

# A critique of a World Health Organization-commissioned report and associated paper on electronic cigarettes

## SUMMARY

The World Health Organization (WHO) recently commissioned a report reviewing evidence on electronic cigarettes and making policy recommendations. A version of it was subsequently published as an academic paper. We identify important errors in the description and interpretation of the studies reviewed, and find many of its key conclusions misleading.

## INTRODUCTION

The WHO has played an important role in attempts to combat the tobacco pandemic. It recently commissioned a review of the evidence on electronic cigarettes (e-cigarettes) [1], which was widely circulated; a version of this review was also subsequently published in the academic journal *Circulation* [2]. E-cigarettes vapourize nicotine from a liquid rather than using combustion, so while cigarette smoke contains thousands of constituents, including 70 known carcinogens, e-cigarettes potentially offer a much less harmful form of nicotine delivery.

This paper addresses the ways in which the review and subsequent *Circulation* paper misrepresent the evidence, misinterpret it or frame it in a way that is misleading. Our critique is structured around the first nine statements in the executive summary of the report, many of which were repeated in the paper. We present each main statement, an alternative statement that we believe reflects more accurately the state of evidence, and a commentary addressing the differences between the two.

## EXECUTIVE SUMMARY STATEMENTS

### Original statement 1

- E-cigarettes are evolving rapidly and being marketed as cigarettes were in the 1950s and 1960s
  - Marketing is back on television and radio
  - Aggressive placement in convenience stores (next to candy) and in other stores (next to medications)

### Alternative statement 1

- E-cigarettes are evolving rapidly and in some cases are being marketed in a way that is reminiscent of cigarette advertising

- There is as yet no evidence as to the importance of different marketing strategies to optimize the benefits to public health (such as encouraging smokers to stop smoking) while minimizing unintended effects (such as appealing to non-smokers)

### Comment

Use of the language 'marketing is back' is polemic, and has no place in an academic report. Reference to placement near 'candy' and 'medicines' similarly seems intended to create an emotional response and lacks reference to evidence on what the significance might be of such placement.

The important issue to consider is the role of marketing in encouraging existing smokers to move away from smoking while not attracting non-smokers. There is evidence that smokers are trying e-cigarettes because of their concern about the health risks of smoking and a desire for safer alternatives [3,4], rather than as a result of pernicious marketing.

### Original statement 2

- Youth are rapidly adopting e-cigarettes
  - E-cigarettes contain candy flavours (e.g. cherry, chocolate, turkish delight)
  - High levels of dual use
  - Youth who use e-cigarettes are heavier (not lighter) smokers
  - Youth who use e-cigarettes are much less likely to have stopped smoking (OR 0.1–0.2)
  - The temporal and causal relationships between e-cigarette use and smoking have not been determined

### Alternative statement 2

- Current use of e-cigarettes in non-smoking youth is very low and there is currently virtually no regular use in children who have never smoked or never used tobacco
- Young smokers who also use e-cigarettes tend to be those with higher cigarette consumption
- The advent of e-cigarettes on the market has been accompanied by a continued reduction in youth smoking prevalence

- It is not clear whether use of e-cigarettes by adolescent smokers and non-smokers inhibits or promotes smoking

#### Comment

The statements misrepresent the existing evidence using vague language that is likely to be misinterpreted. The report cites the cross-sectional Centers for Disease Control (CDC) US National Youth Tobacco Surveys, in which much was made of a doubling of e-cigarette experimentation between 2011 and 2012 [5]. However, current use of e-cigarettes was very low and a striking feature of the data was a fall in smoking prevalence over the same period [6] (similar to recent observations in French youth [7]). The latest CDC report shows that high school smoking is at a 22-year low [8] suggesting that, currently, e-cigarette use is not encouraging uptake of cigarette smoking. Despite the final statement containing a caveat about causality, the statement that youth who use e-cigarettes are less likely to have stopped smoking creates the impression that use of e-cigarettes may deter quitting.

The report also cites the authors' own research, including an analysis of the CDC youth surveys [9] and a study of Korean adolescents [10] which, again, used cross-sectional data (although both press releases were suggestive of causality [11,12]). E-cigarette use is found mainly in youth who are smokers and particularly in those who are heavier smokers, suggesting that e-cigarettes may appeal to smokers trying to reduce their cigarette consumption or that they may try e-cigarettes for the same underlying reasons that caused them to smoke. This may be positive, if it provides an alternative to smoking.

Crucially, the report treats 'ever use', which captures any use including one-off experimentation as though it were current regular use; e.g. with reference to a North Carolina study, the report claimed that: 'Importantly, they found that 12% of e-cigarette users (*sic*) were never smokers' [p. 30] when in fact these were respondents reporting that they had ever used e-cigarettes. Other surveys confirm that, to date, there have been hardly any instances of non-smokers becoming regular users of e-cigarettes (e.g. [3]).

The listing of flavours has the appearance of being a polemic device to arouse an emotional reaction. A study of adult e-cigarette users suggests that flavours are important in efforts to switch from smoking to e-cigarette use and to remain smoke-free [13].

#### Original statement 3

- E-cigarettes have not been proven to help people quit smoking

- Longitudinal population studies show that e-cigarette use is associated with a lower odds of quitting
- The randomized trial comparing e-cigarettes to nicotine patch shows that in the context of low-level behavioural support, the quit rate for those using e-cigarettes is low and similar to those using a nicotine patch

#### Alternative statement 3

- Evidence from randomized controlled trials (RCTs) and population-level observational studies suggests that, overall, the effect of e-cigarettes is similar to the effect of licensed nicotine products used with minimal health professional supervision, but the popularity of e-cigarettes means that they may have a large impact upon population quit rates

#### Comment

The statement misrepresents the consistent picture emerging from a variety of studies using different designs, that e-cigarettes can help smokers to stop, even though the effect is not strong (e.g. [[14–18]). These studies mainly used products with no or low nicotine delivery which are now obsolete. Newer types of e-cigarettes may be more effective, as they have improved nicotine delivery and sensorial effects [19].

The statement that e-cigarette use is associated with lower odds of successful quitting is only meaningful if it implies at least the possibility of a causal connection. In fact, it is based on misrepresentation of two longitudinal studies. In the first [20], reasons for e-cigarette use as well as measurement of current e-cigarette use were assessed at the follow-up wave, not at the initial wave. The odds ratio (OR) of quitting over a 1-year period is thus inappropriate. In the second study [21], the 'e-cigarette users' consisted of people calling a quitline for help with stopping smoking, and who were asked whether they had ever used e-cigarettes at a 7-month follow-up point only. This means that those who quit smoking successfully with the help of e-cigarettes and therefore not needing the quitline were, of course, not included in the sample. A significant minority of the 'e-cigarette users' reported not using e-cigarettes over the follow-up period (but instead before calling the quitline). For the remainder it is unknown whether they used e-cigarettes in their quit attempt. Callers who reported having ever used e-cigarettes for 1 month or more were more likely to have made multiple previous quit attempts compared with never users, indicating prior difficulty in quitting smoking. In summary, the same logic that the report authors apply here would reliably associate quit failure with use of any stop-smoking medication or device, however effective.

The authors also misinterpret findings from studies showing that e-cigarette users are heavier smokers than non-users and that a history of trying an e-cigarette is not related to future quitting. They ignore the fact that the same pattern applies to licensed nicotine products and to behavioural support for smoking cessation, as these are more likely to be used by heavier, more dependent smokers [22,23].

Moving forward, studies need to distinguish clearly the frequency and recency of e-cigarette use when discussing quitting [24]. It is therefore important that observational studies adjust for characteristics associated with people who use e-cigarettes. Matching of participants (e.g. using a technique such as propensity scoring) at baseline prior to using e-cigarettes could also control for selection biases, by showing whether the e-cigarette initiators differ in some other ways.

Recent cross-sectional data from representative population samples in England actually show higher motivation to quit among smokers who also use e-cigarettes [25], and that smokers using e-cigarettes in quit attempts are more likely to report continuing abstinence from smoking than those using nicotine replacement therapy purchased over-the-counter or who tried to quit unaided [26].

#### Original statements 4/5

- There is a high level of dual use of e-cigarettes and conventional cigarettes among adults
- The hope that e-cigarettes will reduce harm by delivering 'clean' nicotine will not be realized in continuing dual users
  - Continuing to smoke any conventional cigarettes confers essentially the full cardiovascular risk
  - Cancer risk may only be modestly affected because smoking duration is more important than intensity

#### Alternative statements 4/5

- Surveys show that the majority of e-cigarette users are current smokers (dual users)
- It is not known whether and by how much using an e-cigarette to reduce cigarette consumption provides a health benefit, or promotes or inhibits smoking cessation

#### Comment

These statements are misleading, as they suggest that there is no benefit of cutting down cigarettes alongside e-cigarette use. There is a strong relationship between the number of cigarettes smoked daily and all-cause mortality, i.e. a strong exposure–risk relationship [27]. However, this relationship may be different when smokers cut down

their cigarette consumption, although using a nicotine product alongside cigarette reduction may reduce inhalation and hence reduce risk.

There is, in fact, a clear dose–response relationship between amount smoked and cardiovascular disease, but it is non-linear [28], although this relationship may alter when smokers cut down. The statement that cancer risk may be only modestly affected by reduction in toxin intake from cigarettes is highly misleading. The fact that duration is believed to play a more important role than dose is being misused in this context, because duration and dose are two complementary metrics.

The correct interpretation of the evidence is that there is likely to be at least some benefit from smoking reduction if that is achieved through use of e-cigarettes, but the amount is unknown and this may be less than users would hope for. More importantly, use of nicotine medications by smokers who are unwilling to quit promotes smoking cessation in this group [29,30], and one may hypothesize that this effect also applies to e-cigarettes [31].

#### Original statement 6

- E-cigarettes deliver lower levels of toxins than conventional cigarettes, but they still deliver some toxins

#### Alternative statement 6

- E-cigarettes tested so far deliver much lower levels of toxins than conventional cigarettes

#### Comment

The conclusion as phrased is misleading, in that it crucially does not communicate the huge difference in toxin delivery between cigarettes and e-cigarettes. The statement incorrectly summarizes the presentation of the studies in the body of the report, where the authors acknowledged that it was unknown whether the much lower levels of toxin delivery from e-cigarettes indicated an actual health risk.

In the body of the report some studies are misrepresented. The finding presented as showing significant risk suggests that daily exposure to tobacco-specific nitrosamines (TSNAs) from e-cigarette use is 76–142-fold lower compared with smoking one cigarette [32] and approximately 1800-fold lower compared to an average smoker's daily exposure [33]. Levels of potentially toxic compounds found in e-cigarette vapour were, in many cases, comparable to those present in the licensed nicotine inhalator [32,34]. Additionally, the units of exposure in one study [35] were misread, giving the findings as  $10^5$ – $10^6$  times higher than those actually reported. The reference to Food and Drug Administration (FDA) reports

of the presence of amino-tadalafil and rimonabant in cartridges [36] is reported as if this was unintentional contamination, when actually this was a misguided commercial initiative.

#### Original statements 7/8

- E-cigarettes pollute the air less than conventional cigarettes, but they pollute the air
  - They do not just emit 'harmless water vapor'
- People passively exposed to e-cigarettes aerosol absorb nicotine (measured as cotinine), with one study showing levels comparable to passive smokers

#### Alternative statements 7/8

- Exposure of bystanders to chemicals in e-cigarette vapour is not at levels that would be expected to cause health problems

#### Comment

The failure to report the magnitude of the difference in concentrations of potential toxins between cigarette smoke and e-cigarette vapour is highly misleading. Policymakers reading the statement could easily form the impression that there was a significant risk from being in the vicinity of someone using an e-cigarette. As there is no side-stream vapour, bystanders are only exposed to the vapour that e-cigarette users exhale into the air which disappears very rapidly compared with cigarette smoke; exposure to nicotine and other chemicals is negligible [37]. With regard to passive exposure to nicotine, the authors of the report should have been aware that it is not nicotine which is harmful in passive smoking, but the other smoke components. However, policymakers reading the report would not necessarily know this, so the statement creates a false impression of harm.

The discussion in the main body of the report about 'particulate matter' emitted from e-cigarettes fails to acknowledge the differences between particles. Environmental pollution microparticles from tobacco smoke are mainly carbon, metal, acid and organic, many of which result from combustion. In the case of e-cigarettes, microparticles are expected to consist mainly of propylene glycol, glycerol, water and nicotine droplets. While metal and silica nanoparticles may also be present [38], emissions from e-cigarettes are not comparable to environmental or cigarette smoke microparticles.

#### Original statement 9

- There is little research on direct health effects
  - One study shows short-term pulmonary effects
  - Evidence of cytotoxicity in animal and human *in vitro* test systems

#### Alternative statement 9

- As long as e-cigarettes continue to deliver concentrations of chemicals similar to what has been shown in tests so far, an understanding of the toxicology of these chemicals indicates a risk to users much lower than from tobacco cigarettes

#### Comment

These statements are factually uninformative while creating an impression of alarming possibilities. The report focuses on one short-term study that reported an increase in airways resistance post-e-cigarette use, associated with a 16% decrease in fractional exhaled nitric oxide (FeNO), a marker of bronchial inflammation, which the authors of the original study stated was not clinically significant [39]. Another study did not find a significant change in FeNO [40], yet only the 'alarming' study is mentioned in the summary. A more recent study found an increase in FeNO levels after e-cigarette use [41,42], suggesting considerably lower risk. A further study has shown a reduction in asthmatic symptoms in both quitters and dual users, suggesting some immediate health benefits for asthmatic smokers of e-cigarette use [43].

The report also fails to mention that the majority of studies have found that e-cigarette use is well tolerated, at least with short- to moderate-term use. No experimental (e.g. [39]) or prospective follow-up study (e.g. [18]) has reported serious adverse events attributable to e-cigarettes; only one randomized controlled trial [14] did so, but these did not differ between groups and were deemed to be unrelated to e-cigarettes.

Concerning cytotoxicity, a study [44] is emphasized despite its marginal relevance. It exposed cells to e-cigarette liquids rather than the vapour, which is what users are actually exposed to. There is no question at all that e-cigarette vapour shows much less toxicity than cigarette smoke [45,46].

## CONCLUSION

The language of the report, the selective use and misrepresentation of evidence is problematic in a major policy-relevant document. Policymakers and the public require scientists to present evidence objectively, and when they offer unsubstantiated opinions, scientists should make it clear that this is what they are doing.

#### Declaration of interests

A.M. has no competing interests. J.F.E. was reimbursed by a manufacturer of e-cigarettes and e-liquids for travelling to London and to China to visit e-cigarette factories, but

received no honoraria for these meetings; he has no competing interests with the tobacco and pharmaceutical industries. Some studies performed by K.F. were carried out using funds provided to his institution (Onassis Cardiac Surgery Center) by e-cigarette companies. P.H. received research funding from and provided consultancy to manufacturers of stop-smoking medications. J.LeH. has received speaker honoraria and consultancy fees from Johnson & Johnson, Novartis, Pfizer and Pierre Fabre; he has never worked for tobacco or electronic cigarettes companies. H.M. was an investigator in a public-good-funded ASCEND e-cigarette trial for which PGM International provided products at no cost, and has undertaken research on Ruyan e-cigarettes, for which the University of Auckland was funded by Health New Zealand, independently of Ruyan; he has provided consultancy for and received research funding from manufacturers of smoking cessation medications (Pfizer, Johnson & Johnson and GlaxoSmithKline).

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