Human lungs are created to breathe clean air: the questionable quantification of vaping safety “95% less harmful”

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ABSTRACT
The New Zealand government is aiming for Smokefree Aotearoa, equivalent to a reduction in smoking prevalence to 5% or less by 2025. E-cigarettes may be one tool to meet this target, but how safe are they? Little is known about their long-term health implications in humans. In 2015, Public Health England commissioned a report summarising the available literature on e-cigarettes and coined the now well-known quantification that “e-cigarettes are 95% less harmful to your health than normal cigarettes”. In this article, we argue that this is an unfounded quantification because the data required to make this quantification are not yet available. The value of ‘95% safer’ was based on a study estimating the relative harms of nicotine-containing products that utilised scoring from a selected panel of experts. One of the key limitations of this quantification is that while the scores provided by the panelists were informed by knowledge, they are fundamentally value judgements and are not an exact science. E-cigarettes are probably safer than conventional cigarettes, however, there is mounting evidence that they are not without harm and the long-term health impacts are not yet known.
shown no significant reduction particularly in unmotivated smokers, and despite widespread availability and promotion in the UK since 2006 a recent report has demonstrated no significant reduction in population cigarette consumption attributable to e-cigarette availability.\(^{10}\) More long-term research into the effectiveness of e-cigarettes with regard to smoking cessation and long-term outcomes is needed.

E-cigarettes are not without risk.\(^{11}\) It is difficult balancing the potential usefulness of e-cigarettes as a smoking cessation tool with the harm they may have on the airways themselves. It is also important to be mindful of nicotine addiction, as it is becoming apparent that nicotine can have significant health risks on its own.\(^{12,13}\) E-cigarettes are designed to enable the inhalation of nicotine, which is associated with the accompanying nicotine addiction. A detailed summary of arguments against a tobacco harm reduction strategy as a population-based strategy can be found in the European Respiratory Society (ERS) position paper on ENDS.\(^{14}\) The accompanying editorial summarises the seven key arguments\(^{15}\) which include: a lack of evidence for effective smoking cessation; the fact that most e-cigarette users (60–80%) continue to smoke; uncertainty around the safety of these products—with the uncertainty being the degree of harm rather than the presence of harm; and finally consideration of the impact of the entire population—with reference to uptake of e-cigarette use among adolescents/non-smokers.

In contrast in August 2015, Public Health England (PHE) commissioned a report of the available evidence related to e-cigarettes.\(^{16}\) This review built on previous evidence summaries in a report in 2014 also by PHE.\(^{17}\) The 2015 report can be largely summarised by the following quote: “In a nutshell, 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”. Since the release of this report, this questionable quantification of vaping safety has been widely utilised, including in the 2018 updated Public Health Report reviewing evidence related to e-cigarettes and heated tobacco products.\(^{18}\)

How did the quantification of 95% safer emerge and why is it unfounded?

This quantification of safety was largely based on two reports.\(^{15,19,20}\) The first, a report estimating the harms of nicotine-containing products by Nutt et al.\(^{19}\) In this study, a multi-criteria decision analysis model (MCDA) including 14 harm criteria was applied to 12 nicotine-containing products. An international expert panel convened over two days to create a score of the harm of each of these nicotine-containing products.

Several limitations of this approach have been acknowledged by the authors themselves, others have been discussed in an editorial by The Lancet.\(^{21}\) Some of the limitations includes “…lack of hard evidence for the harms of most products on most of the criteria”. Components of the total product harm scoring included categories such as ‘product-related mortality’ and ‘product-specific morbidity’—these relating to death or disease due to the use of a nicotine-containing product. It makes sense that e-cigarettes scored low in these main categories because aspects of disease or death related to vaping had not yet emerged at the time of this evaluation.

Another weakness was the panel of experts used in evaluating these measures with the authors acknowledging that there “was no formal criterion for the recruitment of the experts”. In addition, at least two authors had affiliations with e-cigarette distributors. In fact, the editors added a note to this report relating to this conflict of interest and concluding that “the scientific community has to discuss the demarcation between potential conflicts of interest related to companies producing addictive drugs and companies producing therapeutics”.\(^{17}\)

Finally, part of the evaluation of the measures of harm in this study are based on value judgements. The quantification of harm can be informed by data; however, the weighting requires value judgements to be made. This means that these measures are not an exact science and can be easily influenced by the opinions and values of the panel as well as by their opinion of the harms of each product evaluated.
The second paper referenced in the original report was a summary of evidence by West et al.20 This report was co-authored by the two prominent authors from the 2015 PHE report—McNeill and Hajek—making it a somewhat circular argument. The West report provides a short summary of selected literature that was presented to the UK All-Party Parliamentary Group on Pharmacy in July 2015. The section related to safety in this document references the above paper by Nutt et al19 quoting the estimated extent of harm to be “around 1/20th” compared to that of conventional cigarettes. The minimal incidence of harm as of 2015 was also mentioned, including a small number of people who reported acute adverse reactions to vaping, poisoning due to consumption of nicotine liquid and sequelae of exploding e-cigarette batteries and devices.

Toxicity of e-cigarettes aerosols

An author’s note related to the 2015 PHE report specified that the ‘95% safer than smoking’ quantification was based on the facts that: “harmful, including carcinogenic, chemicals are either absent or found at much lower levels (<5% or <1%) compared to cigarette smoke and that the main chemicals present in e-cigarettes have not been associated with any serious risk”.22 While this information can substantiate a valid claim that e-cigarettes have lower levels of harmful chemicals, it is difficult to validate a claim that they are 95% safer. Many toxicological studies have found evidence that harmful and hazardous chemicals are present in e-liquids and aerosols. So far, several known carcinogens have been found in e-cigarette aerosols, including formaldehyde, acetaldehyde, acrolein and heavy metals to name a few. As a result, most reports conclude a high level of uncertainty regarding the safety of e-cigarettes.11

The key components of e-liquid are propylene glycol, glycerol, flavourings and nicotine—although without any regulations in place and no requirement for labelling exactly what chemicals are within the e-liquid other chemicals could be added. The number of chemicals within the aerosol itself has been found to be much greater than this seemingly simple list, with some studies showing upwards of 50 different chemicals within e-cigarette aerosol.23 Compounds that have been identified include tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), phenolic compounds, polycyclic aromatic hydrocarbons (PAHs), flavorings, tobacco alkaloids and drugs.11 Determining the chemical composition of >400 brands and >15,500 flavours available is challenging.24 Another complexity is the large variation in vaporising temperatures due to user preference, device and variable power settings. Coils can reach temperatures of 300°C–350°C or higher under certain conditions and vary between different e-cigarettes.4 When heating occurs, the liquid undergoes a phase change to a vapour to enable inhalation. At these high temperatures, it is likely that the chemicals undergo a range of chemical reactions changing the composition of the vapour, and possibly producing hazardous chemicals and degradation products. Finally, the vaping topography (the inhalation pattern) can vary widely depending on the user (and the experimental protocol) and has been found to alter the chemical composition of e-cigarette aerosol.25

The National Academies of Sciences, Engineering and Medicine (NASEM) report, released in 2018, implemented an extensive systematic review of the literature across several aspects of e-cigarettes.11 In surveying the literature for the toxicity of e-liquid chemicals, the NASEM report concluded that propylene glycol is unlikely to be associated with adverse health impacts.11 Glycerol appears to be generally safe, however pyrolysis (that is, the thermal decomposition of chemicals at high temperatures) of propylene glycol and glycerol results in the creation of toxic carbonyl compounds, including formaldehyde, acetaldehyde and acrolein.26 In addition, carbon monoxide can be formed as a degradation product and has recently been found in e-cigarette aerosol.27 It has also been detected in exhaled breath of EC users, although at levels substantially lower (around 20%) of that seen in cigarette smokers.18 The absence of carbon monoxide in e-cigarettes was thought to be particularly positive as the presence of this gas in conventional cigarettes reduces oxygen uptake28 and is thought to be linked to cardiovascular disease, however the
health implications at these lower levels remains to be determined.\textsuperscript{29,30} E-liquid flavourings in most cases are considered GRAS—generally recognised as safe—for ingestion, although their impact on health during long-term repeated inhalation is unknown. Some flavourings have already been identified as dangerous, for example cinnamon (cinnamaldehyde)\textsuperscript{31} and buttered popcorn (diacetyl). Diacetyl is considered safe to ingest, however inhalation of diacetyl has been associated with bronchiolitis obliterans, a rare and serious disease of the lungs.\textsuperscript{32} Metals found within e-cigarette aerosol include cadmium, chromium, lead, manganese and nickel.\textsuperscript{33} These metals are thought to arise from the heating coil and soldered material within the e-cigarette device. These metals are highly toxic for multiple organs through inhalation, however only a few studies have evaluated the specific health effects of metals in e-cigarettes. Exceptions are the studies on copper nanoparticles from e-cigarettes on mitochondrial oxidative stress and DNA fragmentation\textsuperscript{34} and cobalt exposure with giant cell interstitial pneumonia.\textsuperscript{35} To assist with navigating this often-contradictory topic the NASEM report provided a “levels of evidence framework for conclusions”, which quantified the level of evidence. Below we include the conclusions from the chapter related to the toxicology of e-cigarette constituents, highlighting that to date e-cigarettes produce lower levels of toxic substances compared to conventional cigarettes but should not be considered harmless (Figure 1).

Since the publication of the NASEM report several studies in human airways have demonstrated e-cigarettes damage to airways in novel ways compared to traditional cigarettes, for example Ghosh et al\textsuperscript{36} and Butt et al.\textsuperscript{37} In addition, e-cigarettes produce a similar imbalance in proteases and anti-proteases that are seen in traditional cigarettes.\textsuperscript{36,38} The imbalance of proteases and anti-proteases is associated with long-term emphysema. A recent animal study demonstrated a significant increase in lung cancer development as a result of exposure to nicotine containing e-cigarette aerosol when compared to those exposed to ambient air or an e-liquid aerosol not containing nicotine,\textsuperscript{13} once again raising concerns about the long-term effects from e-cigarette exposure.

The outbreak of lung injury associated with vaping in the US has documented 2,809 hospitalised cases of severe lung illness with 68 of these fatal, according to the CDC as of February 18, 2020. The terms ‘vaping-associated lung injury’\textsuperscript{37} or ‘vaping-related acute lung injury’ (VpALI) have been coined for patterns of acute lung injury consistent with e-cigarette users.\textsuperscript{39} The most common symptoms are shortness of breath, which may be accompanied by a dry cough and eventually could lead to severe respiratory distress as seen in the cases in the US. A recent assessment of the pathology in the New England Medical Journal\textsuperscript{37} suggests that VpALI represents a form of chemical pneumonitis due to one or more inhaled toxic substances contained within e-cigarette aerosol. A number of different types of lung

\textbf{Figure 1:} Conclusions from the National Academies of Sciences, Engineering and Medicine (NASEM) report related to the toxicology of e-cigarette constituents, indicating evidence of harmful chemicals within aerosols.\textsuperscript{11}

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\textbf{Conclusion 5-1.} There is \textbf{conclusive evidence} that in addition to nicotine, most e-cigarette products contain and emit numerous potentially toxic substances. \\
\textbf{Conclusion 5-2.} There is \textbf{conclusive evidence} that, other than nicotine, the number, quantity, and characteristics of potentially toxic substances emitted from e-cigarettes are highly variable and depend on product characteristics including device and e-liquid characteristics and how the device is operated. \\
\textbf{Conclusion 5-3.} There is \textbf{substantial evidence} that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes. 
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damage have been observed and a standard definition for VpALI is still awaited. Vitamin E acetate has been proposed as a significant culprit behind many of these VpALI cases. A lot is still unknown about this outbreak of respiratory disease and one needs to keep an open mind that it may be caused by any one of a large number of chemicals in the inhaled vapour. The large heterogeneity of both the construction of e-cigarettes and the substances aerosolised could mean that other pulmonary manifestations may still become uncovered.

**A consensus of the science**

The current scientific consensus is that e-cigarettes are probably safer than conventional cigarettes, but e-cigarettes are not without harm! This highlights the need for regulations relating to the manufacturing and sales of these products. In addition, safe operating conditions of e-cigarettes need to be developed, for example having restrictions of the power/temperature as higher temperatures increase the creation of more dangerous chemicals. Non-factual based predictions of comparative safety, such as the ‘95% safer’ quantification, are not helpful for the risk estimation of e-cigarettes and should not be used when discussing or promoting e-cigarettes. Taking up vaping is not safe. A quote from the recent ERS recommendation related to tobacco harm reduction using e-cigarettes sums up its recommendations: “The human lungs are created to breathe clean air, not ‘reduced levels of toxins and carcinogens’, and the human body is not meant to be dependent on addictive drugs. ERS cannot recommend any product that is damaging to the lungs and human health”.

**Competing interests:**
Nil.

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