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COMMENTARY

Electronic cigarettes: proceed with great caution

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On 29 May 2014, 53 people, including scientists, clinicians and advocates, signed a letter[1] addressed to Margaret Chan, the Director General of the World Health Organisation (WHO). It sought to dismiss WHO's known concerns about electronic cigarettes (e-cigarettes) and, despite omitting any references to the scientific literature, the signatories hailed them as an innovation with potential to save many millions of lives. A slick campaign by a professional public relations firm ensured that the letter attracted extensive global publicity. The same day, British American Tobacco issued its own press release[2], making many of the same arguments, and arguing that, as a manufacturer of e-cigarettes, it should be viewed as part of the solution to smoking-related disease rather than, as the entire industry had become, a pariah excluded from discussions on smoking and health by the Framework Convention on Tobacco Control.

Three weeks later, with much less publicity, 129 others, this time primarily public health professionals, paediatricians, and cardiologists, including many leaders of national, regional and global organisations, wrote another letter[3] to Dr Chan, this time fully referencing the scientific literature, and taking a very different view. These signatories supported the WHO's current approach, based on an independent systematic review (Grana et al. 2014), that expresses great caution about the potentially serious hazards associated with the promotion of e-cigarettes. How can it be that informed individuals can reach such different conclusions?

The clue is in the nature of the signatories. Many of the former have backgrounds in addiction, either to nicotine or other substances. Others have promoted harm reduction, known to be effective in relation to narcotics. Inevitably, their focus is on the individual smoker, especially those who are most addicted to nicotine. A few others may have more questionable motives given their links to the tobacco industry. In contrast, signatories of the second letter are worried about the overall impact on the population. They share the concerns of Dr Haik Nikogosian, charged by WHO with monitoring the Framework Convention on Tobacco Control, who believes that e-cigarettes "could result in a new wave of the tobacco epidemic" (Robinson 2014). Although the advocates of e-cigarettes portray the growth in sales as consumer led, the reality is that the manufacturers have spent enormous sums, estimated to be $60 million in the USA alone in 2013, much of which seems designed to appeal not only to smokers but also to non-smokers, including children. The critics are also concerned about the safety of what at present are largely unregulated and unevaluated products. So what does the evidence tell us?

The first question is whether e-cigarettes are safe. There are two considerations here, the safety of nicotine and the

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[1] http://nicotinepolicy.net/documents/letters/MargaretChan.pdf.

[2] http://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DO9KJJX5?opendocument&SKN=1.

[3] https://tobacco.ucsf.edu/129-public-health-and-medical-authorities-31-countries-write-who-dg-chan-urging-evidence-based-appro.

safety of the other substances, including an increasingly diverse array of flavourings and contaminants arising during manufacturing. Nicotine is a poison and there are increasing reports, from several countries, of poisoning in young children who swallow nicotine-containing fluid (Chatham-Stephens et al. 2014)which is hardly surprising given their attractive packaging and flavours, such as bubble gum, that seem designed to appeal to children. However, there is also growing concern about the long-term effects of inhaling nicotine, something that previously had attracted little attention given the known hazards of the tar and carbon monoxide that usually accompanies it. Use of e-cigarettes achieves similar levels of serum cotinine, a marker of nicotine absorption, as are seen with normal cigarettes (Flouris et al. 2013). Recent research has shown how nicotine regulates several genes associated with the development of cancer in normal cells (Bavarva et al. 2013) and promotes tumour progression and metastases in smoking-related cancers (Schaal and Chellappan 2014). Given its many effects on cellular messaging, there are particular concerns about exposure of children, pregnant women, breastfeeding mothers, and those with pre-existing disease (WHO 2013). A particular concern relates to the effects of the ultrafine particles, which are produced by e-cigarettes at similar levels to conventional cigarettes (Zhang et al. 2013). Inhalation of e-cigarette vapour is associated with release of the inflammatory signalling molecule Nitric Oxide (Schober et al. 2013). There are also concerns about the levels of cytotoxic metals in e-cigarette vapour, which are typically at higher concentrations than from conventional cigarettes because they are mainly produced by the heating elements (Williams et al. 2013).

The second question is whether they actually work as an aid to quitting. Remarkably, there is only one published randomised controlled trial and it found no significant difference from nicotine replacement therapy (Bullen et al. 2013). Advocates of e-cigarettes argue that the devices used were early versions and newer ones are more effective, but present no evidence that this is the case. They also ignore the barriers placed in the path of those randomised to nicotine replacement therapy, who had to take a voucher to a pharmacy to obtain the nicotine replacement therapy. In the absence of robust evidence of effectiveness, the advocates of e-cigarettes selectively cite observational data. Yet they conveniently ignore those findings that do not fit their arguments. They use the analogy of smokeless tobacco, or snus, which is sold legally in Sweden. A widely used graph shows a decline in smoking coinciding with increased use of snus. Yet, as Swedish academics have noted, disaggregation by sex shows similar changes in smoking by men and women, yet snus use among women is extremely rare (Galanti et al. 2010). They also cite findings from England showing that, among those who intend to quit, success is greater with e-cigarettes than with nicotine replacement therapy but ignore the counterintuitive finding that the success rate among the latter was lower than those whose attempts were unassisted (Brown et al. 2014). They also ignore the possibility that use of e-cigarettes may reduce the desire to quit.

A third question is whether young people who would not otherwise have smoked to take up e-cigarettes and, in due course, conventional cigarettes. Here too, the evidence is lacking. As noted above, e-cigarette manufacturers have engaged in intensive marketing that gives every impression of being targeted at young people. The imagery employed by e-cigarette manufacturers now is almost identical to that used by tobacco companies in the 1950s and 1960s, except that the clothing of the models and accessories used are more modern (CECD 2014). A report by a group of US senators catalogued the use of sponsorship of youth oriented sports events, use of flavours designed to appeal to youth, and using celebrity spokespersons that appeal to youth (Durbin et al. 2014). These tactics have been described in more detail by research in the USA (Grana and Ling 2014) and UK (Andrade et al. 2013). Particular concern has arisen from US data showing a significant increase in use among middle school and high school students (CDC 2013) from 0.6 to 1.1 %, and from 1.5 to 2.8 %, respectively. Similar findings have been reported among adolescents in Korea (Lee et al. 2014). E-cigarette advocates note that the changes in the USA have coincided with a fall in smoking prevalence but ignore the long-term downward trend, as well as the impact of austerity, given that smoking rates fell during the Cuban economic crisis in the 1990s only to increase when recovery came about (Franco et al. 2013) as well as evidence that alcohol consumption, which might be expected to behave similarly to tobacco, has fallen during the current economic crisis (Harhay et al. 2014, Bor et al. 2013).

In summary, e-cigarettes may turn out to be effective in increasing quitting but that has yet to be shown. However, if this is shown to be the case, then, just like any other system delivering an active, and potentially toxic substance, they must be subject to appropriate regulation. This should ensure that they are consistent in quality and deliver nicotine as effectively and safely as possible and clearly indicate the addictive nature of nicotine and encourage smoking cessation by providing links to appropriate resources. Moreover, marketing, in any media, should not target children and young people or other non-smokers (including through sponsorship of sporting events, product placement, use of flavours designed to appeal to youth, or use of celebrity spokespersons) and should not 'renormalise' or 're-glamourise' smoking or undermine smoking prevention policies (which implies a ban on their use in enclosed public places). This balanced, evidence-based

approach would ensure that any potential benefits are realised while avoiding, as far as possible, the harms. It contrasts with the current position of the advocates, which is akin to calling for WHO to promote the roll out of a new drug before it has undergone phase I, II or III testing, even though there are well-established methods, such as restrictions on marketing, standardised packaging, and tax rises that are extremely effective in reducing smoking without the risks of e-cigarettes.

Any analysis of e-cigarettes would be incomplete without two final points. The first is the nature of the debate. Many of those who have had the temerity to question the portrayal of e-cigarettes as a miracle solution to the tobacco epidemic have been subject to vicious and sustained hate campaigns on social media (Mills 2014). Yet, so far, those health professionals who support e-cigarettes have felt unable to condemn these attacks and, in some cases, they too have joined in, labelling those calling for caution as criminals. Second, the move of the transnational tobacco companies into the e-cigarette market must not be used as a reason to give them a seat at the policy table. If they are serious about reducing tobacco-related harm they will stop manufacturing cigarettes. Anything less is just another example of their shameless hypocrisy.

Additional reference list available as electronic supplementary material at [URL]

Conflict of interest MM has no financial or other relationship with tobacco companies nor with manufacturers of e-cigarettes.

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