



There can be smoke without fire: warranted caution in promoting electronic cigarettes and heat not burn devices as a safer alternative to cigarette smoking

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The tobacco industry is now shifting its focus from combustible cigarettes to promoting the “safer” electronic nicotine delivery alternatives. This editorial presents emerging challenges these devices pose to human health. <http://bit.ly/2xdAjD0>

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The damaging health effects of active and second-hand cigarette smoking are well documented. Tobacco smoke exposure is the primary cause of COPD, which is estimated to become the third leading cause of global mortality by 2030 [1]. In 2012 it was estimated that 1.8 million new cases of lung cancer occurred globally, making it the most common form of cancer [1]. Maternal smoking and intrauterine exposure to tobacco smoke and nicotine have been linked not only to negative pregnancy outcomes such as miscarriage and preterm birth, but also to numerous adverse pathophysiological outcomes in the child, including an increased risk of developing asthma and COPD due to impaired lung development [2]. The global rates of smoking during pregnancy, particularly in the lower socioeconomic status countries, remain too high [3]. The World Health Organization estimates that in 2015, ~20% of the world’s adult population were current smokers; fortunately, the prevalence of tobacco smoking is on a gradual decline [4]. The tobacco industry is currently changing strategies, shifting the focus from tobacco cigarettes, and promoting the “safer” alternative in electronic cigarettes (e-cigarettes) and now heat not burn (HNB) devices [5]. These devices still deliver nicotine and the rise in the number of dual users (of both traditional cigarettes and e-cigarettes) is alarming [6, 7].

The popularity and growth of vaping is increasing globally, with the sales of e-cigarettes expected to surpass the sales of traditional cigarettes in the next 5 years [8]. Figures published in 2018 in the *New England Journal of Medicine* reveal that in the USA alone, there were 1.3 million additional adolescents who vaped nicotine-containing products and 25% of high school seniors (a 10% rise from 2017) had vaped (with or without nicotine) in the prior 30 days of being surveyed [9]. In New Zealand, the numbers of teenagers that had tried e-cigarettes had tripled between 2012 and 2014 [10]. A COMPASS study with a large longitudinal sample size examined the emerging major public health concern in Canadian youth (grade 9–11 never-smoking students), with e-cigarette use largely associated with the development of a



new population of cigarette smokers. Among the sample of never-smoking adolescents, 45.2% of current e-cigarette users reported trying a cigarette after 2 years compared with 13.5% of non-current e-cigarette users [11]. In December 2018, tobacco giant Altria, the parent company of Philip Morris International, invested \$12.8 billion in Juul, taking a 35% stake in the e-cigarette company and offering overly generous bonuses to existing Juul employees [12]. Many countries are now waking up to the dangers of the flourishing e-cigarette market; for example, the US Food and Drug Administration (FDA) chief recently weighed in on the e-cigarette epidemic and threatened the industry with action if the use in youth rises and the marketing to youth continues. The US Surgeon General was quoted in 2018, in the midst of the rise in American youth e-cigarette, use as saying, “less harm does not equal harmless” and that “we need to lean in to get e-cigarettes out of the hands of our children.”

Recently, attention has been brought to the appropriate manufacturing of e-liquids. Concentrations of nicotine found in e-liquids have been found to vary from the labelled concentration or even been incorrectly labelled as being absent. CHIVERS *et al.* [13] raised the concern of the frequency with which nicotine is found in “nicotine-free” products along with the unknown effects of an array of substances when heated, aerosolised and inhaled.

The effects of e-cigarette vaping on lung pathophysiology are slowly emerging, which counter the unsupported claims of the nicotine industry. A single session of e-cigarette vaping has been shown to negatively affect lung function, which is accentuated in people living with asthma [14], and the inflammatory profile of e-cigarette users has been shown to be higher than in never-smokers [15]. Vaping has now also been linked to an increase in the risk of pneumonia [16], macrophage phagocytic dysfunction [17], and in a mouse model, e-cigarette vapour exposure has been shown to induce systemic inflammation and multiorgan fibrosis [18]. Exposure to e-cigarette aerosol impairs lung function in young mice [19], and our own data have shown that maternal vaping can affect the offspring’s lung function as it potentiated key features of allergic asthma, and worsening of these symptoms was partly mediated by mitochondrial dysfunction [20]. Short-term exposure to e-cigarette vapour, whilst having no immediate effect on cardiac function, was shown to increase heart tissue angiogenesis in mice [21]. The identification of this pathophysiological effect from acute e-cigarette exposure elucidates further research into the possible involvement in promotion of tumour growth. Ultimately, long-term studies of e-cigarette exposure are currently lacking, thus limiting our understanding of the role of e-cigarettes in the development and progression of disease.

The latest nicotine delivery systems to arrive on the market are the HNB tobacco products that have been branded as IQOS by Philip Morris (figure 1). Previous HNB products failed to take off but IQOS is dominating the market. IQOS has just received FDA approval for sale within the USA. In this device, ground tobacco is reconstituted into sheets with water, glycerine, guar gum and cellulose fibres. The tobacco sheets are fashioned into small plugs that are contained within products sold as HEETS or mini cigarettes and inserted into the device where they are heated but not ignited at a temperature of up to 350° C, which generates an aerosol. These devices are still quite new but their rising popularity is spreading



FIGURE 1 Heat not burn devices are becoming increasingly popular. As shown in the picture, these devices generate enormous aerosols that are very similar to the smoke emitted by a combustible cigarette.

globally: in 2017, a 10-fold increase in current users of the HNB devices was recorded in Japan in just a single year [22].

Studies looking into the effects of HNB devices on human health are limited due to the infancy of their availability on the market but we recently published a study that investigated the effects of HNB devices on human lung cells, and compared them directly with e-cigarettes and conventional cigarettes [23]. Cigarette smoke, e-cigarette vapour and HNB aerosol all displayed cellular toxicity with increasing concentration in both human bronchial epithelial cells (Beas-2B) and primary human airway smooth muscle cells, along with the release of inflammatory mediators, greater deposition of extracellular matrix proteins and mitochondrial dysfunction [23]. Interestingly, HNB exposure was shown here to be as detrimental to human lung cells as smoking and vaping, and thus the use of HNB devices is not safer than e-cigarette or cigarette smoking.

Clinical studies with HNB exposure must be conducted to further unravel its potential impact on airway remodelling, oxidative stress, infections and inflammation in users of these devices. These devices are available for purchase in 43 countries, predominantly in Europe, and as we stated earlier, the FDA has only just permitted their sale in the USA. Organisations pushing the legalisation and promotion of e-cigarettes, and now HNB products, do not have a clear understanding of the potential risks of these devices, especially for our youth, pregnant women and the unborn.

A recent publication in the *New England Journal of Medicine* claimed that e-cigarettes are the most effective smoking cessation aid following the results from a trial in UK National Health Service “Stop Smoking” services [24]. Two editorials by BORELLI and O’CONNOR [25] and DRAZEN *et al.* [26] followed, raising the concerns that this behavioural paper fails to address. The 1-year abstinence rate of 18% in the e-cigarette group is better than the regular nicotine replacement group (9.9%) in this trial, yet this rate is comparable to other combinations of nicotine replacement with accompanied professional support from previous trials. Alarming, 80% of the e-cigarette group were still using e-cigarettes at the end of the trial, whereas only 9% of the nicotine replacement group still required aids. The success rate for being nicotine free with the aid of an e-cigarette was only 3.7% in this trial, which clearly suggests that e-cigarettes may not be an effective smoking cessation aid [24]. BORELLI and O’CONNOR [25] point out that this trial lacked information on the presence of asthma or COPD following the short-term exposure to e-cigarettes and the exclusion of pregnant women in the e-cigarette group does not provide reassurance that e-cigarettes are the best cessation aid. They conclude by stating that the efficacy and safety of e-cigarettes needs further research if they are to be approved for cessation use [25]. DRAZEN *et al.* [26] also point out that there is a lack of long-term data on the effects of vaping on health whilst raising the fear that the “creation of a generation of nicotine-addicted teenagers will lead to a resurgence in the use of combustible tobacco in the decades to come”. They too are wary of the possibility of e-cigarettes as an addictive gateway that will eventuate in a new population of smokers and called for the removal of flavoured e-liquids from the market [26]. They say, “even though our smoking rates have fallen, they’re going to go up again.”

We as a research community have not yet thoroughly investigated the health risks of these products and great caution must be taken with promoting these as safe smoking cessation tools. It was decades before the link between lung cancer and tobacco cigarettes was exposed [27, 28], and as long-term e-cigarette users are likely to be only nearing the end of a decade of use, then unidentified e-cigarette-driven pathogenesis may yet to have eventuated and been identified.

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