# An opportune and unique research to evaluate the public health impact of electronic cigarettes

***Running title:*** *Health risks or benefits of vaping*

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**ABSTRACT**

**Prelude:** In response to the growing public health concern regarding the risks or benefits of electronic cigarettes use relative to smoking, the National Institute on Drug Abuse (NIDA) has recently introduced the first standardized- and fully characterized e-cig device to the research community (*see*, https://www.drugabuse.gov/funding/supplemental-information-nida-e-cig).

Electronic cigarettes (e-cig) are promoted as safe alternatives to conventional tobacco cigarettes and/or as aides to smoking cessation. E-cig are highly popular among cigarette smokers who are unable/unwilling to quit but are willing to switch to putatively less-harmful tobacco substitutes. E-cig are also becoming increasingly popular among youth who have never experimented with combustible cigarettes. However, chemical analyses of e-cig juices (both in liquid form and after being heated into vapor) have shown that many carcinogens present in cigarette smoke are also found in a range of e-cig products. To date, the cancer-causing potential of e-cig has not been investigated in e-cig users (*i.e.*, vapers). Use of e-cig without a prior history of smoking is currently a rare phenomenon in adults, but is increasingly common among youth. Consequently, investigating the carcinogenic potential of e-cig in nonsmoking youth provides a unique opportunity to verify the health impact of e-cig use, without the confounding effects of cigarette smoking. Within this context, the availability of the NIDA Standard Research e-cig offers a unique research opportunity with tremendous public health implications. Comparing and contrasting the cancer-causing potentials of standard vaping and smoking in youth will help determine the health risks or benefits of e-cig use relative to cigarette smoking. This information will be instrumental in making scientifically-based decisions on the development and evaluation of policies and regulations on e-cig manufacture, marketing and distribution. Ultimately,

evidence-based guidelines and legislations on e-cig will help reduce the burden of tobacco-related diseases, particularly on minors and vulnerable populations.

**1. Electronic cigarette use is a significant and growing public health concern**

Electronic cigarettes (e-cig) are battery-powered devices that heat solutions, usually containing nicotine and flavorings, into inhalable vapor (1). E-cig emerged several years ago as a putatively less-harmful tobacco substitute for cigarette smokers and/or as aides to smoking cessation (1). Over the past 6 years, there has been an evolution in the epidemiology and marketplace of e-cig, with up to 10-fold increases in the prevalence of e-cig use among adults seeking to transition from smoking to vaping (2), adolescent nonsmokers, and teens experimenting with tobacco products (3). Simultaneously, there has been a huge proliferation in the number and type of e-cig products available for purchase without systematic regulation of sales (4). Recent estimates show that over 4 million Americans use e-cig. The 2014 National Health Information Survey reported that 16% of current adult smokers and 22% of recent former smokers regularly use e-cig (2). Alarmingly, there is a growing trend of e-cig use among youth. Since 2011, there have been steady increases in e-cig use among US middle school- and high school students. Approximately 4.3% and 11.3% of all surveyed middle school- and high school students, respectively, reported in 2016 that they used e-cig in the past 30 days—a significant rise from 0.6% and 1.5%, respectively, in 2011 (5-7). US retail sales for e-cig have steadily increased in the past several years, and are estimated to approach $10 billions by 2017. The sales of e-cig are expected to further grow over the next decade, and surpass those of conventional cigarettes by year 2023 (8).

Currently, e-cig use is a significant public health issue due to the uncertainties surrounding its potential health consequences. To date, there is very limited scientific evidence to support the safety of e-cig or the efficacy of these products to aid in smoking cessation. The existing data show that e-cig vapor is not merely "water vapor" as is often claimed or implied in the marketing of these products (9, 10). Chemical analyses of e-cig vapor and liquid have

confirmed the presence of many of the same toxicants and carcinogens as those found in cigarette smoke, albeit in generally lower concentrations (11-13). The presence of carcinogenic compounds in e-cig products is alarming and deserves further investigation as to whether it may constitute a cancer risk to humans. From the standpoint of public health, it is important to determine whether e-cig use poses a cancer risk to regular users of these products and/or to those who involuntarily inhale/ingest the residual e-cig compounds released into the environment. Equally important is to determine the magnitude of cancer risk associated with e-cig use relative to tobacco smoking. The latter will help establish whether e-cig use is as harmful, equally harmful, or less or no harmful compared to conventional smoking.

To generate foundational evidence that can guide future public health policies on e-cig, it is imperative to establish the biological effects of e-cig in regular users of these products as well as in non-users exposed to e-cig contaminants in the environment. Toward this goal, research studies should provide scientific knowledge on the biological effects of e-cig as determined by molecular changes linked to risk of cancer. Many carcinogens present both in e-cig vapor and cigarette smoke (11-13) can cause signature changes that are known to contribute to cancer development (14, 15). Of these, molecular changes impacting cancer-relevant gene networks and functional pathways are of paramount importance. Because these molecular changes occur in the early stages of carcinogenesis, they may serve as biomarkers for cancer (14, 15). Quantification of functionally important molecular changes in tissues and organs of e-cig users can help determine possible cancer risk associated with the use of e-cig. Comparing the results to those already known for smokers can help verify the health risks or benefits of e-cig use relative to cigarette smoking. These investigations should provide timely information about the possible carcinogenic effects of e-cig use years prior to onset of cancer if e-cig are ultimately proven to

cause cancer. This information will be instrumental in developing and evaluating evidence-based policies and regulations on e-cig manufacturing, marketing, and distribution, which will serve the ultimate goal of protecting the public's health.

**2. Novelty of investigating the carcinogenic potential of e-cig use in youth**

Youth is generally considered as a period of transition from the dependence of childhood to adulthood's independence and awareness of our interdependence as members of a community. Youth is a more fluid category than a fixed age-group. However, age is the easiest way to define this group, particularly with regard to social life. The United Nations, for statistical consistency across regions, defines 'youth', as those persons between the ages of 15 and 24 years, without prejudice to other definitions by Member States (16). Youth is a particularly vulnerable developmental period (17). Youth are known to have high vulnerability to carcinogenic assaults (18). Use of e-cig without a prior history of smoking is currently a rare phenomenon in adults (2) , but is increasingly common among youth (3). Thus, investigating the carcinogenic potential of e-cig exposure in nonsmoking youth provides a unique opportunity to verify the health impact of e-cig use during a crucial developmental stage, without the confounding effects of cigarette smoking. Importantly, the cancer-causing effects of smoking are known to remain persistent (to varying extent), even long after quitting smoking (19).

**3. Scientific rationale for studying the cancer-causing potential of e-cig use**

There is a strong scientific foundation for research studies to determine the potential of e-cig to cause biological effects of relevance to cancer. E-cig use could presumably lead to cancer due to the following three reasons. (1) Many e-cig solutions have compounds with known carcinogenic effects when inhaled, *e.g.*, carbonyl compounds (formaldehyde, acetaldehyde, acrolein, and o-methylbenzaldehyde), volatile organic compounds (toluene and p,m-xylene), tobacco-specific nitrosamines (TSN), and metals (cadmium, nickel, and lead) (11, 20-23). The average ratios of carcinogenic compounds in e-cig vapor to those in cigarette smoke are 1:9 for formaldehyde, 1:15 for acrolein, 1:120 for toluene, 1:40-380 for TSN, and 1:450 for acetaldehyde (11, 20-23). The detected levels of lead and chromium in e-cig vapor are within the ranges known for cigarette smoke; however, nickel concentrations are 2-100 times higher than those in cigarette smoke (13). Although opponents and proponents of e-cig differently interpret the comparative levels of carcinogens in e-cig vapor and cigarette smoke, it is widely accepted that there is no minimum threshold of toxicity for carcinogens; in other words, *lower levels of carcinogens in e-cig vapor do not equate to no carcinogenic potential*. A review of over 50 publications on e-cig toxicity has concluded that e-cig vapor as a whole (contaminants plus declared ingredients) creates personal exposure that would justify health surveillance among regular users (24). (2) Certain e-cig devices with powerful batteries can heat solutions to the point of causing chemical reactions resulting in the release of other carcinogens, *e.g.*, formaldehyde-containing hemiacetals (21). (3) *In vitro,* e-cig vapor extracts have been shown to cause DNA strand breaks and cell death independently of nicotine content (25).

## 4. Knowledge gaps

According to the World Health Organization (WHO), the safety of e-cig and their efficacy in aiding smoking cessation have not been scientifically demonstrated, yet (9). A recent WHO report on e-cig states that while e-cig represent an evolving frontier filled with promise and threat for tobacco control, additional research is needed on the safety and efficacy of e-cig, and regulations are required to address the health concerns surrounding the use of these products (10). The report stresses that while e-cig vapor is likely to be less toxic than cigarette smoke, e-cig use poses threats to adolescents and fetuses of pregnant mothers using these devices, as well as increases the exposure of nonsmokers and bystanders to nicotine and numerous toxicants and carcinogens (10). There is also concern that e-cig may serve as a gateway to nicotine addiction and smoking, especially among minors and vulnerable populations (26, 27). The latter is ascribed to the large assortment of e-cig flavorings, many of which (*e.g.*, chocolate- and candy-flavors) being highly attractive to children and youth; currently, there are 7,764 e-cig flavors in the market (10).

## 5. Methodology gaps

The safety of e-cig as a putative harm-reducing tobacco substitute and their efficacy in smoking cessation can be addressed empirically in research studies. So far, however, the published studies, whose primary outcomes were related to cigarette smoking cessation, have used e-cig products that had unknown nicotine delivery profiles, and, in some cases, the product seemed ineffective in delivering nicotine to participants (28, 29). Considering the role of nicotine delivery in withdrawal suppression and product acceptability for cigarette smokers (30, 31), an

ideal research study should include e-cig products that can approximate the nicotine delivery profile of conventional tobacco cigarettes. Apart from nicotine concentrations in e-cig liquid, other product characteristics, such as propylene glycol/vegetable glycerin ratio, device battery, device voltage, etc. may also influence e-cig effects on toxicant exposure, user health, and concurrent tobacco use (32, 33). Previous qualitative and survey-based studies have shown that there are significant differences in the effects of different e-cig products (34, 35). This underscores the need for investigating e-cig product characteristics, acceptability, and nicotine delivery prior to selection of an appropriate model(s) for use in research studies. The existing data provide a rationale for conducting research studies in which nicotine concentration and other product characteristics of e-cig can be held constant. Another important design consideration for research studies on e-cig is selection of the study population. While '*adult*' e-cig users are likely to be current or former cigarette smokers or users of other tobacco products (2), '*youth*' e-cig users mostly do not have a history of exposure to any other tobacco products (3). Thus, a well-designed research study on e-cig may focus on youth who are exclusive users of e-cig and have no prior history of consuming any other tobacco products. The latter will ensure elimination of the confounding effects of exposure to other tobacco products, while investigating the effects of e-cig use *per se*.

**6. Technology gaps:**

There is limited publicly available information on the product characteristics of hundreds of e-cig devices and thousands of e-cig solutions currently available in the market. This makes it difficult, if not impossible, for researchers to know which e-cig product(s) is the most

appropriate to use in their studies. Furthermore, the design and conduct of a research study is often a multi-year process and there is no certainty that any chosen e-cig product will remain available for the entire study considering the constantly evolving e-cig market. The probability of the same e-cig product remaining available for follow up studies, therefore, becomes even more uncertain. The recently announced National Institute on Drug Abuse (NIDA) Standard Research E-cigarette (SREC) has addressed the above concerns by providing a unique opportunity for investigators to study a reference e-cig whose product characteristics are fully described (36). The SREC has an accompanying data package, which describes the chemical composition of the e-liquid and vapor, the reproducibility of its puff-to-puff output, and the human pharmacokinetics of its nicotine delivery (36). These data should empower researchers who will use the SREC as a model e-cig in studies to evaluate the value and limitations of e-cig as a tobacco risk reduction tool. It is intended that the SREC will remain available for an extended period of time, thereby allowing its use in multiyear studies. The long-term availability of the SREC will also allow it to be used in follow up studies and as a comparator to other devices. Data derived using the SREC may also be useful in "bridging" studies, which extrapolate existing data to project the expected performance of other devices.

**7. Scientific premise of studying e-cig carcinogenicity**

Notwithstanding the above-specified gaps, comprehensive studies to objectively assess the health impact of e-cig use are lacking. More specifically, no research study has been conducted on the association of e-cig use, users' characteristics, and e-cig product characteristics with markers of carcinogenesis despite the alarming detection of carcinogens in e-cig products (11-13). As such,

the cancer risk due to e-cig use and the characteristics of e-cig products that may be most harmful and worthy of regulatory action due to carcinogenic potential are not known. Furthermore, there is no empirical data on the relative risk of cancer in e-cig users as compared to cigarette smokers. Future research should fill the above gaps by using cutting-edge technologies to quantify molecular changes linked to risk of cancer in well-defined populations who exclusively use e-cig devices with fully described product characteristics, *e.g.*, the NIDA Standard Research E-cig (SREC) (36).

**8. Perspectives of research on e-cig carcinogenicity**

With the advent of the NIDA standardized- and fully characterized reference e-cig (36) and the growing population of youth who exclusively use e-cig (3), a new era of research with enormous public health implications is awaiting us. The utility of a standard research e-cig for investigating the carcinogenic potential of an increasingly popular tobacco product is highly significant. The impact of research on the cancer-causing potential of a reference e-cig in a highly vulnerable population (*i.e.*, youth) is expected to be high because the data obtained by the culmination of these investigations will inform regulatory agencies and general public, in particular millions of e-cig users, of the potential health risks or benefits of e-cig use relative to cigarette smoking. These urgently needed data can help raise awareness of the *pros* and *cons* of e-cig use, and lay the foundation for development of scientifically based regulations on e-cig manufacturing, marketing and distribution. Ultimately, these data can facilitate implementation of public education campaigns to prevent and/or reduce tobacco-related diseases. It is envisioned that results pointing to a carcinogenic effect of e-cig could be used to counter the prevailing

perception that vaping is healthier than smoking. Conversely, if the data support no or less carcinogenic potential of e-cig as compared to smoking, they could lead to evidence-based promotion of vaping as an alternative nicotine delivery method or smoking cessation approach. Lastly, the global impact of research on e-cig carcinogenicity could be tremendous considering the translatability of the findings to tobacco prevention and control programs currently in place or underway in many national and international organizations and government agencies throughout of the world.

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## AUTHOR CONTRIBUTIONS

Both authors (A.B. and S.T.) have directly participated in the planning, execution, and analysis of this study. They have read and approved the final version submitted. They had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

## CONFLICT OF INTEREST STATEMENT

Both authors declare no conflict of interest.

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