others suggest negative effects on resting heart rate, blood pressure and the cells that line the blood vessels. **More extensive research is needed to gain perspective on the long-term effects of e-cigarette use on heart health**, which have yet to be identified.[6]
- Another pressing concern of e-cigarette use on cardiovascular health is the creation of **carbonyl compounds from e-cigarette aerosol**. Carbonyls are created when propylene glycol and glycerol — common solvents in e-liquid — are exposed to the high heat of an e-cigarette coil. Many of these carbonyl compounds have been previously associated with an increased risk of **blood clot and atherosclerosis** — a disease in which plaque builds on the walls of arteries, narrowing blood flow.[6]

More research over a longer time period is needed to understand the full breadth of health consequences associated with the use of e-cigarettes as well as how their use compares to the well-established negative effects of long-term combustible cigarette use.

Federal investigations into vaping-related illnesses

The emergence of vaping-related illnesses, which have prompted federal health agencies' investigations and advisories, underscores the urgency of research.

As of November 5, 2019, more than **2,000 vaping-related illnesses and 39 deaths have been reported** to the CDC.[26] A review of some of the affected e-cigarette users in two states reported that a majority of patients were experiencing cough, labored breathing, reduced blood oxygen levels and elevated white blood cell counts.[27]

Research by Mayo Clinic of 17 patients with vaping related lung issues found that the injuries resembled "exposures to toxic chemical fumes, poisonous gases and toxic agents."[92] Because a large proportion of the cases with specific substance use information available involved individuals who vaped THC (either exclusively or along with nicotine), the FDA has recommended that consumers not purchase vaping products of any kind on the street and avoid using THC oil or modifying store-bought products.[93] The CDC has also recently identified vitamin E acetate, a chemical found most often in illegal THC vaping products, as a primary chemical of concern in the outbreak.[93]

The CDC has recommended that those who use vapes consider not using them and that children and women who are pregnant should not use e-cigarettes regardless of the outcome of this investigation. For those who vape and experience similar symptoms, the CDC recommends seeking prompt medical care.[94] It is important to note, though, that the CDC continues to state, "it is possible that more than one compound or ingredient could be a cause of lung injury, and evidence is not yet sufficient to rule out contribution of other toxicants."[95]

ADDICTION AND BRAIN DEVELOPMENT

Nicotine is an addictive substance, but its **level of addictiveness can vary substantially depending on its mode of delivery**. Nicotine delivered by the combustion of tobacco is the most addictive form.[96] The rise in popularity of e-cigarettes that can deliver levels of nicotine similar to combustible cigarettes is causing concern about the potential risk for addiction.[32]

- Exposure to nicotine among youth is particularly dangerous since it has been shown to have an effect on key brain receptors, making **young people more susceptible to nicotine addiction**.[41]
- There is some evidence that the effect of nicotine on developing brains may prime not just nicotine addiction, but **greater vulnerability to addiction to other drugs** as well.[97]

In young people, the amount of nicotine needed to establish an addiction has been estimated at around 5 mg a day, or roughly one-quarter of an e-cigarette pod.[21,98] In recognition of these and other risks related to e-cigarettes, the U.S. surgeon general issued an advisory on e-cigarette use among youth, urging **parents, teachers, health professionals and states to take action to stop the epidemic among youth**.[51]

PREGNANCY

- Because most e-cigarettes contain nicotine, which can alter nerve cell functioning in developing organisms, especially during fetal development, **they should not be used by youth or pregnant women**.[99,100]
- **Pregnant women** who use nicotine are also at a greater risk for **stillbirth** and **preterm delivery**.[32]

CHEMICALS

While e-cigarettes may contain fewer toxins than combustible cigarettes, short and long-term effects of their use are unclear. What we do know is that they are not free of toxins and still **deliver harmful chemicals**.

- **At least 60 chemical compounds** have been found in e-liquids, and still more are present in the aerosol produced by e-cigarettes.[2]
- **Heavy metals** such as cadmium, lead, nickel, tin and copper have all been detected in aerosols produced by e-cigarettes.[30]
- E-cigarettes produced fewer free-radicals than combustible cigarettes, however, even low levels of **repeated exposure to free-radicals** can cause oxidative stress, which increases the risk for cardiovascular and respiratory diseases.[101]
- Researchers have identified several substances which are either harmful or potentially harmful to e-cigarette users, including **delivery solvents and propylene glycol**, which can cause dry mouth and **upper respiratory infections** as well as pulegone, a known **carcinogen**.[2,90]

EXPOSURE TO E-LIQUID

- Accidental exposure or ingestion of **e-liquids** can be very dangerous and, in the case of **accidental swallowing or injection**, even **fatal**.[2]
- More than **8,000 accidental liquid nicotine exposures** were reported by U.S. poison control centers between 2012 and 2017 in **children aged 6 or younger**.[102]

- Nearly 5,000 (**4,745**) **children under the age of 5** were treated in U.S. emergency rooms for **e-liquid nicotine exposure** from 2013 to 2017. More than half (56.2%) of the children were aged 2 or younger.[103]

EXPLOSIONS

- **Defective, poorly manufactured and improperly modified e-cigarettes have also been known to explode and cause injury.** The rate of explosions is unknown, but both hospitals and burn centers have reported injuries from e-cigarettes.[2]

SECONDHAND AEROSOL EXPOSURE

- **Exposure to aerosol from e-cigarettes** may expose non-users to nicotine, but research indicates that secondhand aerosol results in substantially lower exposure to toxicants and carcinogens than cigarette smoke. However, exposure among **vulnerable populations, including pregnant women and children, could still be dangerous**.[2]

LUNG ILLNESS AND SEIZURES

- The FDA is investigating whether a direct relationship exists between the use of e-cigarettes and **seizure risk or other neurological symptoms**. As of August 2019, the agency had received **127 reports** of seizure or other neurological symptoms that occurred between 2010 and 2019.[104]

- The CDC, FDA and state and local health departments are investigating a **multistate outbreak of severe lung injury** associated with e-cigarette or vaping product use. As of **November 5, 2019**, more than 2000 cases of this disease, which CDC is calling **"EVALI" (E-cigarette or Vaping product use-Associated Lung Injury)** in 49 states, D.C. and the U.S. Virgin Islands. **Thirty-nine deaths** in 24 states have been confirmed.[26]

INDUSTRY MARKETING AND YOUTH TARGETING

The introduction of e-cigarettes has allowed companies to advertise through traditional outlets that have been heavily regulated to reduce combustible cigarette marketing to children. For example, e-cigarette advertising appears on television and radio, despite the ban on cigarette advertising in both outlets since Congress passed the Public Health Cigarette Smoking Act in 1970. The FDA also banned flavors, except menthol, in combustible cigarettes in 2009 to curb youth appeal, whereas **e-cigarettes capitalize on offering many kid-friendly flavors, such as mint, cotton candy and gummy bear**.[105]

MARKETING TACTICS

- Individuals aware of e-cigarettes report that the most common platforms to hear about e-cigarettes are through in-person communications, by seeing them for sale and through **online and television advertisements**, in which some **celebrities** have endorsed the products.[106-110]

- E-cigarettes are **promoted heavily online**[111] through e-cigarette company-sponsored advertisements,[112] and on **YouTube**[112-115] and **Twitter**.[116]

E-cigarettes capitalize on offering many kid-friendly food flavors, such as mint, cotton candy and gummy bear.

Photo: U.S. Food and Drug Administration

- More recently, **mobile ads** have become a popular place to advertise e-cigarettes. Mobile ads, or **paid advertisements on smartphone applications** and websites optimized for mobile, have the potential to **reach millions of young people**.[117]

- **Some e-liquids have been marketed to look like common food items — many of which appeal to kids.** Early examples included marketing e-liquids as **"Thin Mints,"** after the Girl Scouts' cookie and **"Tootsie Roll"** after the iconic candy. Those were removed, or at least renamed, after the companies owning those copyrights took action to protect their intellectual property. Other food and candy flavors remained on the market.

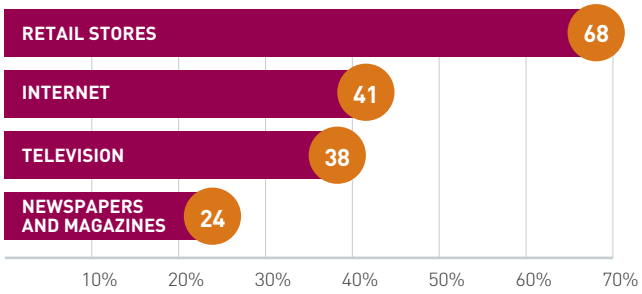
  - Since May 2018, the FDA, often in conjunction with the FTC, has taken action against several **e-liquid companies that marketed their products to look like candy or other kid-friendly food items, such as Reddi-wip, Nilla wafers and Warheads candy**.[118] The FDA has also recently announced moves to restrict the sale of candy- or fruit-flavored e-cigarettes. For more, see "Policy Environment" on page 24.

YOUTH EXPOSURE TO ADVERTISING

- **Youth may be exposed to pro-tobacco content and advertising on social media** through various sources, including commercial **brands** as well as their own **peers** or **influential accounts** they follow. The nature of social sharing allows branded or promotional content to virally spread across platforms, which can increase youth exposure to overt marketing and pro-tobacco content posted by influential peer network members.[75,119-121]

- By 2016, nearly **4 out of 5 middle and high school students**, or more than 20 million youth, **saw at least one e-cigarette advertisement**.[122]

Where young people are most likely to see e-cigarette ads



- Young people were most likely to see ads at **retail stores** (68%), followed by the **internet** (41%), **television** (38%) and **newspapers** and **magazines** (24%).[122] Between 2014 and 2016, exposure to retail e-cigarette advertising among young people jumped nearly 20%.[122]

- Mobile device ownership is most prevalent among young people, and research has shown that **mobile ads may attempt to capitalize on young audiences** by highlighting the product as "cool" or "high tech" and by featuring flavored ads.[117]

- A recent study conducted by Stanford University School of Medicine found **JUUL advertisements strikingly similar to traditional tobacco advertising** in tone and imagery (smoking as pleasurable, relaxing, stylish or romantic).[75]

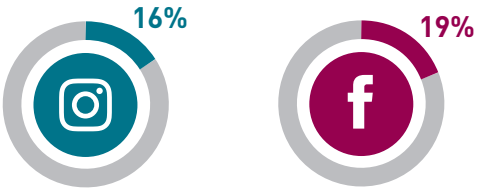
- **JUUL has also targeted children as young as third grade by funding summer camps, visiting schools and paying community and church groups to distribute their materials**, according to recent congressional testimony.

- On Oct. 17, 2019, JUUL announced that it would "suspend all broadcast, print and digital advertising in the U.S." It was not clear from the announcement how long that suspension would last.[74]

E-CIGARETTES ON SOCIAL MEDIA

- **JUUL spent more than $1 million to market its products on the internet** and has paid for campaigns on Twitter, Instagram and YouTube.[73]
- Because JUUL relied heavily on social media advertising for its launch, unlike other e-cigarette brands who focused their marketing through traditional outlets (e.g., TV), **teen and young adults made up a significant majority of JUUL's social media audience**.[123]
- **JUUL also hired social media influencers for product promotion.**[75] They had an entire department dedicated to influencer marketing and **specifically looked for influencers under 30** and created a "VIP Portal" for celebrities.[76]
- As of October 2018, 11 **JUUL-centric YouTube videos from users had more than 1 million total views**. In November 2018, JUUL's Instagram account had 77,600 followers and #juul had 260,866 postings. By January 2019, JUUL's hashtag had 336,308 posts.[75]
- **On Nov. 13, 2018, JUUL Labs announced they would be shutting down their U.S.-based Facebook and Instagram accounts in an effort to curb youth e-cigarette interest and use.** The official Twitter account remains active.[124]
- There were 366,786 JUUL-related tweets in 2017, 17 times more than the previous year. A 2018 study found the **surge of tweets mirrored JUUL's sizable growth in retail sales**.[125]
- A 2018 study found that **exposure to e-cigarette advertisements on social media among young adults was strongly associated with positive expectations of e-cigarette use** — like the idea that using e-cigarettes would provide a pleasurable taste and smell and that it was safe and socially acceptable. These outcomes were also found to be directly correlated with current use.[119]
- **Even among non-smokers, exposure and marketing through social media linked e-cigarettes with increased perceptions of stylishness and popularity.**[119] Of the study participants, 19% regularly saw e-cigarette ads on Facebook and 16% on Instagram. Even more reported seeing posts about e-cigarettes.[119]

Non-smokers regularly saw e-cigarette ads on social media



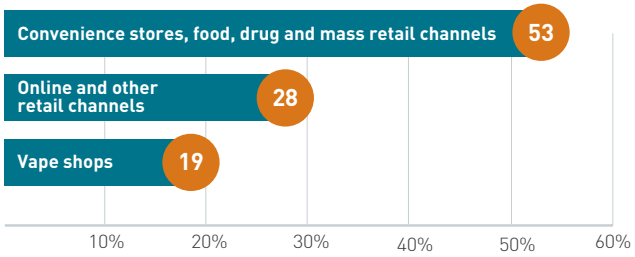
Source: Lin X, Spence PR, Lachlan KAJCiHB. Social media and credibility indicators: The effect of influence cues. 2016;63:264-271.

- The largest e-cigarette forum (/r/electronic_cigarette) on **reddit** has **150,000 subscribers**.[123]
- Another **subreddit**, titled **/r/UnderageJUUL**, at one point contained 844 members before it was shut down by reddit. Posts included discussions of flavors as well as methods of obtaining JUULs or pods. Most posts in this thread did not reference age, but those that did mentioned ages from 13 to over 21.[127]
- A study found that **e-cigarette users who are male and younger** were the most likely to participate in **discussion forums online** related to e-cigarettes.[126]
- Another study analyzed all public active profiles following **JUUL's official Twitter** account in April 2018. Of the 9,077 active individual followers, researchers estimated that **80.6% were aged 13-20**, despite the account stating that one must be 21+ to follow.[128]
- Additional research has shown that **celebrity endorsements of e-cigarettes on social media** can have an impact on young adults. A study of college undergraduates found that the appearance of celebrities on an e-cigarette social media brand page **significantly increased intentions to use e-cigarettes** and positive attitudes towards the devices. This effect was not seen in those who saw non-celebrity endorsers or pages displaying only the product.[129]

WHERE E-CIGARETTES ARE SOLD

- It is difficult to monitor and analyze the market due to differences in the tracking of e-cigarette sales. Common **sales-tracking and retail measurement companies like Nielsen do not examine vape shop data**, which may constitute as much as 20% of the market.
- E-cigarettes are sold at **conventional tobacco retailers**, such as convenience stores, gas stations, pharmacies and tobacco shops. They are also sold at **non-traditional retailers such as online retailers or vape shops**.
- In 2018, the FDA contacted eBay and raised concerns about the site's continued sales of JUUL and other tobacco products — something that was against their company policy.[130] As a result, eBay agreed to work with the FDA and has tried to remove those listings from its website. It also published an explicit policy outlining the reasons why tobacco products cannot be sold on their site.[131] However, recent **reviews of eBay found the site still sells accessories for JUUL**, such as chargers and "skins" that wrap around JUULs to personalize them.
- Because these non-traditional sources are not tracked by scanner data or other tracking, it is difficult to know how much of the market they represent. However, analysts have made some estimates. One paper noted that in 2014, traditional tobacco outlets accounted for less than one-third of the $2.5 billion e-cigarette market. According to one recent estimate, the **breakdown of retail channels for the 2019 e-cigarette market** is:
  - Vape shops: 19%[132]
  - Convenience stores, food, drug and mass retail channels: 53%[132]
  - Online and other retail channels: 28%[132]

Retail channels of the e-cigarettes market



POTENTIAL PUBLIC HEALTH IMPACT

The potential public health impact of e-cigarettes is a subject of hot debate. Despite inconclusiveness about their short- and long-term health effects, **e-cigarettes remain largely unregulated and their popularity among youth and young adults continues to rapidly escalate**. At the same time, serious illness and deaths have been linked to their use and recent research could not conclusively determine that they posed fewer health risks than combustible cigarettes.[27]

Moreover, their potential positive public health impact will be limited if they are not considered as part of comprehensive product regulation, including **actions such as reducing nicotine to non-addictive levels in the most dangerous products, such as cigarettes, and eliminating flavors and marketing practices that attract youth**. Continuous and rigorous implementation of traditional tobacco control measures, such as **taxation**, **clean indoor air policies** and public **education** is also essential. Additionally, an **overarching nicotine regulatory policy** is needed to help improve quitting drugs and to ensure that the FDA reviews tobacco products, including e-cigarettes, so that consumers better understand what can help them quit or completely switch from combustible cigarettes. Finally, the recent news of **vaping-related illnesses requires swift research** and effective guidance to protect the public's health.

POLICY ENVIRONMENT

FDA REGULATION

In May 2016, the FDA finalized its "deeming" regulation, asserting the agency's authority to regulate e-cigarettes and any product meeting the definition of "tobacco product" under the Tobacco Control Act.[133] The **FDA can now establish product standards and regulate the manufacture, import, packaging, labeling, advertising, promotion, sale and distribution of e-cigarettes**, including components and parts of e-cigarettes.[133] Some of these regulations are outlined below.

- The deeming regulation also includes **requirements for pre-market review for e-cigarettes as new tobacco products**. In order to receive marketing approval for a new product, a manufacturer would need to demonstrate that the new product would be "appropriate for the protection of the public health," taking into account both the likelihood of new tobacco product initiation and the increased or decreased likelihood that existing users of current tobacco products would stop using such products.[133]
- It is important to note that because virtually every e-cigarette on the market was introduced after Feb. 15, 2007, technically only those e-cigarettes that have gone through an FDA review to determine whether they benefit public health should be on the market now. However, when the agency finalized the deeming regulation, the FDA issued a "compliance policy" that would give e-cigarette manufacturers more time to prepare those submissions and still allow the products to be on the market. In other words, every e-cigarette on the market right now is illegal because it has not gone through an FDA review, and is only allowed to be sold because the FDA gave them a temporary pass.
- Additionally, when the deeming regulation was finalized, the FDA indicated that no products could come on the market after August 2016 without pre-market review and authorization by the FDA. Many companies have not complied with that and the FDA has sent warning letters to these companies. For example, in October 2019, the FDA sent a letter to Eonsmoke regarding nearly 100 flavored e-cigarette products that came on the market after August 2016 without pre-market review and authorization.[134]
- In 2017, the **FDA pushed back the compliance date for e-cigarette manufacturers to submit pre-market applications even more to August 2022**. This delay in the compliance deadline enabled the proliferation of e-cigarettes that have never undergone an FDA review.
- In March 2018, a group of public health organizations, including Truth Initiative, sued the FDA for unlawfully delaying the implementation of the deeming rule. In

Legal challenges to e-cigarettes

A series of **lawsuits** in recent years have also been brought **against JUUL and other e-cigarette manufacturers** by young people who became addicted to JUUL, claiming **JUUL's marketing was aimed at youth** and instigated these plaintiffs' use. California, North Carolina, Illinois, Connecticut, Colorado, Massachusetts and the District of Columbia have announced either litigation or investigation into JUUL's marketing practices and/or health claims.[136-141]

May 2019, a federal judge ruled that the FDA had acted illegally by allowing e-cigarettes, including those with flavors that appeal to youth, to remain on the market without formally reviewing their impact on public health.[135] The **judge ordered the FDA to commence the statutorily required review by May 2020**. The FDA appears to have accepted this timetable, although industry groups are still challenging the federal judge's decision.

- In addition, the **Trump administration has indicated it will take all flavored e-cigarettes off the market if they have not undergone premarket review**. By early November, the Administration had signaled it may walk back from that policy. As of November 8, 2019, no policy has been released.

FLAVORS

- There are currently **no federal restrictions on flavored e-cigarettes**.
- In March 2018, the FDA issued an advance notice of proposed rulemaking to **request public comment to better understand the role that flavors in tobacco products play in attracting youth**, as well as the role they may play in helping some smokers switch to potentially less harmful forms of nicotine delivery. However, this request for comment is not a guarantee of agency action on this issue and no further rule-making action on flavors has been taken or announced by the FDA as of this writing.
- In March 2019, the FDA proposed to **restrict the sales of flavored e-cigarettes, except mint, menthol and tobacco flavors**, to age-restricted locations and online retailers that place a limit on the quantity that a customer may purchase within a certain time period and have independent, third-party age-verification services.[142] As of October 2019, a final guidance had not yet been issued by the FDA.
- As of Aug. 28, 2019, **220 localities had prohibited the sale of flavored tobacco products, including flavored e-cigarettes**.

220 localities have prohibited the sale of flavored tobacco products, including flavored e-cigarettes.

These include Berkeley, Oakland, Sacramento and San Francisco, California; Aspen, Colorado; Chicago, Illinois; Boston, Massachusetts; Minneapolis and St. Paul, Minnesota; and Providence, Rhode Island.[143] However, a large majority of the U.S. population — more than 90% — is not covered by such restrictions.[144]

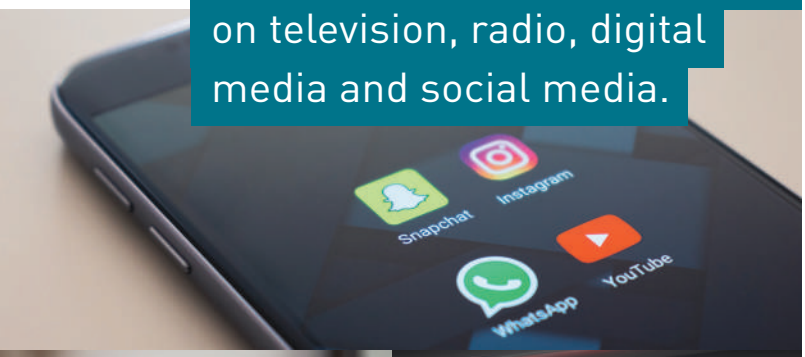
- In September and October 2019, **governors in several states (Michigan, Montana, New York, Oregon, Rhode Island and Washington) used their emergency executive powers or directed their state health departments to temporarily ban in-store and online sales of flavored e-cigarettes**, citing the youth e-cigarette epidemic and recent health concerns regarding seizures and lung illnesses.[145-150] As of late October 2019, however, the **New York**, **Michigan** and **Oregon bans had been temporarily suspended**.[151-153] In **Massachusetts**, the governor took the extraordinary step of **suspending the sale of all e-cigarettes**.[154] And while the ban has not been overturned, a judge recently ruled that it must be resubmitted with an opportunity for public comment.[155] Several other governors have ordered their legislatures to consider legislation to restrict e-cigarette sales. The Utah Department of Health also issued a temporary emergency rule to restrict the sale of flavored e-liquids to licensed specialty tobacco stores.[156]

- On Sept. 11, 2019, in light of significant signs of increased youth uptake of e-cigarettes and the lung illnesses and deaths associated with vaping, the **administration announced that it would not extend the compliance period described above to flavored e-cigarette products (other than tobacco flavor), effectively removing all but tobacco-flavored e-cigarettes from the market.**[35] Manufacturers would be able to submit flavored e-cigarette premarket applications to the FDA for review to determine whether they provide any public health benefit.[35,157] By early November, there were signs the Administration may water down that strong policy. At the time of this writing, the FDA has not yet finalized this action and flavored e-cigarettes remain on the market.

LICENSING

- Licensing and commercial zoning are areas of local concern. The federal government has **no regulations** affecting tobacco retailer licensing.
- As of June 15, 2019, **24 states and the District of Columbia require licenses for the retail sales of e-cigarettes.**[158] Delaware requires retailers to obtain a license to sell e-cigarette liquids, but not e-cigarette devices themselves. In North Carolina, e-cigarette retailers who buy their stock directly from a North Carolina distributor/wholesale dealer or manufacturer do not need to obtain a license, while those who obtain their stock directly from manufacturers outside of North Carolina do need a license.

Unlike traditional cigarettes, e-cigarettes can be advertised on television, radio, digital media and social media.



MARKETING

- There are **few federal restrictions on the marketing of e-cigarettes**, and, unlike traditional cigarettes, e-cigarettes can be advertised on television and radio, in print, and through digital and social media.
- **Marketing materials of e-cigarettes cannot make claims that their product exposes users to fewer toxins or reduces harm unless the FDA grants an order allowing such claims.** In September 2019, the FDA sent JUUL a warning letter cautioning against unauthorized cessation claims and questioning recent marketing practices that appeared to be targeted to youth.[159] In October 2019, the FDA sent Eonsmoke a warning letter for, among other things, marketing their products with unauthorized claims of reduced harm of their products, and for advertisements through social media influencers that do not carry the required warning label.[134]
- **E-cigarette products whose labeling or advertising is misleading can be considered to be misbranded under the Tobacco Control Act.** This includes e-cigarette marketing that imitates food or beverages, as mentioned above.
- **States have the ability to regulate the time, place and manner of tobacco marketing, including e-cigarettes.**[133,160] For example, California and Delaware prohibit websites and online and mobile applications directed at minors from marketing or advertising e-cigarettes. California also prohibits advertisements of tobacco products, including e-cigarettes, on any outdoor billboard located within 1,000 feet of a school or public

playground.[161]

- Recently, the **FTC announced it was requiring marketing data for the years 2015-2018 from six of the top-selling e-cigarettes in the U.S.** The companies will be required to provide data such as how much the companies spent on various types of advertising and promotions, product placement in media, as well as social media and influencer marketing. This is the first time such information will be collected by FTC.

PRODUCT PACKAGING

- The FDA deeming regulation, effective Aug. 10, 2018, established a **nicotine warning label** that must appear on all tobacco products, including **e-cigarettes**:

  WARNING: This product contains nicotine. Nicotine is an addictive chemical.[162]

  The warning label must comprise 30% of the two principal display panels and be in a large, legible font.

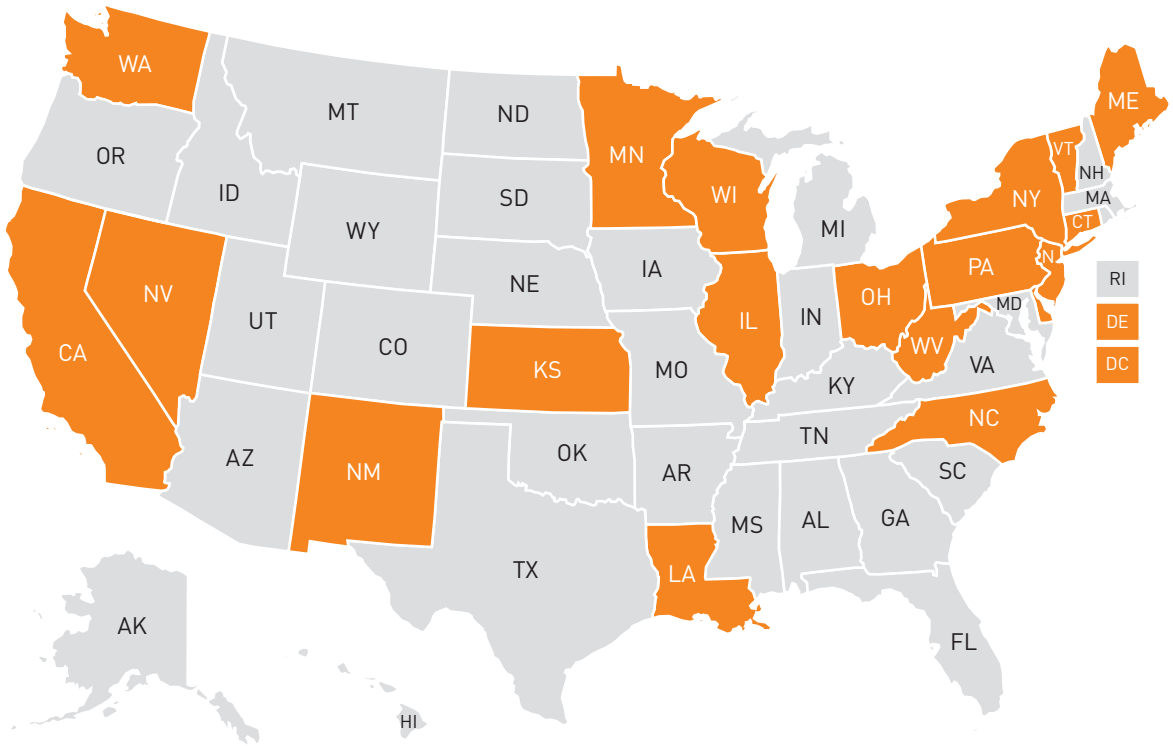
- **The Child Nicotine Poisoning Prevention Act of 2015 requires the Consumer Safety Product Commission to establish requirements for child-resistant packaging for e-cigarettes and e-liquids.** The law, passed before the deeming regulation gave the FDA authority over e-cigarettes, maintains the FDA's ability to regulate such packaging. The FDA has indicated that it will also issue regulations requiring child-resistant packaging for e-cigarettes and e-liquids, but has not yet done so.

TAXATION

- There is **no federal excise tax on e-cigarettes**.
- States have the authority to tax e-cigarettes. **Nineteen states and the District of Columbia have imposed a tax on e-cigarettes.**[161]

Taxes are a particularly **effective tool** for discouraging youth use of tobacco products. **Youth**

Nineteen states and Washington, D.C., have imposed a tax on e-cigarettes.



and young adults are two to three times more likely to respond to changes in prices than adults, and studies examining the effect of price increases on combustible cigarettes estimate that raising the cost of cigarettes to $10 per pack nationwide would result in 4.8 million fewer smokers between the ages of 12 and 25.

YOUTH ACCESS AND MINIMUM AGE OF SALE

- **The FDA deeming regulation established a federal minimum age of 18 for the sale of all tobacco products, including e-cigarettes.** Retailers must check photo IDs of everyone under age 27 who attempts to purchase tobacco products, including e-cigarettes.
  - **Pennsylvania is the only state that does not have a law** restricting youth access to e-cigarettes.[163]
- **Vending machine sales of e-cigarettes are prohibited**, except in facilities where only those over 18 are allowed.
- **Free samples of e-cigarettes and their components are also prohibited** as of Aug. 8, 2016.[133]
- The Tobacco Control Act required the FDA to issue regulations to **establish age verification requirements for the internet and other non-face-to-face purchases of any tobacco products**. However, the FDA has yet to implement this set of regulations.
  - A 2014 study of internet tobacco vendors selling e-cigarettes found that 52.3% of vendors had an age warning on the homepage of their website. However, **51.9% exclusively used age-verification methods that could not effectively verify the age of a consumer**. Additionally, 11.3% made no attempts to verify age at all.[164]
- The Tobacco Control Act prohibits the FDA from further raising the federal minimum legal age of sale.[165] However, states and some localities have the ability to establish a higher age of sale for tobacco products beyond the federal requirement. As of Sept. 18, 2019, **18 states — Arkansas, California, Connecticut, Delaware, Hawaii, Illinois, Maine, Maryland, Massachusetts, New Jersey, New York, Ohio, Oregon, Texas, Utah, Vermont, Virginia and Washington — and at least 505 localities have established a minimum age of 21** for the sale of tobacco products.[166] As of this writing, the federal government is also considering proposals for adopting a nationwide minimum age of 21 for the sale of tobacco products, but those proposals are not yet law.
- Tobacco 21 laws, which forbid the sale of tobacco to anyone under age 21, have **gained in popularity** in recent years. Tobacco companies have increasingly indicated their support for such laws, but they often simultaneously support and help to develop policies that weaken the impact of other

Tobacco 21 laws have gained in popularity in recent years.

effective tobacco control laws.

INTERNATIONAL POLICIES

International regulation of e-cigarettes **varies widely**, and, due to the relatively recent introduction of the product category, is rapidly changing.

- As of November 2018, 98 countries had national laws regulating e-cigarettes and 29 countries had banned the sale of e-cigarettes completely. **A significant portion of countries with e-cigarette policies** (67) **prohibit or regulate e-cigarette marketing**.[167] The European Union has enacted standards for e-cigarettes, including restricting the strength of nicotine fluids (2% maximum), limiting tank size on vaping devices (2 ml maximum), requiring child-resistant packaging and prohibiting cross-border advertising of e-cigarettes.[168] Some member states have further restrictions on the age of sale and taxes.[169]

- The Institute for Global Tobacco Control at the Johns Hopkins Bloomberg School of Public Health keeps a database of international e-cigarette laws.[170] Notably, the **United Kingdom has been most active in promoting e-cigarettes as a reduced harm alternative to cigarettes**.[171] Public Health England has encouraged the National Health Service to make e-cigarettes available to smokers looking to quit or switch.[171] The U.K. allows for the licensing of e-cigarettes as medicinal quitting aids, but no manufacturer has yet taken this route to product approval.[172]

- **The World Health Organization (WHO) recently warned governments, as well as the public, not to trust the tobacco industry's latest health claims regarding e-cigarettes.**[173] The WHO also released a set of recommendations around e-cigarettes to protect public health, including advertising and flavor restrictions to prevent youth sales, plain packaging policies, and awareness around the danger of tobacco use becoming re-normalized.[174]

Unlike in the U.S., a significant portion of countries with e-cigarette policies prohibit or regulate e-cigarette marketing.

Photo: Stanford Research into the Impact of Tobacco Advertising

REFERENCES

1 Moritz ED, Zapata LB, Lekiachvili A, et al. Update: Characteristics of Patients in a National Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injuries — United States, October 2019. MMWR Morb Mortal Wkly Rep. ePub: 28 October 2019. DOI: http://dx.doi.org/10.15585/mmwr.mm6843e1external

2 National Academies of Sciences E, Medicine. *Public Health Consequences of E-Cigarettes*. Washington, DC: The National Academies Press; 2018.

3 Bowen A XC, Inventor; PAX Labs, Inc., assignee. Nicotine Salt Formulations for Aerosol Devices and Methods Thereof. 2015.

4 Romberg AR, Lo EJM, Cuccia A, et al. Patterns of nicotine concentrations in electronic cigarettes sold in the United States, 2013-2018. 2019.

5 Hammond D, Reid JL, Rynard VL, et al. Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. 2019;365:l2219.

6 Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ. Impact of Electronic Cigarettes on the Cardiovascular System. *J Am Heart Assoc*. 2017;6(9).

7 Kennedy CD, van Schalkwyk MC, McKee M, Pisinger CJPm. The cardiovascular effects of electronic cigarettes: A systematic review of experimental studies. 2019:105770.

8 Regan AK, Promoff G, Dube SR, Arrazola R. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette' in the USA. *Tobacco control*. 2013;22(1):19-23.

9 Zhao J, Pyrgiotakis G, Demokritou P. Development and characterization of electronic-cigarette exposure generation system (Ecig-EGS) for the physico-chemical and toxicological assessment of electronic cigarette emissions. *Inhalation toxicology*. 2016;28(14):658-669.

10 Nielsen. Tobacco "All Channel" Data Thru 10/5 - Cig Vol Declines Moderate. In:2019.

11 Kaplan S. 'Juul-alikes' Are Filling Shelves With Sweet, Teen-Friendly Nicotine Flavors. 2019; https://www.nytimes.com/2019/08/13/health/juul-flavors-nicotine.html. Accessed October 23, 2019.

12 Elias J, Dutra LM, St. Helen G, Ling PM. Revolution or redux? Assessing IQOS through a precursor product. *Tobacco control*. 2018;27(Suppl 1):s102.

13 Food and Drug Administration. Premarket Tobacco Product Applications. 2019; https://www.fda.gov/tobacco-products/tobacco-product-review-evaluation/premarket-tobacco-product-applications. Accessed May 9, 2019.

14 McGinley L WW. FDA clears Philip Morris's heat-not-burn IQOS tobacco device for sale. 2019; https://www.washingtonpost.com/health/2019/04/30/fda-clears-philip-morris-heat-not-burn-iqos-tobacco-device/?utm_term=.c6b2ab7c557b. Accessed May 9, 2019.

15 McKelvey K, Popova L, Kim M, et al. Heated tobacco products likely appeal to adolescents and young adults. *Tobacco control*. 2018;27(Suppl 1):s41-s47.

16 Wang JB, Olgin JE, Nah G, et al. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. 2018;13(7):e0198681.

17 Goniewicz ML, Gupta R, Lee YH, et al. Nicotine levels in electronic cigarette refill solutions: A comparative analysis of products from the US, Korea, and Poland. *The International journal on drug policy*. 2015;26(6):583-588.

18 Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tobacco control*. 2014;23(suppl 2):ii4.

19 Belluz J. Juul, the vape device teens are getting hooked on, explained. 2018; https://www.vox.com/science-and-health/2018/5/1/17286638/juul-vaping-e-cigarette. Accessed October 1, 2019.

20 Brown A, Xing C, Inventors. Nicotine salt formulations for aerosol devices and methods thereof. US patent U.S. Patent 9,215,8952015.

21 Jackler RK, Ramamurthi DJTc. Nicotine arms race: JUUL and the high-nicotine product market. 2019:tobaccocontrol-2018-054796.

22 Jeffrey Willett P, Morgane Bennett, MPH, Elizabeth C. Hair, PhD, Haijun Xiao, MS, Marisa Greenberg, MA, Emily Harvey, MA, Jennifer Cantrell, DrPH, and Donna Vallone, PhD, MPH. Recognition, use, and perceptions of JUUL among youth and young adults. *Tobacco control*. 2019.

23 Klass P. Helping Teenagers Quit Vaping. 2019; https://www.nytimes.com/2019/10/14/well/family/helping-teenagers-quit-vaping.html. Accessed October 21, 2019.

24 Gutierrez L. 'I was so naive': Student from JoCo tells of his vaping addiction. Will teens listen? 2019; https://www.kansascity.com/news/business/health-care/article235766207.html. Accessed October 21, 2019.

25 Strick K. E-cigarettes: time to realign our approach? *The Lancet*.

26 Centers for Disease Control and Prevention. Outbreak of Lung Illness Associated with Using E-cigarette Products. 2019; https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed November 8, 2019.

27 Gotts JE, Jordt S-E, McConnell R, Tarran RJB. What are the respiratory effects of e-cigarettes? 2019;366:l5275.

28 McKee M, Capewell SJB. Evidence about electronic cigarettes: a foundation built on rock or sand? 2015;351:h4863.

29 National Academies of Sciences E, Medicine. *Public health consequences of e-cigarettes*. National Academies Press; 2018.

30 Mishra VK, Kim K-H, Samaddar P, Kumar S, Aggarwal M, Chacko KJEER. Review on metallic components released due to the use of electronic cigarettes. 2017;22(2):131-140.

31 Jamal A. Tobacco Use Among Middle and High School Students — United States, 2011–2016. *MMWR Morb Mortal Wkly Rep*. 2017;66.

32 U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. In: General OotS, ed. Rockville, MD2016.

33 Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the Future national survey results on drug use, 1975-2018: Volume I, secondary school students. 2019; http://monitoringthefuture.org/pubs.html#monographs

34 Miech RA, Schulenberg, J. E., Johnston, L. D., Bachman, J. G., O'Malley, P. M., & Patrick, M. E. . National Adolescent Drug Trends in 2018. 2018; http://www.monitoringthefuture.org/data/18data.html#2018data-drugs. Accessed January 11, 2019.

35 U.s. Department of Health and Human Services. Trump Administration Combating Epidemic of Youth E-Cigarette Use with Plan to Clear Market of Unauthorized, Non-Tobacco-Flavored E-Cigarette Products. 2019; https://www.hhs.gov/about/news/2019/09/11/trump-administration-combating-epidemic-youth-ecigarette-use-plan-clear-market.html. Accessed October 2, 2019.

36 Cullen KA AB, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students — United States, 2011–2018. *MMWR Morb Mortal Wkly Rep*. 2018;67:1276–1277.

37 Arrazola RA, Neff LJ, Kennedy SM, Singh T, Holder-Hayes E, Jones C. Tobacco use among middle and high school students--United States, 2013 [published correction appears in MMWR Morb Mortal Wkly Rep. 2015 Aug 28;64(33):924]. MMWR Morb Mortal Wkly Rep. 2014;63(45):1021–1026. 2014.

38 Singh TJMM, report mw. Tobacco use among middle and high school students—United States, 2011–2015. 2016;65.

39 Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. *JAMA*. 2019.

40 Johnston LD OMP, Miech RA, Bachman JG, Schulenberg J 2014 Overview: Key Findings on Adolescent Drug Use. *Monitoring the Future: National Results on Adolescent Drug Use*. 2015.

41 US Department of Health Human Services. T*he health consequences of smoking—50 years of progress: a report of the surgeon general*. Citeseer;2014.

42 Berry KM, Fetterman JL, Benjamin EJ, et al. Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. 2019;2(2):e187794-e187794.

43 Marynak KL, Gammon DG, Rogers T, Coats EM, Singh T, King BA. Sales of Nicotine-Containing Electronic Cigarette Products: United States, 2015. (1541-0048 (Electronic)).

44 Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Trends in Adolescent Vaping, 2017–2019. *New England Journal of Medicine*. 2019;381(15):1490-1491.

45 Leventhal AM, Miech R, Barrington-Trimis J, Johnston LD, O'Malley PM, Patrick ME. Flavors of e-Cigarettes Used by Youths in the United States. *JAMA*. 2019.

46 Tsai J, Walton K, Coleman BN, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(6):196-200.

47 Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine & Tobacco Research*. 2015;17(7):847-854.

48 Food and Drug Administration. Modifications to Compliance Policy for Certain Deemed Tobacco Products. 2019; https://www.fda.gov/media/121384/download. Accessed September 11, 2019.

49 Marynak KL, Gammon DG, Rogers T, Coats EM, Singh T, King BAJAjoph. Sales of nicotine-containing electronic cigarette products: United States, 2015. 2017;107(5):702-705.

50 Nielsen. Tobacco "All Channel" Data Thru 7/13 - Cig Vol Declines Moderate. . In:2019.

51 Centers for Disease Control and Prevention. Surgeon General's Advisory on E-cigarette Use Among Youth. 2019; https://www.cdc.gov/tobacco/basic_information/e-cigarettes/surgeon-general-advisory/index.html. Accessed October 2, 2019.

52 Wang TW, Asman K, Gentzke AS, et al. Tobacco Product Use Among Adults - United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(44):1225-1232.

53 Dai H, Leventhal AM. Prevalence of e-Cigarette Use Among Adults in the United States, 2014-2018. *JAMA*. 2019.

54 Mirbolouk M, Charkhchi P, Kianoush S, et al. Prevalence and Distribution of E-Cigarette Use Among U.S. Adults: Behavioral Risk Factor Surveillance System, 2016Prevalence of E-Cigarette Use Among U.S. Adults. *Annals of Internal Medicine*. 2018;169(7):429-438.

55 McClelland E, Valentine N, McMillen R. *JUUL Awareness, Trial, and Continued Use among Undergraduate Students in Mississippi*. Vol 602019.

56 Barrington-Trimis JL, Urman R, Berhane K, et al. E-Cigarettes and Future Cigarette Use. *Pediatrics*. 2016.

57 Bold KW, Kong G, Camenga DR, et al. Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics*. 2018;141(1).

58 Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700-707.

59 Miech R, Patrick ME, O'Malley PM, Johnston LD. E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students. *Tobacco control*. 2017.

60 Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. (2168-6211 (Electronic)).

61 Unger JB, Soto DW, Leventhal A. E-cigarette use and subsequent cigarette and marijuana use among Hispanic young adults. (1879-0046 (Electronic)).

62 Wills TA, Knight R, Sargent JD, Gibbons FX, Pagano I, Williams RJ. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. *Tobacco control*. 2016.

63 National Center for Health Statistics. National Health Interview Survey 2018 Data Release internal calculation. In. Washington DC.

64 QuickStats: Cigarette Smoking Status Among Current Adult E-cigarette Users, by Age Group — National Health Interview Survey, United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(1177).

65 King JL, Reboussin D, Cornacchione Ross J, Wiseman KD, Wagoner KG, Sutfin EL. Polytobacco Use Among a Nationally Representative Sample of Adolescent and Young Adult E-Cigarette Users. *Journal of Adolescent Health*. 2018;63(4):407-412.

66 Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. 2017;171(8):788-797.

67 Kasza KA, Ambrose BK, Conway KP, et al. Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014. *The New England journal of medicine*. 2017;376(4):342-353.

68 Collins LK, Villanti AC, Pearson JL, et al. Frequency of Youth E-Cigarette, Tobacco, and Poly-Use in the United States, 2015: Update to Villanti et al., "Frequency of Youth E-Cigarette and Tobacco Use Patterns in the United States: Measurement Precision Is Critical to Inform Public Health". *Nicotine & Tobacco Research*. 2017;19(10):1253-1254.

69 Olfson M, Wall MM, Liu S-M, Sultan RS, Blanco C. E-cigarette Use Among Young Adults in the U.S. *American journal of preventive medicine*. 2019;56(5):655-663.

70 Kaplan SaR, Matt. Juul Closes Deal with Tobacco Giant Altria. *New York Times*. December 20, 2018, 2018.

71 Maloney JaL, Cara. Juul CEO Exits; Altria, Philip Morris End Talks in Vaping Fallout. 2019; https://www.wsj.com/articles/juul-ceo-kevin-burns-to-step-down-11569411372. Accessed October 22, 2019.

72 Willett JG, Bennett M, Hair EC, et al. Recognition, use and perceptions of JUUL among youth and young adults. *Tobacco control*. 2018:tobaccocontrol-2018-054273.

73 Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tobacco control*. 2019;28(2):146-151.

74 JUUL Labs. JUUL LABS NAMES NEW LEADERSHIP, OUTLINES CHANGES TO POLICY AND MARKETING EFFORTS. *JUUL Newsroom* 2019; https://newsroom.juul.com/juul-labs-names-new-leadership-outlines-changes-to-policy-and-marketing-efforts/.

75 Jackler R CC, Getachew B, Whitcomb M et al. JUUL Advertising Over its First Three Years on the Market. 2019; http://tobacco.stanford.edu/tobacco_main/publications/JUUL_Marketing_Stanford.pdf.

76 U.S. House Committee on Oversight and Reform. 2019; https://oversight.house.gov/sites/democrats.oversight.house.gov/files/JLI-HOR-00144802_Redacted.pdf.

77 U.S. House Committee on Oversight and Reform. Insightpool Research: Identifying Social Media Influencers From Email Subscriber List. 2019; https://oversight.house.gov/sites/democrats.oversight.house.gov/files/JLI-HOR-00169561_Redacted.pdf.

78 Caraballo RS, Shafer PR, Patel D, Davis KC, McAfee TA. Quit Methods Used by US Adult Cigarette Smokers, 2014-2016. *Preventing Chronic Disease*. 2017;14:E32.

79 Giovenco DP, Lewis MJ, Delnevo CD. Factors associated with e-cigarette use: a national population survey of current and former smokers. (1873-2607 (Electronic)).

80 Kalkhoran S, Grana RA, Neilands TB, Ling PM. Dual use of smokeless tobacco or e-cigarettes with cigarettes and cessation. (1945-7359 (Electronic)).

81 Kasza KA, Bansal-Travers M, O'Connor RJ, et al. Cigarette Smokers' Use of Unconventional Tobacco Products and Associations With Quitting Activity: Findings From the ITC-4 U.S. Cohort. *Nicotine & Tobacco Research*. 2014;16(6):672-681.

82 Ramo DE, Young-Wolff KC, Prochaska JJ. Prevalence and correlates of electronic-cigarette use in young adults: findings from three studies over five years. (1873-6327 (Electronic)).

83 Hartmann-Boyce J MH, Bullen C, Begh R, Stead LF, Hajek P. . Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews 2016*. 2016; CD010216(9).

84 Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. 2019;380(7):629-637.

85 Weaver SR, Huang J, Pechacek TF, Heath JW, Ashley DL, Eriksen MP. Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015–2016. *PloS one*. 2018;13(7):e0198047.

86 Farsalinos KE, Romagna G, Voudris V. Factors associated with dual use of tobacco and electronic cigarettes: A case control study. (1873-4758 (Electronic)).

87 Soneji SS, Knutzen KE, Villanti AC. Use of Flavored E-Cigarettes Among Adolescents, Young Adults, and Older Adults: Findings From the Population Assessment for Tobacco and Health Study. P*ublic Health Reports*. 2019;134(3):282-292.

88 Tang M-s, Wu X-R, Lee H-W, et al. Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. 2019:201911321.

89 Lee WH, Ong SG, Zhou Y, et al. Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell-Derived Endothelial Cells. *Journal of the American College of Cardiology.* 2019;73(21):2722-2737.

90 Jabba SV, Jordt S-EJJim. Risk Analysis for the Carcinogen Pulegone in Mint-and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. 2019.

91 Muthumalage T, Prinz M, Ansah KO, Gerloff J, Sundar IK, Rahman I. Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine. *Frontiers in Physiology.* 2017;8:1130.

92 Yasmeen M. Butt MLS, Henry D. Tazelaar, Laszlo T. Vaszar, Karen L. Swanson, Matthew J. Cecchini, Jennifer M. Boland, Melanie C. Bois, James H. Boyum, Adam T. Froemming, Andras Khoor, Isabel Mira-Avendano, Aiyub Patel, Brandon T. Larsen. Pathology of Vaping-Associated Lung Injury. 2019;New England Journal of Medicine.

93 Blount BC, Karwowski MP, Morel-Espinosa M, et al. Evaluation of Bronchoalveolar Lavage Fluid from Patients in an Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injury — 10 States, August–October 2019. MMWR Morb Mortal Wkly Rep. ePub: 8 November 2019. DOI: http://dx.doi.org/10.15585/mmwr.mm6845e2

94 Centers for Disease Control and Prevention. Outbreak of Lung Injury Associated with E-Cigarette Use, or Vaping. 2019; https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#recommendations-public, 2019.

95 Centers for Disease Control and Prevention. Outbreak of Lung Illness Associated with Using E-cigarette Products. 2019; https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed September 10, 2019.

96 U.S. Department of Health and Human Services. H*ow Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2010.

97 Kandel. A Molecular Basis for Nicotine as a Gateway Drug. *New England Journal of Medicine.* 2014;371(21):2038-2039.

98 Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *The New England journal of medicine.* 1994;331(2):123-125.

99 Suter MA, Abramovici AR, Griffin E, et al. In utero nicotine exposure epigenetically alters fetal chromatin structure and differentially regulates transcription of the glucocorticoid receptor in a rat model. *Birth Defects Research Part A: Clinical and Molecular Teratology.* 2015;103(7):583-588.

100 Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *The Journal of physiology.* 2015;593(16):3397-3412.

101 Bitzer ZT, Goel R, Reilly SM, et al. Emissions of free radicals, carbonyls, and nicotine from the NIDA Standardized Research Electronic Cigarette and comparison to similar commercial devices. 2018;32(1):130-138.

102 Govindarajan P, Spiller HA, Casavant MJ, Chounthirath T, Smith GAJP. E-cigarette and liquid nicotine exposures among young children. 2018;141(5):e20173361.

103 Chang JT, Wang B, Chang CM, Ambrose BKJIE. National estimates of poisoning events related to liquid nicotine in young children treated in US hospital emergency departments, 2013–2017. 2019;6(1):10.

104 Felberbaum M. FDA In Brief: FDA encourages continued submission of reports related to seizures following e-cigarette use as part of agency's ongoing scientific investigation of potential safety issue. 2019; https://www.fda.gov/news-events/fda-brief/fda-brief-fda-encourages-continued-submission-reports-related-seizures-following-e-cigarette-use. Accessed October 2, 2019.

105 Keller K. Ads for E-Cigarettes Today Hearken Back to the Banned Tricks of Big Tobacco. 2018; https://www.smithsonianmag.com/history/electronic-cigarettes-millennial-appeal-ushers-next-generation-nicotine-addicts-180968747/.

106 Pepper JK, Emery SL, Ribisl KM, Brewer NT. How U.S. Adults Find Out About Electronic Cigarettes: Implications for Public Health Messages. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2014.

107 Zhu SH, Gamst A, Lee M, Cummins S, Yin L, Zoref L. The Use and Perception of Electronic Cigarettes and Snus among the U.S. Population. *PloS one.* 2013;8(10):e79332.

108 Morris DS, Fiala SC. Online electronic cigarette retailers can do more to prevent accidental poisonings. *Tobacco control.* 2015;24(4):415-416.

109 Campaign for Tobacco-Free Kids. 7 ways e-cigarette companies are copying Big Tobacco's playbook (or 7 reasons FDA should quickly regulate e-cigarettes). 2013; http://www.tobaccofreekids.org/tobacco_unfiltered/post/2013_10_02_ecigarettes. Accessed November 8.

110 Kamerow D. Big Tobacco lights up e-cigarettes. *BMJ (Clinical Research Ed).* 2013;346:f3418.

111 Ayers JW, Ribisl KM, Brownstein JS. Tracking the rise in popularity of electronic nicotine delivery systems (electronic cigarettes) using search query surveillance. *American journal of preventive medicine.* 2011;40(4):448-453.

112 112. Paek HJ, Kim S, Hove T, Huh JY. Reduced harm or another gateway to smoking? source, message, and information characteristics of E-cigarette videos on YouTube. *Journal of health communication.* 2014;19(5):545-560.

113 Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. *Tobacco control*. 2013;22(2):103-106.

114 Cranwell J, Murray R, Lewis S, Leonardi-Bee J, Dockrell M, Britton J. Adolescents' exposure to tobacco and alcohol content in YouTube music videos. *Addiction (Abingdon, England)*. 2014.

115 Luo C, Zheng X, Zeng DD, Leischow S. Portrayal of electronic cigarettes on YouTube. *BMC public health*. 2014;14:1028.

116 Huang J, Kornfield R, Szczypka G, Emery SL. A cross-sectional examination of marketing of electronic cigarettes on Twitter. *Tobacco control*. 2014;23 Suppl 3:iii26-iii30.

117 Cantrell J, Ganz O, Emelle B, et al. Mobile marketing: an emerging strategy to promote electronic nicotine delivery systems. *Tobacco control*. 2017;26(e2):e1-e3.

118 FDA, FTC take action against companies misleading kids with e-liquids that resemble children's juice boxes, candies and cookies [press release]. Washington, DC: US Department of Health and Human Services,2018.

119 Pokhrel P, Fagan P, Herzog TA, et al. Social media e-cigarette exposure and e-cigarette expectancies and use among young adults. 2018;78:51-58.

120 Chu K-H, Colditz JB, Primack BA, et al. JUUL: spreading online and offline. 2018;63(5):582-586.

121 Lin X, Spence PR, Lachlan KAJCiHB. Social media and credibility indicators: The effect of influence cues. 2016;63:264-271.

122 Marynak K, Gentzke A, Wang TW, Neff L, King BA. Exposure to Electronic Cigarette Advertising Among Middle and High School Students—United States, 2014–2016. *Morbidity and Mortality Weekly Report*. 2018;67(10):294.

123 Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. 2019;28(2):146-151.

124 Burns K. JUUL LABS ACTION PLAN. 2018; https://newsroom.juul.com/2018/11/13/juul-labs-action-plan/, 2019.

125 Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tobacco control*. 2018;28:tobaccocontrol-2018.

126 Zhan Y, Etter J-F, Leischow S, Zeng DJJotAMIA. Electronic cigarette usage patterns: a case study combining survey and social media data. 2018;26(1):9-18.

127 Zhan Y, Zhang Z, Okamoto J, Zeng DD, Scott L. *Content Analysis of Reddit Messages about Underage JUUL Use (Preprint)*. 2018.

128 Kim AE, Chew R, Wenger M, et al. Estimated Ages of JUUL Twitter FollowersEstimated Ages of JUUL Twitter FollowersLetters. *JAMA Pediatrics*. 2019.

129 Phua J, Jin SV, Hahm JM. Celebrity-endorsed e-cigarette brand Instagram advertisements: Effects on young adults' attitudes towards e-cigarettes and smoking intentions. *Journal of Health Psychology*. 2017;23(4):550-560.

130 Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on new enforcement actions and a Youth Tobacco Prevention Plan to stop youth use of, and access to, JUUL and other e-cigarettes. 2018; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm605432.htm. Accessed April 26, 2019.

131 Ebay. Tobacco and smoking accessories policy. 2019; https://www.ebay.com/help/policies/prohibited-restricted-items/tobacco-smoking-accessories-policy?id=4273. Accessed April 26, 2019.

132 Wells Fargo Securities. *Nielsen: Tobacco "All Channel" Data. Equity Research*. San Francisco, CA: Wells Fargo Securitiess;2019.

133 Food and Drug Administration. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. 2016; https://www.federalregister.gov/articles/2016/05/10/2016-10685/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the. Accessed Jun 20, 2016.

134 Food and Drug Administration. FDA notifies Eonsmoke LLC to remove nearly 100 flavored electronic nicotine delivery system products from the market for not having required marketing authorization, among other violations. 2019; https://www.fda.gov/news-events/fda-brief/fda-brief-fda-notifies-eonsmoke-llc-remove-nearly-100-flavored-electronic-nicotine-delivery-system. Accessed October 24, 2019.

135 American Academy of Pediatrics. Federal Judge Rules FDA Acted Illegally in Delaying Required Review of E-Cigarettes, Cigars. 2019; https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/FDAECigReviewRuling.aspx. Accessed October 23, 2019.

136 Healey OoAGM. AG Healey Announces Investigation into JUUL, Other Online E-Cigarette Retailers Over Marketing and Sale to Minors. 2019; https://www.mass.gov/news/ag-healey-announces-investigation-into-juul-other-online-e-cigarette-retailers-over-marketing. Accessed October 22, 2019.

137 Paul J. Colorado's attorney general will investigate whether Juul marketed to kids, misled on smoking cessation. 2019; https://coloradosun.com/2019/09/18/colorado-juul-investigation-vaping-attorney-general/. Accessed October 22, 2019.

138 Brone A. Connecticut investigating Juul Labs over health claims, marketing. 2019; https://www.courant.com/news/connecticut/hc-news-attorney-general-juul-investigation-20190731-jq4grrl2kzdd5notsuctp2njru-story.html. Accessed October 22, 2019.

139 Press A. E-cigarette maker Juul facing mounting scrutiny by state AGs. 2019; https://www.latimes.com/business/story/2019-08-30/e-cigarette-maker-juul-facing-mounting-scrutiny. Accessed October 22, 2019.

140 Maloney J. Federal Prosecutors Conducting Criminal Probe of Juul. 2019; https://www.wsj.com/articles/federal-prosecutors-conducting-criminal-probe-of-juul-11569268759. Accessed October 22, 2019.

141 Sheeler A. E-cigarette-maker Juul agrees to avoid targeting minors amid wave of vaping illnesses. 2019; https://www.sacbee.com/news/local/health-and-medicine/article236319588.html. Accessed October 22, 2019.

142 U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on advancing new policies aimed at preventing youth access to, and appeal of, flavored tobacco products, including e-cigarettes and cigars. 2019; https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-advancing-new-policies-aimed-preventing-youth-access. Accessed May 8, 2019.

143 Campaign for Tobacco-Free Kids. STATES & LOCALITIES THAT HAVE RESTRICTED THE SALE OF FLAVORED TOBACCO PRODUCTS. 2019; https://www.tobaccofreekids.org/assets/factsheets/0398.pdf.

144 2016: ACS 5-Year Estimates Data Profiles. In: US Census Bureau, ed. internal calculation ed2019.

145 Whitmer TOoGG. Governor Whitmer Takes Bold Action to Protect Michigan Kids from Harmful Effects of Vaping. 2019; https://www.michigan.gov/whitmer/0,9309,7-387-90499_90640-506450--,00.html. Accessed October 22, 2019.

146 Bullock MGS. Governor Bullock Directs Ban on Flavored E-Cigarettes to Address Public Health Emergency. 2018; http://governor.mt.gov/Pressroom/governor-bullock-directs-ban-on-flavored-e-cigarettes-to-address-public-health-emergency. Accessed October 22, 2019.

147 State NY. Governor Cuomo Announces Emergency Executive Action to Ban the Sale of Flavored E-Cigarettes. 2019; https://www.governor.ny.gov/news/governor-cuomo-announces-emergency-executive-action-ban-sale-flavored-e-cigarettes. Accessed October 22, 2019.

148 Office Gs. Governor Brown Issues Temporary Ban on Flavored Vaping Products, Convenes Vaping Public Health Workgroup. 2019; https://www.oregon.gov/newsroom/Pages/NewsDetail.aspx?newsid=3448. Accessed October 22, 2019.

149 1Raimondo GM. Protecting Rhode Island Youth Against the Harms of Vaping. 2019; http://www.governor.ri.gov/documents/orders/Executive-Order-19-09.pdf. Accessed October 22, 2019.

150 Inslee WGJ. Inslee issues executive order to change how state will regulate vaping industry in light of recent health crisis. 2019; https://www.governor.wa.gov/news-media/inslee-issues-executive-order-change-how-state-will-regulate-vaping-industry-light-recent. Accessed October 22, 2019.

151 Singh K. New York court blocks state ban on flavored e-cigarettes. 2019; https://www.reuters.com/article/us-health-vaping-new-york/new-york-court-blocks-state-ban-on-flavored-e-cigarettes-idUSKBN1WJ0IK. Accessed October 22, 2019.

152 The Office of Governor Gretchen Whitmer. Governor Whitmer to Seek Supreme Court Ruling to Protect Michigan Kids, Public Healt. 2019; https://www.michigan.gov/whitmer/0,9309,7-387-90499_90640-510074--,00.html. Accessed October 22, 2019.

153 Peel S. Oregon Court of Appeals Blocks Flavored Vaping Ban for Nicotine-Containing Vapes. 2019; https://www.wweek.com/news/state/2019/10/17/oregon-court-of-appeals-blocks-flavored-vaping-ban/. Accessed October 22, 2019.

154 Mass.gov. Guide Vaping Public Health Emergency. 2019; https://www.mass.gov/guides/vaping-public-health-emergency. Accessed October 22, 2019.

155 Raymond N. Massachusetts vaping sales ban can stand but needs fixes: judge. 2019; https://www.reuters.com/article/us-health-vaping-massachusetts/judge-orders-massachusetts-to-redo-parts-of-vaping-ban-idUSKBN1X01SL. Accessed October 22, 2019.

156 Health UDo. Emergency Rule to Address Vaping-related Illnesses. 2019; https://health.utah.gov/featured-news/emergency-rule-to-address-vaping-related-illnesses. Accessed October 22, 2019.

157 HHS Secretary Alex Azar: FDA will finalize new e-cigarette rules. CNBC Television 2019; https://www.youtube.com/watch?v=U0DQUS8XVk0.

158 Public Health Law Center. States with Laws Requiring Licenses for Retail Sales of E-Cigarettes. 2019; https://www.publichealthlawcenter.org/sites/default/files/States-with-Laws-Requiring-Licenses-for-Retail-Sales-of-ECigarettes-June152019.pdf. Accessed October 2, 2019.

159 Food and Drug Administration. FDA warns JUUL Labs for marketing unauthorized modified risk tobacco products, including in outreach to youth. 2019; https://www.fda.gov/news-events/press-announcements/fda-warns-juul-labs-marketing-unauthorized-modified-risk-tobacco-products-including-outreach-youth. Accessed October 22, 2019.

160 Food and Drug Administration. *Transcript for FDA's media briefing on electronic cigarettes. Moderator: Judy Leon. July 22, 2009. 1:30 pm CT*. 2009.

161 Tobacco Control Legal Consortium. U.S. E-Cigarette Regulation: A 50-State Review. 2017; http://www.publichealthlawcenter.org/resources/us-e-cigarette-regulations-50-state-review.

162 Food and Drug Administration. FDA's Plan for Tobacco and Nicotine Regulation. 2017; https://www.fda.gov/TobaccoProducts/NewsEvents/ucm568425.htm.

163 Public Health Law Center. States with Laws Restricting Youth Access to E-Cigarettes. 2019; https://www.publichealthlawcenter.org/sites/default/files/States-with-Laws-Restricting-Youth-Access-to-ECigarettes-June152019.pdf. Accessed October 2, 2019.

164 Williams RS, Derrick J, Liebman AK, LaFleur K, Ribisl KM. Content analysis of age verification, purchase and delivery methods of internet e-cigarette vendors, 2013 and 2014. *Tobacco control.* 2018;27(3):287.

165 Family Smoking Prevention and Tobacco Control Act. In. *Public Law No: 111-31.* Vol HR 12562009.

166 Campaign for Tobacco-Free Kids. States and Localities that have Raised the Minimum Legal Sales Age for Tobacco Products to 21. 2019; https://www.tobaccofreekids.org/assets/content/what_we_do/state_local_issues/sales_21/states_localities_MLSA_21.pdf.

167 Institute for Global Tobacco Control. Country Laws Regulating E-cigarettes: A Policy Scan 2018; https://www.globaltobaccocontrol.org/e-cigarette/country-laws/view. Accessed October 2, 2019.

168 European Commission. Electronic cigarettes. https://ec.europa.eu/health/tobacco/ecigarettes_en.

169 Kennedy RD, Awopegba A, De Leon E, Cohen JE. Global approaches to regulating electronic cigarettes. T*obacco control.* 2017;26(4):440-445.

170 Johns Hopkins Bloomberg School of Public Health Institute for Global Tobacco Control. Country Laws Regulating E-cigarettes.http://globaltobaccocontrol.org/e-cigarette/country-laws-regulating-e-cigarettes.

171 Public Health England. Press release: PHE publishes independent expert e-cigarettes evidence review. February 6, 2018; https://www.gov.uk/government/news/phe-publishes-independent-expert-e-cigarettes-evidence-review.

172 Public Health England. Evidence review of e-cigarettes and heated tobacco products 2018: executive summary. March 2, 2018; https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review/evidence-review-of-e-cigarettes-and-heated-tobacco-products-2018-executive-summary.

173 Miles T. WHO says e-cigarettes, 'smoke-free' products do not help reduce cancer. 2019; https://www.reuters.com/article/us-health-tobacco/who-says-e-cigarettes-smoke-free-products-do-not-help-reduce-cancer-idUSKCN1UL29C. Accessed October 22, 2019.

174 World Health Organization. WHO report on the global tobacco epidemic 2019. 2019; https://www.who.int/tobacco/global_report/en/. Accessed October 22, 2019.

truth initiative®

INSPIRING TOBACCO-FREE LIVES

900 G Street, NW
Fourth Floor
Washington, DC 20001
202.454.5555

truthinitiative.org
/truthinitiative
@truthinitiative

THE TIMES

EU ruling on vaping and addiction to tobacco

February 18 2016, 12:01am, The Times
https://www.thetimes.co.uk/article/eu-ruling-on-vaping-and-addiction-to-tobacco-x5zv75d28

Sir,
Matt Ridley's analysis and conclusion concerning e-cigarettes must not be allowed to go unchallenged ("Threat to vaping is a backward step for UK", Feb 15).

Although we share the hope that vaping might provide a safer alternative to conventional tobacco smoking, the statement by Public Health England (which Ridley quotes) that vaping is 95 per cent safer than [tobacco] smoking is **groundless. We, and others, have shown that there is insufficient scientific evidence of an acceptable quality or quantity, or relevance and reliability, to permit an objective and meaningful risk assessment.**
Also, it is known that, in addition to nicotine, e-cigarette vapour contains a number of harmful chemicals at potentially significant levels.

The human respiratory system is a delicate vehicle, on which the length and quality of our lives depend. For governments and companies to condone, or even suggest, the regular and repeated inhaling of a complex mixture of chemicals with addictive and toxic properties, but without comprehensive data, is irresponsible and could have serious consequences.

Far from "*leading the way*, with more people having quit smoking by taking up vaping than in other countries", **there is a danger that Britain may be laying the foundations for a public health disaster, albeit one that may not become apparent for decades**. Only one piece of advice is worth giving: quit smoking anything.

Michael Balls
Emeritus professor of medical cell biology, University of Nottingham

Dr Robert Combes
Independent consultant in toxicology

The debate on electronic cigarettes

We were surprised to read in *The Lancet* (Nov 1, p 1576),[1] Lorien Jollye's criticisms of the public health community for, as she alleges, insulting and ignoring the supporters of electronic cigarettes (e-cigarettes). A recent *Lancet*–London School of Hygiene & Tropical Medicine Global Health Lab (held in London, on Nov 4, 2014) debating the tobacco endgame, that was widely advertised, was an opportunity to engage on this issue. Yet rather than put forward their arguments, advocates of e-cigarettes instead chose to remain silent in the lecture theatre while insulting the participants on twitter. Two things are now clear. First, the advocates of e-cigarettes seem only willing to engage on their own terms. Second, anyone with the temerity to suggest that e-cigarettes are anything other than the game changing solution to the problem of tobacco will be subject to grossly offensive attacks,[2] with growing evidence that these are being orchestrated.[3] One recent example, a tweet directed at two of us, contained a picture of a noose with the caption "your days are numbered". The public health community has listened, but it has also systematically reviewed the evidence.[4] Numerous national and international organisations have reached the conclusion that it is possible that these products might help some people who are heavily addicted to nicotine but there are many very serious concerns about their effectiveness, safety, and potential to renormalise smoking.[5] Moreover, there are real concerns that they are introducing non-smoking adolescents to nicotine addiction,[6] so it is certainly premature to encourage their use. However, the very effective campaign waged by their supporters has ensured that other measures of known effectiveness have almost disappeared from the debate on tobacco control.

We declare no competing interests.

*Martin McKee, Simon Chapman, Mike Daube, Stanton Glantz
martin.mckee@lshtm.ac.uk

European Centre on Health of Societies in Transition, London School of Hygiene & Tropical Medicine, WCIE 7HT London, UK (MM); Sydney School of Public Health, University of Sydney, Sydney, Australia (SC); Curtin University, Perth, Australia (MD); and Center for Tobacco Control Research and Education, University of California, San Francisco, CA, USA (SG)

1 Jollye L. E-cigarettes in the UK: a more inclusive debate is needed. *Lancet* 2014; **384:** 1576.
2 Mills D. Opponents of e-cigarettes bombarded with abusive 'four-letter emails starting with C and F' in bitter row with online cult groups. http://www.dailymail.co.uk/news/article-2656160/Health-campaigners-receiving-incredibly-abusive-emails-bitter-row-alternative-smoking.html (accessed Nov 27, 2014).
3 Harris JK, Moreland-Russell S, Choucair B, et al.Tweeting for and against public health policy: response to the Chicago Department of Public Health's electronic cigarette twitter campaign. *J Med Internet Res* 2014; **16:** e238.
4 Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation* 2014; **129:** 1972–86.
5 de Andrade M, Hastings G, Angus K. Promotion of electronic cigarettes: tobacco marketing reinvented? *BMJ* 2013; **347:** f7473.
6 Dutra LM, Glantz SA. High international electronic cigarette use among never smoker adolescents. *J Adolesc Health* 2014; **55:** 595–97.

Prevalence of overweight and obesity in children and adults

The global burden of overweight and obesity study by Marie Ng and colleagues (Aug 30, p 766)[1] will be crucial to drive political change. We emphasise two important additional steps in global obesity surveillance to inform action.

First, obesity trends should be reported stratified by socioeconomic position. A socioeconomic gradient in obesity has been reported in most developed countries; greater prevalence of overweight and obesity is seen in more disadvantaged groups.[2] Although levelling off of the obesity epidemic has been reported in some countries, preliminary evidence suggests that this has not been shared across all socioeconomic levels.[3] Obesity is one of the few preventable risk factors with increasing prevalence worldwide. Reduction of socioeconomic inequalities in obesity is an opportunity to reduce future social disparities in health. Routine monitoring of obesity trends by socioeconomic position should be introduced to make inequalities central to policy making.


B Boissonnet BSIP/Science Photo Library

Second, the composition of the obese population should be described with respect to the degree of severity. During the past three decades, increases have been reported in overall obesity prevalence, with the largest increases in the most severe obesity subgroups.[4,5] Consequently, cases of severe obesity (body mass index [BMI] more than 35 kg/m^2) account for an increasingly large proportion of the obese population over time. One in seven Americans are now severely obese, and the total obesity prevalence is 35% in the USA.[6] Severe obesity is associated with greater adverse consequences than mild obesity (BMI between 30·0 and 34·9 kg/m^2). Monitoring trends in the severity composition of the obese population is essential to predict the associated disease burden and inform options for intervention.

We declare no competing interests.

*Catherine Keating, Kathryn Backholer, Anna Peeters
catherine.keating@bakeridi.edu.au

Obesity and Population Health, Baker IDI Heart and Diabetes Institute, Melbourne VIC 3004, Australia (CK, KB, AP); and Deakin Health Economics, Deakin University, Melbourne VIC, Australia (CK)

1 Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384:** 766–81.
2 Devaux M, Sassi F. Social inequalities in obesity and overweight in 11 OECD countries. *Eur J Public Health* 2013; **23:** 464–69.
3 Rokholm B, Baker JL, Sorensen TI. The levelling off of the obesity epidemic since the year 1999—a review of evidence and perspectives. *Obes Rev* 2010; **11:** 835–46.
4 Sturm R. Increases in morbid obesity in the USA: 2000–2005. *Public Health* 2007; **121:** 492–96.

E-cigarettes: Public Health England's evidence-based confusion

Last week, Public Health England (PHE) reported what it described as a "landmark review" of evidence about e-cigarettes. The headline in their press release quoted their top-line finding—"E-cigarettes around 95% less harmful than tobacco". Kevin Fenton, Director of Health and Wellbeing at PHE, commented that, "E-cigarettes are not completely risk free but when compared to smoking, evidence shows they carry just a fraction of the harm". Indeed, the 95% figure was widely picked up in news media. The BBC, for example, reported with certainty that "E-cigarettes are 95% less harmful than tobacco". So what was the allegedly "game-changing" evidence that e-cigarettes are so safe?

In the "evidence update" published by PHE, written by Ann McNeill (King's College London) and Peter Hajek (Queen Mary University of London), the safety of e-cigarettes "in the light of new evidence" is summarised in this way: "While vaping may not be 100% safe, most of the chemicals causing smoking-related disease are absent and the chemicals that are present pose limited danger. It had previously been estimated that EC [e-cigarettes] are around 95% safer than smoking (10, 146). This appears to remain a reasonable estimate." The headline conclusion of the PHE report was a judgment relying on two references from 2014. One (reference 146) was a briefing report to the UK All-Party Parliamentary Group on Pharmacy. The other (reference 10) was a paper by David Nutt and colleagues published in *European Addiction Research*. It is from this paper that the 95% figure derives. McNeill and Hajek are clear about the importance of this work: "There is a need to publicise the current best estimate that using EC is around 95% safer than smoking." PHE immediately acted on this recommendation. But with undue haste.

It is worth reading the paper on which PHE has based its latest advice carefully. Nutt and colleagues describe how the Independent Scientific Committee on Drugs, which Nutt founded in 2010, convened an international expert panel to consider the "relative importance of different types of harm related to the use of nicotine-containing products". During a two-day workshop in July, 2013, the panel met in London to review the context of perceived harms from nicotine products, the range of products (including "electronic nicotine delivery system products"), and the criteria of harms. The group scored the products for harm, and weightings were applied to the results. Based on the opinions of this group, cigarettes were ranked as the most harmful nicotine product with a score of 99·6. E-cigarettes were estimated to have only 4% of the maximum relative harm. It is this result that yields the "95% less harmful" figure reported last week.

But neither PHE nor McNeill and Hajek report the caveats that Nutt and colleagues themselves emphasised in their paper. First, there was a "lack of hard evidence for the harms of most products on most of the criteria". Second, "there was no formal criterion for the recruitment of the experts". In other words, the opinions of a small group of individuals with no prespecified expertise in tobacco control were based on an almost total absence of evidence of harm. It is on this extraordinarily flimsy foundation that PHE based the major conclusion and message of its report.

The study led by Nutt was funded by Euroswiss Health and Lega Italiana Anti Fumo (LIAF). Riccardo Polosa, one of the authors of the Nutt paper, is the Chief Scientific Advisor to LIAF. In the paper, he reports serving as a consultant to Arbi Group Srl, an e-cigarette distributor. His research on e-cigarettes is currently supported by LIAF. Another author reports serving as a consultant to manufacturers of smoking cessation products. The editors of the journal added a note at the end of the paper warning readers about the "potential conflict of interest" associated with this work.

Tobacco is the largest single cause of preventable deaths in England—e-cigarettes may have a part to play to curb tobacco use. But the reliance by PHE on work that the authors themselves accept is methodologically weak, and which is made all the more perilous by the declared conflicts of interest surrounding its funding, raises serious questions not only about the conclusions of the PHE report, but also about the quality of the agency's peer review process. PHE claims that it protects and improves the nation's health and wellbeing. To do so, it needs to rely on the highest quality evidence. On this occasion, it has fallen short of its mission. ■ *The Lancet*

Charles Platiau/Reuters/Corbis

For the **Public Health England report** see https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update

Experts criticise Public Health England e-cigarettes review

theguardian.com/society/2015/sep/15/experts-criticise-public-health-england-e-cigarettes-review

Press Association

September 15, 2015

Claims by a government-funded agency that e-cigarettes are 95% less harmful than smoking arose from a meeting of 12 people, some with links to the tobacco industry, researchers have said.

Experts writing in the British Medical Journal (BMJ) joined the Lancet in criticising the evidence used by Public Health England (PHE) in its report on e-cigarettes.

PHE published the "landmark" report last month, describing it as a "comprehensive review of the evidence". But several researchers have questioned the robustness of the data and pointed to links between some experts and the tobacco industry.

An editorial in the Lancet medical journal last month attacked the "extraordinarily flimsy foundation" on which PHE based its main conclusion. Writing in the BMJ, two further researchers have questioned whether the claims were "built on rock or sand".

Martin McKee, professor of European public health at the London School of Hygiene and Tropical Medicine, and Simon Capewell, professor of clinical epidemiology at the University of Liverpool, said: "A fundamental principle of public health is that policies should be based on evidence of effectiveness."

They said the public would expect PHE's claims that "the current best estimate is that e-cigarettes are around 95% less harmful than smoking" would be based on a detailed review of evidence and modelling.

"In fact, it comes from a single meeting of 12 people convened to develop a multi-criteria decision analysis (MCDA) model to synthesise their opinions on the harms associated with different nicotine-containing products; the results of the meeting were summarised in a research paper."

McKee and Capewell said one sponsor of the meeting was a company called EuroSwiss Health, whose chief executive was reported to have previously received funding from British American Tobacco for an independent study. He also endorsed BAT's public health credentials in a sustainability report, they said.

One of the 12 people at the meeting declared funding from an e-cigarette manufacturer but not the funding he was reported to have received previously from the tobacco company Philip Morris International, they added.

"The rationale for selecting the members of the panel is not provided, but they include several known e-cigarette champions, some of whom also declare industry funding in the paper. Some others present at the meeting are not known for their expertise in

tobacco control. The meeting was also attended by the tobacco lead at PHE."

The research paper produced by the group "tellingly concedes" there is a lack of "hard evidence for the harms of most products on most of the criteria", McKee and Capewell wrote. "However, none of these links or limitations are discussed in the PHE report."

McKee and Capewell said PHE's claims that "there is no evidence so far that e-cigarettes are acting as a route into smoking for children or non-smokers" were premature.

Prof Kevin Fenton, director of health and wellbeing at PHE, said the claims in the BMJ had been responded to before. He said: "E-cigarettes are significantly less harmful than smoking. One in two lifelong smokers dies from their addiction. All of the evidence suggests that the health risks posed by e-cigarettes are small by comparison, but we must continue to study the long-term effects.

"PHE has a clear duty to inform the public about what the evidence shows and what it does not show, especially when there was so much public confusion about the relative dangers compared to tobacco.

"Nearly 80,000 people a year die of a smoking-related illness and smoking costs the NHS £2bn a year. By spelling out clearly the current evidence – that while e-cigarettes are not risk-free, they carry only a fraction of the harm caused by smoking – we are fulfilling our national remit."

Vaping: e-cigarettes safer than smoking, says Public Health England

theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking

James Meikle

August 19, 2015

Vaping is safer than smoking and could lead to the demise of the traditional cigarette, Public Health England (PHE) has said in the first official recognition that e-cigarettes are less damaging to health than smoking tobacco.

The health body concluded that, on "the best estimate so far", e-cigarettes are about 95% less harmful than tobacco cigarettes and could one day be dispensed as a licensed medicine in an alternative to anti-smoking products such as patches.

Relative harm

While stressing that e-cigarettes are not free from risk, PHE now believes that e-cigarettes "have the potential to make a significant contribution to the endgame for tobacco".

The message was backed by the government's chief medical officer, Dame Sally Davies, who nevertheless cautioned that "there continues to be a lack of evidence on the long-term use of e-cigarettes". She said they should only be used as a means to help smokers quit.

"I want to see these products coming to the market as licensed medicines. This would provide assurance on the safety, quality and efficacy to consumers who want to use these products as quitting aids, especially in relation to the flavourings used, which is where we know least about any inhalation risks."

The 111-page review raises concerns about the length and cost of the the government's licensing process, which is a key part of the revised strategy to cut tobacco use.

No e-cigarettes have yet been licensed, unlike other nicotine-replacement therapies such as gums, lozenges and patches. Pilot schemes in Leicester and the City of London allow stop-smoking specialists to offer free e-cigarette starter kits, but smokers elsewhere cannot be offered e-cigarettes on prescription.

The Medicines and Healthcare Products Regulatory Agency began its work in this area more than two years ago, and manufacturers have complained that it costs them millions to go through the process.

Jane Ellison, the public health minister in England, reminded smokers that the best thing they could do to avoid falling victim to the country's number one killer was to quit completely.

“Although we recognise the e-cigarettes may help adults to quit, we still want to protect children from the dangers of nicotine, which is why we have made it illegal for under-18s to buy them,” she said.

The review found that almost all of the 2.6 million adults in the UK now thought to be using e-cigarettes are current or former conventional smokers, most using them to help them quit tobacco or to prevent them going back to smoking.

There was no suggestion that the products were a gateway into tobacco smoking, with less than 1% of adults or young people who had never smoked becoming regular cigarette users.

The PHE decision comes after carefully choreographed moves by anti-tobacco campaigners and public health specialists to help move the NHS towards offering better smoking cessation support and to be less negative about e-cigarettes.

Services are being urged to follow those in the north-east of England in offering behavioural support to those wanting to quit tobacco and using e-cigarettes to try to do so.

Smoking kills about 100,000 people a year in the UK, most of those in England where there are thought to be eight million tobacco users. But official figures suggest smoking is now at its lowest prevalence since records started in the 1940s.

Rates are highest in many of the most deprived areas of England, and getting smokers off tobacco is increasingly seen as one of the best ways of reducing health inequalities.

Worryingly for many of those behind the policy change, increasing numbers of people – up to 22%, compared with 8% two years ago – think e-cigarettes are equally or more harmful than tobacco. This is leading some smokers to avoid switching, studies have suggested.

Tobacco reduction campaigners say the public needs to be educated to recognise that although e-cigarettes, like tobacco cigarettes, contain addictive nicotine, they do not contain more dangerous chemicals such as tar and arsenic.

PHE is also advocating careful monitoring of the e-cigarette market, particularly of companies closely involved with or part of big tobacco companies. It says the government must meet its obligations “to protect public health policy from commercial and other vested interests of the tobacco industry”.

Kevin Fenton, director of health and wellbeing at PHE, said: “E-cigarettes are not completely risk-free but when compared to smoking, evidence shows they carry just a fraction of the harm.

“The problem is people increasingly think they are at least as harmful and this may be keeping millions of smokers from quitting. Local stop-smoking services should look to support e-cigarette users in their journey to quitting completely.”

Peter Hajek, of Queen Mary University, London, one of the independent authors of the review, said: “My reading of the evidence is that smokers who switch to vaping remove almost all the risks smoking poses to their health. Smokers differ in their needs and I would advise them not to give up on e-cigarettes if they do not like the first one they try. It may take some experimentation with different products and e-liquids to find the right one.”

Ecita, a trade association of e-cigarette manufacturers, said: “There could be huge long-term benefits to taxpayers and the NHS as well as to former smokers and their families. The proposed ban in public places across Wales is very worrying, as are many of the bans in pubs and restaurants across the UK. This appears to be driving a growing number of people to think the harm is the same, deterring smokers from moving to e-cigarettes, and damaging public health.”

The smokers group Forest questioned whether prescribing e-cigarettes on the NHS would be a justifiable use of taxpayers’ money. Simon Clark, its director, said promoting them “as a state-approved smoking cessation aid ignores the fact that many people enjoy vaping in its own right and use e-cigs as a recreational not a medicinal product.”

He said e-cigarettes had been successful because the consumer, not the state, was in charge. “If they want more smokers to switch to e-cigarettes, public health campaigners should embrace consumer choice and oppose unnecessary restrictions on the sale, marketing and promotion of this potentially game-changing product.”

The switch in policy towards e-cigarettes coincided with publication in the Journal of the American Medical Association of research from Los Angeles suggesting that high school students who had use e-cigarettes are more likely to go on to try tobacco.

But Hajek said this did not show that vaping leads to smoking. “It just shows that people who are attracted to e-cigarettes are the same people who are attracted to smoking. People who drink white wine are more likely to try red wine than people who do not drink alcohol.”

BMJ 2015;351:h4863 doi: 10.1136/bmj.h4863 (Published 15 September 2015)

ANALYSIS

Evidence about electronic cigarettes: a foundation built on rock or sand?

Public Health England recently endorsed the use of e-cigarettes as an aid to quitting smoking. **Martin McKee** and **Simon Capewell** question the evidence on safety and efficacy underpinning the recommendations

Martin McKee *professor of European public health*[1], Simon Capewell *professor of clinical epidemiology*[2]

[1]London School of Hygiene and Tropical Medicine, London WC1H 9SH, UK; [2]Department of Public Health and Policy, Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK

Those responsible for safeguarding the health of the public must often tackle complex and controversial issues. Public Health England (PHE) has been courageous in entering the debate on the role of electronic cigarettes in tobacco control. In a new report it concludes that e-cigarettes are much safer than conventional cigarettes,[1] and one of its author is quoted as describing them as a potential "game changer" in tobacco control.[2] Media coverage suggests that the debate is now over, with a BBC correspondent describing the evidence as "unequivocal."[2] However, although British organisations such as the Royal College of Physicians of London[3] and ASH UK,[4] have endorsed some of the report's conclusions, albeit with caveats, many others have come to the opposite opinion. These include the British Medical Association, the UK Faculty of Public Health, the US Centers for Disease Control and Prevention, the American Lung Association, the World Health Organization,[5] the European Commission,[6] and other leading international health bodies.[7] The available evidence about e-cigarettes suggests that the debate is far from over and questions remain about their benefits and harms.

Defining the role of e-cigarettes

Fundamental divisions seem to exist between those engaged in this debate. Supporters of e-cigarettes focus narrowly on existing smokers, comparing the devices' effects with those of smoking conventional cigarettes. As well as being an aid to quitting, e-cigarettes are seen as having a role for people who do not want to quit, offering a safer substitute for some of the cigarettes they would otherwise smoke.

Meanwhile, those on the other side of the debate express concern about uptake of e-cigarettes among people, especially children and adolescents, who would not otherwise smoke and about their long term health effects. They argue that although e-cigarettes do not contain some of the most harmful substances found in conventional cigarettes, such as tar, they do contain other substances such as formaldehyde (a carcinogen) and diverse flavourings. Thus, it is equally important to include non-smoking as a comparator. They also draw attention to important epidemiological evidence that contrary to what is widely believed, reduced smoking (as opposed to quitting) may not reduce overall risk of death.[8] The expression "dual use," which acknowledges that two thirds of e-cigarette users also smoke, rarely occurs in the PHE report. Although some dual use is inevitable during the quitting process, if this persists long term health concerns remain. A recent cohort study by McNeill and colleagues showed that dual use among daily "vapers" apparently remained above 80% after 12 months follow-up, which is worrying.[9]

Quality of the evidence

A fundamental principle of public health is that policies should be based on evidence of effectiveness. So does the available evidence show clearly that e-cigarettes are as effective as established quitting aids? Unfortunately not. The recent Cochrane review is widely cited,[10] but it included only two randomised controlled trials, both with important limitations, and concluded that the evidence was of "low or very low quality by GRADE standards." The PHE report authors concede the weakness of the evidence, noting how a single observational study with substantial limitations offers "some of the best evidence to date on the effectiveness of e-cigarettes for use in quit attempts."

Where there is uncertainty about risks, the precautionary principle should apply. Thus, in the absence of scientific consensus that the substance is not harmful to the public, the burden of proof that it is not harmful falls on those taking an action. The quality of the evidence cited by PHE therefore becomes crucial. The headline message from the PHE report, widely quoted in the media, is that "best estimates show

Correspondence to: M McKee martin.mckee@lshtm.ac.uk

e-cigarettes are 95% less harmful to your health than normal cigarettes," seemingly leaving little room for uncertainty about long term risks. Yet a recent systematic review,[11] which the PHE report surprisingly fails to cite, came to a different conclusion. It found serious methodological problems in many of the 76 studies it reviewed, and one third of the studies (34%) were published by authors with conflicts of interest. The systematic review also expressed concern about the effects of various substances in e-cigarettes, some but not all of which are also found in conventional cigarettes. It concluded that "due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of e-cigarettes. However, they can hardly be considered harmless."

We might also expect that the prominently featured "95% less harmful" figure was based on a detailed review of evidence, supplemented by modelling. In fact, it comes from a single meeting of 12 people convened to develop a multicriteria decision analysis (MCDA) model to synthesise their opinions on the harms associated with different nicotine containing products; the results of the meeting were summarised in a research paper.[12] The authors state: "The sponsor of the study had no role in any stage of the MCDA process or in the writing of this article, and was not present at the workshop." However, given the importance of complete transparency in an area as controversial as this, it is legitimate to ask about the sponsors. One is a company called EuroSwiss Health.[13] An internet search reveals little about its activities other than that it funded the meeting, but it is one of several companies registered at the same address in a village outside Geneva with the same chief executive. He is reported to have previously received funding from British American Tobacco (BAT)[14] for writing a book on nicotine as a means of harm reduction,[15] although the book states that "the statements, findings, conclusions and recommendations contained in the book were developed independently of BAT." He also endorsed BAT's public health credentials in its 2013 sustainability report.[16]

The paper also acknowledges support from Lega Italiana Anti Fumo (Italian Anti-Smoking League), whose chief scientific adviser was one of the 12 people attending the meeting. He declares funding from an e-cigarette manufacturer but not the funding he is reported elsewhere to have received previously from tobacco company Philip Morris International.[17] The rationale for selecting the members of the panel is not provided, but they include several known e-cigarette champions, some of whom also declare industry funding in the paper.[12] Some others present at the meeting are not known for their expertise in tobacco control. The meeting was also attended by the tobacco lead at PHE. Furthermore, their paper tellingly concedes that "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria." However, none of these links or limitations are discussed in the PHE report.

Uncertainty around harms

The PHE report asserts that the available evidence suggests that e-cigarettes are not currently re-normalising smoking among children and young people in the UK. However, this remains a major concern for health professionals and parents. In England, experimentation with e-cigarettes among young people is worrying high, with over one fifth of 11-15 year olds having ever used e-cigarettes[18]; 73% of the young people surveyed who had tried e-cigarettes were non-smokers. Uptake of e-cigarettes among young non-smokers is a particular concern, given that nicotine use in young people may disrupt brain development with long term, irreversible consequences for brain function.[19] The authors categorically dismiss the possibility that e-cigarettes may be a gateway to smoking, arguing that even the concept of a children's gateway should be rejected. This view seems premature, particularly given recently emerging evidence[20] such as an American study, published after the PHE report, which concluded that "those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year."[21] Furthermore, none of the research so far can be considered conclusive, and longer term studies are needed.

Evidence on the risk of e-cigarette aerosol to bystanders in enclosed public spaces is sparse. However, the PHE report seems to equate lack of evidence with evidence of lack of effect. It claims that there is "no identified risk to bystanders," a view that may be premature.

The report has many other omissions, such as concerns about product safety, including forged safety certificates reported by a BBC *Fake Britain* documentary in December 2014, and the lack of evidence of risks from long term dual use with conventional cigarettes.[22] Yet perhaps its most striking feature is its consistent adoption of the most optimistic position on the limited evidence available. To take one example, the report offers reassurance that e-cigarettes when "used as intended pose no risk of nicotine poisoning to users." This is true, but it is equally true of all poisons. The report rightly calls for nicotine to be in child-proof containers given the attraction of colourful packaging. However, it quotes a report of over 2400 poisoning cases in the United States up to February 2014[23] as saying "none resulted in any serious harm," although the US report included reference to a death attributed to suicide. Nor does it cite the report's conclusion that "the public should be aware that e-cigarettes have the potential to cause acute adverse health effects and represent an emerging public health concern."

The PHE authors also fail to consider the practical consequences of their recommendations. If e-cigarettes are so safe, presumably there will be no restriction on using them in cars. This will make the forthcoming ban on smoking in cars with children virtually unenforceable because it will be extremely difficult to determine what is causing a cloud of smoke or vapour in a moving car.

Finally, the PHE summary states, "The accuracy of nicotine content labelling currently raises no major concerns." Surely, England's leading public health agency cannot be indifferent to a situation where consumer product information is known to be wildly inaccurate?[6 24]

Where next for policy on e-cigarettes?

In 2016, the European Union Tobacco Products Directive[25] will come into force despite some of the most intensive tobacco industry lobbying ever seen.[26] Most of the lobbying effort concerned packaging of conventional cigarettes. However, there was also a powerful attack on the directive's substantial restrictions on e-cigarettes. These restrictions will hopefully limit the negative effect of this flawed PHE report. Meanwhile, directors of public health and the wider community desperately need advice on e-cigarettes that is evidence based and free from any suspicion of influence by vested interests.

Happily, a consensus may be emerging. The English chief medical officer (CMO) recently said that, if e-cigarettes have a role in smoking cessation that should be as "licensed medicines. This would provide assurance on the safety, quality, and efficacy to consumers who want to use these products as quitting aids."[27] That would, of course, require data to show that they were both

safe and effective because, as the CMO also notes, "there continues to be a lack of evidence on the long-term use of e-cigarettes." We agree with this view.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 McNeill A, Brose LS, Calder R, et al. E-cigarettes: an evidence update: a report commissioned by Public Health England. Public Health England, 2015.
2 Brimelow A. E-cigarettes could be prescribed by the NHS to help smokers quit, report says. *BBC News* 2015 Aug 19. www.bbc.co.uk/news/health-33978603.
3 Royal College of Physicians of London. RCP statement on e-cigarettes. 2014. www.rcplondon.ac.uk/press-releases/rcp-statement-e-cigarettes.
4 ASH. Electronic cigarettes 2014.www.ash.org.uk/files/documents/ASH_715.pdf.
5 World Health Organization. Electronic nicotine delivery systems. 2014. http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10Rev1-en.pdf?ua=1.
6 European Commission. E-cigarettes myth buster. 2015. http://ec.europa.eu/health/tobacco/docs/tobacco_mythbuster_en.pdf .
7 McKee M. Electronic cigarettes: peering through the smokescreen. *Postgrad Med J* 2014;90:607-9.
8 Godtfredsen NS, Holst C, Prescott E, et al. Smoking reduction, smoking cessation, and mortality: a 16-year follow-up of 19,732 men and women from the Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol* 2002;156:994-1001.
9 Hitchman SC, Brose LS, Brown J, et al. Associations between e-cigarette type, frequency of use, and quitting smoking: findings from a longitudinal online panel survey in Great Britain. *Nicotine Tob Res* 2015:ntv078.
10 McRobbie H, Bullen C, Hartmann-Boyce J, et al. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev* 2014;12:CD010216.
11 Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. *Prevent Med* 2014;69:248-60.
12 Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA approach. *Eur Addict Res* 2014;20:218-25.
13 Moneyhouse Commercial Register and Business Information. EuroSwiss Health. 2015. www.moneyhouse.ch/en/u/v/euroswiss_health_sa_CH-550.1.035.243-5.htm.
14 Delon Human. *Tobacco Tactics* 2015. www.tobaccotactics.org/index.php/Delon_Human.
15 Human D. *Wise nicotine* . Dennis Barber, 2010.
16 British American Tobacco. Why it matters. Sustainability focus report 2013: how we address the public health impact of our products. 2013. www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DO964UGU/$file/A_Focus_on_Harm_Reduction_Report_2013.pdf.
17 Riccardo Polosa. *Tobacco Tactics* 2015. www.tobaccotactics.org/index.php/Riccardo_Polosa.
18 Health and Social Care Information Centre. More than a fifth of young people have tried e-cigarettes. 23 Jul 2015. www.hscic.gov.uk/article/6555/More-than-a-fifth-of-young-people-have-tried-e-cigarettes.
19 Goriounova NA. Long-term consequences of nicotine exposure during adolescence: synaptic plasticity in rodent and human cortical neuronal networks. PhD thesis. Vrije Universiteit Amsterdam, 2012.
20 Chapman S. Are e-cigarettes a gateway to smoking in 14-year-olds? New US data. *The Conversation* 2015 Aug 21. https://theconversation.com/are-e-cigarettes-a-gateway-to-smoking-in-14-year-olds-new-us-data-46468.
21 Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA* 2015;314:700-7.
22 Chapman S. E-cigarettes: the best and the worst case scenarios for public health-an essay by Simon Chapman. *BMJ* 2014;349:g5512.
23 Chatham-Stephens K, Law R, Taylor E, et al. Notes from the field: calls to poison centers for exposures to electronic cigarettes—United States, September 2010-February 2014. *MMWR* 2014;63:292-3.
24 Yang L, Rudy SF, Cheng JM, Durmowicz, EL. Electronic cigarettes: incorporating human factors engineering into risk assessments. *Tob Contr* 2014;23(suppl 2):ii47-53.
25 European Union. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the member states concerning the manufacture, presentation and sale of tobacco and related products and repealing directive 2001/37/EC. European Commission, 2014.
26 Peeters S, Costa H, Stuckler D, et al. The revision of the 2014 European Tobacco Products Directive: an analysis of the tobacco industry's attempts to "break the health silo." *Tob Contr* 2015 Feb 24. [Epub ahead of print.] doi:10.1136/tobaccocontrol-2014-051919.
27 Meikle J. Vaping: e-cigarettes safer than smoking, says Public Health England. *Guardian* 2015 Aug 19. www.theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking.

Cite this as: *BMJ* 2015;351:h4863

Key messages

- Public Health England's endorsement of the safety and efficacy of e-cigarettes is based on uncertain evidence
- The quality of evidence that e-cigarettes help smokers to quit is weak
- Recent evidence questions the conclusion that e-cigarettes are not a gateway to smoking
- Until better evidence is available public health strategies should follow the precautionary principle

I chair the Royal College of Physicians Tobacco Advisory Group, co-chair the Public Health England Tobacco Control Implementation Board and am a member of the board of trustees at Action on Smoking and Health.

John Britton
j.britton@outlook.com

UK Centre for Tobacco and Alcohol Studies, Division of Epidemiology and Public Health, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, UK

1 The Lancet. E-cigarettes: Public Health England's evidence-based confusion. *Lancet* 2015; **386:** 829.
2 McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P, McRobbie H. E-cigarettes: an evidence update. Public Health England, August 2015. https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update (accessed Sept 1, 2015).
3 Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA Approach. *Eur Addict Res* 2014; **20:** 218–25.

Electronic cigarettes: we need evidence, not opinions

We read with interest the recent *Lancet* Editorial on e-cigarettes (Aug 29, p 829)[1] and the accompanying Letter by Ann McNeill and colleagues.[2]

McNeill and colleagues[2] criticise the Editorial on their e-cigarettes report[3] for focusing on one[4] of its 185 references. However, that reference was the only substantive reference cited in their report to justify the message that e-cigarettes are 95% safer than conventional cigarettes reported so prominently in the media (the other was simply a fact sheet that cited the first reference). Although McNeill and colleagues did review other evidence that e-cigarettes are safer (a view not in dispute), there was no independent attempt to verify the figure.

Crucially, many of the studies they used were also included in a recent systematic review,[5] although they failed to cite it. It concluded that much research on the health effects of e-cigarettes was methodologically weak, 34% of papers they reviewed were subject to conflicts of interest, and the evidence was inadequate to conclude that they were harmless. No-one can know the long-term effects of inhaling many of the substances present in e-cigarettes, particularly flavourings, because these chemicals have never been tested in that context.

It is particularly unfortunate that McNeill and colleagues failed to address the conflict of interests in a paper which played such a prominent role in the headlines they generated, which now appear even greater than reported by *The Lancet*.[6]

Finally, McNeill and colleagues simplify the issue by only contrasting vaping and smoking. It is essential to consider long-term dual use, and initiation of vaping among children and adults who would not otherwise smoke.

We declare no competing interests.

**Martin McKee, Simon Capewell*
Martin.McKee@lshtm.ac.uk

London School of Hygiene & Tropical Medicine, London WC1H 9SH, UK (MM); and University of Liverpool, Department of Public Health & Policy, Institute of Psychology, Health & Society, Liverpool, UK (SC)

1 The Lancet. E-cigarettes: Public Health England's evidence-based confusion. *Lancet* 2015; **386:** 829.
2 McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P, McRobbie H. E-cigarettes: the need for clear communication on relative risks. *Lancet* 2015; published online Aug 31. http://dx.doi.org/10.1016/S0140-6736(15)00079-3.
3 McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P, McRobbie H. E-cigarettes: an evidence update. Public Health England, August 2015. https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update (accessed Sept 1, 2015).
4 Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA Approach. *Eur Addict Res* 2014; **20:** 218–25.
5 Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. *Prev Med* 2014; **69:** 248-60.
6 Boseley S. Public Health England under fire for saying e-cigarettes are 95% safer. *The Guardian*, (London): 2015. http://www.theguardian.com/society/2015/aug/28/public-health-england-under-fire-for-saying-e-cigarettes-are-95-safer (accessed Sept 1, 2015).

Renal denervation for resistant hypertension


Ian Hooton/Science Photo Library

The DENERHTN trial (May 16, p 1957)[1] reported that renal denervation was associated with a baseline-adjusted difference of −5·9 mm Hg in daytime ambulatory systolic blood pressure after 6 months in favour of interventional treatment. Surprisingly, and in stark contrast with the results from the Symplicity HTN-2 and HTN-3 trials, the blood pressure response with ambulatory blood pressure measurements was as high as with office blood pressure measurements.[1–3] Specifically, in the Symplicity HTN-2 trial, office blood pressure was reduced by 32/12 mm Hg and 24 h ambulatory blood pressure was reduced by only 11/7 mm Hg after 6 months with renal denervation, and in the Symplicity HTN-3 trial, systolic office blood pressure changed by 14·1 mm Hg and 24 h ambulatory systolic blood pressure by only 6·7 mm Hg after 6 months with renal denervation.

Furthermore, despite the blood pressure difference between denervation and control groups, the amount of additional antihypertensive drugs added in standardised stepped care was not higher (as expected) in controls. What is the explanation for this discrepancy? Since five patients who were randomly assigned to the renal denervation group were not included in the modified intention-to-treat analysis, baseline patient characteristics should have also been reported for the 48 remaining patients. The authors have to be applauded for adding a measure of adherence rates in their study in view of the very high rate of non-adherence in patients with treatment-resistant hypertension.[4] Nevertheless, increases in adherence after renal denervation not detected by the eight-item Morisky Medication Adherence Scale score could still contribute to improved blood pressure control.

We declare no competing interests.

Published **Online** September 4, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00146-4

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

1. Executive Summary

- As professional toxicologists interested in improving testing methods for assessing the safety to humans of chemicals, we starting collaborating with the tobacco industry, to help identify promising new methods, beginning with tobacco smoking harm reduction products and then e-cigarettes.
- We soon became perplexed over the FDA's tobacco deeming regulations and then became even more-concerned about the way in which the UK authorities were laying the foundations for using e-cigarettes in the fight against smoking-related disease. We are especially surprised by the lack of scholarship and scientific rigour that is being applied to the safety assessment of these products, and feel it important to exploit our independence by speaking out.
- The current stipulations regarding the regulatory control and authorisation of electronic cigarettes (ECs) and vaping in the UK are scientifically flawed, as they are based on little more than conjecture and value judgment, backed only by poor science.
- There has been over-reliance on chemical analysis, the use of incomplete data, and risk assessments confused with the perceived benefits of vaping versus smoking, all of which bear little resemblance to standard approaches in toxicological risk assessment.
- The authorities, and other stakeholders, have systematically ignored, or erroneously dismissed, basic principles of pharmacology and toxicology, and inconvenient scientific observations, while promoting vaping as a way of ceasing smoking, instead of discouraging the use of nicotine in any form.
- The research being overlooked includes evidence of the many pleiotropic adverse biological effects of nicotine, more of which continue to be revealed with increasing frequency, which are likely to be highly relevant to carcinogenicity and disease.
- We discuss this very serious situation, and offer some suggestions for a better way forward, for the benefit of individual humans, now and in the future.

2 Introduction

Electronic cigarettes (e-cigarettes; ECs) are handheld, electronic devices that vaporise a liquid (e-liquid) containing nicotine with a other additives (e.g. propylene glycol or glycerol, and flavouring agents), and deliver the vapour to the lungs via inspiration and inhalation (a process called vaping).

In August 2015, Public Health England (PHE) declared that, in principle, ECs should be made available on prescription to reduce tobacco smoking (https://www.theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking). It was also made clear that ECs will be regulated as new medicines by the Medicines and Healthcare products Regulatory Agency (MHRA). This was followed by the news of the first e-cigarette (Evoke) to receive marketing authorisation from the agency.

These announcements have proved to be highly controversial, especially since they were justified by an estimate of there being 95% less harm from vaping than from tobacco smoking (https://www.gov.uk/government/news/e-cigarettes-around-95-less-harmful-than-tobacco-estimates-landmark-review). This submission explains why we believe that the decision by PHE is, in the light of current knowledge, irresponsible and unacceptable. We

Comment [RD]: https://www.theguardian.com/society/2015/aug/19/public-health-england-e-cigarettes-safer-than-smoking

also propose some recommendations to avoiding the potentially very serious consequences, if this situation is allowed to continue.

3 Ignoring basic principles of toxicology

This is the most common characteristic exhibited by individuals, reports and publications discussing safety issues relating to ECs (Table 1; 1-3). The main consequences are: a) the belief that it is legitimate to base safety studies on analytical chemistry to determine the presence or absence of specific chemicals, and that data on their relative concentrations in e-liquids and emissions are sufficient to provide a quantitative measure of harm; b) the belief that the route of exposure has little effect on nicotine toxicity, and that, as few toxic effects have been observed since the times when various nicotine delivery devices were first introduced (ranging from 10 years for ECs to 30 years or more for nicotine replacement therapies {NRTs]), nicotine must be relatively inactive; and c) the belief that long-term toxicity can be predicted on the basis of acute effects.

The idea of deriving quantitative information on risk, while having only qualitative supporting data for ECs, originated from a Multiple-criteria decision analysis (MCDA) study (4). Our concerns about this are summarised in Table 2. Nutt *et al.* must have settled on 95% as a convenient comparative number, which PHE eventually simply expressed differently, ever since which the figure has been quoted *ad nauseam*, without any supporting data.

Overlooking the effect of route of administration is exemplified by a report of the Royal College of Physicians (4) which stated: *There are, however, no grounds to suspect that inhaled nicotine will have an appreciably different risk profile from nicotine delivered via other routes of absorption.* This statement is imprecise, and was not backed by any references. There are many reasons why toxicity can depend greatly on route, rather than merely on target organ(s). Another important factor is the possibility of drugs going into systemic circulation, once entering the body, usually by routes other than orally, before passing through the liver first - the organ which normally reduces systemic concentrations of parent compounds and which alters them to produce various metabolites, which can be more toxic or less toxic than the parent compound.

4. Superficial and inaccurate reporting of supporting evidence

A paper by Cheng (6), cited in a report commissioned by PHE, written by McNeill et al. (7), provides evidence of the presence in vapours of some potentially carcinogenic tobacco-specific nitrosamines (TSNAs) at widely different levels (RF), but McNiell et al. did not mention the evidence in relation to safety, even though they made some other statements on the issue. This contrasts with another PHE-Commissioned report focusing on safety, (8), authored by Britton and Bogdanovica. These authors did not mention the extensive analytical data for such chemicals, as Cheng's paper was omitted in favour of one by Goniewicz et al describing that only very low levels of these chemicals are associated with ECS (9).

In a highly critical editorial (10), *The Lancet* noted that the PHE report was evidence-based confusion rather than being a *"landmark review"*, as referred to by Kevin Fenton, PHE's Director of Health and Wellbeing. When commenting on a paper purporting to demonstrate a link between DNA damage in lung cells and exposure to EC vapour,

Comment [RD]: Nutt, D.J., Phillips, L.D., Balfour, D., Curran, H.V., Dockrell, J.M., Foulds, J., Fagerstrom, K., Letlape, K., Milton, A., Polosa, R., Ramsey, J. & Sweanor, D. (2014). Estimating the harms of nicotine-containing products using the MCDA approach. E. Addiction Research 20, 218–225.Nutt et al 2014

Comment [RD]:

Fenton, replied that *Public Health England has always been clear that e-cigarettes are not 100 per cent safe and we will carefully consider this new study and continue to be vigilant. But our major world leading review, published recently, found that e-cigarettes carry a fraction of the risk of smoking' [underlining added]…..'.* (http://www.telegraph.co.uk/science/2016/03/12/e-cigarettes-are-no-safer-than-smoking-tobacco-scientists-warn/). The so-called 'world-leading review' by PHE was nothing of the sort – it was essentially a very poor appraisal of the situation.

We also note that, while Nutt *et al.,* in 2014 (4), urged caution when interpreting their MCDA data, they supported PHE's 95% safer value in a letter published two years later (11). The MCDA paper (4) is also superficial, especially with respect to criteria for calculating maximum relative harm (MRH) and on how the inescapable problem of the huge bias in data for tobacco smoking compared with ECs was corrected for. This bias is due to the much shorter time for which ECs have been available for use and for testing, meaning that more subjectivity would have been required when assessing ECs to reach consensus at the decision conference, an even greater problem in 2013, when the discussions took place. This problem was also noted in a review on ECs, published in April 2014 (12), which concluded that *"Existing evidence suggests that these products [ECs] are by far a less harmful alternative …."*, although it was admitted that only a very few toxicological studies were available.

Despite searching background literature on the MCDA technique, some of it recommended by Nutt *et al.*, and after watching seminars (13-15) by the two leading authors, we have not found any convincing explanations for our concerns about MCDA. Other critics of the MCDA approach include: Kujawski (16), who commented that the specific MCDA model used can greatly influence the rankings of the alternatives for a given set of criteria; and Rolles and Measham (17), who were highly critical of the criteria and weighting used for ranking.

5. Nicotine - an inconvenient truth?

There is widespread agreement in the various reports supporting ECs that, apart from its addictivity, nicotine, is otherwise non-toxic at its in-use concentrations. Nicotine is actually one of the most toxicologically and pharmacologically active substances known (see reviews cited in ref 1). Structural alerts for DNA and protein binding were identified (unpublished studies by us, by using Toxtree, a decision-tree expert system for structure-activity relationships [SAR]), explaining the observed genotoxicity in the literature, and raising questions about respiratory sensitization (mediatied by DNA binding), and other mechanistically-related diseases, such as Chronic Obstructive Pulmonary Disease (COPD). Of interest is the fact that propylene glycol and glycerine lacked these alerts, although they might be precursors for toxic carbonyl compounds, the generated amounts of which increased with heater settings in one study (18), but it is possible to generate them without the excessive levels causing dry puff.

The literature on nicotine carcinogenicity and reproductive toxicity, reviewed by us in ref 1 [18 references cited therein], at the very least, suggests that, if not a complete carcinogen (acting as an itiator and promoter, nicotine acts on a variety of key post-initiation stages of the multi-step process of carcinogenesis (Fig. 1), including inhibition of apoptosis and immune system suppression, tumour promotion, cell proliferation, progression, stimulation of specific cell activating factors, angiogenesis, and the induction of unique patterns of

Comment [RD]: Ther Adv Drug Saf. 2014 Apr; 5(2): 67–86.
doi: 10.1177/2042098614524430
PMCID: PMC4110871

Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review

Konstantinos E. Farsalinos and Riccardo Polosa

differential gene expression (see also 19). The drug also activates at least five mitogenic signaling pathways and cooperates with TSNAS toward the carcinogenic activity of tobacco smoke (20), and is also embryotoxic and modulates fertilization.

6. Cardiovascular disease (CVD) effects

Nicotine and ultra-fine fibres in the particulate matter in tobacco smoke have been implicated separately to be involved in smoking related CVD via their ability to induce inflammation in the endothelial layer in blood vessel walls, a first step in atherogenesis leading to CVD (21, 22). The fibres increase the surface area for reactive oxygen species (ROS), and possibly act also by causing some physical damage to the cells

It is possible that the two components have to interact synergistically for an effect. Such a model would explain the lack of association between NRT usage and CVD, and would suggest that EC use would also not be linked to NRT, unless some other component could mimic the effect of the fibres. Candidates for this role are the nanoparticles generated from the heating elements in e-liquid reservoirs. Some of the fibres have overlapping dimensions with NPs (23), but their surface chemistry needs to be characterised, and further work is needed to see if they interact with nicotine to induce atherosclerosis. Interestingly, Zhao *et al.* (24) recently demonstrated ROS generation by e-cigarettes, which was highly dependent on brand, flavour, puffing pattern, and voltage.

7. Basing the safety of nicotine on human studies of NRT users and snus takers

Often, the results from epidemiological studies of users of NRT, and of smokeless tobacco (e.g. 'snus', which is popular in Scandinavia, the device being a pouch of tobacco, maintained in the mouth for extended periods), without increases in the incidence of conditions like cancer, COPD or CVD, in device-users compared with matched non-users, are used to argue against nicotine being toxic. However, such arguments fail to explain all of the evidence and/or do not accord with all of the facts.

While the 30-year or so period during which NRT products have been available would seem to be a sufficiently long time for the lack of increased susceptibility to cancer to be attributed to the non-carcinogenicity of nicotine, it is a collective figure for all users, which should not be confused with individual treatment durations for a course of NRT (typically 8-12 weeks per patient) – too short a duration for assuming non-carcinogenicity.

With regard to snus, careful reading of the statistics in the annual Swedish Cancer Registry (http://www.socialstyrelsen.se/english) reveals a complex relationship between snus-taking, lung cancer and other cancers. Two key conclusions from the statistics, a) that the use of snus almost halved lung cancer incidence in males in Sweden, and b) that it is not associated with increases in the occurrence of a range of other 'common' cancers, do not agree with all the available evidence, some of which suggests that snus usage has had only a minimal effect on lung cancer incidence overall, in males, and that increases in a range of other cancers (including oral and pancreatic) can be linked to exposure to snus.

Therefore, the statistics on the change in cancer incidence in relation to snus-taking in Sweden need to be interpreted carefully. Some other published analyses of population studies, including that by Lee *et al.* (25), essentially giving snus the all-clear, were criticised by Tomar *et al.* (26). Finally, if nicotine were a tumour promoter, a long period

Comment [RD]:
Benowitz, N.L. & Burbank, A.D. (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends k Cardiovasc. Med. 26, 515-523.

Comment [RD]:

Comment [RD]:
https://doi.org/10.1016/j.jhazmat.2017.10.057

between exposure to an initiator and promoter is just what would be expected to still potentially result in tumorigenesis.

8. An attempt to obtain long-term data on ECS

A so-called 'long-term' biomonitoring study, published in March 2017 (27), allegedly demonstrating the much greater safety of vaping compared with smoking, has been hailed as being the closest yet to endorsing the 95% less harmful value and PHE's policy on ECs.

Biomonitoring assesses internal exposure to, and the possible systemic effects of, a substance to which an individual is exposed, thereby strengthening the link between exposure and effect. The study in question analysed urine samples obtained from smokers, vapers and those on various types of other NRT devices, for the presence of biomarkers of exposure to several carcinogens found in tobacco smoke and linked to lung cancer. The key criterion for inclusion in the study was the daily use of the same broad category of device for at least six months prior to sampling. This allowed conventional NRT users to use devices with varying routes of administration, introducing a further source of variability. Levels of biomarkers were detected and quantified by using highly sensitive methods for chemical analysis.

The lowest concentrations of all the biomarkers were found in the samples from the EC-only users. As the differences were quoted as being between 90-100%, the authors interpreted this as vindication of the 95% figure.

However, the study was flawed in its rationale (it relied on chemical analysis), and its design (small numbers of volunteers and wide differences in gender ratios between some of the cohorts and only one timepoint). Conventional long-term toxicity testing involves repeat exposure studies and continual surveillance of laboratory animals, for at least several months. The tests are designed to detect chemicals that might not specifically exhibit acute effects. Therefore, this study, with only one sampling, should not be regarded as being equivalent to a repeat-dose toxicity study. There was also no control of fluid and nutrient intake on the day of sampling, let alone of the type of device, and no determination of the various e-liquid compositions. At best, the study could have provided only a snapshot of what was happening during the period involved.

9. A role for non-animal methods

Regulatory test batterles for new drugs include subchronic and chronic tests that are specifically designed to predict repeat-dose toxicity (<90 days) and longer-term toxicity, some studies of which take some 2-3 years to complete. Long-term models of respiratory diseases also exist (2, 28). An example of one of these has recently been published (29), in which mice were exposed by inhalation to nicotine-containing EC fluids for one hour daily over four months. The exposures induced effects associated with the onset of COPD, including cytokine expression, airway hyper-reactivity, and lung tissue destruction. These effects were nicotine-dependent in the mouse lung, suggesting that inhaled nicotine contributes to airway and lung disease.

However, our suggestion of the need for more hazard data for ECs does not necessarily mean more animal testing, since many *in vitro* methods exist (see citations in refs 1-3)

These offer many advantages over their *in vivo* counterparts, ranging from more-precise dosimetry to advantages in data interpretation. This is especially true for inhalation testing (28).

Monolayer-cultures of cells from target airway sites can be used. For example, in the four-month COPD study mentioned above, the same results were obtained when normal human bronchial epithelial [NHBE] airway cells were cultured at an air-liquid interface (ALI) and exposed to EC vapours or nicotine solutions by using a Vitrocell smoke exposure robot.

It should be possible to obtain more-reliable and more-relevant data expeditiously through the application of integrated testing strategies involving advanced human cell-based tissue culture systems, in which their differentiated status is retained in culture, and which are representative of the major target sites in the airways for respiratory toxicity and disease, by using ALI exposure. Moreover, some of the toxicity endpoints (e.g. DNA damage) can be measured *in situ* in the tissue construct (several reviews have been published over the past year).

The tobacco industry has been active in this area, holding workshops and various integrated tiered testing strategies have emerged for improving and expediting hazard identification. We present a generalized strategy, based on this type of approach (Figure 2). The strategy also includes a repeat-dose toxicity testing stage involving the use of hollow fibre technology for maintaining the longevity of cells in culture by replacing spent culture medium with fresh medium.

It is also possible to develop *in vitro* micro-culture models of whole organs, in order to predict the effects of exposure at several different sites within the same organ, simultaneously. A pertinent example is a small 'airway-on-a-chip' device developed by Benam and coworkers (30). This system is lined by living human bronchiolar epithelium from normal or COPD patients. The device is connected to an instrument that delivers whole cigarette smoke in and out of the chips, to permit the study of smoke-induced pathophysiology *in vitro*.

10. Smoking cessation versus nicotine quitting

We also note that the rationale for NRT was originally geared toward the ultimate goal of detoxication from nicotine drug dependency. In other words, it was intended that treatment would progress from a phased withdrawal, from dual usage via exclusive NRT usage to no usage. The current emphasis ion smoking cessation is regrettable, since it would greatly prolong exposure to nicotine. While this might not increase drug dependency, it could result in many other adverse effects, including tumour promotion and progression of initiated cells already formed in smokers before they started to quit.

11. Discussion

The argument for encouraging the use of ECs is based on: a) the apparent lack of association between nicotine exposure and carcinogenesis, CVD and other respiratory diseases, interpreted as meaning that they can be regulated lightly by waiving the batteries of preclinical and clinical tests to which most new medicines are subjected; b) an estimate with no scientific basis that vaping is 95% less harmful than tobacco smoking; and c) the belief that the focus should be on achieving tobacco smoking cessation, rather than drug independence. Our investigations have encouraged us to conclude that all these assumptions are spurious when considered with respect to principles of toxicology involving hazard prediction and risk assessment.

The safety assessment of ECs should, in principle, be no different from that required for other new medicines. No good reasons for by-passing the risk assessment and risk-benefit procedures normally required for registering pharmaceuticals have been made public, and we also note that PHE mandated itself to publish its decision, without first having a public consultation stage.

We also consider that the use of panels of experts to decide, largely on the basis of opinion and value judgment, especially for ECS, about the 'relative harms' of nicotine-release devices, without relevant and reliable quantitative data about the harms resulting from exposure especially to EC vapour, was unwise and unnecesdsary, especially when non-animal testing strategies are available to generate meaningful hazard information and to fill data gaps, to be used, with other information, in a convincing weight-of-evidence assessment.

Finally, we stand by our belief, expressed in a letter published in *The Times* on 18 February 2016, that *"The human respiratory system is a delicate vehicle, on which the length and quality of our lives depend. For governments and companies to condone, or even suggest, the regular and repeated inhaling of a complex mixture of chemicals with addictive and toxic properties, but without comprehensive data, is irresponsible and could have serious consequences."*

12. Recommendations

1. Good Manufacturing Practice guidelines should specify device design, capability, construction, mode of nicotine delivery and permissible ingredients, and their maximum amounts.
2. The designs should avoid the potential for excessive customisation.
3. Professional toxicologists should be involved in advising on safety issues relating to regulation of the use of ECs.
4. The intrinsic risks from vaping should be investigated and calculated separately, before comparison with the risks from tobacco smoking.
5. ECs should be considered as NRT products, rather than for prolonged recreational usage, until more long-term safety data have become available.
6. The toxicity of nicotine should be investigated further, as should the ability of nanoparticles in EC emissions to mimic the effects on CVD of particulate matter in tobacco smoke.
7. Threshold values for nicotine toxicity should be identified.

8. The end-game should be total cessation of the use of nicotine, beginning with tobacco smoking, but proceeding to cessation of the use of NRTs and ECs.
9. POS (point of sale) literature should emphasise the importance of nicotine quitting.
10. The MHRA should be more transparent about how ECs will be regulated via a 'light-touch" approach, especially by applican of the concept of bioequivalence.
11. We strongly urge that further *in vitro* methods for detecting long-term toxicity and chronic disease conditions as a result of inhalation, should be developed and validated and accepted for use as soon as possible.
12. Several prospective long-term epidemiological studies should be initiated in the near future, to assess the adverse clinical and toxic effects from vaping. These should involve biomarkers of exposure and effect, such as DNA adducts, chemically-modified bases, and genotoxicity of body fluids.

December 2017

13. References

1. Combes, R.D. & Balls, M. (2016). Draft response regarding comments made by Clive Bates about one of our publications on the safety of electronic cigarettes and vaping. https://www.researchgate.net/publication/307958871_Draft_Response_regarding_comments_made_by_Clive_Bates_about_one_of_our_publications_on_the_safety_of_electronic_cigarettes_and_vaping
2. Combes, R.D. & Balls, M. (2015). On the safety of e-cigarettes: "I can resist anything except temptation". ATLA 43, 417-425.
3. Combes, R.D. & Balls, M. (2015). A critical assessment of the scientific basis, and implementation, of regulations for the safety assessment and marketing of innovative tobacco-related products. ATLA 43, 251–29.
4. Nutt, D.J., et al. (2014). Estimating the harms of nicotine-containing products using the MCDA approach. E. Addiction Research 20, 218–225.
5. Anon (2016). Nicotine without smoke: Tobacco harm reduction, Royal College of Physicians 206p. (https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0).
6. Cheng, T. (2014). Chemical evaluation of electronic cigarettes. Tobacco Control, 23, ii11–ii17. http://doi.org/10.1136/tobaccocontrol-2013-051482.
7. McNeill, A. et al. (2015). E-cigarettes: an evidence update. A report commissioned by Public Health England (https://casaa.org/e-cigarettes-an-evidence-update-report-commissioned-by-public-health-england/).
8. Britton, J. & Bogdanovica, I. (2014). Electronic Cigarettes, 30p. A report commissioned by Public Health England. London, UK: Public Health, England https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/311887/Ecigarettes_report.pdf
9. Goniewicz, M.L, et al. (2014). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tobacco Tob Control. 2014 Mar;23(2):133-9. doi: 10.1136/tobaccocontrol-2012-050859. Epub 2013 Mar 6.
10. Anon (2016). E-cigarettes: Public Health England's evidence-based confusion. http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)00042-2.pdf
11. Nutt, D.J. et al. (2016). E-cigarettes are less harmful than smoking. Lancet. 2016 Mar 19;387(10024):1160-2. doi: 10.1016/S0140-6736(15)00253-6.
12. Farsalinos, K.E. & Polosa, R. (2014). Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther. Adv. Drug Safety. 5, 67-86.
13. Nutt, D.J. (2015). Drug harms in the UK: a multicriteria decision analysis. slideplayer.com/slide/4959201/ORSCriminalJustice2015_09122015112340(1).pptx
14. Phillips, L. (2015). Psychoactive drugs: modelling their harm and policies for their control. http://www.theorsociety.com/DocumentRepository/Browse.aspx?DocID=698&drct=true
15. Phillips, L. (2006). Decision Conferencing, http://eprints.lse.ac.uk/22712/1/06085.pdf

16. Kujawski, E. (20114). Multi-Criteria Decision Analysis: Limitations, Pitfalls, and Practical Difficulties. Version of Record online: 4 NOV 2014 DOI: 10.1002/j.2334-5837.2003.tb02692.x
17. Rolles, S. & Measham, F. (2011). Questioning the method and utility of ranking drug harms in drug policy. Int. J. Drug Policy 22, 243-246.
18. Wang, P. et al. (2017) A device-independent evaluation of carbonyl emissions from heated electronic cigarette solvents. PLoS ONE 12(1):e0169811. doi:10.1371/journal.pone.0169811
19. Nouri-Shiraz, M. & Guinet, E. (2003). Evidence for the immunosuppressive role of nicotine on human dendritic cell functions. J. Immunology 109, 365–373.
20. Nishioka, T. et al. (2010). Nicotine, through upregulating pro-survival signaling, cooperates with NNK to promote transformation. Cell Biochem. 109, 152–161.
21. Benowitz, N.L. & Burbank, A.D. (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc. Med. 26, 515-523.
22. Csordas, A. & Bernhard, D. (2013). The biology behind the atherothrombotic effects of cigarette smoke. Nature Revs. Cardiol. 10, 219-230.
23. Zhang, Y. et al. (2013). In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. Nicotine Tob. Res.15, 501-5085
24. Zhao, J. et al. (2018). Assessment of reactive oxygen species generated by electronic cigarettes using acellular and cellular approaches. Journal of Hazardous Materials 344, 549-557.
25. Lee, P.N. (2013). The effect on health of switching from cigarettes to snus – A review. Regulatory Toxicology and Pharmacology 66 (2013) 1–5.
26. Tomar, S.L. et al. (2003). Declining smoking in Sweden: is Swedish Match getting the credit for Swedish tobacco control's efforts? Tob. Control. 12, 368-371.
27. Shahab, L. et al. (2017). Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. Annals of Internal Medicine. 166, 390-400.
28. Bérubé, K. et al. (2009). In vitro models of inhalation toxicity and disease. The Report of a FRAME workshop. ATLA 37, 89–141.
29. Garcia-Arcos, I. et al. (2016). Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax, 71, 1119–1129.
30. Benam, K.H., et al. (2016). Matched-comparative modelling of normal and diseased human airway responses using a microengineered breathing lung chip. http://www.cell.com/cell-systems/fulltext/S2405-4712(16)30322-2 http://dx.doi.org/10.1016/j.cels.2016.10.003

14. Tables and figures:

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

Table 1

Ten principles of toxicology being ignored in the debate in the UK concerning electronic cigarettes

1. There can be synergistic or antagonistic effects between constituents of complex mixtures.
2. Non-linear dose-responses are often exhibited.
3. There can be lag periods of many years between exposure and effect, e.g. for some cancers.
4. Analytical chemistry is of limited value for predicting non-toxicity.
5. Some chemicals and endpoints lack thresholds of toxicological concern, and toxicity can occur at very low concentrations.
6. Long-term effects are just as important as acute ones.
7. Quantitative expressions of safety should *always* be based on numerical data.
8. Route of entry/administration can have a large effect on toxicity.
9. Acute toxicity data should be used with great care, when attempting to predict long-term effects.
10. When in doubt, adopt the precautionary approach.

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

Table 2

Ten problems with the MCDA study (Nutt et al., 2014)* on Maximum Relative Harms (MRHs) for nicotine devices, and its subsequent interpretation

---

1. Insufficient information available to repeat study closely with a completely different panel of experts (e.g. criteria for MRH unclear).
2. Panel did not have on it a toxicologist experienced in risk assessment (the focus was not on comparison of hazard compared with exposure).
3. Huge bias of harm information available for tobacco smoking compared with vaping, (meaning much more conjecture in scoring the latter).
4. Therefore, although scoring in general based on opinion, this would have been less so for tobacco smoking.
5. Since 2013/4, much more safety data have become available for vaping, and such information should inform fresh new discussions.
6. No explanation as to how consensus was achieved between the panelists (no proceedings of face-face workshop).
7. No numerical hazard data to support the quantitative estimate made for relative harm of vaping versus tobacco smoking (resulting in a false impression of accuracy).
8. Insufficient focus on the toxicity of nicotine and its contribution to harms (leading to a possible under-estimation of harm from vaping).
9. Harms from smoking based on short-term and chronic effects, whereas, for vaping, no chronic data available (long-term safety cannot be accurately predicted from acute effects).
10. MRH values were based on wide range of criteria, other than safety *per se*,** meaning use of the term 'harm' in the paper is misleading ('harm' has been used to infer safety, when the terms are not synonymous).

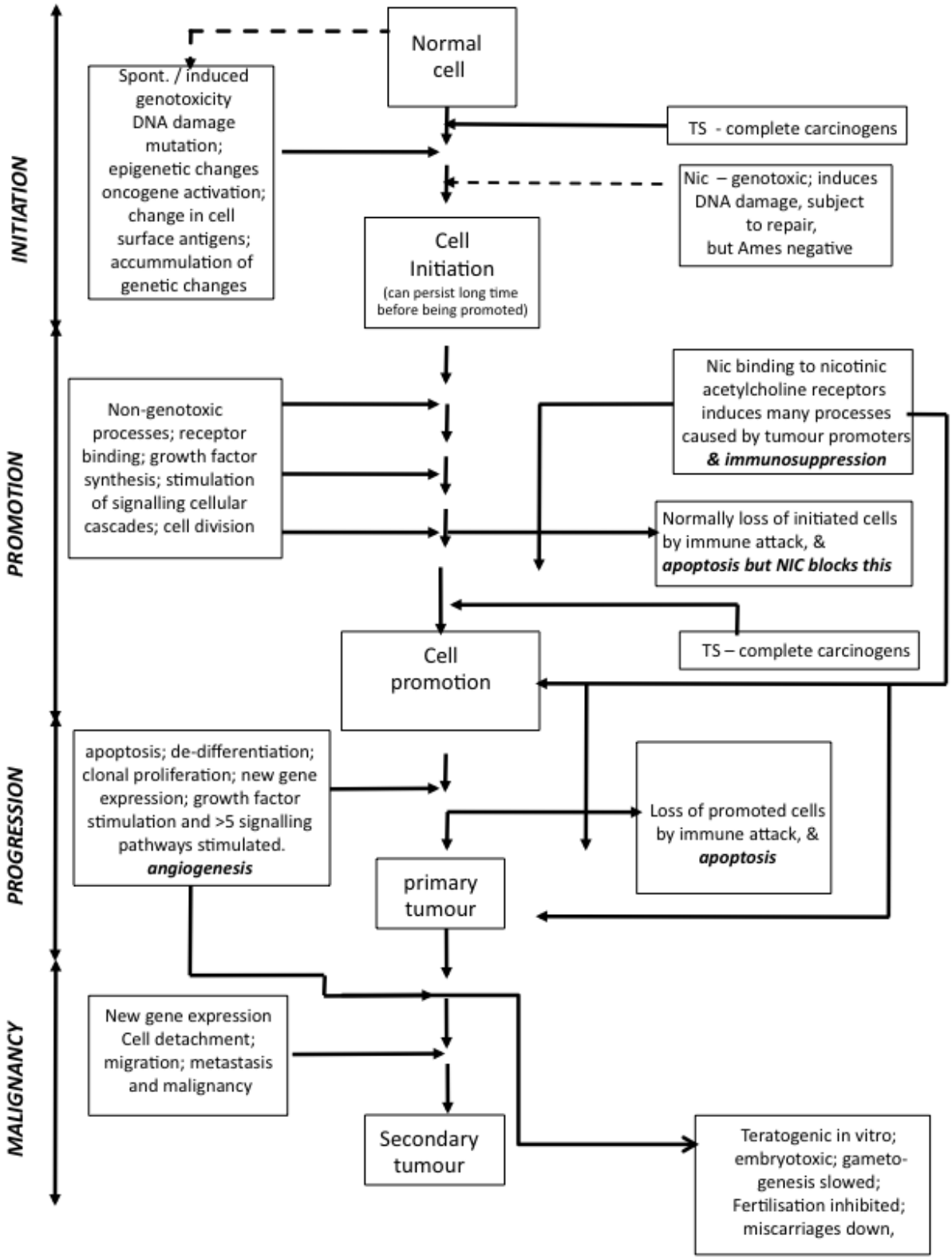
---

* reference 4 in References

**only 5/14 harm criteria were related to personal user adverse effects, and one of these was drug dependency;

Written evidence submitted by Dr Robert D Combes and Professor Michael Balls (ECG0080)

Figure: 1 Multi-stage carcinogenesis – effects of tobacco smoke (TS) & nicotine (NIC)



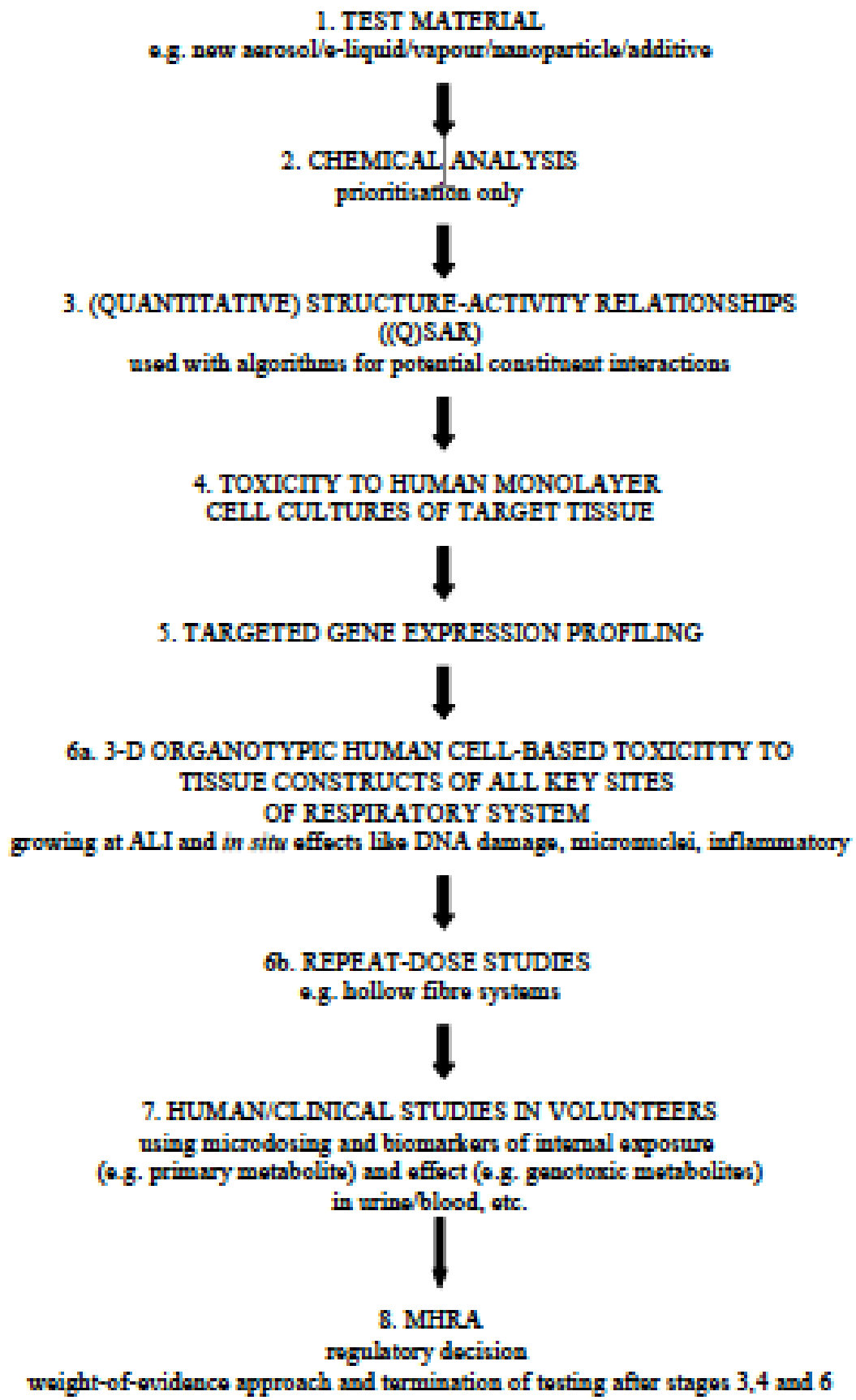


FIGURE 2 A GENERALISED INTEGATED TOXICITY TESTING STRATEGY FOR E-CIGARETTES

CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

REFERENCES

1. Cabrera de León A, Rodríguez IM, Gannar F, et al. Austerity policies and mortality in Spain after the financial crisis of 2008. *Am J Public Health*. 2018;108(8):1091–1098.

2. Hernández-Quevedo C, Lopez-Valcarcel BG, Porta M. Short-term adverse effects of austerity policies on mortality rates: what could their real magnitude be? *Am J Public Health*. 2018;108(8):983–985.

3. Galea S, Vaughan RD. Making the invisible causes of population health visible: a public health of consequence, August 2018. *Am J Public Health*. 2018;108(8):985–986.

4. Lopez-Valcarcel B, Barber P. Economic crisis, austerity policies, health and fairness: lessons learned in Spain. *Appl Health Econ Health Policy*. 2017;15(1):13–21.

5. Rajmil L, Fernandez de Sanmamed MJ. Austerity policies and mortality rates in European countries, 2011–2015. *Am J Public Health*. 2019;109(5):768–770.

Evidence and E-Cigarettes: Explaining English Exceptionalism

See also Fairchild et al., p. 1000.

What should health professionals advise about e-cigarettes? In this issue of *AJPH*, Fairchild et al. (p. 1000) compare reports offering two very different perspectives. One is by Public Health England (PHE), the body charged with protecting the health of the population, which has promoted e-cigarettes, or vaping, enthusiastically as a means to reduce the harm associated with smoking (for additional reading, see the Appendix, available as a supplement to the online version of this article at http://www.ajph.org). The other, by the US National Academies of Science, Engineering, and Medicine (NASEM), takes a much more cautious view, noting the large gaps in the available research as well as the warning signs in studies that have been undertaken. Fairchild et al. attributed this difference primarily to PHE's focus on the potential benefits to existing smokers in England, whereas the US report emphasizes the protection of nonsmokers, including children, who may be attracted to e-cigarettes and thus at risk for nicotine addiction, including, potentially, cigarette smoking. They also point to other differences, such as the priority given to randomized control trials in the NASEM report, whereas the PHE report questions their value, seeing them as inconsistent with the real-life situation.

The situation in which two groups assessing the same evidence reach differing conclusions is not unique and can be attributed to differing weights placed on particular issues. For example, perspectives on genetically modified food may differ depending on whether one views it as an issue of consumer safety, biodiversity, or the power of multinational producers over small farmers. But is it simply a question of different perspectives that explains the markedly divergent conclusions about e-cigarettes? To answer this question, it is necessary to recognize, as Fairchild et al. note, that England really is quite exceptional in its approach to e-cigarettes. Thus, another report, written by the Australian Commonwealth Scientific and Industrial Research Organization and stretching to 394 pages,[1] reaches conclusions that are broadly similar to those of the NASEM Report. So does a statement by the Forum of International Respiratory Societies, bringing together nine of the leading professional organizations worldwide working on respiratory health.[2]

The European Public Health Association, representing 40 national associations of public health, is similarly concerned, as are the European Commission, the World Health Organization, and many others (see Appendix). Thus, rather than comparing just two reports, surely the more important question is why PHE, along with some other English organizations, such as the Royal College of Physicians and the English advocacy organization Action on Smoking and Health, takes a view that is so much at odds with those in the rest of the world?

DIFFERENT PROFESSIONAL PERSPECTIVES

It does seem that the backgrounds of those assessing the evidence matters. Some of the strongest advocates of e-cigarettes in England are respiratory physicians (although, as noted, the leading respiratory organizations do not share their views). They are confronted daily with individuals addicted to nicotine who seem unable to quit smoking. They hear compelling stories from individuals who have found e-cigarettes an aid to quitting. Yet many studies find that the net result is a reduction in quitting, whereas dual users, who are typically the majority, are more likely to transition to exclusive cigarette use than to either sole e-cigarette use or complete abstinence.[3] They may also believe in the "hardening" hypothesis, whereby it is thought that as smoking rates decline, those few smokers who remain are especially resistant to quitting, although the most recent, thorough review shows that evidence does not support this.[4] Other strong supporters have worked with drug users and are familiar with methadone and needle exchanges being used as established means of harm reduction. Yet the approach advocated by e-cigarette enthusiasts lacks some of the core elements employed in the narcotics field (see Appendix).

Those favoring a much more cautious approach to e-cigarettes are, by contrast, drawn primarily from the public health community, which focuses on the overall population impact, anticipating the ability of e-cigarettes to recruit a new generation of smokers; pediatricians, who share

ABOUT THE AUTHOR

Martin McKee is with European Public Health, London School of Hygiene & Tropical Medicine, London, UK.

Correspondence should be sent to Martin McKee, Department of Public Health and Policy, London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, United Kingdom (e-mail: martin.mckee@lshtm.ac.uk). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted April 14, 2019.

doi: 10.2105/AJPH.2019.305132

those concerns; and cardiologists, who recognize the growing evidence linking components of e-cigarette vapor to endothelial damage in particular.

LACK OF HARD EVIDENCE FOR HARMS

It seems necessary to look beyond these differences in emphasis. PHE was one of the first organizations to support e-cigarettes. It has actively promulgated the claim that they are 95% safer than conventional cigarettes. Crucially, that claim is derived not from empirical evidence but from a meeting attended by 12 people, many who had previously expressed support for e-cigarettes. The report, often referred to as the "Nutt report" after its lead author, provided this remarkably precise and memorable figure even though their article conceded, "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria."[5(p224)] Despite this most fundamental of caveats, a senior PHE official told an Australian parliamentary inquiry, "We are very clear that this is just one of the figures that we have used, and there are plenty more. *We say what really matters is the evidence underlying this figure came from the Nutt report.*"[6] [emphasis added] To complicate matters further, there are important questions about the funding of the meeting, specifically any role of the tobacco industry, that are yet to be answered satisfactorily.[7]

Of course, considering how little time has elapsed since e-cigarettes entered widespread use, it is impossible to put a precise figure on harm, and the emerging evidence indicates that it is inappropriate to view them as a safer form of cigarette, as both types contain substances not found in the other, ensuring that dual users will have the worst of both worlds. But, because of the prominence of this claim, now afforded extensive visibility via e-cigarette industry promotion, it has been hard to retreat from it.

This is an example of what is termed "escalation of commitment" or, by economists and behavioral scientists, "sunk cost fallacy" (see Appendix). Once embarked on a course of action or line or argument, it is difficult to extract oneself. It leads to a situation in which evidence that supports the position being held is promoted, whereas that which challenges it is dismissed. Thus, even though Juul e-cigarettes—which have come to dominate the US market in just three years—are only now entering the UK market—with evidence already of an increase in adolescent e-cigarette use—we are to believe that the situation is somehow completely different from that in the United States, where adolescent vaping has assumed epidemic proportions. Considering a common language and the strong cultural links between the two countries, the idea that the powerful provaping imagery on the Internet will somehow disperse in a puff of smoke on its journey across the Atlantic seems, to say the least, implausible. So, as we seek to explain this example of English exceptionalism, the answer may lie in the growing literature on cognitive biases. AJPH

Martin McKee, MD, DSc

CONFLICTS OF INTEREST

M. M. is immediate past president of the European Public Health Association, which has expressed major concern about the promotion of e-cigarettes.

REFERENCES

1. Byrne S, Brindal E, Williams G, et al. *E-cigarettes, smoking and health: a literature review update*. Canberra, Australia: Commonwealth Scientific and Industrial Research Organisation; 2018.

2. Ferkol TW, Farber HJ, La Grutta S, et al. Electronic cigarette use in youths: a position statement of the Forum of International Respiratory Societies. *Eur Respir J*. 2018;51(5):1800278.

3. Coleman B, Rostron B, Johnson SE, et al. Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) study, waves 1 and 2 (2013–2015). *Tob Control*. 2019;28(1):50–59.

4. Fernandez E, Lugo A, Clancy L, Matsuo K, La Vecchia C, Gallus S. Smoking dependence in 18 European countries: hard to maintain the hardening hypothesis. *Prev Med*. 2015;81:314–319.

5. Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA approach. *Eur Addict Res*. 2014;20(5):218–225.

6. Parliament of Australia. Standing Committee on Health, Aged Care and Sport: 18/10/2017: use and marketing of electronic cigarettes and personal vaporisers in Australia. 2017. Available at: https://parlinfo.aph.gov.au/parlInfo/search/display/display.w3p. Accessed April 4, 2019.

7. Gornall J. Public Health England's troubled trail. *BMJ*. 2015;351:h5826.

Public Health, Politics, and the Creation of Meaning: A Public Health of Consequence, July 2019

See also Jakubowski et al., p. 1034.

Our health is the product of the social, economic, and environmental context within which we live. The air we breathe, the water we drink, our education, our friend networks, the places where we live, and the conditions of our work are foundational drivers of our health. This observation, perhaps obvious at this point in time for the readers of *AJPH,* has one fundamental implication that colors the science of population health and the practice of public health. It suggests, centrally, that the health of populations is inherently political.

It is impossible to separate our social, economic, and environmental conditions from the political decisions and actions that create this context. Decisions that drive quality and availability of housing, for example, inevitably pertain to the allocation of resources and must rest on prioritization of the same through political processes. The conditions of our employment are inextricable from economic circumstance and the motives—including financial—that inform occupational structures, salaries, and

ABOUT THE AUTHORS

Sandro Galea is with the School of Public Health, Boston University, Boston, MA. Roger D. Vaughan is an AJPH *associate editor and is with The Rockefeller University, New York, NY.*

Correspondence should be sent to Roger D. Vaughan, The Rockefeller University, 1230 York Ave, Box 327, New York, NY 10065 (e-mail: roger.vaughan@rockefeller.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted April 11, 2019.

doi: 10.2105/AJPH.2019.305128

Facts and fiction on e-cigs

What are they?

Electronic cigarettes, also known as e-cigarettes, e-cigs or, most accurately, Electronic nicotine delivery systems (ENDS), are devices that deliver an aerosol (incorrectly called 'vapour'), inhaled by the users and created by heating a solution, usually composed of propylene glycol or glycerol (glycerin) and flavourings, generally with nicotine. While they both contain nicotine, e-cigarettes and traditional cigarettes are entirely different products. Thus, while the vapour from e-cigarettes does not contain some of the harmful substances in traditional cigarettes, it does contain different harmful substances not found in traditional cigarettes, so the health effects of using both can be expected to be greater than either alone. ENDS have been heavily marketed in some countries in recent years. In 2017, about 15% of the European population had tried e-cigs at least once in their life.[1]

The WHO view on e-cigs

In 2016, the World Health Organization (WHO)[2] noted that, while e-cigarettes *might* be less harmful than conventional cigarettes, e-cigarettes still pose important risks to health, and that ENDS regulation should:

- Deter e-cigarette promotion to non-smokers and young people;
- Minimise potential health risks to e-cigarette users and nonusers;
- Prohibit unproven health claims about e-cigarettes;
- Prevent/Bar/Ban involvement of the tobacco industry in the marketing and promoting of e-cigarettes.

The legislative situation in Europe

As of May 2016 all European Union (EU) countries must comply with the EU Tobacco Products Directive that includes regulations for ENDS. The Directive[3] states that their packaging should provide information on toxicity and addictiveness, health warnings, and a list of all the substances contained in the product, including the exact level of nicotine (that should be in a concentration level of no more than 20 mg/mL). The Directive also requires that advertising and promotion rules for tobacco products also apply to electronic cigarettes.

Answering key-questions about e-cigs

Are e-cigs safe?

- E-cigs have only recently been used widely so there are limited long term data. Consequently, as noted by the WHO, it is impossible to say if and by how much they are safer or more dangerous than traditional cigarettes. The widely cited figure of 95% safer[4] emerged from a discussion among individuals, most of whom had previously advocated for these products,[5] who conceded the lack of evidence on which to base their conclusion.[6]
- E-cigs do not produce the tar produced by traditional cigarettes that is the main cause of lung cancer. However, they do produce formaldehyde, a known carcinogen at levels above recommended levels.[7] In addition, nicotine acts in ways that may encourage spread of established tumours[8] and reduce the effects of cancer chemotherapy.[9] Overall, however, the risk of cancer is unknown, though likely to be lower.
- E-cig use has been tied to lung disease, with a growing body of research, including laboratory studies, case reports and population epidemiology, reporting adverse effects of e-cig vapour, potentially linked to flavourings not found in traditional cigarettes that have been tested.[10,11,12]
- E-cig use adversely affects the cardiovascular system, with a number of studies linking them to impaired functioning of blood vessels. A recent cross-sectional study found that daily e-cigarette use is associated with increased risk of heart attacks, with an additional effect in those also smoking, and while the authors were careful not to claim a causal relationship, they noted that the findings are consistent with the growing body of research on the effects of e-cigarettes on the vascular system.[13]
- The level of nicotine and other components released varies greatly among products, even at equal levels of nicotine in the refill liquid, due to the considerable differences among the different types and brands of e-cigs. The voltage of the system also affects nicotine delivery. Consequently, it is not possible to extrapolate findings from one product to another.

Conclusion:

The health risks associated with e-cigarettes remain uncertain but they cannot be considered safe. What is certain is that statements that they are some percentage safer than conventional cigarettes are so far unjustified.

Are e-cigs effective in helping to quit smoking?

- E-cigarettes are promoted in some countries as a tool to quit conventional smoking. However a recent meta-analysis of 27 studies reports that smokers (the whole population, including heavy smokers and all other smokers) who use e-cigarettes are about 1/3 less likely to quit smoking, compared to smokers who do not use e- cigarettes.[14]
- These findings are consistent with a study using survey data from all 28 EU Member States, which also found that e-cigarette use was associated with reduced quitting.[15]
- A Cochrane Review of the small number of randomized trials concluded that the evidence for their effectiveness was of low quality[16] and a subsequent large randomised controlled trial found that they were of no additional benefit when added to provision of information and motivational text messages.[17]
- One large US study following exclusive e-cig and dual users over a year found that, while some of each group did quit or moved from dual use to sole e-cig use, more than twice as many continued to smoke, with a net increase in risk.[18]

- The largest review to date, conducted by the US National Academies of Science, Engineering and Medicine,[19] concluded that "For youth and young adults, there is substantial evidence that e-cigarette use increases the risk of ever using combustible tobacco cigarettes. For e-cigarette users who have also ever used combustible tobacco cigarettes, there is moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco cigarette smoking."

Conclusion:

Overall, e-cigarettes may help some smokers quit but, for most, e-cigarettes depress quitting.

Do e-cigarettes act as a gateway to tobacco consumption?

- Evaluating the association between e-cig use and subsequent smoking is complicated by the fact that smoking rates among young people are falling in many countries, regardless of whether e-cigs are available or not.
- A recent meta-analysis reports never-smoking adolescents and young adults who have at least tried e-cigarettes have a greater risk of starting conventional smoking (quadruple the odds compared to those that did not try e-cigarettes).[20] This cannot be explained by arguments that these young people would otherwise have started smoking.[21]
- The overall evidence has recently been summarised in a major report for the Australian government as follows: "The evidence for a strong positive relationship between use of e-cigarettes and later cigarette smoking amongst youth continues to accumulate. The evidence is consistent in observational studies and across different countries. A plausible biological pathway from use of e-cigarettes to conventional cigarette smoking operates through developing addiction to nicotine. The use of e-cigarettes with higher concentrations of nicotine is observed to have a stronger association to later conventional cigarette use."[22]
- Among adults, dual use is the predominant pattern.

Conclusion:

The net effect of making e-cigarettes widely available, at population level, seems likely to be an increase in sole and dual use of e-cigarettes and sole smoking unless there is very stringent regulation.

What is the role of the tobacco industry?

- The tobacco industry is promoting e-cigs as well as their related heated tobacco products (which they inaccurately label 'heat-not-burn') intensely, especially in smaller countries where tobacco control communities are weaker. One vehicle for this is the Philip Morris-funded Foundation for a Smoke Free World.[23] Consistent with the views of WHO and many Schools of Public Health, EUPHA's view is that public health organisations should not accept funding from this foundation under any circumstances.

Conclusion:

E-cigarettes and "smoke not burn" products are portrayed publicly by the tobacco industry as a means to reduce smoking yet, at the same time, these companies are actively promoting their combustible products.

EUPHA's view on e-cigs:

Given the available evidence, EUPHA strongly supports the precautionary approach taken in the EU Tobacco Products Directive and in statements by WHO. It is not possible, at this point, to make any claims about the relative safety of e-cigs compared to traditional cigarettes. The overall effect may well be to worsen the tobacco epidemic first by deflecting smokers from using proven smoking cessation strategies and shifting them to e-cigs, which, for most smokers, reduce successful smoking cessation, and second by deflecting discussion from measures opposed by the tobacco industry. E-cigarettes are expanding the nicotine market by attracting youth who were at low risk of initiating nicotine use with conventional cigarettes, but many of whom are now moving on to those conventional cigarettes. Even if they do not progress, promoting nicotine use to youth is bad public health policy.

EUPHA also welcomes the recent Bloomberg Stop! Initiative, which will provide important additional information on the strategies used by the tobacco industry, while commending to journalists, researchers and others the important resource Tobacco Tactics.[24]

As The Lancet noted in a recent Editorial,[25] referring to a heavily criticized UK House of Commons Science and Technology Committee report on e-cigarettes, it is "naive and premature… to confuse an absence of evidence with an absence of harm."

Meantime, the tobacco industry continues to promote its "core product", traditional cigarettes globally, and with a special focus on low and middle income countries: EUPHA urges all concerned to reduce smoking to maintain their focus on evidence-based measures that will reduce smoking.

"The market competes on addiction—the most addictive products win out. With research, they [firms], like the cigarette companies, may find out which of their ingredients is most effective in increasing sales/addiction. […]they are loath to give up these profit opportunities, no matter the costs to society."

Joseph E. Stiglitz, Recipient of the Nobel Memorial Prize in Economic Sciences, 2008

For more information, please contact the EUPHA office at office@eupha.org.

EUPHA
EUROPEAN PUBLIC HEALTH ASSOCIATION

The European Public Health Association, or EUPHA in short, is an umbrella organisation for public health associations in Europe. Our network of national associations of public health represents around 20'000 public health professionals. Our mission is to facilitate and activate a strong voice of the public health network by enhancing visibility of the evidence and by strengthening the capacity of public health professionals. EUPHA contributes to the preservation and improvement of public health in the European region through capacity and knowledge building. We are committed to creating a more inclusive Europe, narrowing all health inequalities among Europeans, by facilitating, activating, and disseminating strong evidence-based voices from the public health community and by strengthening the capacity of public health professionals to achieve evidence-based change.

EUPHA - European Public Health Association
E-mail office@eupha.org
Internet www.eupha.org
Twitter @EUPHActs

1 Special Eurobarometer 458 - Attitudes of Europeans towards tobacco and electronic cigarettes. Available at http://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/Survey/getSurveyDetail/instruments/SPECIAL/surveyKy/2146. (accessed 28th August 2018)

2 WHO Report to COP7 on ENDS/ENNDS. Available at http://www.who.int/tobacco/communications/statements/eletronic-cigarettes-january-2017/en/.

3 European Union. Tobacco Products Directive (2014/40/EU). Available at https://ec.europa.eu/health/tobacco/products/revision. (accessed 28th August 2018)

4 Public Health England. https://www.gov.uk/government/news/phe-publishes-independent-expert-e-cigarettes-evidence-review (accessed 28th August 2018)

5 McKee M, Capewell S. Evidence about electronic cigarettes: a foundation built on rock or sand? BMJ. 2015 Sep 15;351:h4863.

6 Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, Foulds J, Fagerstrom K, Letlape K, Milton A, Polosa R, Ramsey J, Sweanor D. Estimating the harms of nicotine-containing products using the MCDA approach. Eur Addict Res 2014;20(5):218-25

7 Salamanca JC, Meehan-Atrash J, Vreeke S, Escobedo JO, Peyton DH, Strongin RM. E-cigarettes can emit formaldehyde at high levels under conditions that have been reported to be non-averse to users. Sci Rep. 2018 May 15;8(1):7559.

8 Cardinale A, Nastrucci C, Cesario A, Russo P. Nicotine: specific role in angiogenesis, proliferation and apoptosis. Crit Rev Toxicol. 2012 Jan;42(1):68-89.

9 Sanner T, Grimsrud TK. Nicotine: Carcinogenicity and Effects on Response to Cancer Treatment - A Review. Front Oncol. 2015 Aug 31;5:196.

10 Scott A, Lugg ST, Aldridge K, Lewis KE, Bowden A, Mahida RY, Grudzinska FS, Dosanjh D, Parekh D, Foronjy R, Sapey E, Naidu B, Thickett DR. Pro-inflammatory effects of e-cigarette vapour condensate on human alveolar macrophages. Thorax. 2018 Aug 13. pii: thoraxjnl-2018-211663. doi: 10.1136/thoraxjnl-2018-211663.

11 Viswam D, Trotter S, Burge PS, Walters GI. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. BMJ Case Rep. 2018 Jul 6;2018. pii: bcr-2018-224350. doi: 10.1136/bcr-2018-224350

12 Miyashita L, Suri R, Dearing E, Mudway I, Dove RE, Neill DR, Van Zyl-Smit R, Kadioglu A, Grigg J. E-cigarette vapour enhances pneumococcal adherence to airway epithelial cells. Eur Respir J. 2018 Feb 7;51(2). pii: 1701592. doi: 10.1183/13993003.01592-2017.

13 Alzahrani, T., Pena, I., Temesgen, N., & Stanton Glantz, S. A. Association Between Electronic Cigarette Use and Myocardial Infarction. *Am J Prev Med* 2018; doi: 10.1016/j.amepre.2018.05.004.

14 Glantz SA, Bareham DW. E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications. Annual Review of Public Health 2108; 39(1): 215–235.

15 Kulik MC, Lisha NE, Glantz SA. E-cigarettes Associated With Depressed Smoking Cessation: A Cross-sectional Study of 28 European Union Countries. Am J Prev Med. 2018 Apr;54(4):603-609.

16 McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev. 2014;(12):CD010216. doi: 10.1002/14651858.CD010216.pub2

17 Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. N Engl J Med. 2018 Jun 14;378(24):2302-2310.

18 Coleman B, Rostron B, Johnson SE, Persoskie A, Pearson J, Stanton C, Choi K, Anic G, Goniewicz ML, Cummings KM, Kasza KA, Silveira ML, Delnevo C, Niaura R, Abrams DB, Kimmel HL, Borek N, Compton WM, Hyland A. Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013-2015). Tob Control. 2018 Apr 25. pii: tobaccocontrol-2017-054174. doi: 10.1136/tobaccocontrol-2017-054174.

19 NASEM. Public Health Consequences of E-Cigarettes. Washington DC, NASEM, 2018.

20 Soneji S, Barrington-Trimis JL,Wills TA, Leventhal A, Unger JB, et al. 2017. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. JAMA Pediatr. 171:788–97.

21 Chaffee BW, Watkins SL, Glantz SA. Electronic Cigarette Use and Progression From Experimentation to Established Smoking. Pediatrics. 2018 Apr;141(4). pii: e20173594. doi: 10.1542/peds.2017-3594.

22 Byrne S, Brindal E, Williams G, Anastasiou K, Tonkin A, Battams S, Riley M. E-cigarettes, smoking and Health : A Literature Review Update. Canberra : CSIRO, 2018

23 Daube M, Moodie R, McKee M Towards a smoke-free world? Philip Morris International's new Foundation is not credible. Lancet. 2017 Oct 14;390(10104):1722-1724.

24 http://tobaccotactics.org/index.php?title=Main_Page, last accessed, 29 August 2018

25 The Lancet. E-cigarettes—is the UK throwing caution to the wind? Lancet 2018;192: 614

Who we are

eupha.org/who-we-are

Login to EUPHA

The European Public Health Association, or EUPHA in short, is an umbrella organisation for public health associations and institutes in Europe. EUPHA was founded in 1992 by 15 members (12 countries). EUPHA now has 81 members from 47 countries:

- 40 national associations of public health
- 21 institutional members
- 7 individual members
- 1 global member
- 12 partners

EUPHA is an international, multidisciplinary, scientific organisation, bringing together around 19'000 public health experts for professional exchange and collaboration throughout Europe. We encourage a multidisciplinary approach to public health.

Our vision

Our vision is of improved health and well-being and narrowing health inequalities for all Europeans. We seek to support our members to improve health in Europe, adding value to the efforts of stakeholders in regions and states, in national and international organisations, and individual public health professionals.

Our mission

Our mission is to facilitate and activate a strong voice of the public health network by enhancing visibility of the evidence and by strengthening the capacity of public health professionals.

Working in partnership

Sustainable advancements in public health and health services can only be achieved through collaboration. EUPHA is dedicated to working in partnership with European and international intergovernmental and non-governmental organisations as well as national institutes and organisations that are aligned with EUPHA's values and commitment to improve current and future health in Europe.

Our definition of public health

EUPHA defines public health as: the science and art of preventing disease, prolonging life and promoting health and well-being through the organised efforts and informed choices or society, organisations, public and private, communities and individuals, and includes the broader area of public health, health services research, health service delivery and health systems design.

Our definition of public health professionals

EUPHA defines public health professionals as: all professionals that monitor and diagnose the health concerns of entire communities and promote healthy practices and behaviours to ensure that populations stay healthy. This definition specifically includes health services researchers.

EUPHA Members

eupha.org/eupha-members

Cookies are used for the functionality of our web site. For more information please see our Privacy policy or Ok thanks

You may select from the following member types:

Complete list | Full members | Institutional members | Individual members | Global members

Full members:

Albania

- Albanian Epidemiological Association

Armenia

- Armenian Public Health Association

Austria

- Austrian Public Health Association

Belgium

- Belgian Association of Public Health

Bosnia and Herzegovina

- Society of Social Medicine - Public Health of Bosnia and Herzegovina
- Partnership for Public Health

Bulgaria

- Bulgarian Public Health Association

Croatia

- Croatian Public Health Association

Czech Republic

- Czech Society of Public Health and Management of Health Services

Denmark

- Danish Society of Public Health

Estonia

- Health Promotion Union of Estonia

Finland

Society for Social Medicine in Finland
France
Société Française de Santé Publique
Germany
Kooperationsverbund 'Hochschulen für Gesundheit'
German Society of Medical Sociology
German Public Health Association - DGPH
Hungary
Hungarian Association of Public Health Training and Research Institutions - NKE
Israel
Israeli Association of Public Health Physicians
Italy
Italian Society of Hygiene, Preventive Medicine and Public Health
Kazakhstan
Central Asian Public Health Association
Latvia
Public health Association of Latvia
Lithuania
Lithuanian Public Health Association
Macedonia
Macedonian Association of Social Medicine - SZSM
Malta
Malta Association of Public Health Medicine
Netherlands
Netherlands Public Health Federation
Norway
Norwegian Public Health Association
Poland
Polish Society of Public Health
Portugal
Portuguese Association of Public Health Doctors
Portuguese Association for the Public Health Promotion
Romania
Romanian Association for Public Health

Serbia
Serbian Public Health Association
Slovakia
SAVEZ - Slovak Public Health Association
Slovenia
Slovenian Medical Society - Slovenian Preventive Medicine Society
Chamber of Sanitary Engineers of Slovenia - Institute of Public and Environmental Health
Spain
SESPAS
Sweden
Swedish Association of Social Medicine
Switzerland
Swiss Society for Public Health
Turkey
Turkish Public Health Association
United Kingdom
Society for Social Medicine
Faculty of Public Health

EUPHA partners

Agency for Public Health Education Accreditation
Mr Julien Goodman, Ave de l'Armée / Legerlaan 10, 1040 Brussels, Belgium
julien.goodman@aphea.net, http://www.aphea.net

ASPHER
Mr Robert Otok, UM Brussels Campus, Avenue de l'Armée / Legerlaan 10, 1040 Brussels, Belgium
robert.otok@aspher.org, http://www.aspher.org

EACH
Prof Sandra Van Dulmen, PO Box 1568, 3500 BN Utrecht, Netherlands
s.vandulmen@nivel.nl, http://www.each.eu

ESQH
Mr Noel Harrington, Shelbourne Rd, - Limerick, Ireland
noel.harrington@hse.ie, http://www.esqh.net

European Association of Dental Public Health
Dr Colwyn Jones, c/o 1 South Gyle Crescent, EH12 9EB Edinburgh, United Kingdom
colwyn.jones@nhs.net, http://www.eadph.org

European Centre for Disease Prevention and Control
Mrs Barbora Kinross, Gustav III:s boulevard 40, 169 73 Solna, Stockholm, Sweden
barbora.kinross@ecdc.europa.eu

European Forum for Primary Care
Dr Diederik Aarendonk, Otterstraat 118-124, PO Box 1568, 3500 BN Utrecht, Netherlands
d.aarendonk@euprimarycare.org, http://www.euprimarycare.org

European Health Management Association
Mr Usman Khan, Rue Belliard 15-17, 1040 Brussels, Belgium
usman.khan@ehma.org, http://www.ehma.org

European Pediatrics Association/Union of National Peadiatric Societies and Associations (EPA/UNESPA)
Prof Massimo Pettoello-Mantovani, Viale Pinto, 1, 71121 Foggia, Italy
mpm@unifg.it, http://www.epa-unepsa.org/

European Society for Prevention Research (EUSPR)
Dr David Foxcroft, Marston Campus, OX3 0FL Oxford, United Kingdom
david.foxcroft@brookes.ac.uk

Global Law Enforcement and Public Health Association (GLEPHA)
Prof Nick Crofts, -, - Melbourne, Australia
nick.crofts@unimelb.edu.au, http://www.cleph.com.au

IUHPE - Europe
Dr Ursel Broesskamp-Stone, Dufourstrasse 30, Postfach 311, CH-3000 Bern 6, Switzerland
ullaair99@googlemail.com, http://www.healthpromotion.ch

UEMS - Section for Public Health
Dr Ragnar Westerling, BMC, Box 564, SE 75237 Uppsala, Sweden
Ragnar.Westerling@pubcare.uu.se, http://www.pubcare.uu.se

REVIEW ARTICLE

Harmful effects of nicotine

Aseem Mishra, Pankaj Chaturvedi, Sourav Datta, Snita Sinukumar, Poonam Joshi, Apurva Garg

Department of Surgical Oncology, Head and Neck Services, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Address for correspondence:
Dr. Pankaj Chaturvedi, Professor, Department of Surgical Oncology, Head and Neck Services, Tata Memorial Hospital, Dr. E. Borges Road, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: chaturvedi.pankaj@gmail.com

ABSTRACT

With the advent of nicotine replacement therapy, the consumption of the nicotine is on the rise. Nicotine is considered to be a safer alternative of tobacco. The IARC monograph has not included nicotine as a carcinogen. However there are various studies which show otherwise. We undertook this review to specifically evaluate the effects of nicotine on the various organ systems. A computer aided search of the Medline and PubMed database was done using a combination of the keywords. All the animal and human studies investigating only the role of nicotine were included. Nicotine poses several health hazards. There is an increased risk of cardiovascular, respiratory, gastrointestinal disorders. There is decreased immune response and it also poses ill impacts on the reproductive health. It affects the cell proliferation, oxidative stress, apoptosis, DNA mutation by various mechanisms which leads to cancer. It also affects the tumor proliferation and metastasis and causes resistance to chemo and radio therapeutic agents. The use of nicotine needs regulation. The sale of nicotine should be under supervision of trained medical personnel.

Key words: *Addiction, cancer, cardiovascular, gastrointestinal, nicotine, respiratory*

INTRODUCTION

Tobacco is the leading cause of preventable cancers. WHO estimated around 1.27 billion tobacco users worldwide. Tobacco consumption alone accounts for nearly 5.4 million deaths per year and one billion people may die in this century if global tobacco consumption remained at the current levels.[1] An international treaty spearheaded by WHO in 2003 and signed by 170 countries, aims to encourage governments to reduce the production, sales, distribution advertisement and promotion of tobacco products. Despite strong opposition from the Industry, the treaty has been making steady progress in achieving its goal of comprehensive tobacco control around the world.[2] As tobacco consumption is being curbed, there is a growing demand for cessation. Pharmacological treatment of nicotine addiction remains an active area of research. There are many nicotine preparations (nicotine gums, patches, e cigarettes and inhalational agents) that are freely available in most parts of the world. These products are being heavily promoted and marketed as magical remedies. Nicotine gums are available in 2 mg and 4 mg preparation that deliver around 1 mg and 3 mg nicotine to the blood stream respectively. E-cigarette, a sophisticated nicotine delivery device, delivers nicotine in a vapor form and it closely mimics the act of smoking. Currently, these products constitute approximately 1% of total nicotine consumption and are showing an increasing trend in most countries.[3]

Nicotine is well known to have serious systemic side effects in addition to being highly addictive. It adversely affects the heart, reproductive system, lung, kidney etc. Many studies have consistently demonstrated its carcinogenic potential. [Table 1] The only other known use of nicotine has been as an insecticide since 17th century.[4] After World War II, its use has declined owing to the availability of cheaper, more potent pesticides that are less harmful to mammals. The environment Protection Agency of United States has banned use of nicotine as a pesticide from 1st January 2014.[4] India, one of the largest producer and exporter of nicotine sulphate, has progressively banned its use as agricultural pesticide.[5] We undertook this review to evaluate the systemic adverse effects of nicotine.

Access this article online

Quick Response Code:

Website: www.ijmpo.org

DOI: 10.4103/0971-5851.151771

MATERIALS AND METHODS

A computer aided search of the Medline and PubMed databases was done using different combination of the keywords "nicotine," "chemical composition," "history," "metabolism," "addiction," "cancer," "toxic," "endocrine system," "cardiovascular system," "respiratory system,"

Table 1: Studies showing nicotine as a carcinogen

Author	Model	System	References
Jensen *et al*., 2012	Animal	Gastrointestinal	[50]
Schuller *et al*., 1995	Animal	Lung cancer	[45]
Nakada *et al*. 2012	Human	Tumor promoter in lung cancer	[46]
Al-Wadei *et al*., 2009	Mice	Pancreatic cancer	[56]
Treviño *et al*., 2012	Animal	Pancreatic cancer	[58]
Crowley-Weber *et al*., 2003	Human	Pancreatc cancer	[57]
Chen *et al*., 2011	Human	Breast cancer	[59]
Wassenaar *et al*., 2013	Human	Lung	[44]

"lung carcinogenesis, "gastrointestinal system," "immune system," "ocular," " cataract," "central nervous system," "renal system," " reproductive system," "menstrual cycle," "oocytes," "foetus,". Initial search buildup was done using "Nicotine/adverse effects" [Mesh], which showed 3436 articles. Articles were analyzed and 90 relevant articles were included in the review. All the animal and human studies that investigated the role of nicotine on organ systems were analyzed. Studies that evaluated tobacco use and smoking were excluded. All possible physiological effects were considered for this review. We did not exclude studies that reported beneficial effects of nicotine. The objective was to look at the effects of nicotine without confounding effects of other toxins and carcinogens present in tobacco or tobacco smoke.

CHEMICAL PROPERTIES AND METABOLISM

Nicotine was first extracted from tobacco by German physicians Wilhelm Heinrich Posselt and Karl Ludwig Reimann. Nicotine, a strong alkaloid, in its pure form is a clear liquid with a characteristic odour. It turns brown on exposure to air. It is water soluble and separates preferentially from organic solvents. It is an amine composed of pyridine and pyrrolidine rings.

Nicotine is a dibasic compound and the availability and absorption in human body depends upon the pH of the solution.[7] The absorption can occur through oral mucosa, lungs, skin or gut.[6] The increase in pH of a solution causes an increase in concentrations of uncharged lipophilic nicotine, in this form it can actively pass through all biological membranes.[7] The addition of slaked lime and catechu to tobacco increases the absorption of nicotine from the oral cavity.

Nicotine once ingested, is absorbed and metabolized by the liver. The metabolic process can be categorized into two phases. In phase I there is microsomal oxidation of the nicotine via multiple pathways.[8] This leads to formation of various metabolites like cotinine and nornicotine, demethyl cotinine, trans-3-hydroxy-cotinine and d-(3-pyridyl)-g-methylaminobutyric acid.[9,10] Thereafter in phase II there is N'-and O'-glucuronidation of the metabolites and excretion via urine, feces, bile, saliva, sweat etc.[11,12] 5-10% of elimination is by renal excretion of unchanged nicotine, however there is reabsorption from the bladder when the urinary pH is high.[14] There is evidence that nitrosation of nicotine *in vivo* could lead to formation of N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).[13] which are known to be highly carcinogenic. Inflammation in the oral cavity increases risk of endogenous nitrosation.

MECHANISM OF ACTION

Nicotine acts via 3 major mechanisms, producing physiological and pathological effects on a variety of organ systems.[15,16]

1. Ganglionic transmission.
2. Nicotinic acetylcholine receptors (nAChRs) on chromaffin cells via catecholamines.
3. Central nervous system (CNS) stimulation of nAChRs.

Brain imaging studies demonstrate that nicotine acutely increases activity in the prefrontal cortex and visual systems. There is release of a variety of neurotransmitters important in drug-induced reward. Nicotine also causes an increased oxidative stress and neuronal apoptosis, DNA damage, reactive oxygen species and lipid peroxide increase. nAChRs were originally thought to be limited to neuronal cells, however, studies have identified functional nAChRs in tissues outside the nervous system. Actions on nicotinic receptors produce a wide variety of acute and long-term effects on organ systems, cell multiplication and apoptosis, throughout the body.

IMMEDIATE EFFECTS AND TOXICITY

Nicotine on direct application in humans causes irritation and burning sensation in the mouth and throat, increased salivation, nausea, abdominal pain, vomiting and diarrhea.[17] Gastrointestinal effects are less severe but can occur even after cutaneous and respiratory exposure.[18] Predominant immediate effects as seen in animal studies and in humans consist of increase in pulse rate and blood pressure. Nicotine also causes an increase in plasma free fatty acids, hyperglycemia, and an increase in the level of catecholamines in the blood.[19,20] There is reduced coronary blood flow but an increased skeletal muscle blood flow.[20,22] The increased rate of respiration causes hypothermia, a

hypercoagulable state, decreases skin temperature, and increases the blood viscosity.

Nicotine is one of the most toxic of all poisons and has a rapid onset of action. Apart from local actions, the target organs are the peripheral and central nervous systems. In severe poisoning, there are tremors, prostration, cyanosis, dypnoea, convulsion, progression to collapse and coma. Even death may occur from paralysis of respiratory muscles and/or central respiratory failure with a LD50 in adults of around 30-60 mg of nicotine. In children the LD50 is around 10 mg.[23]

GREEN TOBACCO SICKNESS

This is an acute form of nicotine toxicity that is known to occur due to handling of green tobacco leaves, with symptoms lasting from 12 to 24 h. The acute symptoms include headache, nausea, vomiting, giddiness, loss of appetite, fatigue and tachyarrythmias.[24] No significant mortality has been reported due to green tobacco sickness (GTS) but it significantly affects the health of workers in the tobacco industry.[25]

NICOTINE ADDICTION

Nicotine is one of the most addicting agent. The US surgeon general (2010) has concluded nicotine to be as addictive as cocaine or heroin. Nicotine interacts with the nicotinic acetyl choline receptors and stimulates the dopaminergic transmission.[26] This in turn stimulates the reward centre and is responsible for the mood elevation and apparent improvement in cognitive function.[27] With chronic stimulation by nicotine the GABAergic neurons are desensitized and thus lose their inhibitory effect on dopamine.[28] This in turn reinforces the addiction by inducing craving. This effect has been shown to affect the CYP2A6 gene and leads to heritable dependence to nicotine. Studies have shown the nicotine dependence to be transmitted maternally and grand maternally by epigenetic mechanism.[29]

EFFECTS ON METABOLISM

Nicotine causes catecholamine release and stimulates the autonomic system. There is increased glycogen synthesis due to α-adrenoceptor stimulation. This leads to reduction in the fasting blood glucose levels. It also causes lipolysis thus decreasing body weight. Nicotine affects insulin resistance and predisposes to metabolic syndrome. In an animal study prenatal exposure was toxic to pancreatic β-cell and leads to decreased B cell population, thus increasing the risk of diabetes.[30,31]

NICOTINE AND CANCER

The stimulation of nAChRs by nicotine has biologic effects on cells important for initiation and progression of cancer.[26] It activates signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells. In addition, nicotine is a precursor of tobacco specific nitrosamines (TSNAs), through nitrosation in the oral cavity.[32,33] It is shown that nitrosation of nicotine could lead to formation of NNN and NNK. This effect of nicotine may be important because of its high concentration in tobacco and nicotine replacement products.[13] NNN and NNK are strongly carcinogenic.[34]

Nicotine forms arachidonic acid metabolites which cause increased cell division. Binding to Bcl-2 and action on vascular endothelial growth factor and cyclooxygenase-2 (COX-2) causes increased cancer proliferation and survival.[35,36] Promotion of tumor angiogenesis accelerates tumor growth which is mediated by β-adrenergic activation and stimulation of nAChRs.[35,37-39] Nicotine also suppresses apoptosis by phosphorylation mediated extracellular signal regulated kinases of Bcl-2.[40,41] Recent studies show that nicotine, activates nuclear factor kappa B (NF-kB)-dependent survival of cancer cell and proliferation.[42]

In normal cells, nicotine can stimulate properties consistent with cell transformation and the early stages of cancer formation, such as increased cell proliferation, decreased cellular dependence on the extracellular matrix for survival, and decreased contact inhibition. Thus, the induced activation of nAChRs in lung and other tissues by nicotine can promote carcinogenesis by causing DNA mutations[26] Through its tumor promoter effects, it acts synergistically with other carcinogens from automobile exhausts or wood burning and potentially shorten the induction period of cancers[43] [Table 2].

LUNG CARCINOGENESIS

A study relates lung carcinogenesis by nicotine due to genetic variation in CYP2B6.[44] Its simultaneous exposure with hyperoxia has been found to induce cancer in hamsters.[45] Cotinine has been found to promote lung tumorigenesis by inhibiting anti-apoptotic pathway.[46] Nuclear translocation of ARB1 gene by nicotine has found in proliferation and progression of nonsmall-cell lung cancer. Several Studies have shown that nicotine has significant role in tumor progression and metastasis via CXCR4 and increased angiogenesis.[36,47] Carriers of the lung-cancer-susceptibility loci in their DNA extract more nicotine. Smokers carrying the gene CHRNA3 and CHRNA5 were found to extract more nicotine and cells

Table 2: Studies showing the role of nicotine as tumor promoter

Author	System	References
Chu *et al.*, 2013	Gastrointestinal tumor growth	[71]
Improgo *et al.*, 2013	Lung	[47]
Heusch and Maneckjee, 1998	Lung	[40]
Mai *et al.*, 2003	Lung	[41]
Shin *et al.*, 2005	Gastric	[36]
Heeschen *et al.*, 2001	Tumor growth and angiogenesis	[35]
Zhu *et al.*, 2003	Tumor angiogenesis and growth	[39]
Heusch and Maneckjee, 1998	Lung	[40]
Le Marchand *et al.*, 2008	Lung	[48]
Perez-Sayans *et al.*, 2010	GIT	[51]
Zhang *et al.*, 2010	GIT	[49]
Petros *et al.*, 2012	Chemoresistance	[53]
Trevino *et al.*, 2012	Tumor growth and chemoresistance	[90]

GIT – Gastrointestinal tract

were thus exposed to a higher internal dose of carcinogenic nicotine-derived nitrosamines.[48] Additionally modulation of the mitochondrial signaling pathway leads to resistance to the chemotherapeutic agents.[49]

GASTRO INTESTINAL CARCINOGENESIS

The carcinogenic role may be mediated by the MAPK/COX-2 pathways, α-7 nAchR and β-adrenergic receptor expression, and mi RNAs α-BTX anatagonist.[50] Nicotine forms adducts with liver DNA which enhances its mutagenic potential.[49,51,52] activation of cell-surface receptors by nicotine stimulates downstream kinases that can mediate resistance to chemotherapy. It has been shown by the finding that smokers who continue to smoke during chemotherapy have a worse prognosis. Moreover they also have increased toxicity and lower efficacy of chemo therapeutic drugs.[53] Nicotine affects the periostin gene, α-7-nAChR and e-cadherin suppression which explains the mechanism of gastric cancer growth, invasion and metastasis.[54,55] Nicotine negatively impacts tumor biology by promoting angiogenesis, tumor invasion and increased risk of metastasis.[53]

PANCREATIC CANCER

Nicotine has been found to induce pancreatic adenocarcinoma in mice model, by stimulating the stress neurotransmitters.[56,57] In another study nicotine promoted the growth of nonsmall cell lung cancer and pancreatic cancer in a receptor dependent fashion. It also increased tumor metastasis, and resistance to gemcitabine induced apoptosis, causing chemoresistance.[58] The MUC-4 upregulation, NF-kB and GRP78 activation and Id1 expression by Src dependent manner are the probable mechanism leading to tumor growth, metastasis and chemotherapeutic drug resistance.[57,58]

BREAST CANCER

Nicotine causes α9-nAChR-mediated cyclin D3 overexpression which might cause transformation of normal breast epithelial cells and induce cancer. Nicotine and cotinine has been found to be present in the breast fluid of lactating women.[59] Several studies have found that α9-nAChR mediated mechanism leads to increased tumor growth, metastasis and tumor cells resistant to chemotherapeutic drugs in breast cancer.[59,60]

CARDIOVASCULAR SYSTEM

The acute hemodynamic effects of cigarette smoking or smokeless tobacco are mediated primarily by the sympathomimetic action. The intensity of its hemodynamic effect is greater with rapid nicotine delivery.[61] Nicotine causes catecholamine release both locally and systemically leading to an increase in heart rate, blood pressure and cardiac contractility. It reduces blood flow in cutaneous and coronary vessels; and increases blood flow in the skeletal muscles. Due to restricted myocardial oxygen delivery there is reduced cardiac work. In a study, chewing a low dose (4 mg) of nicotine gum by healthy nonsmokers blunted the increase in coronary blood flow that occurs with increased heart rate produced by cardiac pacing.[21] Thus, persistent stimulation by nicotine can contribute to Coronary Vascular Disease by producing acute myocardial ischemia. In the presence of coronary disease, myocardial dysfunction can be worsened. In a placebo-controlled experiment that produced transient ischemia in anesthetized dogs myocardial dysfunction was produced at doses, that did not alter heart rate, blood pressure, or blood flow or myocyte necrosis.[62]

Nicotine alters the structural and functional characteristics of vascular smooth muscle and endothelial cells.[63] It enhances release of the basic fibroblast growth factor and inhibits production of transforming growth factor-β1.[64] These effects lead to increased DNA synthesis, mitogenic activity, endothelial proliferation and increases atherosclerotic plaque formation.[65] Neovascularization stimulated by nicotine can help progression of atherosclerotic plaques.[66] These effects lead to myointimal thickening and atherogenic and ischemic changes, increasing the incidence of hypertension and cardiovascular disorders. A study on

dogs demonstrated the deleterious effects of nicotine on the heart.[67]

Nicotinic acetylcholine receptor's actions on vascular smooth muscle proliferation and plaque neovascularization increases the risk of peripheral arterial disorders. In a murine model of hind limb ischemia, short-term exposure to nicotine paradoxically increased capillary density and improved regional blood flow in the ischemic hind limb.[35] However, long-term exposure to nicotine for 16 weeks (about one-third of the life span of a mouse) before induction of ischemia obliterated angiogenic response to nicotine.[68]

RESPIRATORY SYSTEM

The effects of nicotine on respiratory system are twofold. One, directly by a local exposure of lungs to nicotine through smoking or inhaled nicotine, and second via a central nervous system mechanism. Nicotine plays a role in the development of emphysema in smokers, by decreasing elastin in the lung parenchyma and increasing the alveolar volume. Nicotine stimulates vagal reflex and parasympathetic ganglia and causes an increased airway resistance by causing bronchoconstriction.[69] Nicotine alters respiration through its effects on the CNS. The simultaneous effect of bronchoconstriction and apnea increases the tracheal tension and causes several respiratory disorders. In a study microinjection of nicotine were administered to the prebotzinger complex and adjacent nuclei in the brain. The firing pattern of the brain signals and breathing pattern were monitored. There was an increased frequency of bursts and decreased amplitude and a shallow and rapid rhythm of respiration.[70]

GASTROINTESTINAL SYSTEM

Nicotine use has been associated with Gastro Esophageal Reflux Disorder (GERD) and peptic ulcer disease (PUD).[36,71] This effect is mediated by increased gastric acid, pepsinogen secretion and stimulatory effects on vasopressin. The action on the cyclo-oxygenase pathway also increases the risk of GERD and PUD.[72] Nicotine causes smooth muscle relaxation by action of endogenous nitric oxide as a nonadrenergic noncholinergic neurotransmitter.[73] The decrease in tone of the colon and gastric motility and reduced lower esophageal sphincteric pressure might be the reason of increased incidence of GERD.[74]

There is an increased incidence of treatment resistant *Helicobacter pylori* infection in smokers. It potentiates the effects of toxins of *H. pylori* by its action on the gastric parietal cells.[75] This effect could be due to histamine mediated response of nicotine.

IMMUNOLOGICAL SYSTEM

Nicotine has been known to be immunosuppressive through central and peripheral mechanisms. It impairs antigen and receptor mediated signal transduction in the lymphoid system leading to decreased immunological response. The T-cell population is reduced due to arrest of cell cycle. Even the macrophage response, which forms the first line defense against tuberculosis becomes dysfunctional and causes increased incidence of tuberculosis.[76] The migration of fibroblasts and inflammatory cells to the inflamed site is reduced. There is decreased epithelialization and cell adhesion and thus there is a delayed wound healing as well as increased risk of infection in nicotine exposed individuals.

The action on the hypothalamo-pituitary adrenal axis and autonomic nervous system stimulation via sympathetic and parasympathetic pathways affects the immune system. The adrenocorticotropic hormone (ACTH) secretion pathway and corticotrophin release is affected and this causes immunosuppression.[77]

OCULAR SYSTEM

Nicotine promotes pathologic angiogenesis and retinal neovascularization in murine models. It causes age-related macular degeneration in mice.[78] In a clinical study, the most virulent form of age-related maculopathy was associated with retinal neovascularization that contributed to visual deterioration. Tobacco smokers are known to be at greater risk of age-related macular degeneration than are nonsmokers.[79] In animal model, spraguely Dawley rats with type 1 diabetes treated with nicotine, developed cataract.[80] Thus the syngergistic relationship between nicotine and glucose metabolism exaggerating diabetes might cause accelerated cataract formation. There is synergistic relationship between nicotine and glucose metabolism which increases the risk of diabetes mellitus. This might cause accelerated cataract formation.

RENAL SYSTEM

Risk of chronic kidney disease in smokers is high. Cigarette smoking has been found to increase albumin excretion in urine, decrease glomerular filtration rate, causes increased incidence of renal artery stenosis and is associated with an increased mortality in patients with end-stage renal disease. The pathogenesis of renal effects is due to the action of nicotine via COX-2 isoform induction. The COX-2

isoforms causes increased glomerular inflammation, acute glomerulonephritis and ureteral obstruction.[81] There is impaired response of kidneys to the increased systemic blood pressure in smokers. This loss of renoprotective mechanism in smokers also leads to pathogenetic effects of nicotine on the renal system.[82]

REPRODUCTIVE SYSTEM – MALES

Nitrous oxide liberated from parasympathetico-nergic nerves plays a pivotal role in generating immediate penile vasodilatation and corpus cavernosum relaxation, and NO derived from endothelial cells contributes to maintaining penile erection. Nicotine causes impairment of NO synthesis. This may lead to loss of penile erections and erectile dysfunction.[83]

Various animal studies suggest that nicotine causes seminiferous tubules degeneration, disrupts the spermatogenesis and at cellular level, affect germ cell structure and function in males.[84] It decreases testosterone levels which is secondary to decreased production of StAR.[85] StAR is the protein which plays an important role in testosterone biosynthesis.

REPRODUCTIVE SYSTEM – FEMALE

Menstrual cycle

Nicotine by inhibiting the 21 hydoxylase causes hypoestrogenic state. It shunts the metabolites to formation of androgen. This leads to chronic anovulation and irregular menstrual cycles. Nicotine can predispose the endometrium to inappropriate cytokine production and irregular bleeding.[86] There is consistent evidence that increase in follicle-stimulating hormone levels and decreases in estrogen and progesterone that are associated with cigarette smoking in women, is atleast in part due to effects of nicotine on the endocrine system.[26]

Effect on oocytes

Nicotine affects the ovaries and alters the production of oocytes in various animal studies. Nicotine-treated oocytes appeared nonspherical with rough surface and torn and irregular zona-pellucida. Nicotine also caused disturbed oocyte maturation. There is a decreased blood flow to the oviducts and thus impaired fertilization.[87]

Peri-natal effects

Maternal smoking has always been known to have deleterious effects on the fetal outcome. There is an increased incidence of intrauterine growth restriction, still birth, miscarriages and mental retardation.[88] Various animal studies show retarded fetal growth and lower birth weight when treated perinatally with nicotine. The lower levels of ACTH and cortisol due to nicotine are probable reasons for the incidence of lower birth weight in the newborns.[89]

Maternal as well as grand maternal smoking has been found to increase risk of pediatric asthma. Another serious and important effect is the transgenic transmission of the addictive pattern.[29]

CONCLUSION

Nicotine is the fundamental cause of addiction among tobacco users. Nicotine adversely affects many organs as shown in human and animal studies. Its biological effects are widespread and extend to all systems of the body including cardiovascular, respiratory, renal and reproductive systems. Nicotine has also been found to be carcinogenic in several studies. It promotes tumorigenesis by affecting cell proliferation, angiogenesis and apoptotic pathways. It causes resistance to the chemotherapeutic agents. Nicotine replacement therapy (NRT) is an effective adjunct in management of withdrawal symptoms and improves the success of cessation programs. Any substantive beneficial effect of nicotine on human body is yet to be proven. Nicotine should be used only under supervision of trained cessation personnel therefore its sale needs to be strictly regulated. Needless to say, that research for safer alternative to nicotine must be taken on priority.

REFERENCES

1. WHO Data. Tobacco Fact Sheet; No. 339. Available from: http://www.who.int/mediacentre/factsheets/fs339/en. [Last accessed on 2015 Jan 29].
2. WHO Framework Convention on Tobacco Control. Available from: http://www.who.int/fctc/about/en. [Last accessed on 2014 Sep 27].
3. Fagerström K. The nicotine market: An attempt to estimate the nicotine intake from various sources and the total nicotine consumption in some countries. Nicotine Tob Res 2005;7:343-50.
4. US Environmental Protection Agency. Nicotine: Product cancellation order.Fed Regist 2009 Available from: http://www.epa.gov/fedrgstr/EPA-PEST/2009/June/Day-03/p12561.htm [Last accessed 2014 Nov 01].
5. APIB. Banned Pesticides. Available from: http://megapib.nic.in/Int_pest_bannedPest.htm. [Last updated on 2002 Mar 25; Last accessed on 2014 Sep 27].
6. Langone JJ, Gjika HB, Van Vunakis H. Nicotine and its metabolites. Radioimmunoassays for nicotine and cotinine. Biochemistry 1973;12:5025-30.
7. Schievelbein H, Eberhardt R, Löschenkohl K, Rahlfs V, Bedall FK. Absorption of nicotine through the oral mucosa I. Measurement of nicotine concentration in the blood after application of nicotine and total particulate matter. Inflamm Res 1973;3:254-8.
8. Armitage AK, Turner DM. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. Nature 1970;226:1231-2.

9. Sobkowiak R, Lesicki A. Absorption, metabolism and excretion of nicotine in humans. Postepy Biochem 2013;59:33-44.
10. Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, Tyndale RF, *et al*. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther 2004;76:64-72.
11. Nakajima M, Tanaka E, Kwon JT, Yokoi T. Characterization of nicotine and cotinine N-glucuronidations in human liver microsomes. Drug Metab Dispos 2002;30:1484-90.
12. Seaton MJ, Kyerematen GA, Vesell ES. Rates of excretion of cotinine, nicotine glucuronide, and 3-hydroxycotinine glucuronide in rat bile. Drug Metab Dispos 1993;21:927-32.
13. Stepanov I, Carmella SG, Briggs A, Hertsgaard L, Lindgren B, Hatsukami D, *et al*. Presence of the carcinogen N'-nitrosonornicotine in the urine of some users of oral nicotine replacement therapy products. Cancer Res 2009;69: 8236-40.
14. Borzelleca JF. Drug movement from the isolated urinary bladder of the rabbit. Arch Int Pharmacodyn Ther 1965;154:40-50.
15. Dani JA, Ji D, Zhou FM. Synaptic plasticity and nicotine addiction. Neuron 2001;31:349-52.
16. Jones S, Sudweeks S, Yakel JL. Nicotinic receptors in the brain: Correlating physiology with function. Trends Neurosci 1999;22:555-61.
17. Smith EW, Smith KA, Maibach HI, Andersson PO, Cleary G, Wilson D. The local side effects of transdermally absorbed nicotine. Skin Pharmacol 1992;5:69-76.
18. Sonnenberg A, Hüsmert N. Effect of nicotine on gastric mucosal blood flow and acid secretion. Gut 1982;23:532-5.
19. Benowitz NL. Nicotine and smokeless tobacco. CA Cancer J Clin 1988;38:244-7.
20. Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron 1996;16:905-8.
21. Kaijser L, Berglund B. Effect of nicotine on coronary blood-flow in man. Clin Physiol 1985;5:541-52.
22. Jolma CD, Samson RA, Klewer SE, Donnerstein RL, Goldberg SJ. Acute cardiac effects of nicotine in healthy young adults. Echocardiography 2002;19:443-8.
23. Centre for Disease Control and Prevention. Available from: http://www.cdc.gov/niosh/idlh/54115.html. [Last accessed on 2014 Sep 27].
24. Parikh JR, Gokani VN, Doctor PB, Kulkarni PK, Shah AR, Saiyed HN. Acute and chronic health effects due to green tobacco exposure in agricultural workers. Am J Ind Med 2005;47:494-9.
25. Weizenecker R, Deal WB. Tobacco cropper's sickness. J Fla Med Assoc 1970;57:13-4.
26. US Department of Health and Human Services. Mental Health. Available from: http://www.samhsa.gov/data/2k12/MHUS2010/MHUS-2010.pdf. [Last accessed on 2014 Sep 27].
27. Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. J Neurobiol 2002;53:606-17.
28. Vezina P, McGehee DS, Green WN. Exposure to nicotine and sensitization of nicotine-induced behaviors. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1625-38.
29. Leslie FM. Multigenerational epigenetic effects of nicotine on lung function. BMC Med 2013;11:27.
30. Bruin JE, Kellenberger LD, Gerstein HC, Morrison KM, Holloway AC. Fetal and neonatal nicotine exposure and postnatal glucose homeostasis: Identifying critical windows of exposure. J Endocrinol 2007;194:171-8.
31. Somm E, Schwitzgebel VM, Vauthay DM, Camm EJ, Chen CY, Giacobino JP, *et al*. Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the control of body weight and glucose metabolism later in life. Endocrinology 2008;149:6289-99.
32. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83:1-1438.
33. Hoffmann D, Adams JD. Carcinogenic tobacco-specific N-nitrosamines in snuff and in the saliva of snuff dippers. Cancer Res 1981;41(11 Pt 1):4305-8.
34. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risk Hum 2007;89:455-7.
35. Heeschen C, Jang JJ, Weis M, Pathak A, Kaji S, Hu RS, *et al*. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med 2001;7:833-9.
36. Shin VY, Wu WK, Chu KM, Wong HP, Lam EK, Tai EK, *et al*. Nicotine induces cyclooxygenase-2 and vascular endothelial growth factor receptor-2 in association with tumor-associated invasion and angiogenesis in gastric cancer. Mol Cancer Res 2005;3:607-15.
37. Natori T, Sata M, Washida M, Hirata Y, Nagai R, Makuuchi M. Nicotine enhances neovascularization and promotes tumor growth. Mol Cells 2003;16:143-6.
38. Wong HP, Yu L, Lam EK, Tai EK, Wu WK, Cho CH. Nicotine promotes colon tumor growth and angiogenesis through beta-adrenergic activation. Toxicol Sci 2007;97:279-87.
39. Zhu BQ, Heeschen C, Sievers RE, Karliner JS, Parmley WW, Glantz SA, *et al*. Second hand smoke stimulates tumor angiogenesis and growth. Cancer Cell 2003;4:191-6.
40. Heusch WL, Maneckjee R. Signalling pathways involved in nicotine regulation of apoptosis of human lung cancer cells. Carcinogenesis 1998;19:551-6.
41. Mai H, May WS, Gao F, Jin Z, Deng X. A functional role for nicotine in Bcl2 phosphorylation and suppression of apoptosis. J Biol Chem 2003;278:1886-91.
42. Tsurutani J, Castillo SS, Brognard J, Granville CA, Zhang C, Gills JJ, *et al*. Tobacco components stimulate Akt-dependent proliferation and NFkappaB-dependent survival in lung cancer cells. Carcinogenesis 2005;26:1182-95.
43. Slotkin TA, Seidler FJ, Spindel ER. Prenatal nicotine exposure in rhesus monkeys compromises development of brainstem and cardiac monoamine pathways involved in perinatal adaptation and sudden infant death syndrome: Amelioration by vitamin C. Neurotoxicol Teratol 2011;33:431-4.
44. Wassenaar CA, Dong Q, Amos CI, Spitz MR, Tyndale RF. Pilot study of CYP2B6 genetic variation to explore the contribution of nitrosamine activation to lung carcinogenesis. Int J Mol Sci 2013;14:8381-92.
45. Schuller HM, McGavin MD, Orloff M, Riechert A, Porter B. Simultaneous exposure to nicotine and hyperoxia causes tumors in hamsters. Lab Invest 1995;73:448-56.
46. Nakada T, Kiyotani K, Iwano S, Uno T, Yokohira M, Yamakawa K, *et al*. Lung tumorigenesis promoted by anti-apoptotic effects of cotinine, a nicotine metabolite through activation of PI3K/Akt pathway. J Toxicol Sci 2012;37: 555-63.
47. Improgo MR, Soll LG, Tapper AR, Gardner PD. Nicotinic acetylcholine receptors mediate lung cancer growth. Front Physiol 2013;4:251.
48. Le Marchand L, Derby KS, Murphy SE, Hecht SS, Hatsukami D, Carmella SG, *et al*. Smokers with the CHRNA lung cancer-associated variants are exposed to higher levels of nicotine equivalents and a carcinogenic tobacco-specific nitrosamine. Cancer Res 2008;68:9137-40.
49. Zhang D, Ma QY, Hu HT, Zhang M. β2-adrenergic antagonists suppress pancreatic cancer cell invasion by inhibiting CREB, NFκB and AP-1. Cancer Biol Ther 2010;10:19-29.
50. Jensen K, Afroze S, Munshi MK, Guerrier M, Glaser SS. Mechanisms for nicotine in the development and progression of gastrointestinal cancers. Transl Gastrointest Cancer 2012;1:81-87.
51. Pérez-Sayáns M, Somoza-Martín JM, Barros-Angueira F, Diz PG, Gándara Rey JM, García-García A. Beta-adrenergic receptors in cancer: Therapeutic implications. Oncol Res 2010;19:45-54.
52. Majidi M, Al-Wadei HA, Takahashi T, Schuller HM. Nongenomic beta estrogen receptors enhance beta1 adrenergic signaling induced by the nicotine-derived carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

in human small airway epithelial cells. Cancer Res 2007;67:6863-71.
53. Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking and nicotine on cancer treatment. Pharmacotherapy 2012;32:920-31.
54. Liu Y, Liu BA. Enhanced proliferation, invasion, and epithelial-mesenchymal transition of nicotine-promoted gastric cancer by periostin. World J Gastroenterol 2011;17:2674-80.
55. Lien YC, Wang W, Kuo LJ, Liu JJ, Wei PL, Ho YS, *et al*. Nicotine promotes cell migration through alpha7 nicotinic acetylcholine receptor in gastric cancer cells. Ann Surg Oncol 2011;18:2671-9.
56. Al-Wadei HA, Plummer HK 3rd, Schuller HM. Nicotine stimulates pancreatic cancer xenografts by systemic increase in stress neurotransmitters and suppression of the inhibitory neurotransmitter gamma-aminobutyric acid. Carcinogenesis 2009;30:506-11.
57. Crowley-Weber CL, Dvorakova K, Crowley C, Bernstein H, Bernstein C, Garewal H, *et al*. Nicotine increases oxidative stress, activates NF-κB and GRP78, induces apoptosis and sensitizes cells to genotoxic/xenobiotic stresses by a multiple stress inducer, deoxycholate: Relevance to colon carcinogenesis. Chem Biol Interact 2003;145:53-66.
58. Treviño JG, Pillai S, Kunigal S, Singh S, Fulp WJ, Centeno BA, *et al*. Nicotine induces inhibitor of differentiation-1 in a Src-dependent pathway promoting metastasis and chemoresistance in pancreatic adenocarcinoma. Neoplasia 2012;14:1102-14.
59. Chen CS, Lee CH, Hsieh CD, Ho CT, Pan MH, Huang CS, *et al*. Nicotine-induced human breast cancer cell proliferation attenuated by garcinol through down-regulation of the nicotinic receptor and cyclin D3 proteins. Breast Cancer Res Treat 2011;125:73-87.
60. Nishioka T, Kim HS, Luo LY, Huang Y, Guo J, Chen CY. Sensitization of epithelial growth factor receptors by nicotine exposure to promote breast cancer cell growth. Breast Cancer Res 2011;13:R113.
61. Porchet HC, Benowitz NL, Sheiner LB, Copeland JR. Apparent tolerance to the acute effect of nicotine results in part from distribution kinetics. J Clin Invest 1987;80:1466-71.
62. Przyklenk K. Nicotine exacerbates postischemic contractile dysfunction of 'stunned' myocardium in the canine model. Possible role of free radicals. Circulation 1994;89:1272-81.
63. Csonka E, Somogyi A, Augustin J, Haberbosch W, Schettler G, Jellinek H. The effect of nicotine on cultured cells of vascular origin. Virchows Arch A Pathol Anat Histopathol 1985;407:441-7.
64. Villablanca AC. Nicotine stimulates DNA synthesis and proliferation in vascular endothelial cells *in vitro*. J Appl Physiol. 1998;84:2089-98.
65. Chalon S, Moreno H Jr, Benowitz NL, Hoffman BB, Blaschke TF. Nicotine impairs endothelium-dependent dilatation in human veins *in vivo*. Clin Pharmacol Ther 2000;67:391-7.
66. Lee J, Cooke JP. The role of nicotine in the pathogenesis of atherosclerosis. Atherosclerosis 2011;215:281-3.
67. Sridharan MR, Flowers NC, Hand RC, Hand JW, Horan LG. Effect of various regimens of chronic and acute nicotine exposure on myocardial infarct size in the dog. Am J Cardiol 1985;55:1407-11.
68. Konishi H, Wu J, Cooke JP. Chronic exposure to nicotine impairs cholinergic angiogenesis. Vasc Med 2010;15:47-54.
69. Beck ER, Taylor RF, Lee LY, Frazier DT. Bronchoconstriction and apnea induced by cigarette smoke: Nicotine dose dependence. Lung 1986;164:293-301.
70. Jaiswal SJ, Pilarski JQ, Harrison CM, Fregosi RF. Developmental nicotine exposure alters AMPA neurotransmission in the hypoglossal motor nucleus and pre-Botzinger complex of neonatal rats. J Neurosci 2013;33:2616-25.
71. Chu KM, Cho CH, Shin VY. Nicotine and gastrointestinal disorders: Its role in ulceration and cancer development. Curr Pharm Des 2013;19:5-10.
72. Ogle CW, Qiu BS, Cho CH. Nicotine and gastric ulcers in stress. J Physiol Paris 1993;87:359-65.
73. Irie K, Muraki T, Furukawa K, Nomoto T. L-NG-nitro-arginine inhibits nicotine-induced relaxation of isolated rat duodenum. Eur J Pharmacol 1991;202:285-8.
74. Kadakia SC, De La Baume HR, Shaffer RT. Effects of transdermal nicotine on lower esophageal sphincter and esophageal motility. Dig Dis Sci 1996;41:2130-4.
75. Endoh K, Leung FW. Effects of smoking and nicotine on the gastric mucosa: A review of clinical and experimental evidence. Gastroenterology 1994;107:864-78.
76. Geng Y, Savage SM, Johnson LJ, Seagrave J, Sopori ML. Effects of nicotine on the immune response. I. Chronic exposure to nicotine impairs antigen receptor-mediated signal transduction in lymphocytes. Toxicol Appl Pharmacol 1995;135:268-78.
77. Sopori ML, Kozak W, Savage SM, Geng Y, Soszynski D, Kluger MJ, *et al*. Effect of nicotine on the immune system: Possible regulation of immune responses by central and peripheral mechanisms. Psychoneuroendocrinology 1998;23:189-204.
78. Suñer IJ, Espinosa-Heidmann DG, Marin-Castano ME, Hernandez EP, Pereira-Simon S, Cousins SW. Nicotine increases size and severity of experimental choroidal neovascularization. Invest Ophthalmol Vis Sci 2004;45:311-7.
79. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. JAMA 1996;276:1141-6.
80. Tirgan N, Kulp GA, Gupta P, Boretsky A, Wiraszka TA, Godley B, *et al*. Nicotine exposure exacerbates development of cataracts in a type 1 diabetic rat model. Exp Diabetes Res 2012;2012:349320.
81. Jaimes EA, Tian RX, Joshi MS, Raij L. Nicotine augments glomerular injury in a rat model of acute nephritis. Am J Nephrol 2009;29:319-26.
82. Halimi JM, Philippon C, Mimran A. Contrasting renal effects of nicotine in smokers and non-smokers. Nephrol Dial Transplant 1998;13:940-4.
83. Xie Y, Garban H, Ng C, Rajfer J, Gonzalez-Cadavid NF. Effect of long-term passive smoking on erectile function and penile nitric oxide synthase in the rat. J Urol 1997;157:1121-6.
84. Jana K, Samanta PK, De DK. Nicotine diminishes testicular gametogenesis, steroidogenesis, and steroidogenic acute regulatory protein expression in adult albino rats: Possible influence on pituitary gonadotropins and alteration of testicular antioxidant status. Toxicol Sci 2010;116:647-59.
85. Oyeyipo IP, Raji Y, Bolarinwa AF. Nicotine alters male reproductive hormones in male albino rats: The role of cessation. J Hum Reprod Sci 2013;6:40-4.
86. Jin Z, Roomans GM. Effects of nicotine on the uterine epithelium studied by X-ray microanalysis. J Submicrosc Cytol Pathol 1997;29:179-86.
87. Hammer RE, Mitchell JA, Goldman H. Effects of nicotine on concept us cell proliferation and oviductal/uterine blood flow in the rat. In: Cellular and Molecular Aspects of Implantation. US: Springer; 1981. p. 439-42.
88. Chen M, Wang T, Liao ZX, Pan XL, Feng YH, Wang H. Nicotine-induced prenatal overexposure to maternal glucocorticoid and intrauterine growth retardation in rat. Exp Toxicol Pathol 2007;59:245-51.
89. Liu L, Liu F, Kou H, Zhang BJ, Xu D, Chen B, *et al*. Prenatal nicotine exposure induced a hypothalamic-pituitary-adrenal axis-associated neuroendocrine metabolic programmed alteration in intrauterine growth retardation offspring rats. Toxicol Lett 2012;214:307-13.

How to cite this article: Mishra A, Chaturvedi P, Datta S, Sinukumar S, Joshi P, Garg A. Harmful effects of nicotine. Indian J Med Paediatr Oncol 2015;36:24-31.
Source of Support: Nil. **Conflict of Interest:** None declared.

Comment

On the Safety of E-cigarettes: "I can resist anything except temptation"[1]

Robert D. Combes and Michael Balls

Strategic policy decisions are being made about e-cigarettes, based on the plausibility of their greater safety, rather than on essential scientific evidence which would permit a proper risk assessment. If e-cigarettes are *really 'safer', then their use should be recommended, but only after an intelligent analysis of their risk to human health, based on integrated* in silico, in vitro *and clinical studies for both scientific and logistical reasons*

Concern Raised by Public Health England's Proposal for ECs to be Available on the NHS

In a Comment article published in the September 2015 issue of *ATLA*,[2] we expressed our concern that, although we welcomed the prospect of new tobacco-related products aimed at reducing harmful exposures, it appeared that new regulations would require that their relatively greater 'safety' would have to be established via complex testing regimes which would be heavily reliant on traditional animal procedures of doubtful relevance and reliance. We argued that, instead, the focus should be on the intelligent and integrated use of non-animal *in silico*, *in vitro* and clinical studies.

Just before our article went to press for publication, Public Health England (PHE; a UK executive agency, sponsored by the Department of Health) proposed that electronic cigarettes (ECs), a non-tobacco alternative to smoking, should be made available via the NHS (National Health Service),[3] as a means of reducing the general incidence of disease and harm attributable to conventional smoking.

We found that there was an increasingly heated debate about the safety of ECs, between those that want their use encouraged and endorsed with little delay, and others who urge caution. The PHE proposal is a classic example of the temptation of short-term gain irrespective of the possibility of long-term pain.[4] It is dangerous, because the relatively greater safety of ECs has not been scientifically established — and regrettable, because it is likely that other authorities, notably those on the other side of the Atlantic, are likely to insist on the introduction of complex testing regimes which will require animal testing, as is the case for new smoking materials.[2]

Background

PHE's proposal is a matter of concern, mainly because of the lack of safety data and the resulting inability to perform any sort of risk assessment of the type normally undertaken for consumer products, as well as doubts concerning the relevance of the data on the impact of ECs on smoking habits. In addition, our review was not specifically on ECs, as a consequence of which there is other, relevant published information on usage and safety, which needs to be considered. We now take this opportunity to elaborate on our initial response, and on our reasons for urging caution, in the light of recent developments regarding ECs, both at home and in the USA.

This issue needs to be resolved urgently, since the popularity of ECs is rapidly gaining ground, especially with young people, at the expense of tobacco smoking, largely on the assumption that ECs either lack many of the toxic constituents, contaminants and by-products to which conventional smokers are exposed, or that these substances are encountered at sufficiently low concentrations so as to cause no health problems. Moreover, an update on the situation with ECs is timely since: a) the FDA is about to be charged with responsibility for regulating ECs in the USA (http://www.fda.gov/TobaccoProducts/ Labeling/ ucm388395.htm); b) as we write, the *Third Summit on Electronic Cigarettes* has just taken place in London (http://www.e-cigarette-summit.com/); and c) the UK (via the Department of Health and the Medicines and Healthcare Products Regulatory Agency [MHRA]) has a deadline of May 2016 to complete the process of transposing into its national legislation, the EU revised Tobacco Products Directive (http://ec.europa.eu/health/ tobacco/ docs/ dir_201440_en.pdf), which came into force in May 2014.

The situation regarding ECs is also highly relevant to the Three Rs, since we have the prospect of significant levels of safety testing, some of which could involve traditional animal tests, highly invasive procedures and the use of non-human primates, to satisfy new regulatory requirements in Europe and the USA.[2] Although, after careful consideration, we believe that more information is required before ECs become incorporated into strategies for tackling the burden of disease and ill-health due to tobacco smoking, we feel that most, if not all, of the required data could be obtained in a more-timely way by implementing a strategy focused on the coordinated use of chemical, *in vitro* and clinical methods. Moreover, because the information will have largely been obtained by using organotypic tissue culture systems comprised of cells from the target tissues and species, it will be of direct relevance to assessing risk levels arising from the use of ECs.

The Controversy

Understandably, PHE's suggestion has provoked considerable discussion and controversy, while being generally welcomed by those who see ECs as a quick solution to the smoking and health problem. To illustrate the type of approach being taken by some stakeholders to address the EC issue, we quote the opening sentence of what looks like an internal report on the burdens of regulating ECs, but dated September 2013,[5] which states that: *E-cigarettes are very low risk alternatives to cigarettes, used by smokers as a pleasurable way of taking the relatively harmless recreational drug, nicotine*. However, we were unable to find any evidence, or citations to original articles presenting toxicity data, in support of such a potentially far-reaching statement by the authors in their 26-page document, which, essentially, urges the UK Government to resist being overburdened with EU regulations for ECs — requirements which, in the authors' opinion, are unnecessary, because they could delay the take-up of ECs by the public. The authors qualify the risk level, by claiming it is 'very low', again without any reference to quantitative hazard data — most extraordinary!

In direct contradiction, and two years following publication of that statement, our in-depth appraisal[2] of the use, safety assessment and regulatory control of tobacco-related products in general, including ECs, leads us to believe that, whatever the long-term consequences of any such policy, or however worthy the ultimate objective of PHE may be, it is, *in the light of current knowledge*, a reckless and irresponsible suggestion.

Poor Reporting

PHE's justification for its proposal relies heavily on two reports which it commissioned, and which were not peer-reviewed.[6,7] It ignores the possibilities that users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation.[8] Also, the PHE report contains information on the likely adoption and use of e-cigarettes by existing and potential smokers that could be of questionable relevance to the UK. This is because this information is derived from experience in other countries, with differing attitudes to smoking, or it applies to other tobacco-related products that are used mainly elsewhere, or it is conflicting, or merely circumstantial.

On comparing our Comment[2] with the PHE document, as well as looking at data that were published before the document was released, we have found that some key references are missing from it, or have been selectively covered, with the omission of some important information. For example, we have previously discussed evidence of the presence in vapours of some tobacco-specific nitrosamines (TSNAs), but the PHE report, which included the same reference,[9] omitted any mention of the analytical data for such chemicals. There are several other reports of the detection of TSNAs in ECs,[10,11] but there is no discussion in the PHE report of the potential role of such contaminants, some of which are highly-potent genotoxins[12] in the aetiology of lung cancer. In fact, cancer is not specifically mentioned anywhere in relation to safety, and there is no record of published reports of exposure to additional substances, such as nanoparticles (NPs) derived from metals[13] (also see Combes and Balls[2]). NPs, together with certain other chemicals, have been linked to respiratory sensitisation and mechanistically-related diseases, such as chronic obstructive pulmonary disease. Sensitisation is another endpoint for which clear thresholds for induction doses are difficult to identify.[14] This might be because they do not exist, as with genotoxins, or because of technical deficiencies, but either way, this complicates risk assessment.

The omission by PHE of several key papers and information from a report that was intended to be used to determine public health policy on the basis of the evidence available, is completely inexcusable. This is especially the case, as the above facts combined suggest that there is a tangible, and, at

present, unquantifiable, risk that repeated and prolonged exposure to even low doses of such chemicals, as would be expected to occur as a result of using ECs, could be sufficient to trigger cellular changes eventually culminating in serious conditions, sometimes not manifested until some considerable time following the onset of exposure.

With regard to the possibility of the presence of undetected chemicals, some of which could be toxic, it is worth noting that very few of the analytical methods in use have been validated for the purpose in question, which could, in part, explain the relatively high levels of variation seen between EC brands, and which also could account for the variation experienced within experiments.

The PHE report also fails to mention one of the main findings of the earlier investigations into the safety of ECs, namely, that different brands can vary substantially in the levels of contaminants, by-products and active components (e.g. nicotine), such that there is an urgent need for more harmonisation of the different products available.[3]

A reminder of how difficult it can be to predict the adverse effects of complex mixtures, such as EC aerosols and liquids, is provided by a recent study[15] on the potential modulating influence of nicotyrine, a product present in tobacco which also arises in EC fluids as a result of slow oxidation of nicotine. This chemical is an inhibitor of cytochrome (CYP) isozymes (CYP P450 mixed function oxidases), which clear nicotine from the body and are active in both hepatic and extrahepatic systems. The authors noted that the metabolism of all of the substrates of the respective isozymes will be affected by nicotyrine. It so happens that one of these substrates is the TSNA, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK),[12] one of the most potent of the known lung carcinogens in tobacco smoke. This substance is activated in airway cells, both *in vitro* and *in vivo*, by CYP2A13,[12] suggesting a potential anti-carcinogenic effect of nicotyrine, at least for this particular mechanistic pathway.

Neither our Comment,[2] nor the PHE report, referred to a review, published in April 2014, on the toxicity of ECs.[16] The authors of this review concluded that: *The available evidence suggests that these products are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes.* However, while this seems to be good news, the authors admitted that only very few toxicological studies were available to them. Also missing from the PHE report is reference to an unpublished, but comprehensive 19-page document, available on the Internet,[17] which summarises various aspects of ECs, including safety issues.

The PHE report went considerably further than merely saying that ECs are safer than conventional smoking, by providing a quantitative estimate of the extent of this alleged greater safety. It claimed that ECs are up to 95% safer than conventional smoking, and that: *Best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether*. Later on, the report states that: *Acknowledging that the evidence base on overall and relative risks of EC in comparison with smoking was still developing, experts recently identified them as having around 4% of the relative harm of cigarettes overall (including social harm) and 5% of the harm to users.*

Misuse of Information

While these two statements are not referenced, it emerges later in the report that they are based on the outcome of a multi-criteria decision analysis (MCDA) study, in which a small group of experts considered the harms to human health and well-being posed by using a wide range of tobacco products.[18] Each product was ranked on a scale which put cigarette smoking top at almost 100% for several properties, including addiction and cancer. The authors stated that: *Within the tobacco products there was a gradual reduction in harm from water pipe, smokeless unrefined, smokeless refined to snus that has 5% of MRH. Among the purer non-tobacco vehicle products ENDS were rated to have only 4% of MRH and for the even purer NRTs the MRH was only rated at about 2%.* [where ENDS = electronic nicotine delivery systems; MRH = maximum relative harm; and NRTs = pharmacological replacement products.]

PHE then used the outcome of this study, as if it were equivalent to experimental data, to derive the 95% figure. Apart from being baffled by how any quantitative risk assessment can be made with the paucity of available hazard data, we are uncertain as to how to interpret the intended meaning of such a statement, other than by concluding that PHE believes that ECs are almost twice as safe as tobacco smoking. The quantification of risk in toxicology, although not a precise process by any means, implies some greater confidence in a particular prediction than is conveyed by a mere qualitative statement, and it has to be derived from detailed quantitative hazard data. However, in this case, the information was merely generated by an *ad hoc* group of experts, and was based on opinions, rather than being grounded in scientific observation.

Moreover, there are many difficulties with the MCDA approach in general, and in particular, with the above application of it.[2,19] This implies that the validity of its outcome is very questionable, being dependent on the amount and rele-

vance of pre-existing information, subject to much value judgement, and difficult to reproduce with a different set of experts, and with the same ill-defined criteria used to assess relative harm. We also noted one inescapable problem, which relates to the large bias in the overwhelming amount of available data on cigarette smoking compared to that on ECs. It is difficult to see how such an imbalance could be compensated for in practice, but it greatly complicates any comparison of the two types of products. The results from an MCDA study should be used only for what they are, that is, *predictions*, rather than as novel experimental data, which they certainly are not. MCDA is part of the analysis of evidence, rather than being an additional source of evidence *per se*.

Another UK study, investigating the perception of relative harm from the use of ECs,[20] involved recording the views of cohorts of smokers and ex-smokers given ECs, and involved standard statistical methods to estimate changes in perception over a three-year period. It was found that the proportion perceiving ECs to be less harmful than cigarettes decreased significantly over the period 2013 to 2014. Unsurprisingly, a major preliminary conclusion of the study was that: *Clear information on the relative harm of cigarettes and e-cigarettes is needed*. Another human study, a randomised controlled trial,[21] found that ECs, with or without nicotine, were only moderately good at assisting smokers to quit. The authors noted that: *Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms.*

Like McKee and Capewell,[22] we doubt that the 95% figure can be given any scientific credibility, mainly due to the way in which it was derived. We go further, in saying that the statement is misguided and misleading. It is tempting to even suspect that the latter was used intentionally, as intimated by Kirby,[23] who summed up the situation well, if somewhat rather benevolently, thus: *While the PHE report contains many caveats, albeit subtle and largely missing from the media coverage, it has uniformly adopted the most favourable interpretation of the very limited evidence, rejecting the precautionary principle.*

In response to criticism of the 95% figure,[24] Professor John Britton (chair of the Royal College of Physicians Tobacco Advisory Group and co-chair of the PHE Tobacco Control Implementation Board, and also a co-author of one of the reports on ECs that was commissioned by PHE), suggested that, rather than dwell on an exact percentage figure, the real point is that ECs are substantially safer than tobacco smoking.[25] This begs the following question: If the 95% figure is not meant to be interpreted literally, why include it in the report, unless the aim was to have a headline for gaining publicity, with a view to persuading us all to accept the proposal without further questioning? However, in truth, as we have argued above, there is no *evidence* for the 95% estimate. Moreover, doubts have been expressed about the integrity and objectiveness of the MCDA study, due to the alleged conflicts of interest of some of its authors.[26] Unfortunately, little further information is available, and this fact, together with the other general drawbacks of implementing MCDA, discussed earlier, suggest that extreme caution should be exercised when considering the outcome. A similar issue with conflict of interest was encountered by Pisinger and Døssing,[27] when they found the problem to have arisen in some 34% of the 76 studies relating to EC safety that they reviewed. These authors could draw no firm conclusions from the information, due to high levels of data inconsistency, but they did state that: *Electronic cigarettes can hardly be considered harmless.* This study, incidentally, is yet another key publication missing from the PHE document.

What is Needed is a Role for Alternative Methods

Predictably, few, if any, of the small number of toxicity studies that have been published to date consist of medium-term to long-term investigations. The issue of chronic toxicity due to vaping has been noted by others, including, for example, Rowell and Tarran,[28] who recently discussed the lack of data relating to the ability of chronic exposures to ECs to induce serious lung disease. The need to take into account long-term consequences of EC use also applies to efficacy as well as safety, as Unger notes in a recent editorial: *Longitudinal studies are not yet available to assess the long term effects of e-cigarettes on health or their usefulness as a cessation tool*.[29] Some four years ago, Etter *et al.*[30] stated that ECs had not been adequately tested for safety or efficacy, and the situation has not altered very much since then. Until further studies of high quality and integrity are conducted, the marketing of ECs poses unknown health and safety concerns, particularly because the products available are extremely diverse, many of them on the market are not regulated, and no oversight of quality control is in operation.

While we understand that there is an urgent need to have more safety information, we believe that there is a better way of obtaining it than having several individuals sitting at a table trying to predict the harms of these products, when they have very little reliable information on which to base their decisions. Instead, we suggest the strategy which we have outlined previously,[2] involving an intelligent, integrated testing scheme, comprised mainly of chemical analysis, *in vitro*

methodologies and human/clinical studies. Such an approach would also expedite testing, particularly since traditional *in vivo* methods are often lengthy and their relevance and reliability are highly questionable.

The numbers of publications on *in vitro* studies with EC vapours are increasing (http://www.ashscotland.org.uk/what-we-do/supply-information-about-tobacco-and-health/tobacco-related-research/research-2015/e-cigarettes-2015/). In general, the data are promising, in that, for example, one paper[31] shows that several vapours exhibit substantially less activity in cytotoxicity testing and in a range of genotoxicity assays, compared with that exhibited by cigarette smoke. Other, more-recent studies, one involving the MatTek™ epithelial airway model, confirm the substantially lower cytotoxicity of vapours, and also demonstrate that this applies to airway cells in culture[32] (http://vaperanks.com/big-tobacco-study-claims-e-cigarette-vapor-is-as-harmless-to-human-airway-tissue-as-plain-air/).

However, while all this is encouraging, a glance at the Vape Ranks website (presenting news on ECs, rankings and reviews [www.http://vaperanks.com/]) shows that there is no shortage of other reports which raise legitimate safety concerns relating to ECs, that warrant further investigation. Among such reports are an increasing number of cases where ECs are being used to 'smoke' marijuana, a potentially worrying development (see, for example, Murphy[33]). Some of the investigations conducted *in vitro* also suggest that acute toxic effects could be caused by vaping. For example, a study in which cultures of human gingival fibroblasts were exposed to nicotine-containing or nicotine-free EC fluids, increased the production of reactive oxygen species (ROS) after 24 hours, along with an elevated expression of the *Bax* gene (an early indicator of apoptosis), followed by apoptosis itself, after 48 hours of exposure.[34] The authors concluded that such exposures could lead to periodontitis, but, in addition, the induction of such cellular changes could presage other, more-serious long-term toxicity.

An important part of the integrated testing strategy that we have proposed, involves human clinical studies, which have been undertaken for both efficacy and safety testing (the latter uniquely possible with tobacco and tobacco-related products, at an early stage), rather than following extensive preclinical testing, as with pharmaceuticals (see Combes and Balls[2]). Encouraging results were obtained in some of the first human studies (reviewed in Caponnetto *et al.*[35]), with high levels of tolerance and acceptance of the new products by existing smokers and non-smokers, as well as low incidences of side-effects or of overt signs of toxicity.

However, some subsequent studies have revealed several potential effects which cause concern. One example is an investigation[36] with smokers and non-smokers that involved monitoring changes in plasma nicotine and carbon monoxide (CO) concentration, and heart rate. One brand of ECs increased each of these parameters within the first five minutes of administration, an example of an acute adverse effect caused by vaping. Other evidence that ECs can exert acute effects on users, following brief exposures, was clearly demonstrated in a clinical study,[37] in which: a) non-smokers, using an EC for ten minutes, experienced elevated airway resistance; b) current regular smokers exhibited a significant rise in airway resistance after using an EC for ten minutes; and c) neither COPD nor asthma patients were affected (www.medicalnewstoday.com/articles/ 249784.php). In a blog, Phillips has questioned the relevance of these results.[38] However, although chemicals causing this effect may not elicit an immune response, the changes seen serve as biomarkers of lung exposure and of changes therein that could result in serious health consequences.

Another investigation, still ongoing, involves cohorts of smokers and non-smokers. At the 12-month stage, the results suggest that vaping has little effect on helping smokers to quit.[39] However, the trial is not scheduled to be completed until 2019. It is monitoring self-reported side-effects, and, hopefully, will include an assessment of biomarkers of disease and toxicity.

Nowhere are conflicting views regarding the safety of ECs more sharply delineated than by the different approaches to their use and regulation that are emerging in markets on either side of the Atlantic (reviewed in Combes and Balls[2]). On the one hand, in the UK, some Government agencies appear too ready to approve and promote the use of such products, without going through the necessary standard checks and balances, while, on the other hand, in the USA, the FDA is about to take over the regulation of ECs by subjecting them to a rigorous and formal assessment.

It was on 25 April 2014 that the FDA published a proposed rule, *Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act*. The period between then and now has been taken up by: a) a 75-day public comment period, which ended on 9 July 2014; b) an extension of the public comment period by 30 days, taking us to 8 August 2014; c) an unknown time delay for consideration and decision by the Agency of additional requests to extend the comment period a second time (which was not granted); and d) the analysis of comments (undisclosed time). Despite these delays, the question concerning the FDA's regulation of ECs is 'when', rather than 'if'. The latest information we can find is an entry in *The Hill* (the website presenting news of US Congress activities) in May 2015, where it is reported that Senator

Richard Blumenthal (D-Conn.) is giving the FDA until the end of the summer 2015 to finalise its deeming regulations for all tobacco products, including ECs and cigars (http://thehill.com/regulation/242125-fda-has-summer-to-finalize-tobacco-deeming-regs-sen-dem-says).

Once the FDA assumes responsibility for ECs for recreational use (it already regulates such products intended for therapeutic purposes), its approach to ECs would appear to be clear from its website (http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm172906.htm). This states that: *E-cigarettes have not been fully studied, so consumers currently don't know: the potential risks of e-cigarettes when used as intended; how much nicotine or other potentially harmful chemicals are being inhaled during use, or whether there are any benefits associated with using these products. Additionally, it is not known whether e-cigarettes may lead young people to try other tobacco products, including conventional cigarettes, which are known to cause disease and lead to premature death.*

This viewpoint is essentially one that we share, and, although we are not in favour of testing just for the sake of it, we fervently believe that it is very simplistic and premature, at this time, to base important public health decisions of the sort currently being proposed by PHE, on inadequate evidence of safety and/or potentially irrelevant and unreliable extrapolation. On the other hand, while we concur with FDA's overall assessment of the situation regarding ECs, we take issue with the way in which the Agency intends to regulate tobacco-related products, especially via the use of the substantial equivalence concept.[2] In addition, our views on the availability of data are shared by other organisations, notably the American Association for Cancer Research and the American Society of Clinical Oncology,[40] and the BMA.[41]

The official EU position on ECs is not clear at this time. The revised EU Directive on the marketing and use of tobacco products merely requires that manufacturers take responsibility for the safety of such products. However, we understand that, in the UK, once the Directive has been transposed into UK legislation, a process that will be facilitated by the Department of Health, the MHRA will become the competent authority (Dr Ian Hudson, personal communication, 2015) for ECs intended for medicinal purposes, which include quitting smoking. Accordingly, the MHRA will regulate such products in the same way that it does medicines. Indeed, the MHRA website has now documented data requirements for ECs (http://www.mhra.gov.uk/home/groups/commsic/documents/websiteresources/con454361.pdf), where it is stated (for preclinical studies) that: *The potential transformation of the formulation on thermal decomposition, and the potential for the heating element and associated components (including adhesives and solder) to shed metallic and other particles on heating, would warrant further investigation by the applicant to assess the inhalation safety risks and to limit exposure where necessary. In addition, the applicant should provide a detailed safety review of all the components in the formulation from the available literature; in particular a review of the safety following inhalation exposure (including long-term exposure) would be relevant. A comprehensive evaluation of the potential extractables and leachables originating from all components of the electronic cigarette should also be provided, with associated toxicological review.* For clinical studies, for some unaccountable reason, the focus is on the levels of nicotine in the body and its pharmacodynamics, to ensure that endogenous levels do not exceed maximum safe levels. We feel that this represents a missed great opportunity for undertaking biomarker and biomonitoring safety studies on vapours in the clinical setting, as we have explained in more detail elsewhere.[2]

How these regulations are going to be applied in practice after the various stakeholders and pressure groups, including the tobacco industry, have argued their various standpoints remains to be seen. However, if the MHRA sticks to its procedures and requirements for new medicines, it should be the case that: a) if the supporting toxicological data are deemed relevant and suitable, there will be no need for further testing and/or review; and b) where this is not so, or where data are missing, such information would have to be obtained by toxicity testing, according to International Conference on Harmonisation (ICH)-approved regulatory test methods for new medicinal products. Whether any products currently on the market will receive exemption is a matter of conjecture at this time. Therefore, we are now confronted by a ludicrous situation, whereby two UK Government authorities, the MHRA and PHE, both with the responsibility for safeguarding public health, are giving out different messages — the former has the remit of controlling the sale of the ECs according to international regulatory requirements, while the latter endorses the use of ECs now. Furthermore, the PHE report and its associated documents can be downloaded from the MHRA website — no wonder there is so much confusion!

Some notes on the presentations given at the Third E-Cigarette Summit, have been posted on the web (http://www.ecigarettedirect.co.uk/ashtray-blog/wp-content/uploads/2015/11/E-Cig-Summit-3-PDF.pdf). The notes provide a preliminary impression that the debate shows no signs of letting up, although it would appear that there is a growing admission among the protagonists that ECs are not harmless, and, among those looking at health

effects, that they are probably safer than smoking, but by how much it is difficult to tell. Perhaps we could be heading in the right direction, after all. We should get a better idea once the presentations have been uploaded to the resources section of the summit's website.

Concluding Comments

We are puzzled by: a) why there is such a gulf between the UK and the USA in approaches to regulating ECs; and, more importantly, b) why the fundamentals of toxicology, underpinning public health and safety, involving hazard identification and risk assessment,[42] seem to have been ignored by PHE, and are being overlooked in the ongoing debate by a growing number of stakeholders and so-called experts, when the same are usually so rigorously applied to other consumer products.

Calls endorsing the wider usage of ECs are being driven by two main factors, both of which cannot be supported on scientific grounds: a) an understandable, but misguided, wish for having a quick fix for the major health problems associated with smoking; and b) a mistaken belief that there is no need to test complex mixtures, such as EC liquids and vapours, when the levels of ingredients, whose presence and contribution to toxicity are known, are at very low concentrations. If this were possible, most of toxicology would now merely consist of chemical analysis of test samples, except in rare cases where the threshold of regulation concept[43] can legitimately be applied — for example, when synergistic or antagonistic effects between constituents can be accommodated.

One way in which risk assessment can be approached is to derive likely exposure levels from analytical data on the constituents of vapours and compare them with recommended maximum allowable daily intake figures for humans, obtained from safety tests. However, since most of the information relates to data obtained under laboratory conditions, mainly with rodents, sometimes involving different routes of exposure, it has to be extrapolated and scaled up to be relevant to human populations, and adjusted to provide for an extra margin of safety. Moreover, predicting exposure levels is confounded by individual differences in the way in which ECs are used, the extent to which they are used, the differences in design and composition of ECs, the degree of vapour inhalation, and variation in the biotransformation of inhaled constituents, and also by the possible endogenous generation of more TSNAs from vaped nicotine.[44]

It has been noted elsewhere (http://www.tobacco.ucsf.edu/9-chemicals-identified-so-far-e-cig-vapor-are-california-prop-65-list-carcinogens-and-reproductive-t) that nine constituents variously found in EC fluids and/or aerosols, are listed by the Environmental Protection Agency (EPA) of the US State of California as being of concern with regard to human safety, as part of the Agency's drive to improve and simplify the regulation of environmental chemicals. These chemicals are: acetaldehyde, cadmium, formaldehyde, isoprene, lead, nickel, nicotine, N-nitrosonornicotine (NNN) and toluene. NNN is widely considered to be a carcinogen in tobacco smoke. As a worse-case scenario, we have taken the threshold value of concern for this chemical (which the EPA has identified from rodent carcinogenicity studies, after adjustments for species and test system extrapolation), to have a NSRL (non-significant risk level) of 0.5μg/day (NSRL is the level of exposure that would result in no more than one excess case of cancer in 100,000 individuals exposed to the chemical). We have compared this figure with the amount of NNN that different ECs users might be expected to be exposed to, based on the maximum levels of chemical reported in Gureckis and Love,[4] which is 4.3μg/150 puffs (equivalent to 14.3μg/day for a user taking 500 puffs/day). As the respective NSRL value is 0.5μg/day, the expected exposure under these conditions exceeds the level of concern by almost 30-fold. Presumably, such a result would raise the possibility that ECs with similar constituent profiles could prompt the EPA in California to require appropriate product labelling as a precondition for marketing approval. We stress, however, that these are preliminary data, subject to several uncertainties, not the least of which are vaping behaviour and individual susceptibility, and we plan to investigate risk assessment in more detail for more ECs, and also for other risk assessment methods, such as the Margin of Exposure (see Hahn *et al.*[45]).

The more and more we read, the more convinced we are that the whole debate about ECs is premature, and would not be happening with other, equally dangerous consumer products, in the absence of powerful lobbying on behalf of industry. The title of the PHE report includes the phrase *...foundation for evidence-based policy and practice.* This sounds great, until one realises that the foundation is very weak indeed, having been built on sand, in the words of McKee and Capewell,[22] and that the evidence used was incomplete, conflicting, and used selectively. It is crucial that these new types of products are labelled appropriately and accurately, not only with regard to their benefits, but also with appropriate and proportionate warnings of any hazards to which users may be exposed. This will only be possible after there has been a full and scientifically-sound investigation of the toxicity of these products.

We seem to be living in a world now where the term *evidence-based* increasingly seems to be being used to imply some new revelatory approach to

scientific activity that guarantees high quality. We have 'evidence-based medicine' and, more-recently, 'evidence-based toxicology', and now: 'evidence-based public health' and 'evidence-based regulation'. But, in truth, of course, *evidence-based* is not a new concept, nor is it a panacea for quality — any thorough scientific piece of work is only as good as the evidence on which it is based. What does appear to be new is the attempt to use the phrase as a smokescreen for sub-standard scientific investigation, otherwise there would be no need to use it at all!

We leave the last word to the British Heart Foundation (BHF), by quoting from a booklet entitled *10 Minutes to Change Your Life — Time to Quit*, which is available in its high-street charity shops or from its website (https://www.bhf.org.uk/~/media/files/publications/smoking/g925_time_to_quit_01_14_booklet_chart.pdf). This states that: *E-cigarettes allow you to breathe in nicotine vapour. Unlike tobacco smoke, this nicotine [vapour] doesn't contain many of the chemicals that cause cancer and heart disease. But scientists don't know yet if e-cigarettes can help you quit or if they cause any long-term damage to your health.*

Simple, clear, informative and correct — this is where the debate needs to start and it is why the temptation for a quick fix to the smoking issue must be resisted!

Author for correspondence:
Robert D. Combes
Independent Consultant
Norwich
UK
E-mail: robert_combes3@yahoo.co.uk

Michael Balls
c/o FRAME
Russell & Burch House
96–98 North Sherwood Street
Nottingham NG1 4EE
UK

References and Notes

[1] Wilde, O. (1892). A quotation from *Lady Windermere's Fan*, a play first performed in 1892 and first published in written form in 1893.
[2] Combes, R.D. & Balls, M. (2015). A critical assessment of the scientific basis, and implementation, of regulations for the safety assessment and marketing of innovative tobacco-related products. *ATLA* **43**, 251–290.
[3] Anon. (2015). *E-cigarettes: A new foundation for evidence-based policy and practice,* 6pp. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/454517/Ecigarettes_a_firm_foundation_for_evidence_based_policy_and_practice.pdf (Accessed 19.08.15).
[4] Gureckis, T.M. & Love, B.C. (2009). Short term gains, long term pains: How cues about state aid learning in dynamic environments. *Cognition* **113**, 293–313.
[5] Bates, C. & Stimson, G. (2013). *Costs and Burdens of Medicines Regulation for e-Cigarettes. A Report: 20 September 2013*, 26pp. Available at: http://www.e-cigarette-summit.com/files/2014/07/Impacts-of-medicines-regulation-V4-22-09-2013.pdf (Accessed 06.11.15).
[6] McNeill, A., Brose, L.S., Calder, R., Hitchman, S.C., Hajek, P. & McRobbie, H. (2015). *E-cigarettes: An evidence update. A report commissioned by Public Health England*, 113pp. London, UK: Public Health England. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINL.pdf (Accessed 07.11.15).
[7] Britton, J. & Bogdanovica, I. (2014). *Electronic Cigarettes. A report commissioned by Public Health England*, 30pp. London, UK: Public Health England. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/311887/Ecigarettes_report.pdf (Accessed 07.11.15).
[8] Hengstler, J.G., Bogdanffy, M.S., Bolt, H.M. & Oesch, F. (2002). Challenging dogma: Thresholds for genotoxic carcinogens? The case of vinyl acetate. *Annual Reviews of Pharmacology* **43**, 485–520.
[9] Cheng, T. (2014). Chemical evaluation of electronic cigarettes. *Tobacco Control* **23**, Suppl. ii, 11–17.
[10] Williams, M. (2013). *Electronic cigarette liquids and vapors: Is it harmless water vapor?* Webinar presentation. Available at: http://www.trdrp.org/files/e-cigarettes/williams-slides.pdf (Accessed 07.11.15).
[11] Kim, H.J. & Shin, H.S. (2013). Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A* **1291**, 48–55.
[12] Akopyan, G. & Bonavida, B. (2006). Understanding tobacco smoke carcinogen NNK and lung tumorigenesis. *International Journal of Oncology* **29**, 745–752.
[13] Neuberger, M. (2015). The electronic cigarette: A wolf in sheep's clothing. *Wiener Klinische Wochenschrift, Central European Journal of Medicine,* doi: 10.1007/s00508-015-0753-3. Available at: http://www.forte.or.at/download.php?id=1725 (Accessed 06.11.15).
[14] Cochrane, S.A., Arts, J.H.E., Ehnes, C., Hindle, S., Heli, M., Hollnagel, S.H.M., Poole, A. Suto, H. & Kimber, I. (2015). Thresholds in chemical respiratory sensitisation. *Toxicology* **333**, 179–194.
[15] Megaraj, V., Zhou, X., Xie, F., Liu, Z., Yang, W. & Ding, X. (2014). Role of CYP2A13 in the bioactivation and lung tumorigenicity of the tobacco-specific lung procarcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone: *In vivo* studies using a CYP2A13-humanised mouse model. *Carcinogenesis* **35**, 131–137.
[16] Farsalinos, K.E., & Polosa, R. (2014). Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: A systematic review. *Therapeutic Advances in Drug Safety* **5**, 67–86.
[17] Gardiner, P. (2013). *E-Cigarettes: The Vapor This Time?* 18pp. Available at: www.trdrp.org/files/e-cigarettes/e-cigarettes-the-vapor-this-time.pdf (Accessed 07.11.15).
[18] Nutt, D.J., Phillips, L.D., Balfour, D., Curran, H.V., Dockrell, J.M., Foulds, J., Fagerstrom, K., Letlape, K., Milton, A., Polosa, R., Ramsey, J. & Sweanor, D. (2014). Estimating the harms of nicotine-containing products using the MCDA approach. *European*

Addiction Research **20**, 218–225.

[19] Kujawski, E. (2002). *Multi-criteria decision analysis: Limitations, pitfalls, and practical difficulties*, 9pp. Berkeley, CA, USA: eScholarship, University of California. Available at: http://escholarship.org/uc/item/0cp6j7sj (Accessed 07.11.15).

[20] Brose, L.S., Brown, J., Hitchman, S.C. & McNeill, A. (2015). Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug & Alcohol Dependence* **157**, 106–111.

[21] Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Williman, J. & Walker, N. (2013). Electronic cigarettes for smoking cessation: A randomised controlled trial. *The Lancet* **382**, 1629–1637.

[22] McKee, M. & Capewell, S. (2015). Evidence about electronic cigarettes: A foundation built on rock or sand? *BMJ* **351**, h4863.

[23] Kirby, T. (2015). E-cigarettes declared 95% less harmful than tobacco by UK health body. *The Lancet Respiratory Medicine* **3**, 750–751.

[24] Culpan, D. (2015). *E-cigarettes 'safer than tobacco' study faces Lancet criticism*. Wired.co.uk, 4 September 2015. Available at: http://www.wired.co.uk/news/archive/2015-09/04/e-cigarette-report-criticised-the-lancet (Accessed 07.11.15).

[25] Britton, J. (2015). E-cigarettes, Public Health England, and common sense. *The Lancet* **386**, 1238–1239.

[26] Knapton, S. (2015). *E-cigarette 'safety' study was written by industry funded scientists, Lancet warns*. The Telegraph, Science News, 28 August 2015. Available at: http://www.telegraph.co.uk/news/science/science-news/11830029/E-cigarette-safety-study-was-written-by-industry-funded-scientists-Lancet-warns.html (Accessed 07.11.15).

[27] Pisinger, C. & Døssing, M. (2014). A systematic review of health effects of electronic cigarettes. *Preventive Medicine* **69**, 248–260.

[28] Rowell, T.R. & Tarran, R.A. (2015). Will chronic e-Cigarette use cause lung disease? *American Journal of Physiology — Lung Cellular & Molecular Physiology*, doi: 10.1152/ajplung.00272.2015. [E-pub ahead of print.]

[29] Unger, J.B. (2015). E-Cigarettes: Introducing new complexities and controversies to the field of nicotine and tobacco research. *Nicotine & Tobacco Research* **17**, 1185–1186.

[30] Etter, J-F., Bullen, C., Flouris, A.D., Laugesen, M. & Eissenberg, T. (2011). Electronic nicotine delivery systems: A research agenda. *Tobacco Control* **20**, 243–248.

[31] Misra, M., Leverette, R.D., Cooper, B.T., Bennett, M.B. & Brown, S.E. (2014). Comparative *in vitro* toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: E-liquids, extracts and collected aerosols. *International Journal of Environmental Research & Public Health* **11**, 11,325–11,347.

[32] Neilson, L., Mankus, C., Thorne, D., Jackson, G., DeBay, J. & Meredith, C. (2015). Development of an *in vitro* cytotoxicity model for aerosol exposure using 3D reconstructed human airway tissue; application for assessment of e-cigarette aerosol. *Toxicology in Vitro* **29**, 1952–1962.

[33] Murphy, N. (2015). *5 Marijuana Vaporizers Offering a Better, Healthier High*. The Cheat Sheet, 28 October 2015. Available at: http://www.cheatsheet.com/business/5-marijuana-vaporizers-offering-a-better-healthier-high.html/?a=viewall#ixzz3lBQ3vxHd (Accessed 06.11.15).

[34] Sancilio, S., Gallorini, M., Cataldi, A. & di Giacomo, V. (2015). Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clinical Oral Investigations*, 2015 Aug 4. [E-pub ahead of print.]

[35] Caponnetto, P., Campagna, D., Papale, G., Russo, C. & Polosa, R. (2012). The emerging phenomenon of electronic cigarettes. *Expert Review of Respiratory Medicine* **6**, 63–74.

[36] Vansickel, A.R., Cobb, C.O., Weaver, M.F. & Eissenberg, T.E. (2010). A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": Nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiology, Biomarkers & Prevention* **19**, 1945.

[37] Palamidas, A., Gennimata, S.A., Kaltsakas, G., Tsikrika, S., Vakali, S., Gratziou, C. & Koulouris, N. (2014). Acute effect of an e-cigarette with and without nicotine on lung function. *Tobacco Induced Diseases* **12**, Suppl. 1, A34.

[38] Phillips, C.V. (2012). *The biomarkers lie*. Tobacco Harm Reduction Blog at WordPress.com. Available at: http://antithrlies.com/2012/09/07/the-biomarkers-lie/ (Accessed 06.11.15).

[39] Flacco, M.E., Fiore, M., La Vecchia, C., Marzuillo, C., Gualano, M.R., Liguori, G., Cicolini, G., Capasso, L., Boccia, S., Siliquini, R., Ricciardi, W., Villari, P. & Manzoli, L. (2015). Electronic cigarettes: Efficacy and safety at 12 months: Cohort study. *European Journal of Public Health* **25**, Suppl. 3, 254.

[40] Brandon, T.H., Goniewicz, M.L., Hanna, N.H., Hatsukami, D.K., Herbst, R.S., Hobin, J.A., Ostroff, J.S., Shields, P.G., Toll, B.A., Tyne, C.A., Viswanath, K. & Warren, G.W. (2015). Electronic nicotine delivery systems: A policy statement from the American Association for Cancer Research and the American Society of Oncology. *Journal of Clinical Oncology* **33**, 952–963.

[41] Anon. (2015). *Vaping needs stronger regulation, say doctors leaders*. London, UK: British Medical Association. Available at: http://bma.org.uk/news-views-analysis/news/2015/august/vaping-needs-stronger-regulation-say-doctors-leaders (Accessed 06.11.15).

[42] Combes, R., Balls, M., Illing, P., Bhogal, N., Dale, J., Duvé, G., Feron, V., Grindon, C., Gülden, M., Loizou, G., Priston, R. & Westmoreland, C. (2006). Possibilities for a new approach to chemicals risk assessment. The Report of a FRAME Workshop. *ATLA* **34**, 621–649.

[43] Combes, R.D. (1997). Defining a 'threshold of regulation' the ultimate alternative for safety assessment? *ATLA* **25**, 187–191.

[44] Sepanov, I., Carmella, S.G., Han, S., Pinto, A., Strasser, A.A., Lerman, C. & Hecht, S.S. (2009). Evidence for endogenous formation of N´-nitrosonornicotine in some long-term nicotine patch users. *Nicotine & Tobacco Research* **11**, 99–105.

[45] Hahn, J., Monakhova, Y.B., Hengen, J., Kohl-Himmelseher, M., Schussler, J., Hahn, H., Kuballa, T. & Lachenmeier, D.W. (2014). Electronic cigarettes: Overview of chemical composition and exposure estimation. *Tobacco Induced Diseases* **12**, 23.

Australian Government
National Health and Medical Research Council

NHMRC CEO Statement: Electronic Cigarettes (E-Cigarettes)

Summary

Electronic cigarettes (e-cigarettes, also known as electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS)) are often marketed as a method to assist smokers to quit, or as a 'safe alternative' to conventional tobacco cigarettes. However, there is currently insufficient evidence to support claims that e-cigarettes are safe and further research is needed to enable the long-term safety, quality and efficacy of e-cigarettes to be assessed.

Key messages

- E-cigarettes may expose users to fewer toxic chemicals than conventional tobacco cigarettes; however the extent to which this reduces harm to the user has not been determined.
- E-cigarettes may expose users to chemicals and toxins such as formaldehyde, heavy metals, particulate matter and flavouring chemicals, at levels that have the potential to cause adverse health effects.
- There is currently insufficient evidence to conclude whether e-cigarettes can assist smokers to quit. Smokers wishing to quit should consult the Quitline or their general practitioner.
- There is some evidence from longitudinal studies to suggest that e-cigarette use in non-smokers is associated with future uptake of tobacco cigarette smoking.
- Health authorities and policy-makers should act to minimise harm to users and bystanders, and to protect vulnerable groups such as young people, until evidence of safety, quality and efficacy can be produced.
- NHMRC is currently funding a number of studies into the safety and efficacy of e-cigarettes.
- Consumers should seek further information about e-cigarettes from reliable sources, such as the relevant State or Territory Health Department or quit smoking services.

E-cigarettes are battery operated devices that heat a liquid (called 'e-liquid') to produce a vapour that users inhale. Although the composition of this liquid varies, it typically contains a range of chemicals, including solvents and flavouring agents, and may or may not contain nicotine. E-cigarettes have evolved as a product group since first entering the market, with products now ranging from early 'first generation' devices that resemble cigarettes, to second and third generation devices that enable users to modify characteristics of the device, such as adjusting the voltage.[1]

This wide variation in products, and the ability of users to customise their vaping experience, makes it difficult to assess the safety and efficacy of e-cigarettes as a group, because the results from research involving one particular product may not be applicable to all e-cigarettes or all users. However, by examining the evidence to identify common findings across a range of different products, or results that are replicated in a number of studies, it is possible to gain some insight into the efficacy of e-cigarettes, their potential harms, and areas where further research is required.

NHMRC recognises the need for high-quality research in this area and is currently funding a number of studies investigating the effects of e-cigarettes.

The following information is provided to assist consumers and policy-makers in understanding the current evidence about the safety and efficacy of e-cigarettes. This information is current at the time of writing but is subject to change as more research becomes available.

Health and safety

Potential health risks

It is widely believed that e-cigarettes are likely to be less harmful than tobacco cigarettes, because they expose users to fewer toxic chemicals.[2, 3, 4] However, there is insufficient evidence to quantify the reduction in risk when e-cigarettes are used instead of tobacco cigarettes.[1, 5] Although a 2014 study reported that e-cigarettes are 95% less harmful than tobacco cigarettes,[6] this finding was based on opinion rather than empirical evidence, and concerns have been raised about potential conflicts of interest.[7, 8] The World Health Organisation has stated that "no specific figure about how much 'safer' the use of these products is compared to smoking can be given any scientific credibility at this time."[1]

E-cigarettes are not likely to be risk free, and may expose users to chemicals and toxins at levels that have the potential to cause health effects. These include solvents such as propylene glycol, glycerol or ethylene glycol, which may form toxic or cancer-causing compounds when vaporised.[9, 10, 11, 12, 13, 14, 15, 16, 17] Although these chemicals are typically found in lower concentrations than in tobacco cigarettes,[3, 4, 10, 15] in some studies e-cigarettes and tobacco cigarettes were found to produce similar levels of formaldehyde,[11, 14] which is classified as a cancer-causing agent.[18] E-cigarette liquids or vapour may also contain potentially harmful chemicals which are not present in smoke from tobacco cigarettes.[1, 11, 19]

While some of the chemicals in e-liquid are also used in food production and are generally considered safe when eaten, this does not mean that these chemicals are safe when inhaled as a vapour directly into the lungs. A number of studies have reported harmful effects when certain flavourings that are approved for use in food production, including cherry, cinnamon and popcorn flavours, are inhaled.[20, 21, 22, 23] There is growing evidence to suggest that the long-term inhalation of flavourings used in most e-liquids is likely to pose a risk to health.[1]

Studies also show that e-cigarettes expose both users and bystanders to particulate matter (very small particles)[16, 24, 25, 26, 27] that may worsen existing illnesses or increase the risk of developing diseases such as cardiovascular or respiratory disease.[28] The World Health Organisation has warned that exposure to any level of particulate matter may be harmful and that levels of exposure should be minimised.[29]

E-cigarettes may also expose users to metals such as aluminium, arsenic, chromium, copper, lead, nickel and tin,[3, 15, 30, 31, 32] with these elements having been detected in e-liquid and in the vapour produced during use. In some cases these metals have been detected at levels greater than, or similar to, those found in tobacco cigarettes.[1, 30]

Adverse events

Studies that have tested e-cigarettes for use as a smoking cessation tool found that users of e-cigarettes typically experience a low rate of adverse events in the short term,[33, 34] with mouth and throat irritation the most commonly reported symptoms. However, more serious adverse events have also been reported, with over 200 incidents of e-cigarettes overheating, catching fire or exploding reported to date in the US and UK alone.[35] In some cases, these events have resulted in life-threatening injury, permanent disfigurement or disability, and major property damage.

The rising popularity of e-cigarette use internationally has also corresponded with an increasing number of reported nicotine poisonings due to exposure to or ingestion of e-liquids.[36, 37, 38, 39, 40, 41, 42] The effects of exposure range from relatively mild, including irritation of the eyes and skin, nausea and vomiting,[36, 37, 40] to severe life-threatening illness,[39] and in some cases, death.[36, 38, 42]

Passive exposure

A recent systematic review of 16 studies concluded that e-cigarette vapour has the potential to pose a health risk to bystanders, although the risk is likely to be lower than that posed by conventional cigarette smoke.[43] However, exposure to certain metals such as nickel and silver may be greater for e-cigarettes than tobacco cigarettes.[43] A 2016 study found that the most common symptoms reported by those passively exposed to e-cigarettes included respiratory difficulties, eye irritation, headache, nausea and sore throat or throat irritation.[44]

Smoking cessation

Experts disagree about whether e-cigarettes may help smokers to quit, or whether they will become 'dual users' of both e-cigarettes and tobacco cigarettes. There is currently insufficient evidence to demonstrate that e-cigarettes are effective in assisting people to quit smoking[1] and no brand of e-cigarette has been approved by the Therapeutic Goods Administration (TGA) for this purpose. Although a 2016 systematic review conducted by the Cochrane Collaboration[33] found some evidence that e-cigarettes with nicotine may assist smokers to quit, the review authors had a low level of confidence in this finding, due to the small volume of evidence. The review also reported results from one study comparing e-cigarettes with nicotine replacement therapy, which found that both methods resulted in similar rates of smoking cessation at 6 months follow-up. However, the reviewers noted that more research is required to enable confidence in these estimates and that further research is likely to change the estimate of effect.[33]

Smokers wishing to quit are advised to consult their general practitioner. First-line treatments include a range of TGA-approved nicotine replacement therapies and prescription medications that have been tested for safety and efficacy. Support and information are also available from the Quitline (13 78 48) or via the Quit Now website (www.quitnow.gov.au).

E-cigarettes and tobacco control policies

Concerns have been raised that the potential benefits of e-cigarettes in reducing harm to smokers may be outweighed by the risks that they may undermine tobacco control efforts. This includes the potential for e-cigarettes to provide a gateway to nicotine addiction or tobacco product use, or that they may renormalise smoking. The appeal of flavoured e-cigarettes to children and adolescents is also of concern, with studies reporting rapid uptake of e-cigarettes among adolescents in many countries, where trend data are available.[45, 46, 47, 48, 49] This provides some cause for concern given uncertainties about the long-term safety of e-cigarettes.

There is some evidence that e-cigarettes could act as a gateway into nicotine addiction or tobacco cigarette smoking. A number of longitudinal studies have reported an association between e-cigarette use in non-smokers and the uptake of tobacco cigarette smoking in the future.[50, 51, 52, 53] This association remained even when the studies controlled for other risk factors that might make people more likely to take up smoking. In some studies, the effect of e-cigarettes on future smoking behaviour was greatest among those who were otherwise at low risk of taking up smoking.[51, 54] A number of studies have also reported an association between e-cigarette use in non-users and future use of marijuana[52] or tobacco products such as hookahs, cigars or pipes.[51, 55, 56]

In view of the above concerns, the World Health Organisation has recommended that policy-makers act to prevent the initiation of e-cigarette use by non-smokers and youth, with special attention given to protecting vulnerable groups.[1]

Manufacturing quality

The manufacturing quality of e-cigarettes is highly variable, with a number of issues relating to quality control reported in the literature. Labelling of e-cigarettes and e-liquids has been found to be incomplete or inaccurate.[57, 58] Products have been found to contain chemicals that were not listed on the label,[57, 58, 59] or to state incorrectly that they did not contain potentially toxic chemicals, despite analyses confirming their presence.[60, 61]

There may also be wide variation between the levels of nicotine declared on packaging and the amount contained in e-liquid.[9, 58, 62, 63, 64, 65] One study that compared identical models of e-cigarettes found that nicotine content varied by up to 20% when the products came from different manufacturing batches, with variation of up to 12% reported for products manufactured in the same batch.[66] Furthermore, some products that are labelled as nicotine free have been found to contain nicotine.[11, 15, 57, 59, 62, 65, 67, 68]

Where can I get more information?

When seeking information about e-cigarettes online, it is important to look at websites that provide a reliable source of information, such as government websites or quit smoking services. Information on websites sponsored by retailers or manufacturers may reflect a commercial interest in promoting the sale of certain products.

Similarly, when reading published research on e-cigarettes it is important to consider whether the authors of the research held any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes, such as e-cigarette manufacturers.[69]

The following websites may provide further information of use to consumers:

Evidence-based reports

World Health Organisation – *Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS)*
http://www.who.int/fctc/cop/cop7/FCTC_COP_7_11_EN.pdf

Information, fact sheets and FAQs from government departments

ACT Health – *Electronic Cigarettes*
http://www.health.act.gov.au/public-information/public-health/tobacco-and-smoke-free/electronic-cigarettes

New South Wales Department of Health – *Electronic Cigarettes*
http://www.health.nsw.gov.au/tobacco/Pages/electronic-cigarettes.aspx

Product Safety Australia – *Electronic Cigarette Safety*
http://www.productsafety.gov.au/news/electronic-cigarette-safety

Therapeutic Goods Administration – *Electronic Cigarettes*
https://www.tga.gov.au/community-qa/electronic-cigarettes

Western Australia Department of Health – *Electronic cigarettes (e-cigarettes)*
http://healthywa.wa.gov.au/Articles/A_E/Electronic-cigarettes-e-cigarettes

State and Territory Health Departments – *Contact Details*
http://www.health.gov.au/internet/main/publishing.nsf/Content/health-related.htm#state

Position statements

Australian Medical Association – *Tobacco Smoking and E-cigarettes (2015) – The AMA Position*
https://ama.com.au/position-statement/tobacco-smoking-and-e-cigarettes-2015

Cancer Council Australia and The Heart Foundation – *Joint Position Statement on Electronic Cigarettes*
http://wiki.cancer.org.au/policy/Position_statement_-_Electronic_cigarettes

Public Health Association of Australia – *Statement by the Public Health Associations of Australia on Electronic Cigarettes*
https://www.phaa.net.au/documents/item/704

References

1 World Health Organisation, "Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS)" WHO Framework Convention on Tobacco Control, Geneva, 2016.

2 World Health Organisation, "Electronic Nicotine Delivery Systems" WHO Framework Convention on Tobacco Control, Geneva, 2014.

3 M. L. Goniewicz , J. Knysak , M. Gawron, L. Kosmider, A. Sobczak and J. Kurek, "Levels of Selected Carcinogens and Roxicants in Vapour from Electronic Cigarettes" *Tobacco Control,* vol. 23, no. 2, pp. 133-139, 2014.

4 S. S. Hecht, S. G. Carmella, D. Kotandeniya, M. E. Pillsbury, M. Chen, B. W. Ransom, R. Isaksson Vogel, E. Thompson, S. E. Murphy and D. K. Hatsukami, "Evaluation of Toxicant and Carcinogen Metabolites in the Urine of e-Cigarette Users Versus Cigarette Smokers" *Nicotine & Tobacco Research,* pp. 1-6, 2014.

5 N. Lindson-Hawley, J. Hartmann-Boyce, T. R. Fanshawe, R. Begh, A. Farley and T. Lancaster, "Interventions to Reduce Harm from Continued Tobacco Use" *Cochrane Database of Systematic Reviews,* no. 10, 2016.

6 D. J. Nutt, L. D. Phillips, D. Balfour, H. V. Curran, M. Dockrell, J. Foulds, K. Fagerstrom, K. Letlape, A. Milton, R. Polosa, J. Ramsey and D. Sweanor, "Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach" *European Addiction Research,* vol. 20, no. 5, pp. 218-225, 2014.

7 The Lancet, "Public Health England's Evidence-Based Confusion" *The Lancet,* vol. 386, p. 829, 2015.

8 M. Mckee and S. Capewell, "Evidence about Electronic Cigarettes: Foundation Built on Rock or Sand?" *BMJ,* vol. 351, 2015.

9 T. Cheng, "Chemical Evaluation of Electronic Cigarettes" *Tobacco Control,* vol. 23, no. Suppl 2, pp. ii11-7, 2014.

10 O. Geiss, I. Bianchi and J. Barrero-Moreno, "Correlation of Volatile Carbonyl Yields Emitted by E-cigarettes with the Temperature of the Heating Coil and the Perceived Sensorial Quality of the Generated Vapours" *International Journal of Hygiene and Environmental Health,* vol. 219, no. 3, pp. 268-277, 2016.

11 C. Hutzler, M. Paschke, S. Kruschinski, F. Henkler, J. Hahn and A. Luch, "Chemical Hazards Present in Liquids and Vapors of Electronic Cigarettes" *Archives of Toxicology,* vol. 88, pp. 1295-1308, 2014.

12 R. P. Jensen, W. Luo, J. F. Pankow, R. M. Strongin and D. H. Peyton, "Hidden Formaldehyde in E-cigarette Aerosols" *The New England Journal of Medicine,* vol. 372, no. 4, pp. 392-394, 2015.

13 M. Sleiman, J. M. Logue, V. N. Montesinos, M. L. Russell, M. I. Litter, L. A. Gundel and H. Destaillats, "Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals" *Environmental Science & Technology,* vol. 50, no. 17, pp. 9644-9651, 2016.

14 L. Kosmider, A. Sobczak, M. Fik, J. Knysak, M. Zaciera, J. Kurek and M. L. Goniewicz, "Carbonyl Compounds in Electronic Cigarette Vapors – Effects of Nicotine Solvent and Battery Output Voltage" *Nicotine & Tobacco Research,* vol. 16, no. 10, pp. 1319-1326, 2014.

15 W. Visser, L. Geraets, W. Klerx, L. Hernandez, E. Stephens, E. Croes, P. Schwillens, H. Cremers, P. Bos and R. Talhout, "The Health Risks of Using E-cigarettes" National Institute for Public Health and the Environment, Bilthoven, 2015.

16 A. El-Hellani, R. Salman, R. El-Hage, S. Talih, N. Malek, R. Baalbaki, N. Karaoghlanian, R. Nakkash, A. Shihadeh and N. A. Saliba, "Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics" *Nicotine & Tobacco Research,* vol. Oct, 2016.

17 A. Khlystov and V. Samburova, "Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping" *Environmental Science & Technology,* vol. 50, no. 23, pp. 13080-13085, 2016.

18 International Agency for Research on Cancer (IARC), "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 100F (29)" WHO, 2012.

19 S. Uchiyama, K. Ohta, Y. Inaba and N. Kunungita, "Determination of Carbonyl Compounds Generated from the E-cigarette using Coupled Silica Cartridges Impregnated with Hydroquinone and 2,4-Dinitrophenylhydrazine, Followed by High-Performance Liquid Chromatography" *Analytical Sciences,* vol. 29, pp. 1219-1222, 2013.

20 K. Kreiss, A. Gomaa, G. Kullman, K. Fedan, E. Simoes and P. Enright, "Clinical Bronchiolitis Obliterans in Workers at a Microwave-Popcorn Plant" *New England Journal of Medicine,* vol. 347, no. 5, pp. 330-338, 2002.

21 P. Harber, K. Saechao and C. Boomus, "Diacetyl-Induced Lung Disease" *Toxicological Reviews,* vol. 25, no. 4, pp. 261-272, 2006.

22 R. Behar, B. Davis, Y. Wang, V. Bahl, S. Lin and P. Talbot, "Identification of Toxicants in Cinnamon-Flavored Electronic Cigarette Refill Liquids" *Toxicology in Vitro,* vol. 28, no. 2, pp. 198-208, 2014.

23 L. Kosmider, A. Sobczak, A. Prokopowicz, J. Kurek, M. Zaciera, J. Knysak, D. Smith and M. L. Goniewicz, "Cherry-flavoured Electronic Cigarettes Expose Users to the Inhalation Irritant, Benzaldehyde" *Thorax,* vol. 71, no. 4, pp. 376-377, 2016.

24 R. M. Pellegrino, B. Tinghino, G. Mangiaracina, A. Marani, M. Vitali, C. Protano, J. F. Osborn and M. S. Cattaruzza, "Electronic Cigarettes: an Evaluation of Exposure to Chemicals and Fine Particulate Matter (PM)" *Annali di Igiene,* vol. 24, no. 4, pp. 279-288, 2012.

25 W. Schober, K. Szendrei, W. Matzen, H. Osiander-Fuchs, D. Heitmann, T. Schettgen, R. A. Jorres and H. Fromme, "Use of Electronic Cigarettes (E-cigarettes) Impairs Indoor Air Quality and Increases FeNO Levels of E-cigarette Consumers" *International Journal of Hygiene and Environmental Health,* vol. 217, pp. 628-637, 2014.

26 T. Schripp, D. Markewitz, E. Uhde and T. Salthammer, "Does E-cigarette Consumption Cause Passive Vaping?" *Indoor Air,* vol. 23, pp. 25-31, 2013.

27 J. Zhao, G. Pyrgiotakis and P. Demokritou, "Development and Characterization of Electronic-Cigarette Exposure Generation System (Ecig-EGS) for the Physico-Chemical and Toxicological Assessment of Electronic Cigarette Emissions" *Inhalation Toxicology,* vol. 28, no. 14, pp. 658-669, 2016.

28 Environmental Protection Agency, "Integrated Science Assessment for Particulate Matter (Final Report)" U.S. Environmental Protection Agency, Washington DC, 2009.

29 World Health Organisation, "WHO Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide: Summary of Risk Assessment" WHO, Geneva, 2006.

30 M. Williams, A. Villarreal, K. Bozhilov, S. Lin and P. Talbot, "Metal and Silicate Particles Including Nanoparticles are Present in Electronic Cigarette Cartomizer Fluid and Aerosol" *PLoS One,* vol. 8, no. 3, p. e57987, 2013.

31 V. B. Mikheev, M. C. Brinkman, C. A. Granville, S. M. Gordon and P. I. Clark, "Real-Time Measurement of Electronic Cigarette Aerosol Size Distribution and Metals Content Analysis" *Nicotine & Tobacco Research,* vol. May, 2016.

32 C. A. Hess, P. Olmedo, A. Navas-Acien, W. Goessler, J. E. Cohen and A. M. Rule, "E-cigarettes as a Source of Toxic and Potentially Carcinogenic Metals" *Environmental Research,* vol. 152, pp. 221-225, 2017.

33 J. Hartmann-Boyce, H. McRobbie, C. Bullen, R. Begh, L. F. Stead and P. Hajek, "Electronic Cigarettes for Smoking Cessation (Review)" *Cochrane Database of Systematic Reviews,* no. 9, 2016.

34 M. R. Gualano, S. Passi, F. Bert, G. La Torre, G. Scaioli and R. Siliquini, "Electronic Cigarettes: Assessing the Efficacy and the Adverse Effects through a Systematic Review of Published Studies" *Journal of Public Health,* vol. 37, no. 3, pp. 488-497, 2015.

35 S. F. Rudy and E. L. Durmowicz, "Electronic Nicotine Delivery Systems: Overheating, Fires and Explosions" *Tobacco Control,* vol. Mar, 2016.

36 K. Chatham-Stephens, R. Law, E. Taylor, S. Kieszak, P. Melstrom, R. Bunnell, B. Wang, H. Day, B. Apelberg, L. Cantrell, H. Foster and J. G. Schier, "Exposure Calls to U. S. Poison Centers Involving Electronic Cigarettes and Conventional Cigarettes-September 2010-December 2014" *Journal of Medical Toxicology,* 2016.

37 F. Davanzo, L. Settimi, G. Milanesi, F. Giordano, F. M. Sesana, A. Celentano, E. Urbani, G. Panzavolta, L. Cossa, A. Tomoiaga, A. Travaglia and V. Dimasi, "Surveillance of Hazardous Exposures to Electronic Cigarettes in Italy" *Clinical Toxicology,* vol. 52, no. Supp, pp. 336-337, 2014.

38 A. Kamboj, H. A. Spiller, M. J. Casavant, T. Chounthirath and G. A. Smith, "Pediatric Exposure to E-Cigarettes, Nicotine, and Tobacco Products in the United States" *Pediatrics,* vol. 137, no. 6, 2016.

39 S. W. Lindberg, N. Ebbehoej, J. Bang and L. B. Christensen, "Nicotine Poisoning Related to the Use of E-cigarettes" *Clinical Toxicology,* vol. 53, no. 4, 2015.

40 S. Pajarre-Sorsa, M. Saukkonen and K. Hoppu, "Calls Concerning Electronic Cigarettes to the Finnish Poison Information Centre" *Clinical Toxicology,* vol. 52, no. Supp, p. 337, 2014.

41 E. Thomas, R. A. Spears, G. Alldridge, C. V. Krishna, J. P. Thompson, M. Eddleston, J. A. Vale and S. H. L. Thomas, "E-cigarette Liquid Refills – a Safe Beverage? Analysis of Enquiries to the UK National Poisons Information Service from 2007 to 2013" *Clinical Toxicology,* vol. 52, no. Supp, pp. 338-339, 2014.

42 J. P. Vakkalanka, L. S. Hardison and C. P. Holstege, "Epidemiological Trends in Electronic Cigarette Exposures Reported to U.S. Poison Centers" *Clinical Toxicology,* vol. 52, no. 5, pp. 542-548, 2014.

43 I. M. R. Hess, K. Lachireddy and A. Capon, "A Systematic Review of the Health Risks from Passive Exposure to Electronic Cigarette Vapour" *Public Health Research and Practice,* vol. 26, no. 2, 2016.

44 E. L. Durmowicz, S. F. Rudy and I. L. Chen, "Electronic Cigarettes: Analysis of FDA Adverse Experience Reports in Non users" *Tobacco Control,* vol. 25, no. 2, p. 242, 2016.

45 S. Lee, R. Grana and S. Glantz, "Eletronic Cigarette Use Among Korean Adolescents: A Cross-Sectional Study of Market Penetration, Dual Use, and Relationship to Quit Attempts and Former Smoking" *J Adolesc Health,* vol. 54, pp. 684-690, 2014.

46 B. Eastwood, M. J. Dockrell, D. Arnott, J. Britton, H. Cheeseman, M. J. Jarvis and A. McNeill, "Electronic Cigarette Use in Young People in Great Britain 2013-2014" *Public Health,* vol. 129, no. 9, pp. 1150-1156, 2015.

47 T. Singh, R. A. Arrazola, C. G. Corey, C. G. Husten, L. J. Neff, D. M. Homa and B. A. King, "Tobacco Use Among Middle and High School Students — United States, 2011-2015" *Morbidity and Mortality Weekly Report,* vol. 65, no. 14, 2016.

48 J. White, J. Li, R. Newcombe and D. Walton, "Tripling Use of Electronic Cigarettes Among New Zealand Adolescents Between 2012 and 2014" *The Journal of Adolescent Health,* vol. 56, no. 5, pp. 522-528, 2015.

49 J. M. Kinnunen, H. Ollila, P. L. Lindfors and A. H. Rimpelä, "Changes in Electronic Cigarette Use from 2013 to 2015 and Reasons for Use Among Finnish Adolescents" *International Journal of Environmental Research and Public Health,* vol. 13, no. 11, 2016.

50 K. Chatterjee, B. Alzghoul, A. Innabi and N. Meena, "Is Vaping a Gateway to Smoking: a Review of the Longitudinal Studies" *Int J Adolesc Med Health,* 2016.

51 J. L. Barrington-Trimis, R. Urman, K. Berhane, J. B. Unger, T. B. Cruz, M. A. Pentz, J. M. Samet, A. M. Leventhal and R. McConnell, "E-Cigarettes and Future Cigarette Use" *Pediatrics,* vol. 138, no. 1, 2016.

52 J. B. Unger, D. W. Soto and A. Leventhal, "E-cigarette Use and Subsequent Cigarette and Marijuana Use Among Hispanic Young Adults" *Drug and Alcohol Dependence,* 2016.

53 T. R. Spindle, M. M. Hiler, M. E. Cooke and T. Eissenberg, "Electronic Cigarette Use and Uptake of Cigarette Smoking: A Longitudinal Examination of U.S. College Students" *Addictive Behaviors,* vol. 67, pp. 66-72, 2017.

54 T. A. Wills, J. D. Sargent, F. X. Gibbons, I. Pagano and R. Schweitzer, "E-cigarette Use is Differentially Related to Smoking Onset Among Lower Risk Adolescents" *Tobacco Control,* 2016.

55 J. Huh and A. M. Leventhal, "Progression of Poly-Tobacco Product Use Patterns in Adolescents" *American Journal of Preventive Medicine,* vol. 51, no. 4, pp. 513-517, 2016.

56 A. M. Leventhal, D. R. Strong, M. G. Kirkpatrick, J. B. Unger, S. Sussman, N. R. Riggs, M. D. Stone, R. Khoddam, J. M. Samet and J. Audrain-McGovern, "Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence" *JAMA,* vol. 314, no. 7, pp. 700-707, 2015.

57 J. Hahn, Y. B. Monakhova, J. Hengen, M. Kohl-Himmelseher, J. Schassler, H. Hahn, T. Kuballa and D. W. Lachenmeier, "Electronic Cigarettes: Overview of Chemical Composition and Exposure Estimation" *Tobacco Induced Diseases,* vol. 12, no. 1, p. 23, 2014.

58 S. Han, H. Chen, X. Zhang, T. Liu and Y. Fu, "Levels of Selected Groups of Compounds in Refill Solutions for Electronic Cigarettes" *Nicotine & Tobacco Research,* vol. 18, no. 5, pp. 708-714, 2016.

59 M. E. Hadwiger, M. L. Trehy, W. Ye, T. Moore, J. Allgire and B. Westenberger, "Identification of Amino-tadalafil and Rimonabant in Electronic Cigarette Products Using High Pressure Liquid Chromatography with Diode Array and Tandem Mass Spectrometric Detection" *Journal of Chromatography,* vol. 1217, no. 48, pp. 7547-7555, 2010.

60 J. G. Allen, S. S. Flanigan, M. LeBlanc, J. Vallarino, P. MacNaughton, J. H. Stewart and D. C. Christiani, "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes" *Environmental Health Perspectives,* 2015.

61 Australian Competition and Consumer Commission, "ACCC Takes Action Against E-cigarette Suppliers for Alleged Misleading "No Toxic Chemicals" Claims" 20 June 2016. Online. Available: https://www.accc.gov.au/media-release/accc-takes-action-against-e-cigarette-suppliers-for-alleged-misleading-%E2%80%9Cno-toxic-chemicals%E2%80%9D-claims. Accessed 25 November 2016.

62 K. Buettner-Schmidt, D. R. Miller and N. Balasubramanian, "Electronic Cigarette Refill Liquids: Child-Resistant Packaging, Nicotine Content, and Sales to Minors" *Journal of Pediatric Nursing,* vol. 31, no. 4, pp. 373-379, 2016.

63 B. Davis, M. Dang, J. Kim and P. Talbot, "Nicotine Concentrations in Electronic Cigarette Refill and Do-it-yourself Fluids" *Nicotine & Tobacco Research,* vol. 17, no. 2, pp. 134-141, 2015.

64 M. Williams, A. Villareal, B. Davis and P. Talbot, "Comparison of the Performance of Cartomizer Style Electronic Cigarettes from Major Tobacco and Independent Manufacturers" *PLoS One,* vol. 11, no. 2, 2016.

65 M. Famele, J. Palmisani, C. Ferranti, C. Abenavoli, L. Palleschi, R. Mancinelli, R. M. Fidente, G. de Gennaro and R. Draisci, "Liquid Chromatography with Tandem Mass Spectrometry Method for the Determination of Nicotine and Minor Tobacco Alkaloids in Electronic Cigarette Refill Liquids and Second-hand Generated Aerosol" *Journal of Separation Science,* vol. Dec, 2016.

66 M. L. Goniewicz, P. Hajek and H. McRobbie, "Nicotine Content of Electronic Cigarettes, its Release in Vapour and its Consistency Across Batches: Regulatory Implications" *Addiction,* vol. 109, no. 3, pp. 500-507, 2014.

67 U.S. Food and Drug Administration, "Evaluation of E-cigarettes" U.S. Food and Drug Administration, St Louis, MO, 2009.

68 J. Regueiro, A. Giri and T. Wenzl, "Optimization of a Differential Ion Mobility Spectrometry-Tandem Mass Spectrometry Method for High-Throughput Analysis of Nicotine and Related Compounds: Application to Electronic Cigarette Refill Liquids" *Analytical Chemistry,* vol. 88, no. 12, pp. 6500-6508, 2016.

69 C. Pisinger and M. Døssing, "A Systematic Review of Health Effects of Electronic Cigarettes" *Preventive Medicine,* vol. 69, pp. 248-260, 2014.

WARNING LETTER

JUUL Labs, Inc.

MARCS-CMS 590950 — SEPTEMBER 09, 2019

Delivery Method: VIA UPS and Electronic Mail

Product: Tobacco

Recipient:

Mr. Kevin Burns

CEO

JUUL Labs, Inc.

560 20th Street
San Francisco, CA 94107-4344
United States

kburns@juul.com (mailto:kburns@juul.com)

Issuing Office:

Center for Tobacco Products

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

WARNING LETTER

Dear Mr. Burns:

The Center for Tobacco Products of the U.S. Food and Drug Administration (FDA) reviewed testimony from the July 24-25, 2019 hearing on "Examining JUUL's Role in the Youth Nicotine Epidemic," of the Subcommittee on Economic and Consumer Policy of the Committee on Oversight and Reform of the United States House of Representatives ("House Subcommittee"), documents from FDA's September 24-28, 2018 inspection of JUUL Labs, Inc.'s (JUUL) headquarters in San Francisco, California, JUUL's submissions to the Agency, and JUUL's website, https://www.juullabs.com (https://www.juullabs.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer), and determined that JUUL products, which are electronic nicotine delivery system (ENDS) products, are manufactured, marketed, advertised, labeled, and offered for sale or distribution to customers in the United States. Under section 201(rr) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 321(rr)), as amended by the Family Smoking Prevention and Tobacco Control Act, these products are tobacco products because they are made or derived from tobacco and intended for human consumption. Certain tobacco products, including ENDS products (*e.g.,* e-cigarettes and e-liquids), are subject to FDA jurisdiction under section 901(b) of the FD&C Act (21 U.S.C. § 387a(b)).

Based on our review of the information described above, FDA has determined that JUUL adulterated its products under section 902(8) of the FD&C Act (21 U.S.C. § 387b(8)) by selling or distributing them as modified risk tobacco products without an FDA order in effect that permits such sale or distribution.

Modified Risk Tobacco Products Without an Appropriate FDA Order in Effect are Adulterated

Our review of testimony from the July 24-25, 2019 House Subcommittee hearing, documents from FDA's inspection of JUUL's headquarters, JUUL's submissions to the Agency, and JUUL's website, https://www.juullabs.com (https://www.juullabs.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer), revealed that your firm has engaged in labeling, advertising, and/or other activities directed to consumers, in which JUUL explicitly and/or implicitly has represented that JUUL products are free of a substance, have a reduced level of or exposure to a substance, and/or that JUUL products present a lower risk of tobacco-related disease or are less harmful than one or more other commercially marketed tobacco products.

The July 24-25, 2019 House Subcommittee hearing included the following evidence:

1. A JUUL representative speaking with students at his presentation stated that JUUL "was much safer than cigarettes" and that "FDA would approve it any day."[1]
2. The JUUL representative speaking with students at his presentation called JUUL "totally safe."[2]
3. The JUUL representative speaking with students at his presentation stated that a student "…should mention JUUL to his [nicotine-addicted] friend…because that's a safer alternative than smoking cigarettes, and it would be better for the kid to use."[3]
4. The JUUL representative speaking with students at his presentation stated, "FDA was about to come out and say it [JUUL] was 99% safer than cigarettes…and that…would happen very soon…."[4]

Referring to your ENDS products as "99% safer" than cigarettes, "much safer" than cigarettes, "totally safe," and "a safer alternative than smoking cigarettes" is particularly concerning because these statements were made directly to children in school. Our concern is amplified by the epidemic rate of increase in youth use of ENDS products, including JUUL's products, and evidence that ENDS products contribute to youth use of, and addiction to, nicotine, to which youth are especially vulnerable.[5]
In addition, your "Letter from the CEO" states: "[JUUL's] simple and convenient system incorporates temperature regulation to heat nicotine liquid and deliver smokers the satisfaction that they want without the combustion and the harm associated with it." On April 25, 2018, your letter appeared in an email that JUUL sent to a parent in response to her complaint that the firm sold JUUL products to her child. On May 8, 2018, your letter appeared on JUUL's website, https://www.juullabs.com (https://www.juullabs.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).[6] This letter provides further confirmation of the evidence from the hearing testimony that JUUL has marketed JUUL products as modified risk tobacco products.

A tobacco product is considered a "modified risk tobacco product," *inter alia*, if its label, labeling, or advertising explicitly or implicitly represents that: (1) the product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products; (2) the product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or (3) the product or its smoke does not contain or is free of a substance (section 911(b)(2)(A)(i) of the FD&C Act (21 U.S.C. § 387k(b)(2)(A)(i))); or where the manufacturer has taken any action directed to consumers through media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances (section 911(b)(2)(A)(iii) of the FD&C Act (21 U.S.C. § 387k(b)(2)(A)(iii))).

Under section 911(a) of the FD&C Act (21 U.S.C. § 387k(a)), no person may introduce or deliver for introduction into

interstate commerce any modified risk tobacco product without an FDA order in effect under section 911(g) of the FD&C Act (21 U.S.C. § 387k(g)). A modified risk tobacco product application under section 911(d) of the FD&C Act (21 U.S.C. § 387k(d)) is required to provide scientific evidence and other information to support issuance of an order under section 911(g) of the FD&C Act (21 U.S.C. § 387k(g)). A product that is in violation of section 911(a) of the FD&C Act (21 U.S.C. § 387k(a)) is adulterated under section 902(8) of the FD&C Act (21 U.S.C. § 387b(8)).

JUUL has marketed its ENDS products as modified risk tobacco products because JUUL's labeling, advertising, and/or other actions directed to consumers (examples of which are referenced above), represent, or would be reasonably expected to result in consumers believing, that the products present a lower risk of tobacco-related disease or are less harmful than one or more other commercially marketed tobacco products; contain a reduced level of a substance or present a reduced exposure to a substance; and/or do not contain or are free of a substance or substances. JUUL adulterated its products under section 902(8) of the FD&C Act (21 U.S.C. § 387b(8)) by selling or distributing them as modified risk tobacco products without an appropriate FDA order in effect under section 911(g) of the FD&C Act (21 U.S.C. § 387k(g)) that permits such sale or distribution.

Conclusion

The violations discussed in this letter do not necessarily constitute an exhaustive list. To the extent you have not already done so, you should immediately correct the violations that are referenced above, as well as violations that are the same as or similar to those stated above, and take any necessary actions to bring your tobacco products into compliance with the FD&C Act. It is your responsibility to ensure that your tobacco products, all related labeling and advertising, and all other activities by JUUL directed to consumers, such as in any media in which you advertise and any retail establishments, comply with each applicable provision of the FD&C Act and FDA's implementing regulations. Failure to ensure compliance with the FD&C Act may result in FDA initiating further action, including, but not limited to, civil money penalties, seizure, and/or injunction. Please note that any adulterated and misbranded tobacco products offered for import into the United States are subject to detention and refusal of admission.

Please submit a written response to this letter within 15 working days from the date of receipt describing your corrective actions, including the dates on which you discontinued the violative promotion, labeling, advertising, sale, and/or distribution of these tobacco products. In your written response, please also describe your plan for maintaining compliance with the FD&C Act, including your plan to prevent violations that are the same as or similar to those stated above, such as through, for example, new internal controls and training. You can find the FD&C Act through links on FDA's homepage at http://www.fda.gov (http://www.fda.gov). If you do not believe that your products are in violation of section 911 of the FD&C Act (21 U.S.C. § 387k), please provide us with your reasoning and provide any and all scientific evidence and data, if any, that support that your statements and representations do not explicitly or implicitly convey that JUUL products pose less risk, are less harmful, present reduced exposure, or are safer than other tobacco products.

Please note your reference number, RW1901168, in your response and direct your response to the following address:

Anthony Villa, Senior Regulatory Counsel
Office of Compliance and Enforcement
FDA Center for Tobacco Products
c/o Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions about the content of this letter, please contact Anthony Villa at (301) 796-7385 or via email at Anthony.Villa@fda.hhs.gov (mailto:Anthony.Villa@fda.hhs.gov).

Sincerely,

/s/
Ann Simoneau, J.D.
Director
Office of Compliance and Enforcement
Center for Tobacco Products

VIA Electronic Mail

cc:

Jerry Masoudi
Chief Legal Officer, JUUL Labs, Inc.
jmasoudi@juul.com (mailto:jmasoudi@juul.com)

---

[1] Hearing, July 24, 2019, Testimony of Ms. Meredith Berkman (PAVe co-founder), at minutes 52:27 – 53:31 (https://youtu.be/m3iEMrAd83o (https://youtu.be/m3iEMrAd83o) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)).

[2] Hearing, July 24, 2019, Testimony of Mr. Caleb Mintz (son of Ms. Meredith Berkman, PAVe co-founder), at minutes 1:18:50 – 1:19:11 (https://youtu.be/m3iEMrAd83o (https://youtu.be/m3iEMrAd83o) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)).

[3] Hearing, July 24, 2019, Testimony of Mr. Phillip Fuhrman (son of Ms. Dorian Fuhrman, PAVe co-founder), at minutes 1:20:20 – 1:21:14 (https://youtu.be/m3iEMrAd83o (https://youtu.be/m3iEMrAd83o) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)).

[4] Hearing, July 24, 2019, Testimony of Mr. Phillip Fuhrman, at minutes 1:21:45 – 1:22:02 (https://youtu.be/m3iEMrAd83o (https://youtu.be/m3iEMrAd83o) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)).

[5] As discussed in the March 2019 Draft Guidance: Modifications to Compliance Policy for Certain Deemed Tobacco Products, "[R]ecent data show a significant increase in minors' use of ENDS products…For example, data from the NYTS [National Youth Tobacco Survey] show that, between 2017 and 2018, current e-cigarette use among high school students increased 78 percent (11.7 percent to 20.8 percent, $p<0.05$)…These data represent an increase of an estimated 1.32 million high school students reporting past 30-day e-cigarette use in one year. Current e-cigarette use among middle school students also increased by 48 percent over the same time period (3.3 percent to 4.9 percent, $p<0.05$), an increase of an estimated 180,000 middle school students reporting past 30-day e-cigarette use in one year…[.]" (https://www.fda.gov/media/121384/download (https://www.fda.gov/media/121384/download), at p. 8)

[6] See, *e.g.*, "Letter from the CEO" from Mr. Kevin Burns, CEO, JUUL Labs, Inc. (https://www.juullabs.com (https://www.juullabs.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)) (May 8, 2018).

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)

FDA warns leading e-cigarette maker Juul about its marketing practices

edition.cnn.com/2019/09/09/health/fda-juul-warning-bn/index.html

September 9, 2019

*(CNN)*The US Food and Drug Administration on Monday warned leading e-cigarette maker Juul Labs about illegally marketing its product as a safer alternative to cigarettes.

The FDA ordered Juul to respond within 15 working days with corrective actions and its plan to comply with federal law. The warning letter noted that failure to comply could result in fines, seizures or injunction.

More deaths reported among rising number of lung disease cases that could be due to vaping

"Regardless of where products like e-cigarettes fall on the continuum of tobacco product risk, the law is clear that, before marketing tobacco products for reduced risk, companies must demonstrate with scientific evidence that their specific product does in fact pose less risk or is less harmful. JUUL has ignored the law, and very concerningly, has made some of these statements in school to our nation's youth," Acting FDA Commissioner Dr. Ned Sharpless said in a statement.

"We will continue to scrutinize tobacco product marketing and take action as appropriate to ensure that the public is not misled into believing a certain product has been proven less risky or less harmful," he said. "We've also put the industry on notice: If the disturbing rise in youth e-cigarette use continues, especially through the use of flavors that appeal to kids, we'll take even more aggressive action."

The FDA sent a separate letter to Juul "expressing concern, and requesting more information, about several issues raised in a recent Congressional hearing regarding JUUL's outreach and marking practices, including those targeted at students, tribes, health insurers and employers."

Read More

#Juul: Study makes the case for stricter regulation on e-cigarette marketing

The agency requested documents related to marketing, including scientific evidence and data such as consumer perception studies "related to whether these statements and representations explicitly or implicitly convey that JUUL products pose less risk, are less harmful, present reduced exposure, are safer than other tobacco products or that the products are smoking cessation products."

In November, the FDA revealed that vaping had increased nearly 80% among high schoolers and 50% among middle schoolers since a year earlier. Public health experts have said that Juul has largely propelled the rise, commanding about 75% of the e-cigarette market in the United States.

"We believe you have a continuing responsibility to take action to address the epidemic of youth use of your products, some of which appears to have been a direct result of

your product design and marketing campaigns, whether or not some of these practices have been discontinued," the FDA's separate letter to Juul said.
Juul has maintained that its products are intended to convert adult smokers to what it described in the past as a less-harmful alternative. In other communications, the company says it cannot make claims its products are safer, in line with FDA regulations.
"We are reviewing the letters and will fully cooperate," according to Ted Kwong, a Juul Labs spokesperson.

Calls for action against Juul

Last week, Rep. Raja Krishnamoorthi, chairman of the House Oversight Subcommittee on Economic and Consumer Policy, asked the FDA in a letter to take "appropriate enforcement action" against Juul. He said the agency should "protect the American public from the fraudulent and unapproved medical claims" made by the company.

Juul went into a ninth-grade classroom and called its device 'totally safe,' teens testify

Krishnamoorthi's letter followed a two-day hearing in July, after which the committee concluded that "JUUL appears to be violating FDA regulations against making unapproved express and implied claims that its product helps users stop smoking cigarettes and is safer than cigarettes."
At the subcommittee hearing in July, several people testified that the company was directly marketing to children in high school, to the Cheyenne River Sioux Tribe and to smoking cessation groups.
On Friday, the US Centers for Disease Control and Prevention announced that the agency is now aware of at least 450 possible cases of severe lung disease that could be caused by vaping across 33 states.
There have been at least five deaths across five states -- one each in Illinois, Oregon, Minnesota, Indiana and California -- linked to the illnesses.
US Senate Democratic Whip Dick Durbin pointed out in a press conference on Monday how Sharpless' predecessor, Dr. Scott Gottlieb, called vaping among youth an "epidemic."
"That was his word, and it is an epidemic, and why the FDA refuses to act, I can not answer," Durbin said during the press conference.
After news of additional deaths spread on Friday, Durbin called on Sharpless to act on regulating e-cigarettes and flavors in the next 10 days. Durbin said he would call for Sharpless' resignation if he did not take action.
Then on Monday, Durbin said again that it's time Sharpless "either does something or resigns."
"This is a kids' toy, make no mistake about it, no matter what Juul tells you," he said. "We're naïve to believe that children aren't buying these and using these for purposes that are endangering their health. This ought to be closely regulated by the Food and Drug Administration. We are facing, in their words, an epidemic, taking the lives of children across the United States."
Durbin added during the press conference that public education around this issue is not enough and enforcement is needed.

"We have to send people undercover into these places that are selling these devices, and when we nail them selling them to people underage, they pay a heavy price for it. The word gets out quickly in the retail community," he said.
Sign up here to get **The Results Are In with Dr. Sanjay Gupta** every Tuesday from the CNN Health team.

In response to Durbin's criticism, FDA spokeswoman Stephanie Caccomo said in an emailed statement on Friday that the agency looks forward to "engaging with Senator Durbin, along with all members of Congress, on this ongoing and very serious situation." "Getting to the bottom of this is a top priority for the agency and all of our federal and state partners. We are all working tirelessly to get as much information as possible about any products or substances used. We are leaving no stone unturned in following any potential leads and we're committed to taking appropriate actions as the facts emerge," the statement said in part. "The illnesses under investigation involve the broader use of vaping products — including those being used with substances like THC; e-cigarettes are considered one type of vaping product. With respect to our work to tackle the youth e-cigarette epidemic, we remain committed to our oversight of e-cigarettes and to keeping them out of the hands of youth."