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# How close are we to definitively identifying the respiratory health effects of e-cigarettes?

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## Abstract

**Introduction:** Use of electronic cigarettes (e-cigarettes) is frequently promoted as a less harmful alternative to cigarette smoking. The impact of repeated inhalation of e-cigarette aerosols on respiratory health is not well understood.

**Areas covered:** Using results from laboratory, observational, and clinical studies, we synthesize evidence relevant to potential respiratory health effects that may result from inhalation of e-cigarette aerosols.

**Expert Commentary:** Chemical analyses reveal that e-cigarette aerosols contain numerous respiratory irritants and toxicants. There are documented cytotoxic effects of e-cigarette constituents on lung tissue. Studies among ex-smokers who switched to e-cigarettes note reduced exposure to numerous respiratory toxicants, reduced asthma exacerbations, and COPD symptoms. Regular exposure to e-cigarette aerosols is associated with impaired respiratory functioning. Potential respiratory health risks resulting from secondhand e-cigarette aerosol exposure have not been sufficiently evaluated. Current evidence indicates that although e-cigarettes are not without risk, these products seemingly pose fewer respiratory health harms issues compared to tobacco cigarettes. Data from prospective studies and randomized controlled trials examining the impact of e-cigarette use on lung health are needed to better understand respiratory health risks tied to use of these products.

### Keywords

E-cigarettes; electronic cigarettes; harm reduction; nicotine; smoking; vaping

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Electronic cigarettes (e-cigarettes) have been a topic of controversy among tobacco control researchers, public health professionals, and clinicians alike. These battery-operated devices are designed to deliver nicotine to the body via inhalation without involving a combustion process. While it is common to hear the term "e-cigarettes", this label is a broad term referring to a heterogeneous class of devices that differ in shape, size, and functional characteristics. [1] Common features of e-cigarettes include a heating element that heats a propylene glycol and/or vegetable glycerin based solution ("e-liquid" / "e-juice") that contains stabilizers, flavorings and often, nicotine. [1] Numerous flavorings are available, including tobacco, menthol, fruit, and sweet flavors. [1] Heating of e-liquids produces an aerosol, which is then inhaled by the user.

E-cigarettes were introduced to the global market in the mid 2000's. Since then, awareness and use of e-cigarettes has increased exponentially in many nations, particularly among youth [2]. The prevalence of e-cigarette ever use in 2013–2015 among youth were highest in Poland (62.1%; 95%CI: 59.9–64.2%), and lowest in Italy (5.9%; 95%CI: 3.3–9.2%) [2]. Among non-smoking youth, the prevalence of e-cigarette ever use in 2013–2015 varied, ranging from 4.2% (95%CI: 3.8–4.6%) in the US to 14.0% in New Zealand (95%CI: 12.7–15.4%). The prevalence of e-cigarette ever use among current tobacco smoking youth was the highest in Canada (71.9%, 95%CI: 70.9–72.8%) and lowest in Italy (29.9%, 95%CI: 18.5–42.5%). Between 2008 and 2015, e-cigarette ever use among youth increased in Poland, Korea, New Zealand and the US; decreased in Italy and Canada; and remained stable in the UK [2]. In the US, the popularity of e-cigarettes among youth has already surpassed use of tobacco cigarettes [3]. Among the 5.5% of adult current e-cigarette users in the US, 42.2% reported infrequent use, 36.5% reported moderate use and 21.3% reported daily use [4]. Cigarette smokers who quit in the past year were more likely to report daily e-cigarette use, compared with current smokers (aPR=3.21, 95% CI=2.75 to 3.76) [4]. Data from the UK suggest that e-cigarette use among regular smokers increased from 2.7% in 2010 to 6.7% in 2012 [5]. Market research projections indicate that within the next thirty years, rates of e-cigarette use may exceed those of tobacco cigarettes. Given their increased popularity, there is urgent need to characterize the safety of these products.

Many advocates support e-cigarettes as low-risk products, and promote their use in lieu of conventional cigarettes among smokers as a harm reduction strategy [6,7]. On the other hand, concerns have been raised about the potential long-term health effects from inhaling e-cigarette aerosols [8]. In addition, their increasing popularity and potential for second-hand exposure to aerosols present concerns related to tobacco product initiation and constituent exposure among vulnerable populations, namely, youth and young adults. [9] Due to their relatively short existence, data on the long-term health effects of e-cigarette use are not currently available. In the interim, evidence from animal studies, in vitro and in vivo laboratory studies, observational studies, and small-scale clinical trials may provide important information on the potential harms of e-cigarette use on respiratory health. Using information from the peer-reviewed literature to support our claims, this article provides our perspective on potential risks and benefits related to e-cigarette use, with a focus on concerns related to respiratory health outcomes. Studies included in this review were relevant to respiratory health effects of e-cigarettes. In addition to database searches, we also included key findings for respiratory health outcomes in relation to conclusions drawn from the comprehensive report recently released by the National Academies of Sciences, Engineering, and Medicine (NASEM) entitled, "Public Health Consequences of E-Cigarettes" [9]. The NASEM Committee conducted a comprehensive review of key e-cigarette liquid and aerosol constituents, human health effects, initiation and cessation of combustible cigarette use, and harm reduction from e-cigarette use. The NASEM Report considered the quality of studies and the totality of evidence, and categorized the evidence as conclusive, substantial, moderate, limited, insufficient, or no available evidence. A list of report conclusions pertinent to respiratory health can be viewed in Table 1.

## 1. Evidence from chemical analyses on e-cigarette aerosol emissions

Many studies conducted on e-cigarettes have focused on the generation, inhalation, and measurement of user and bystander exposure to potentially harmful chemical emissions that may be produced by these products. These include nicotine, tobacco-specific nitrosamines (TSNAs), metals, polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), carbonyl compounds, and aldehydes. Within these classes, there are several respiratory irritants and toxicants, as well as carcinogenic substances linked to the development of respiratory cancers [10].

One of the first studies demonstrating presence of potentially toxic chemicals in e-cigarettes was conducted between 2008 and 2009 [11,12]. The concentration of toxic chemicals, including many known carcinogens and respiratory irritants, were measured in an activated e-cigarette set to low temperature. In this study, no toxic heavy metals, PAHs, or phenols were detected. However, the study revealed trace amounts of mercury, formaldehyde, and acetaldehyde emitted from the examined e-cigarettes [11,12].

In 2009, the US Food and Drug Administration (FDA) conducted a similar analysis of 18 brands of e-cigarette liquids popular on the US market [13]. The study confirmed that tested e-cigarettes contained lower levels of potentially harmful chemicals compared to tobacco products. In our work, we have tested emissions from numerous e- cigarette brands [14] and identified the presence of formaldehyde, acetaldehyde, and acrolein in e-cigarette emissions, as well as two VOCs: toluene and xylene. Overall, concentrations of toxicants identified in e-cigarette aerosols were 9 to 450 times lower than in tobacco smoke [14].

Concerns have also been raised about the presence of metal particles in e-cigarette aerosol (particularly nickel and chromium, two main elements in heating coils). The inhalation of these metals in larger quantities may cause respiratory diseases, bronchitis, and pneumonia [15], however, these effects have not been definitively elucidated. Williams et al. found trace levels of metals (including calcium, potassium, aluminum, sodium, tin, silver, iron, cerium, lanthanum, bismuth, and zinc) in aerosols generated from early generation e-cigarette devices [15]. Risk assessments of inhalation exposure to these metals showed that, even in very intensive use and extreme exposure scenarios, respiratory exposure to metals among e-cigarette users are 4 to 40 times lower than the approved maximum daily dose [16]. Notably, the extreme exposure scenario assumes that 100% of the emitted aerosol from e-cigarettes is absorbed by the user. This is extremely unlikely, since a significant portion of the aerosol is exhaled by users. However, some metals (copper, lead, nickel, chromium) have been reported in e-cigarette aerosols in higher levels than previously measured in tobacco cigarette smoke [17–19]. In addition, a recent study by our group has raised some concerns about potential exposure among e-cigarette users to toxic flame retardants [20].

### Summary:

It is crucial to understand that most of chemicals present in tobacco smoke that are harmful to respiratory health are generated primarily during the combustion process - which is absent in the case of e-cigarettes. Evidence from laboratory studies comparing the chemical composition of aerosols emitted from e-cigarettes vs tobacco cigarette smoke largely indicates that e-cigarettes contain far fewer potentially toxic chemicals, many of which are linked to adverse respiratory health effects. What's more, concentrations of those toxicants identified in e-cigarette aerosols are in nearly all cases significantly lower than those measured in tobacco smoke, with exception of some metals.

## 2. Effects of inhaling particulates present in e-cigarette aerosols

The size of particulate matter generated from tobacco products and e-cigarettes affects pulmonary absorption and determines settlement of particulate matter into various parts of the upper or lower airways. Even though the size of airborne particulates matters a great deal for examinations of product and chemical effects on respiratory health, the details of e-cigarette aerosol particle size and absorption remain unexplored. There is likely substantial variation across generations of e-cigarette devices, and across brands. Pellegrino and colleagues [21] tried to address this question and focused on microparticles emission from e-cigarettes. In their work, particulate matter delivered from e-cigarettes was 6 to 18 times lower compared to tobacco cigarettes, which only slightly exceeded WHO air quality guidelines ($PM_{2.5}$ = 25 μg/$m^3$, $PM_{10}$=50 μg/$m^{3)}$ [21, 22]. Similar findings were reported in another study concerning microparticles [23], which estimated the amount of particulate matter inhaled from 10 puffs taken by an average e- cigarette user. Estimation suggested that particulate matter was more than 800 times lower than those found in one tobacco cigarette [23].

### Summary:

These results indicate that e-cigarettes may expose users to smaller particulates, and lower amounts of particulate matter in general. While inhalation of high levels of particulate matter has been linked to greater mortality risk from cardiopulmonary illnesses, the available data indicate that e-cigarette particulate emissions expose users at a level akin to WHO guidelines and are far lower than those of conventional cigarettes. [22] This suggests that e-cigarettes may be a less harmful source of particulate exposure in contrast to tobacco cigarettes, but further research is needed.

## 3. Testing the inhalation toxicity of e-cigarettes using in vitro methods

Issues raised about toxicological effects mostly question effects on cells, with a special interest in lung epithelial cells. For instance, many flavorings used in e-cigarettes (e.g. cinnamaldehyde) are already approved for use in food manufacturing, yet their impact on respiratory health via repeated inhalation is currently unknown. In a study by Lerner et al., the cytotoxic effects of flavorings used in e-liquids substances on human pulmonary fibroblasts were analyzed [24]. That study suggests that e-cigarette flavorings could lead to lung cell damage (mostly by releasing free radicals) and inflammation in lung tissue [24]. In our study, exposure of bronchial epithelial cells to e-cigarette aerosol resulted in decreased metabolic activity and cell viability and increased release of several inflammatory markers (compared to air controls) [25]. We also found that product type, battery output voltage and flavors significantly affected toxicity of e-cigarette aerosol, with a strawberry-flavored product being the most cytotoxic [25].

Regarding the cytotoxic effects of nicotine in e-cigarettes, normal human bronchial epithelial cells exposed to nicotine-containing aerosol from e-cigarettes showed impaired ciliary beat frequency, as well as aberrancies in airway surface liquid volume as well as cystic fibrosis transmembrane regulator channel malfunction. Such defects are usually seen in Chronic Obstructive Pulmonary Disease (COPD) tissue, leading to increased cytokine expression, airway hyper-reactivity, and eventually lung tissue destruction [26].

Studies on cytotoxic effects of e-cigarette chemical constituents have also identified negative effects on DNA. In one in vitro research, e-cigarette liquids aerosolized at biologically relevant doses induced increased DNA strand breaks and apoptosis while decreasing clonogenic survival in both 'normal epithelial' and 'head and neck squamous cell carcinoma cell lines, independently of nicotine concentration [27]. Moreover, in experiments conducted by Yu V at al. [28], e-cigarettes aerosol, both with and without nicotine, has demonstrated cytotoxic effects on epithelial cell lines and acts as a DNA-breaking agent. Exposure to e-cigarette aerosol extracts suppressed the cellular antioxidant defenses and led to significant DNA damage [29]. In many of these studies, potential confounding factors such as aerosol temperature and particle size have not been taken into account [30].

#### Summary:

Rightly, the NASEM report concluded there is limited evidence in this domain [9]. Taken together, flavorings seem to display potentially hazardous effects on lung tissue, which in turn may pose a considerable threat to the respiratory health of users. Cytotoxic effects were nicotine-dependent both in the mouse lung and in human airway cells, suggesting that inhaled nicotine may contribute to adverse effects on airway and lung cells. Similarly, e-cigarette aerosol extracts have been shown to induce DNA damage in a dose-dependent manner, independently of nicotine concentration, pointing out the detrimental role of flavoring substances [9]. In vitro cell studies can be more informative and representative of the human condition if aerosols rather than liquid e-cigarette solutions are used.

## 4. Knowledge on respiratory health effects of e-cigarette using data from animal studies

In experiments where mice were exposed to aerosolized nicotine-free and nicotine-containing e-cigarette fluid, an increased airway hyperreactivity, distal airspace enlargement, mucin production, cytokine, and protease expression was found when nicotine-containing e-cigarettes were used [26,31,32]. Interestingly, exposure to nicotine-free e-cigarettes did not affect these lung parameters [26]. However, the animal studies that have examined the effects of e-cigarettes on respiratory outcomes have used different e-cigarette devices, pumps, solutions, and exposures, limiting the ability to compare results among studies [9].

**Summary:**

The utility of studies using whole-body exposures in animal studies when examining health effects of e-cigarette aerosols is limited because this type of exposure may overestimate or underestimate an exposure in the human condition. This is a general limitation of using animal models to examine the impact of constituent exposures on human health [9].

## 5. Respiratory symptoms in e-cigarette users – what do we know so far?

Several observational studies measuring widespread early generation e-cigarette use have shown that, to date, most users of e-cigarettes continue to smoke tobacco cigarettes. [33,34] However, in several human studies, smokers who completely substitute tobacco cigarettes with e-cigarettes note fewer subjective adverse respiratory health effects (especially in contrast to those related to conventional smoking), thus suggesting the potential benefits that e-cigarettes pose to reducing respiratory related health harms. As an example, Polosa et al. [35] followed a sample of e-cigarette users for 24 months; these patients reported only mild side effects related to their e-cigarette use, including mouth and throat irritation together with dry cough. In another short-term study [36], using exhaled nitric oxide (eNO) as a marker of airway inflammation, results indicate that short-term (5 minutes of exposure) e-cigarette puffing and conventional cigarette smoking pose very similar risks of airway inflammation and obstruction. This effect might be attributed to the propylene glycol irritation properties [36]. Puffing on e-cigarette was shown to increase dynamic airway resistance by 18% [37]. Studies examining the short-term effects of e-cigarettes indicate that nicotine-containing e-cigarettes, but not nicotine-free e-cigarettes, can have short-term adverse effects on lung defense mechanisms, including mucociliary clearance (MCC), urge to cough, and cough sensitivity [38–40]. The observation that e-cigarette use might be associated with both increased respiratory and asthma symptoms and increased asthma-related school absenteeism in adolescents is potentially concerning [41–47] since diminished lung function in later years has been linked to asthma and chronic bronchitis in childhood and adolescence [47,48].

**Summary:**

In line with limited evidence brought forth by the NASEM [9], currently, there is a lack of rigorously designed epidemiologic studies examining the relationship between chronic e-cigarette use (especially in adolescents and young adults) and increased prevalence of respiratory symptoms and chronic respiratory illnesses. Compared to tobacco cigarettes, e-cigarettes may present similar risks in terms of airway inflammatory responses. However, in contrast to cigarette smoking, users who completely substitute with e-cigarette generally report fewer subjective adverse respiratory health effects. Dual use of tobacco cigarettes and e-cigarettes is common – which is, of course, problematic for respiratory health. However, many studies documenting this behavior generally reflected use of earlier (i.e., first, second) generation products. These early devices were limited in their ability to deliver nicotine to users, which may partially explain higher rates of dual use. [49,50] The continued evolution of the e-cigarette market in combination with improvements in product designs and nicotine delivery could shift patterns of dual use downward over time, as users may find newer products (EX: Juul) to be more suitable substitutes for traditional smoking. Promoting completing substitution of tobacco e-cigarettes with e-cigarettes in clinical settings and promoting such messaging through various public health channels could net additional population-level benefits for respiratory health overall.

## 6. E-cigarettes and risk of lung cancer

Given the risk of lung cancer linked with use of tobacco cigarettes, the potential net public health benefit of e-cigarette use as a cancer prevention tool has been discussed [51,52]. However, given multiple potential etiologic mechanisms related to incident case development coupled with the long latency period in developing illness, there is currently no definitive evidence to commenting on the role of e-cigarettes in increasing lung cancer risk, or in their ability to aid in net population reduced risk of incident cases. As an intermediate assessment, cross-sectional biomarker data can be suggestive of possible carcinogen exposures related to cancer development, however, these studies are certainly not causal links and are subject to number of limitations. For instance, Shahab et al. [53] examined a large panel of biomarker data among e-cigarette users, cigarette users, and users of both products (“dual users”). The e-cigarette–only users had significantly lower metabolite levels for tobacco-specific nitrosamines (TSNAs), particularly the 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of potent lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanon (NNK). Several observational longitudinal studies also showed a substantial reduction in exposure to NNK and several VOCs, including respiratory toxicants like acrolein, acrylamide, acrylonitrile, 1,3-butadiene (human carcinogen), and ethylene oxide among smokers who switched to e-cigarette [54–56].

### Summary:

As stated by the NASEM report [9], there is a paucity of information available to demonstrate any linkages between e-cigarette adoption and use, and cancer-causation or prevention related to use of these products. Evidence from biomarker studies are insufficient to evaluate causative mechanisms, but show users of e-cigarettes display lower levels of exposure to biomarkers of lung carcinogens when compared to smokers, such as NNK.

## 7. E-cigarettes and COPD risk

Studies examining the long-term effects of e-cigarette use on the development of chronic respiratory symptoms are, without question, incomplete. However, it is well-known that exposure to various components of e-cigarette aerosol could potentially damage the respiratory system or worsen preexisting lung disease through a multitude of diverse mechanisms. For instance, e-cigarette use may lead to impaired function of the cystic fibrosis transmembrane conductance regulator (CFTR), causing defective mucociliary clearance (MCC) [57]. CFTR dysfunction in humans has been associated with the development of COPD and asthma hyperresponsiveness [58]. Exposure to inhaled nicotine-containing e-cigarette fluids triggered effects typically correlated with the development of COPD, including increased airway hyperreactivity, distal airspace enlargement, mucin production, as well as cytokine and protease expression [26,59,60]. However, exposure to nicotine-free e-cigarettes did not affect these lung parameters, suggesting such effects were rather nicotine dependent [26]. There is limited evidence for reduced COPD exacerbations among adult smokers with COPD who switch to e-cigarettes completely [61].

### Summary:

As brought forth by the NASEM report [9], there is some support for e-cigarettes as tertiary prevention related to COPD in adult smokers. It is still crucial to learn whether chronic e-cigarette use by itself may lead to COPD, and if substitution traditional tobacco products with e-cigarettes can prevent or delay the development of COPD in smokers who quit or reduced cigarette use. At this moment, there is a lack of well-designed epidemiological studies investigating either issue.

## 8. Secondhand vaping and respiratory health – what do we know so far?

The health consequences of inhaling secondhand aerosol have not been thoroughly evaluated. Schober et al. [62] studied a comprehensive exposure assessment of e-cigarette emissions, including respirable particulate matter, particle number concentrations, nicotine, VOCs, PAHs, carbonyls, and metals; findings showed that e-cigarettes emit numerous chemicals that adversely affect indoor air quality. Use of e-cigarettes indoors elevates levels of nicotine, particulate matter, PAHs, and aluminum in the air. Another study by our group has showed that e-cigarettes are a source of secondhand exposure to nicotine but not to many combustion toxicants emitted from conventional tobacco cigarettes [63]. The airborne nicotine concentrations emitted by various brands of e-cigarettes ranged from 0.82 to 6.23 $\mu g/m^3$ [63]. In non-users who are exposed to secondhand aerosols from e-cigarettes, common respiratory endpoints can include an increase in asthma symptoms and severity, and a higher prevalence of upper and lower respiratory tract symptoms and infections [64,65]. Due to observed changes in indoor air quality, it has been recommended restricting the use of e-cigarettes in all indoor public areas [66].

### Summary:

Using e-cigarettes in indoor environments may involuntarily expose nonusers to nicotine and particulates but not to toxic tobacco-specific combustion products such as carbon monoxide. There are no epidemiologic studies reporting on the respiratory effects of exposure to exhaled aerosols on non-users. More research is needed to evaluate short and long-term health consequences of inhaling secondhand emissions from e-cigarettes, especially among vulnerable populations including children, pregnant women and patients with pre-existing respiratory conditions like asthma and COPD.

## 9. Conclusions

What is known for certain about the effects of e-cigarettes on respiratory health? Right now, the answer is --- so far, not much. While the recent report put forth by the NASEM [9] certainly improves our collective understanding related to the impact of e-cigarettes on health, it is clear that there are many deficiencies in the existing literature regarding benefits and risks of e-cigarettes in relation to respiratory health. Further research is needed to more definitively assess the short-term and long-term health effects of using e-cigarettes. Since e-cigarettes have only been on the market for a decade, it is presently not possible to assess all potential long-term harmful effects of e-cigarette use. To date, findings from clinical studies have demonstrated that e-cigarettes are likely less harmful compared to conventional tobacco cigarettes, and any harmful side effects are noticeably milder compared with regular cigarettes. Furthermore, it is also clear that e-cigarette aerosols are not “a harmless water vapor”, as claimed by manufacturers and retailers, and potential respiratory health effects from vaping may emerge after long-term use. This may merit more concern based on the population of users in question – for instance, a recent report by Rubinstein et al (2018) was the first to show the presence of carcinogens in the urine of adolescent exclusive e-cigarette users. [67] This is concerning, given that lifetime tobacco use behaviors are frequently established in youth. [68] Reasonably, it may be the case that youth e-cigarette users could yield a disproportionately greater risk of developing adverse respiratory health effects from use relative to adult cigarette smokers that transition to e-cigarettes in an effort to reduce harms know to be caused by conventional cigarette use. Such issues are complex, and warrant creative approaches from respiratory clinicians and others to advise on the appropriateness of e-cigarette use based on the context of use, as well as the user.

## 10. Expert commentary

Data on short-term health effects from inhaling e-cigarette aerosols are limited, and data regarding long-term respiratory effects are inadequate. There is some coherence across animal, laboratory, and human studies regarding the effect of e-cigarette exposure and respiratory symptoms. Chemical analyses reveal that e-cigarette aerosols contain numerous respiratory irritants and toxicants. There are documented cytotoxic effects of e-cigarette constituents on lung tissue. Studies among ex-smokers who switched to e-cigarettes note reduced exposure to numerous respiratory toxicants, reduced asthma exacerbations, and COPD symptoms. However, regular exposure to e-cigarette aerosols among regular users is also associated with impaired respiratory functions compared to non-users. Potential respiratory health risks resulting from secondhand e-cigarette aerosol exposure have not been sufficiently evaluated.

In summary, current evidence indicates that although e-cigarettes are not without risk, these products seemingly pose fewer respiratory health harms issues compared to tobacco cigarettes. Data from prospective studies and randomized controlled trials examining the impact of e-cigarette use on lung health are needed to better understand respiratory health risks tied to use of these products. The human observational studies examining the effect of switching to e-cigarettes provide support for beneficial health effects among current smokers relative to continued use of combustible tobacco products.

## 11. Five-year view

Our collective knowledge about the potential health effects of e-cigarettes on respiratory health is rapidly expanding. New studies improving our understanding in this area are released on a weekly basis, which will aid in addressing outstanding questions needed to more conclusively state any respiratory health effects linked to e-cigarette use. In the next five years, we hope that new studies will bring forth a better understanding of particulate deposition in the human airways, especially for emerging, popular e-cigarette products, such as Juul. [69,70] This will allow scientists to evaluate whether e-cigarette derived-particles impact the upper versus lower airways and alveoli, and how areas of impaction in the lung may influence any health effects caused by e-cigarettes. Emergence of additional results from long-term animal and human inhalation studies will produce a better understanding of disease risks from inhaling potentially toxic constituents of e-cigarette aerosol, including flavoring chemicals. Perhaps most importantly, as recommended by the NASEM report [9], longitudinal cohort studies are direly needed to assess the association of long-term use of e-cigarettes with clinical and subclinical respiratory health outcomes, especially compared to smoking combustible tobacco cigarettes, dual use of e-cigarettes and combustible tobacco cigarettes, and never smoking or vaping. The effect of e-cigarette aerosol on pulmonary inflammation and clearance of viral and bacterial pathogens in the lungs will be studied. Finally, there are several ongoing randomized controlled trials that will provide evidence about the effectiveness of e-cigarettes as smoking cessation aids. Trials that compare e-cigarettes to FDA-approved smoking cessation pharmacotherapies and other evidence-based cessation treatments can help to develop clinical guidelines regarding whether or not e-cigarettes should be recommended by health care providers for smoking cessation. In the next five years, we are hopeful that science will work to produce a better answer to this question than we can today.

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* Of interest

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(this animal exposure experiment confirms potential detrimental effects of flavorings present in e-cigarettes on respiratory cells)

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[PubMed: 27633767]

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[PubMed: 28166548]

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(this study showed potential secondhand exposure to several respiratory toxicants emitted from e-cigarettes)

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### Key issues

- Data on both short- and long-term respiratory health effects of e-cigarette use are very limited.
- E-cigarette aerosol contains numerous respiratory irritants and toxicants, and have documented cytotoxic effects on lung tissue. Regular exposure to e-cigarette aerosols is associated with impaired respiratory functioning.
- Studies among ex-smokers who switched to e-cigarettes note reduced exposure to numerous respiratory toxicants, reduced asthma exacerbations, and COPD symptoms.
- There is a significant research gap regarding potential respiratory health risks resulting from secondhand e-cigarette aerosol exposure and effects in humans, including children and other vulnerable populations.
- Current evidence indicates that although e-cigarettes are not without risk, these products seemingly pose fewer respiratory health harms issues compared to tobacco cigarettes.
- Data from prospective studies and randomized controlled trials examining the impact of e-cigarette use on lung health are needed to better understand respiratory health risks tied to use of these products.

## Table 1.

Summary of conclusions relevant to respiratory health from the National Academies of Science, Engineering, and Medicine (NASEM) Report "Public Health Consequences of E-Cigarettes" [9].

| Conclusion Number | Respiratory health issue related to e-cigarettes | NASEM Committee Statement* |
|---|---|---|
| 11-1 | Causal links to respiratory disease | There is ***no available evidence*** whether or not e-cigarettes cause respiratory diseases in humans. |
| 11-2 | Lung functioning/respiratory symptoms in asthma patients | There is ***limited evidence*** for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use) |
| 11-3 | Chronic Obstructive Pulmonary Disease (COPD) | There is ***limited evidence*** for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use) |
| 11-4 | Adolescent respiratory health | There is ***moderate evidence*** for increased cough and wheeze in adolescents who use e-cigarettes and an association with e-cigarette use and an increase in asthma exacerbations |
| 11-5 | Effect of e-cigarette aerosols on the respiratory system | There is ***limited evidence*** of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies |

* **Note:**NASEM uses a consistent framework that evaluates both the quality and number of studies, and categorizes evidence for various outcomes into five levels (in descending order of strongest to weakest): conclusive, substantial, moderate, limited, insufficient, or no available evidence