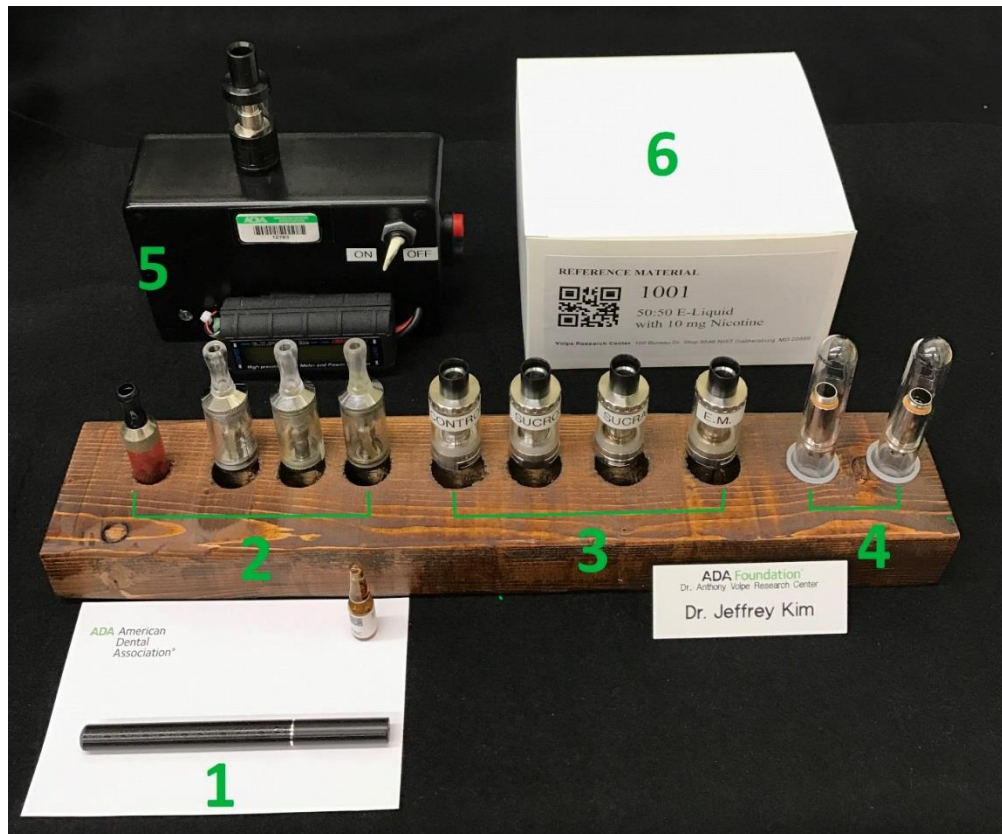


# E-cigarettes, Research and Your Health: What Do We Know About Electronic-cigarettes?

## What is an e-cigarette?

An e-cigarette is a battery-operated device or 'cigarette', that delivers flavored nicotine using vapors instead of smoke. The device uses a power source (e.g. lithium ion battery) to heat a metal element. The element aerosolizes the flavored e-liquids, and the user inhales the resulting aerosol.

First generation e-cigarettes resemble a cigarette, usually are disposable and readily available at U.S. convenience stores, shopping malls, and gas stations. The latest e-cigarettes use a sub-ohm heating element (more power), replaceable atomizer (convenient) and refillable reservoir (customizable). Most e-cigarettes are imported from China which is the largest manufacturer of e-cigarettes, producing 95% of the world's e-cigarettes, primarily for the U.S. and the European consumer markets.



**Electronic cigarettes.** 1: first generation e-cigarette, 2: second generation e-cigarette (AKA tank system), 3: latest generation e-cigarette (AKA sub-ohm system), 4: heating elements, 5: e-cigarette power delivery system, and 6: e-liquid Reference Material (RM).

## What is e-liquid?

Most e-liquids contain four base chemicals: propylene glycol, vegetable glycerin, nicotine, and flavoring(s). In the U.S., over 400 companies distribute thousands of e-liquids through local 'vape shops' and online stores.<sup>1</sup> In 2014, there were over 7,700 different e-liquid formulations available on the market and it is estimated that more than 200 new flavors are being introduced monthly.<sup>1</sup> Quality control and industry standards for e-liquid manufacturing process are not yet fully implemented. Thus, there are significant product and batch variations; and impurities are commonly found in consumer products.<sup>2-12</sup>

The lack of child-proof containers poses a serious threat to infants and toddlers. Sophisticated packaging for candy-flavored e-liquids, which targets youth, can be indistinguishable from real candies which, in part, is responsible for accidental ingestion. The American Association of Poison Control Centers (AAPCC) receives on average 10 calls a day from people regarding children who were accidentally exposed to e-cigarette devices and liquid nicotine.<sup>13</sup>



**E-liquids.** ~10,000 e-liquid formulations are available from local vape shoppes and online stores in U.S. (credits: [www.vaporhq.com](http://www.vaporhq.com), [www.vape.deals.com](http://www.vape.deals.com), [www.vaportrim.com](http://www.vaportrim.com), [www.flavors.com](http://www.flavors.com), and [www.skittlesjuice.com](http://www.skittlesjuice.com)).

## **What are the potential dangers/risks of using e-cigarettes?**

**Chemical analyses of e-cigarette aerosol:** We found that three factors could significantly impact research outcomes: (1) types of e-cigarette devices (e.g. e-cigarette generation and design) used in the study, (2) the amount of power (in wattage) delivered to the system, and (3) composition of e-liquids aerosolized (specifically the types of flavorings used). A consensus on e-cigarette testing standards from the industry, government agencies and academia would be necessary prior to putting the chemical analysis into perspective and to better assess potential health dangers and risks associated with e-cigarette usage.

**Youth:** Currently we do not have long-term data to understand the physiological, psychological, and developmental effects of e-cigarette on youth. Some researchers consider e-cigarettes as ‘gateway devices,’ in that kids are introduced to tobacco products via vaping and once addicted to nicotine, ‘graduate’ to traditional products such as cigarettes, cigars, chewing tobacco and hookah.<sup>14,15</sup> Although the complexity of youth’s vaping/smoking behavior remains to be seen, it is certain that e-cigarette products are easier for children to obtain compared to regular tobacco products.<sup>16</sup> Studies show e-cigarettes have surpassed combustible cigarettes as the most commonly used tobacco product among middle school and high school students.<sup>17-19</sup> Marketing, internet availability and sweet flavorings may have contributed to this shift. In a 2016 report, the U.S. Surgeon General states that e-cigarette usage among youth and young adults has become a public health concern.<sup>20</sup> Regardless of how nicotine is delivered (by e-cigarettes or combustible cigarettes), nicotine negatively affects adolescence brain developmental processes and may lead to psychiatric disorders and cognitive impairment in later life.<sup>20,21</sup> This report and ongoing research will clarify the public’s perceived safety of e-cigarettes in the future.

# STATE LAWS & E-CIGARETTES

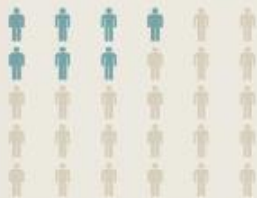
**16 MILLION CHILDREN LIVE  
IN STATES WHERE THEY CAN  
BUY E-CIGARETTES LEGALLY**



10 STATES AND D.C. ALLOW SALES  
OF E-CIGARETTES TO MINORS



ONLY 3 STATES PROHIBIT INDOOR  
E-CIGARETTE USE IN PRIVATE  
WORKPLACES, RESTAURANTS, AND BARS



Over 300 million Americans, including  
70 million children, live in states  
where they could be exposed to either  
secondhand smoke or e-cigarette aerosol  
in worksites, restaurants, and bars.



E-CIGARETTE AEROSOL IS **NOT**  
**HARMLESS WATER VAPOR,**  
IT CAN CONTAIN NICOTINE  
AND OTHER TOXINS.

<http://www.cdc.gov/mmwr/>



Centers for Disease  
Control and Prevention  
National Center for Chronic  
Disease Prevention and  
Health Promotion

**CDC Morbidity and Mortality Weekly Report (MMWR).** A simple and effective message to raise public awareness of e-cigarettes' potential risks (credit: [www.cdc.gov/mmwr/](http://www.cdc.gov/mmwr/)).



**Devices:** According to the latest FDA study, since 2009 there have been 92 overheating, fire and explosion cases involving e-cigarette devices in the U.S.<sup>22</sup> Forty-seven people were injured and 67 cases involved property damage. Injuries overall included chemical and thermal burns, smoke inhalation, fractured neck vertebrae, fractured palate and finger loss, displacement or damage of one or more teeth, lacerations, bruising, psychological distress, sensory disturbances, nicotine overdose and oral discolorations.<sup>22</sup> The causes of the device failures are incompletely defined. However, many of the fire and explosion cases occurred while charging lithium batteries in e-cigarettes. Potential explanations of the fires and explosions may include: (1) user error, (2) lack of a clear charging instruction, (3) faulty charging units, (4) lack of overcharge protection / automatic built-in shut off switch, (5) substandard lithium ion batteries, and (6) counterfeit e-cigarette devices and lithium ion batteries.



**Counterfeit lithium ion batteries.** Substandard, potentially dangerous lithium ion batteries are available from online retail stores. Some counterfeit batteries are so sophisticated that it is almost impossible to distinguish from genuine products by a visual inspection (credit: [www.tasteyourjuice.com](http://www.tasteyourjuice.com)).

## Who regulates e-cigarettes and e-liquids?

Effective August 8, 2016, U.S. Food and Drug Administration (FDA) regulates e-cigarettes under the “Deeming Tobacco Products Amendment” (Docket No. FDA-2014-N-0189). The new rule extends the FDA’s regulatory authority to all tobacco products, including e-cigarettes, cigars, hookah (AKA waterpipe tobacco), pipe tobacco, nicotine gels, and dissolvables.<sup>23</sup> The FDA expects, by 2019, the new regulation will be fully implemented and enforced. The FDA states the rule will help prevent young people from starting to use these products, help consumers better understand the risks of using these products, prohibit false and misleading product claims, and prevent new tobacco products from being marketed unless a manufacturer demonstrates that the products meet the relevant public health standard.<sup>23</sup> The new rule is well-received and welcomed by most U.S. health care professionals and organizations.

**FDA's New Regulations for E-Cigarettes, Cigars, and All Other Tobacco Products**

Tobacco use is the single largest preventable cause of disease and death in the United States. Since 2009, FDA has regulated cigarettes, smokeless, and roll-your-own tobacco. FDA finalized a rule, effective August 8, 2016, to regulate all tobacco products. For background information on this milestone in consumer protection, see [The Facts on the FDA's New Tobacco Rule](#).

Read the [FDA Voice blog post](#) by Center Director Mitch Zeller on Protecting the Public and Especially Kids from Tobacco Products, Including E-Cigarettes, Cigars and Hookah Tobacco.

### How Do the New Regulations Affect You?

Manufacturer? Retailer? Consumer?

**FDA’s new regulations.** FDA finalized a rule that extends its regulatory authority to all tobacco products, including e-cigarettes, cigars, and hookah and pipe tobacco, as part of its goal to improve public health (credit: www.fda.org).

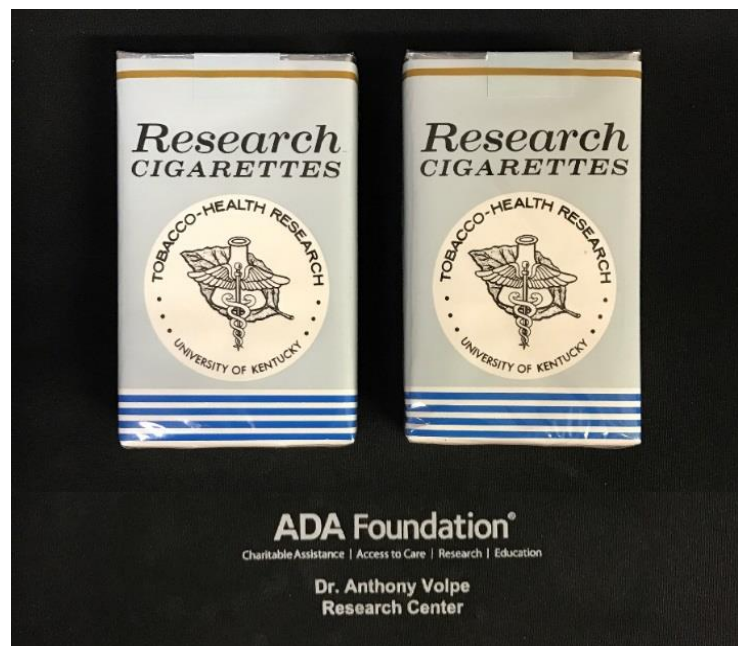
### **What are the challenges associated with e-cigarette research?**

A major challenge in e-cigarette research is that there is no scientific consensus. Misleading, inconsistent and contradictory research findings have polarized scientists, policy makers and the public, leaving them with few scientific facts to evaluate potential risks of using e-cigarettes. Many contributing factors to the inconsistent and contradicting findings include lack of standardized research materials, testing devices and test methods.<sup>24</sup> Several studies in the early phase of e-cigarette research have been financially supported by e-cigarette companies. Although the funding sources were fully disclosed, some scientists still raised their concerns regarding implied conflict of interest. In contrast, various vaping advocacy associations have pointed out that some published studies used unrealistic power settings (e.g. extremely high voltage) to generate carcinogens such as formaldehyde and other toxins in the aerosol.<sup>25-28</sup> Whether the researchers intentionally operated the e-cigarettes to produce hazardous chemical byproducts to inflate the potential danger of e-cigarettes or they mistakenly used the high voltage due to lack of experience in using the device is up for a debate.

Considering there are close to 10,000 different e-liquid formulations and hundreds of e-cigarette devices, many with significant quality variations, it is difficult for researchers to keep up with vast array of products in the e-cigarette consumer market and the rapid changes in e-cigarette technology.<sup>24</sup> Mutually agreed research materials, testing devices and test methods are needed to bring clarity to the current situation.

## How can a Reference Material (RM) help the e-cigarette research?

The challenges of product testing, quality control and quality maintenance are not new to the manufacturing industry. Manufacturers have applied various quality control practices to improve the manufacturing process and product quality. One of the most common methods is implementing a Reference Material (RM) in the quality control process. RM is a matrix-matched material with assigned target values and assigned ranges for each variable, reliably determined from data obtained by repeated analysis.<sup>29</sup> RMs are routinely used to check the quality and metrological traceability of products, as well as for instrument calibration. The Reference Cigarettes produced by the Center for Tobacco Reference Products (University of Kentucky), for example, have provided much needed standards for tobacco manufacturers, government agencies and research institutions. Although the Reference Cigarettes are different from consumer cigarettes (e.g. Marlboro, Lorillard, or Camel), the Reference Cigarettes come with well-characterized and traceable physical properties. Researchers and manufacturers can use them as a consistent baseline or as a control to compare and characterize new products. Scientists at the ADAF Volpe Research Center recently developed three Reference Materials for e-liquid standards.<sup>24</sup> When used appropriately, the reference e-liquids can serve as a control in research experiments and during the manufacturing processes.



**Reference Material (RM).** Implementation of a Reference Material improves product quality for manufacturers and provides research standards for researchers.



## **Where can I get more information about the latest e-cigarette research and reference e-liquid?**

The latest e-cigarette research information can be found from the following peer-reviewed journals:

- Tobacco Induced Diseases: <https://tobaccoinduceddiseases.biomedcentral.com/>
- Tobacco Control: <http://tobaccocontrol.bmj.com/>
- Nicotine and Tobacco Research: <https://academic.oup.com/ntr>

More information on the research grade reference e-liquid can be found here:

- <http://rdcu.be/pkoz> and,
- by contacting Dr. Jeffrey Kim directly at: [jeffrey.kim@nist.gov](mailto:jeffrey.kim@nist.gov)



**E-Liquid Reference Material.** The reference e-liquid can be used to check the quality and metrological traceability of commercial e-liquids during a pre-market testing period, instrument calibration, toxicological risk assessment, and safety and efficacy of e-cigarette devices.

## **References**

1. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23 Suppl 3:iii3-9.
2. Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control*. 2014;23 Suppl 2:ii4-10.
3. Callahan-Lyon P. Electronic cigarettes: human health effects. *Tob Control*. 2014;23 Suppl 2:ii36-40.
4. Orr MS. Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future. *Tob Control*. 2014;23 Suppl 2:ii18-22.
5. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res*. 2013;15(1):158-166.
6. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014;23(2):133-139.
7. Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and vapors of electronic cigarettes. *Arch Toxicol*. 2014;88(7):1295-1308.
8. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the "e-cigarette". *Am J Public Health*. 2010;100(12):2340-2342.
9. Cameron JM, Howell DN, White JR, Andrenyak DM, Layton ME, Roll JM. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tob Control*. 2014;23(1):77-78.
10. Cheah NP, Chong NW, Tan J, Morsed FA, Yee SK. Electronic nicotine delivery systems: regulatory and safety challenges: Singapore perspective. *Tob Control*. 2014;23(2):119-125.
11. Etter JF, Zather E, Svensson S. Analysis of refill liquids for electronic cigarettes. *Addiction*. 2013;108(9):1671-1679.
12. Hadwiger ME, Trehy ML, Ye W, Moore T, Allgire J, Westenberger B. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J Chromatogr A*. 2010;1217(48):7547-7555.
13. <http://www.aapcc.org/alerts/e-cigarettes/>

14. Barrington-Trimis JL, Berhane K, Unger JB, et al. The E-cigarette Social Environment, E-cigarette Use, and Susceptibility to Cigarette Smoking. *J Adolesc Health*. 2016;59(1):75-80.
15. Barrington-Trimis JL, Urman R, Berhane K, et al. E-Cigarettes and Future Cigarette Use. *Pediatrics*. 2016;138(1).
16. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a1.htm>
17. <https://www.cdc.gov/mmwr/volumes/65/wr/mm6514a1.htm>
18. <https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs>
19. <https://www.cdc.gov/mmwr/volumes/65/wr/mm655051a2.htm>
20. <https://www.surgeongeneral.gov/library/2016ecigarettes/index.html>
21. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf>
22. Rudy SF, Durmowicz EL. Electronic nicotine delivery systems: overheating, fires and explosions. *Tob Control*. 2016.
23. <http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm32094909.htm>
24. Kim JJ, Sabatelli N, Tutak W, et al. Universal electronic-cigarette test: physiochemical characterization of reference e-liquid. *Tob Induc Dis*. 2017;15:14.
25. Sodhi SK, Khanna A. More on hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*. 2015;372(16):1576.
26. Thomson RH, Lewis PM. More on hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*. 2015;372(16):1575-1576.
27. Nitzkin JL, Farsalinos K, Siegel M. More on hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*. 2015;372(16):1575.
28. Pankow JF, Strongin RM, Peyton DH. More on hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*. 2015;372(16):1576-1577.
29. [http://www.who.int/water\\_sanitation\\_health/resourcesquality/wqmchap6.pdf?ua=1](http://www.who.int/water_sanitation_health/resourcesquality/wqmchap6.pdf?ua=1)