

COMMENTARY ON WHO REPORT ON ELECTRONIC NICOTINE DELIVERY SYSTEMS AND ELECTRONIC NON-NICOTINE DELIVERY SYSTEMS

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DECLARATION OF INTERESTS OF AUTHORS

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FCTC COMPLIANCE

This report has been prepared in full compliance with Article 5.3 of the Framework Convention on Tobacco Control.

EXECUTIVE SUMMARY

The World Health Organisation has commissioned a scientific assessment and policy options report on electronic cigarettes (referred to in the report as Electronic Nicotine Delivery Systems (ENDS) and Electronic Non-Nicotine Delivery Systems (ENNDS)¹) for the Seventh Conference of the Parties of the Framework Convention on Tobacco Control (FCTC COP-7). This paper provides a critique of that assessment. The main concerns with the WHO report are as follows:

- **Positioning ENDS as a threat rather than opportunity.** Overall, the WHO report does not correctly position ENDS primarily as an *alternative* to smoking and instead focusses excessively on risks of ENDS use without adequately recognising the deep reductions in health risks when a smoker switches to ENDS. The FCTC itself recognises ‘harm reduction’ as a key strategy in tobacco control. But with minor exceptions, the WHO report discusses ENDS as a threat, whereas in fact they represent a major opportunity for public health.
- **Failure to quantify risk.** The WHO paper provides a poor assessment of ENDS risks. In terms of toxicology, the discussion is naïve and places excessive emphasis on negligible risks arising from very low exposures. In toxicology, the presence of a potentially harmful agent does not necessarily establish a material risk. This is because the level of exposure matters and “the dose makes the poison”.
- **Inadequate comparisons with smoking.** The WHO paper systematically does not make relevant comparisons with exposures arising from inhaling tobacco smoke or refer to other useful comparators such as occupational exposure limits. However, data from around the world shows that almost all ENDS users are smokers, ex-smokers or would-be smokers. The most relevant comparison for health policy purposes is with smoking.
- **Misrepresenting second hand ENDS vapour risks.** The section on risks of second-hand exposure to ENDS aerosol provides no evidence that such exposures pose any material risks to bystanders. The claim that ENDS have the “*potential to lead to adverse health effects*” in bystanders does not reflect the science behind the cited source unless ‘potential’ is taken to mean *any exposure*, no matter how trivial. Again, the issue is not the presence of particular chemicals, but the magnitude of exposure.
- **Discounting the evidence that ENDS do help smokers quit.** The WHO paper does not properly assess the role that ENDS play in quitting smoking and uncritically repeats several methodological errors found in the literature. Taking the totality of evidence including controlled trials, observational studies, changes in population smoking and ENDS use, the experience of nicotine replacement therapy, and widely reported user experience, there is confidence that ENDS are helping many smokers to quit smoking and not having negative effects like renormalising smoking, reducing quit rates or creating gateway effects.
- **ENDS marketing can be anti-smoking advertising.** The clear majority of ENDS marketing is truthful promotion of a low-risk alternative to smoking. The evidence cited by WHO has been misrepresented and does not make the case for any systematic malpractice by ENDS vendors. However, the WHO paper overlooks that most fundamental point, which is that ENDS marketing is promoting an *alternative to smoking* and may therefore be promoting desirable changes in smoking behaviour. It may also reach people who do not engage with conventional stop-smoking interventions.
- **Flavours are essential to the appeal of ENDS as alternative to smoking.** The section on ‘product characteristics’ attempts to demonstrate a problem with flavours appealing to

¹ The WHO report refers to ENDS and ENNDS, recognising that not all electronic cigarettes contain nicotine. This is correct, but for ease of reading in our *responses* to the WHO report we use the single acronym ENDS, unless we wish specifically to make the distinction between the product categories which we will then make clear.

teenagers. In fact, flavours are integral to the appeal of ENDS to adults as an alternative to smoking. The citations are selective and findings misinterpreted and do not support this claim. Several citations simply reflect opinions or speculation, while important studies have been overlooked. These do not show that any interest amongst teenagers in ENDS flavours is resulting in regular use of ENDS in this age group.

- **Mischaracterisation of the ENDS market and role of tobacco transnationals.** The WHO paper misinterprets the ENDS market, makes misleading and unreferenced statements about the role of transnational tobacco companies in the market and is not grounded in an understanding of how competitive markets function. The WHO report fails to acknowledge the threat of disruptive technology such as ENDS to the commercial viability of the traditional cigarette business. Ironically, the published papers cited in the report point out how regulations, such as those favoured by WHO, actually help the cigarette trade. WHO should be aware of the danger that its policy proposals may provide the traditional tobacco industry with a twin advantage: (1) slowing down the disruption of the cigarette market by ENDS; (2) shaping the ENDS market to suit the ENDS business model favoured by the tobacco industry.
- **Unjustified support for ENDS prohibition.** In the discussion of policy options, the opening paragraph for each policy set implicitly endorses ENDS prohibition. It does this by stating that *“Parties that have not banned the importation, sale, and distribution of ENDS/ENNDs may consider the following options”*. Prohibition is one regulatory option among many that ought to be discussed on its own merits, not taken as a default. The merits of prohibition are exceedingly poor given the pervasive availability of cigarettes in all jurisdictions. WHO should not be endorsing prohibitions, explicitly or implicitly. It is unethical to deny smokers much lower risk options than cigarettes, and there is no scientific support for ENDS prohibition as a public health intervention. The WHO’s framing suggests that a prohibition is something for Parties to progress towards and should not be undone once done. In fact, it is a policy that should be reversed.
- **Policy proposals made with no supporting policy analysis.** Numerous policies are proposed without any supporting evidence for their effectiveness or cost-effectiveness. Any policy proposal should be subject to evidence-based justification, options appraisal and analysis of trade-offs or distributional effects, and impact assessment. Policies should be tested for proportionality and possible unintended consequences. The WHO has not applied any policy-making disciplines to its menu of proposed policy options.
- **No assessment of unintended consequences.** There is no recognition of the likelihood of ‘unintended consequences’ arising from the policies proposed in the WHO paper. However, it is very likely that some of the proposed policies would have the effect of *increasing* smoking. The Royal College of Physicians explains this in its 2016 *Nicotine without Smoke* report² as follows:

“A risk-averse, precautionary approach to e-cigarette regulation can be proposed as a means of minimising the risk of avoidable harm, e.g. exposure to toxins in e-cigarette vapour, renormalisation, gateway progression to smoking, or other real or potential risks. However, if this approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.” (Section 12.10 page 187)

Almost every policy listed in the WHO’s paper could easily have the effect of protecting the incumbent cigarette trade, promoting smoking rather than vaping, and lead to increases in

² Tobacco Advisory Group of the Royal College of Physicians: *Nicotine without smoke - tobacco harm reduction*. RCP 2016. <https://www.rcplondon.ac.uk/file/3563/download?token=uV0R0Twz>

non-communicable diseases. It is very likely that widespread uptake of WHO's policy proposal would 'reduce harm reduction' and therefore increase harm.

- **Transparency and quality.** The WHO report has been made available without the four supporting papers upon which it is supposed to be based. These papers are still undergoing revision during peer review. This is poor scientific practice and does not provide a reliable basis for policy advice.

COMMENTARY ON WHO REPORT ON ELECTRONIC NICOTINE DELIVERY SYSTEMS AND ELECTRONIC NON-NICOTINE DELIVERY SYSTEMS (ENDS)

The Seventh Conference of the Parties (COP-7) of the Framework Convention on Tobacco Control (FCTC), to be held in Delhi between the 7th and 12th of November 2016, will discuss and formulate future policy on the role of Electronic Nicotine Delivery Systems (ENDS; also known as electronic cigarettes or e-cigarettes) and Electronic Non-Nicotine Delivery Systems (ENNDS) in tobacco control. In preparation for this discussion, and in response to a request made by the COP at its 6th session (COP-6) in Moscow in 2014, the World Health Organisation (WHO) has prepared a report providing updates on evidence of the health impacts of ENDS/ENNDS; on their potential role in smoking cessation and tobacco control; and on policy options to achieve objectives set at COP-6 [1].

In our view, the WHO report [1] succeeds in identifying a range of areas of uncertainty over the potential benefits and risks of ENDS to effective tobacco control policy. However, by doing so from a position of emphasis on the risks and disadvantages of these products which disregards their potential to reduce consumption of smoked tobacco, the report fails to deliver the equipoise required for dispassionate formulation of public health policy. The report also contains factual errors and misinterpretations of evidence available in the public domain; and refers at its outset to four reports, including two systematic reviews, commissioned by the WHO but as yet unpublished and hence unavailable for scrutiny.

We present this commentary on the WHO document in an attempt to provide corrections to the factual errors and misconceptions in the report, and to present some of the arguments suggesting that the availability of ENDS offers an opportunity to prevent some of the otherwise inevitable burden of premature death and disability caused by the global tobacco epidemic. We do using the sequence of headings in the WHO report, with reference to the headings and individual paragraphs (reproduced in italics) of the WHO document.

1. INTRODUCTION

Original text:

1

1. *This document was prepared in response to the request made by the Conference of the Parties (COP) at its sixth session (Moscow, Russian Federation, 13-18 October 2014) to the Convention Secretariat to invite WHO to: (a) prepare a report on Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS) for the seventh session of the COP (COP7), covering updates on the evidence of the health impact of ENDS/ENNDS, their potential role in tobacco cessation and impact on tobacco control efforts; (b) subsequently assess policy options to achieve the objectives outlined in paragraph 2 of decision FCTC/COP6(9); and (c) consider the methods to measure the contents and emissions of these products. Following the terminology approved by COP, this report differentiates between ENDS and ENNDS depending on whether or not the heated solution delivered as an aerosol by the device contains nicotine.*

2. *This report incorporates the December 2015 deliberations and scientific recommendations on ENDS/ENNDS by the WHO Study Group on Tobacco Product Regulation (TobReg) at its*

2

eighth meeting (Rio de Janeiro, Brazil, 9-11 December 2015) , the May 2016 informal consultation on policy options held in Panama (4-5 May 2016, Panama City, Panama) and

four background papers commissioned by WHO . This report does not consider methods to measure the contents and emissions of ENDS/ENNDS. All appendices to this report can be found on the WHO website

Response:

1.1 The policy options outlined in paragraph 2 of the decision made by the Conference of the Parties in 2014 at COP 6 - FCTC/COP6(9) [2] were to:

- (a) prevent the initiation of ENDS/ENNDS by non-smokers and youth with special attention to vulnerable groups;
- (b) minimise as far as possible potential health risks to ENDS/ENNDS users and protect non-users from exposure to their emissions;
- (c) prevent unproven health claims from being made about ENDS/ENNDS; and
- (d) protect tobacco-control activities from all commercial and other vested interests related to ENDS/ENNDS, including interests of the tobacco industry

1.2 The objective of the Framework Convention on Tobacco Control (FCTC), stated in Article 3, is:

“to protect present and future generations from the devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke by providing a framework for tobacco control measures to be implemented by the Parties at the national, regional and international levels in order to reduce continually and substantially the prevalence of tobacco use and exposure to tobacco smoke” [3].

The guiding principles specified in Article 4 refer to the need to take measures to “*protect all persons from exposure to tobacco smoke*”, and *to prevent the initiation, to promote and support cessation, and to decrease the consumption of tobacco products in any form*”.

1.3 The FCTC also states (Article 1d) that: “tobacco control means a range of supply, demand and **harm reduction** [our emphasis] strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco”.

1.4 The objective of the FCTC is thus explicitly and exclusively the prevention of tobacco use, and in particular, tobacco smoking. Preventing and treating nicotine addiction are included in the FCTC as secondary objectives, as a means to prevent smoking [3], and indeed nicotine replacement therapy (NRT) has for years been the pharmaceutical product most widely used to treat tobacco dependence. The logic underpinning this approach is that while nicotine addiction plays a fundamental role in sustaining tobacco smoking, nicotine itself accounts for little if any of the harm from smoking [4, 5]; and therefore that use of NRT as a substitute for tobacco as a source of nicotine enables smokers first to stop using tobacco smoke to obtain nicotine, and then in due course to reduce or completely quit all nicotine use. It is now recognised that smokers who switch completely to a medicinal nicotine product but continue long-term nicotine use achieve similar health benefits to those who quit all nicotine use [4, 5].

1.5 ENDS are not tobacco products: they are nicotine delivery devices, and nicotine delivery devices help smokers to quit smoking. The evidence on the efficacy of nicotine in this indication is of sufficient strength that in recent guidance on medicines licensing for nicotine products, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) requires only data demonstrating bioequivalence with an established NRT product as evidence of clinical efficacy [6]. Any nicotine product, including ENDS, that delivers nicotine in sufficient doses to match the blood levels achieved by conventional NRT is thus deemed to be effective as a smoking cessation therapy [6].

1.6 Smoking is highly addictive, and lethal. Half of all people who smoke throughout their adult life are killed prematurely by smoking [7]; and with an estimated 967 million current smokers in the world in 2012 [8], half a billion people alive today will be killed prematurely by smoking, unless they quit. Since smokers lose approximately one day of life for every four days of smoking after the age of about 35 [7, 9], quitting smoking as quickly as possible is a vital health priority. In addition, as smoking by parents and siblings is a strong cause of smoking initiation among children [10], therefore helping today's smokers to quit also helps to prevent perpetuation of smoking in future generations. Conventional approaches to tobacco control, as articulated in the FCTC, emphasise measures that discourage uptake of smoking, and motivate smokers to try to quit; and these measures are being adopted increasingly widely around the world. However, as means of support for smokers trying to quit, the FCTC relies on traditional medical service models which are well known to be effective, but achieve low population reach even in countries sufficiently wealthy to provide them. ENDS offer the potential to broaden that population reach, by offering a consumer alternative to the cigarette as a means of consuming nicotine that is affordable, effective, and socially acceptable. It is important that policy on ENDS recognises this potential to deliver significant public health benefits, while also identifying and managing any likely risks. In our view the present WHO report [1] fails to recognise this potential, and fails to acknowledge the role that ENDS could play in the harm reduction approach endorsed by the FCTC.

2. ENDS PRODUCTS

Original text:

3. *All ENDS/ENNDS heat a solution (e-liquid) to create an aerosol which frequently contains flavourants, usually dissolved into Propylene Glycol or/and Glycerin. All ENDS (but not ENNDS) contain nicotine. Although generally considered a single product class, these products constitute a diverse group with potentially significant differences in the production of toxicants and delivery of nicotine. There are several coexisting types of devices on the market: first-generation or so-called cigalikes, second-generation tank systems and even larger third-generation or personal vaporizers. Others classify these devices into closed and open systems depending mainly on the degree of control that users have over the e-liquid used and the voltage and resistance applied to heating the e-liquid and ventilation features.*
4. *The choice of e-liquid, the user's puffing style and the device's capacity to aerosolize the e-liquid at increasing temperatures by modulating its wattage and resistance will all determine whether the use of ENDS/ENNDS produces a satisfactory experience to the user in terms of the speedy delivery of sufficient nicotine to mimic the sensory feel of smoking.*

Response:

2.1 We agree that ENDS are a heterogeneous range of products rather than a single product class, and it is important that product characteristics are considered when interpreting evidence on the effectiveness of these products as smoking substitutes, and evidence on emissions. It is well recognised that early or first generation ENDS delivered little (if any) nicotine to the user [11], and hence are typically much less effective as a smoking substitute than second and third generation devices. First generation devices are however cheaper to purchase, and have been available more widely and for longer than second and third generation devices, and hence have tended to be the first product tried by smokers in many countries [12]. Since nicotine delivery from these devices can be poor, they are often tried and abandoned by smokers, who then relapse to smoking. In the UK, however, it is clear that sustained users of ENDS tend to migrate to second and third generation devices [13] to achieve more effective nicotine substitution, and hence sustain abstinence from smoking. It is important to recognise that much of the available

evidence on ENDS is derived from early generation products, and therefore not representative of the more effective products now available on the market, and generally preferred by current and former smokers.

3. POTENTIAL ROLE OF ENDS IN TOBACCO CONTROL

Original text:

5. *If the great majority of tobacco smokers who are unable or unwilling to quit would switch without delay to using an alternative source of nicotine with lower health risks, and eventually stop using it, this would represent a significant contemporary public health achievement. This would only be the case if the recruitment of minors and non-smokers into the nicotine-dependent population is no higher than it is for smoking, and eventually decreases to zero. Whether ENDS/ENNDS can do this job is still a subject of debate between those who want their use to be swiftly encouraged and endorsed on the basis of available evidence, and others who urge caution given the existing scientific uncertainties as well as the performance variability of products and the diversity of user behaviour.*

Response:

3.1 The report acknowledges that widespread switching to alternative sources of nicotine, and in due course quitting all nicotine, would be a significant contemporary public health achievement, but with the caveat that this applies only if recruitment of new nicotine users does not exceed that of smoking and eventually decreases to zero. In practice however, use of nicotine (as distinct from tobacco) by adults causes few if any health problems, so even a high prevalence of nicotine use would generate substantial benefits to public health if accompanied by appreciable reductions in smoking prevalence [14]. Similarly, the proviso that recruitment of new nicotine users should not exceed that of smoking is inappropriate since, whilst undesirable, becoming addicted to nicotine *per se* represents a health hazard of negligible proportion relative to that of tobacco smoking. If, theoretically, smoking was eradicated at the cost of 100% population addiction and use of medicinal grade nicotine, public health would still gain substantially as a result [14]. Levy et al estimate that 80% of otherwise non-smokers would be required to experiment seriously with products such as ENDS if ENDS are 5% as hazardous as tobacco cigarettes; and 30% of otherwise non-smokers would be required to experiment seriously with ENDS to generate overall public health harm if ENDS are 25% as harmful as tobacco [15]. So, depending on the hazard of ENDS relative to tobacco, substantial use among people who would never otherwise have used nicotine is still compatible with overall health gain. That is not intended as an endorsement of nicotine use, but to emphasise that the benefits of reductions in smoking matter for public health far more than detriments arising from increases in nicotine use.

3.2 Paragraph 5 then presents the role of ENDS in tobacco harm reduction and public health as a question of debate, when in fact there is now increasing recognition that the potential benefits of ENDS far outweigh their disadvantages. In the UK, for example, a strong consensus has now formed among health organisations in favour of promoting the use of ENDS to reduce the prevalence of smoking [16]. This position is supported by trends in UK prevalence of ENDS and tobacco use: by the second quarter of 2016 ENDS were being used on a daily basis by around 13% of smokers (equivalent to over 1 million people) [17], and the rise in ENDS use has coincided with steady decline in smoking prevalence which has been particularly marked (and statistically significant) between 2014 and 2015 [18]. Observational data on the association between ENDS use and quitting smoking indicate that, although smokers using ENDS are less likely to quit smoking than if using medical services combining behavioural support and pharmacotherapy, this lower efficacy is almost certainly offset by the greater uptake (reach) of ENDS [5]. That the recent

marked fall in UK smoking prevalence has occurred in a period in which investment in mass media campaigns has been low [19], and provision of medical services to help smokers quit undermined by service reorganisation [20], suggests that ENDS use may have made a significant contribution to the decline in UK smoking prevalence.

3.3 Paragraph 5 does not address the relative effectiveness of other tobacco control policies in promoting smoking cessation, as opposed to preventing smoking uptake. An analysis of smoking rates within birth cohorts in the UK demonstrates clearly that the substantial decline in smoking prevalence achieved in the UK over recent decades by the implementation of highly comprehensive tobacco control policies [21] has been achieved primarily by preventing uptake of smoking among young people, while cessation rates among established smokers have shown little if any improvement over time [21]. This finding highlights the need for new policies and approaches to help established smokers to quit. ENDS are the first new consumer technology to emerge in this respect since the development of NRT four decades ago; and their popularity with smokers demonstrates their potential as a significant complement to more conventional and established tobacco control approaches.

4. ENDS MARKET SIZE

Original text:

6. *The global market for ENDS/ENNDS in 2015 was estimated at almost US \$10 billion. About 56% was accounted for by the United States of America and 12% by the United Kingdom. Another 21% of the market was divided between China, France, Germany, Italy and Poland (3-5% each). It is unclear whether the sales of ENDS/ENNDS will continue to increase. In addition, the market may change since the tobacco industry has launched alternative nicotine delivery systems that heat but do not burn tobacco, and is developing or has bought nicotine inhaler technology that does not require a heating mechanism.*

Response:

4.1 We agree that the global market in ENDS has grown rapidly, and that technological development and product innovation in both ENDS and alternative nicotine devices will generate further growth. Since growth in sales of these products to date has been almost exclusively attributable to use by smokers, in many cases as a means to quit smoking, this is a good thing. However, the ENDS product range is itself evolving rapidly, generating more effective and cleaner systems, and with technological development and product innovation. Quality standards are being developed and implemented by manufacturers [22]. It is likely therefore that, in absence of restriction through inappropriate regulation or misinformation, sales will continue to grow. The emergence of other novel nicotine delivery devices such as nicotine inhalers is likely to generate further growth, as are the heat-not-burn products in development by the tobacco industry. The emergence of medicinally licensed products, of which at least two exist in the UK, will add further growth by providing clinicians with ENDS and alternatives that can be prescribed as part of clinical care. We therefore welcome this growth in the market for ENDS and related products, as it reflects the generation of an increasing range of consumer and medical products providing smokers with less harmful nicotine delivery devices as an alternative to tobacco.

5. HEALTH RISKS OF EXCLUSIVE ENDS USE

Original text:

7. *The typical use of unadulterated ENDS/ENNDS produces aerosol that ordinarily includes glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbon*

(PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles and other elements. Dicarbonyls (glyoxal, methylglyoxal, diacetyl) and hydroxycarbonyls (acetol) also are thought to be important compounds in the aerosol. Many of these substances are toxicants that have known health effects resulting in a range of significant pathological changes.

8. The number and level of known toxicants generated by the typical use of unadulterated ENDS/ENNDS is on average lower or much lower than in cigarette smoke, with a few new toxicants specific to ENDS such as glyoxal. However, the levels of toxicants can vary enormously across and within brands and sometimes reach higher levels than in tobacco smoke. This is probably due, among other things, to the increased thermal decomposition of e-liquid ingredients with rising applied temperatures in open system devices. A number of metals - including lead, chromium, and nickel and formaldehyde - have been found in the aerosol of some ENDS/ENNDS at concentrations equal to or greater than traditional cigarettes under normal experimental conditions of use.
9. ENDS aerosol contains nicotine, the addictive component of tobacco products. In addition to dependence, nicotine can have adverse effects on the development of the foetus during pregnancy and may contribute to cardiovascular disease. Although nicotine itself is not a carcinogen, it may function as a “tumour promoter” and seems to be involved in the biology of malignant diseases, as well as of neurodegeneration. Foetal and adolescent nicotine exposure may have long-term consequences for brain development, potentially leading to learning and anxiety disorders. The evidence is sufficient to warn children and adolescents, pregnant women, and women of reproductive age against ENDS use and nicotine.
10. Close to 8,000 e-liquid unique flavours have been reported. The health effects of heated and inhaled flavourants used in the e-liquids have not been well studied. Heated and inhaled popcorn, cinnamon and cherry flavourants are potentially hazardous, with the limited literature on the topic indicating that most flavourants may pose appreciable health risks from long-term use, especially those that are sweet. Many are irritants which may increase airway inflammation; some are more cytotoxic than unflavoured aerosol although less so than tobacco smoke, or increase the susceptibility of airway cells to viral infection after direct contact with e-liquid, although the relevance of direct effects of contact with e-liquid, as opposed to aerosol, is unclear.
11. Based mostly on the levels and number of toxicants produced during the typical use of unadulterated ENDS/ENNDS made with pharmaceutical-grade ingredients, it is very likely that ENDS/ENNDS are less toxic than cigarette smoke. However, ENDS/ENNDS are unlikely to be harmless, and long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer, and possibly cardiovascular disease as well as some other diseases also associated with smoking. The magnitude of these risks is likely to be smaller than from tobacco smoke, although there is not enough research to quantify the relative risk of ENDS/ENNDS over combustible products. Therefore, no specific figure about how much “safer” the use of these products is compared to smoking can be given any scientific credibility at this time. Existing modelling studies indicate, however, that in order for there to be a potential population-wide net health benefit from ENDS/ENNDS at present usage rates, these products would need to be at least three times “safer” than cigarettes.
12. There is an urgent need to elucidate the range of relative risks when using the diverse ENDS/ENNDS devices and e-liquids, and about user behaviour compared to smoking and use of other nicotine products, recognizing that:
 - a. complex mixtures, such as in ENDS liquids and aerosol, have the potential for toxicological effects even if toxicants are at low or very low concentrations;

- b. predicting adverse health effects of these complex mixtures solely on the basis of aerosol composition might prove futile without solid evidence from the coordinated use of chemical, in vitro, clinical and epidemiological methods; and that*
- c. simple comparisons of toxicant levels in ENDS/ENNDS aerosol to the high levels in tobacco smoke, as advocated by the tobacco industry, may be of little value given the absence of science on safe tolerance limits for smoke constituents or their specific effects on the multiple diseases caused by smoking.*

5.1 This section places a strong emphasis on potential risks of ENDS use without balance or context from comparison with the health risks of tobacco smoke. Thus, whilst the text acknowledges that aerosol emissions from ENDS have much reduced levels and number of toxicants compared to cigarette smoke, disproportionate concern about their absolute harm is conveyed with little or no consideration for the notion of relative risk, either in relation to no use of ENDS, or in relation to smoking.

5.2 In paragraph 7, a list of substances detected in ENDS aerosol emissions is presented, with an assertion that many of these have known health effects and cause a range of significant pathological changes. A basic premise of toxicology is that risk is a function both of the hazardousness of the substance and the exposure to it. Simply listing substances detected in ENDS emissions is, therefore, only part of the process of assessing hazard. It is also essential to look at the levels of exposure generated, both in relation to occupational or other relevant exposure limits, and in relation to tobacco smoke, to give a sense of the magnitude of any risk to health from these exposures, and their hazard to smokers in relation to continued or future tobacco smoking.

5.2.1 Paragraph 7 highlights the presence of propylene glycol in the vapour. Propylene glycol is recognized as safe for human consumption by ingestion [23] and is widely used in foods, cosmetics and pharmaceuticals [23]. In animal studies, exposure to propylene glycol vapour has not been found to cause damage to lung tissues or to have other serious adverse effects [24-27]. A study of the effects of exposure to aviation de-icing aerosol (composed mainly of non-pharmaceutical grade propylene glycol) on 27 healthy volunteers [28] did not show any reduction in lung function. Other findings from this study included self-reported sensations of sore and dry eyes, throat dryness, and cough; and a decrease of tear film stability, which is likely to be related to the humectant effects of propylene glycol. Participants in this study were exposed for 1 minute to mean propylene glycol concentrations of 360 mg/m³, which is more than 3 orders of magnitude higher than the ambient level of propylene glycol (203.6) µg/m³ observed in a study in which 3 participants used ENDS ad lib for 1 hour in a small room [29]. Propylene glycol used in de-icing facilities is of industrial grade [30], and hence less pure than the pharmaceutical grade propylene glycol used in most ENDS. These irritant symptoms are transient and disappear spontaneously over a short period of time [31]. The question of whether such an acute irritation could translate into clinically meaningful lung disease remains unanswered, but there certainly is no evidence to suggest that this is an indication of clinically significant adverse lung effects. Inhaled propylene glycol is thus unlikely to represent a significant hazard to health.

5.2.2 In addition to propylene glycol, analysis of ENDS vapour has detected water, ethylene glycol or glycerine, nicotine and various other chemicals including low levels of formaldehyde, acetaldehyde, acrolein, volatile organic compounds (VOC) and tobacco specific nitrosamines [32]. However the levels of many of these substances are extremely low, ranging between 9 and 450 times lower than those in smoke from conventional cigarettes [32], indicating (though not necessarily guaranteeing) a much lower level of risk. ENDS vapour contains aldehydes (carbonyl compounds) generated through oxidation of e-liquids during heating and vapourisation, to an extent depending on the power levels (i.e. wattage) of the device and on the e-liquid used [33]. Yet as with other chemicals in

vapour, their concentration is between 13 and 807 times lower than those found in tobacco smoke [34]. One study which demonstrated extremely high levels of formaldehyde in ENDS vapour [35] used voltage and heating levels which in practice generate what is known colloquially as a 'dry puff', which is aversive and hence avoided by ENDS users [36]. Although reported to contain a range of metals including cadmium, nickel and lead [32, 37], levels of these metals in ENDS vapour are substantially below permitted levels for daily occupational exposure, and below permissible daily exposure from inhalation medications, and are therefore unlikely to have significant adverse health effects [38]. The presence of potential toxins in ENDS at very low levels does not necessarily preclude safe use in humans: for example, medicinally licensed NRT products contain known carcinogens (TSNAs) [31], but at levels considered negligible to health. The presence of TSNAs in NRT is not used as justification to question their safety or role in public health, since trace levels of impurity are inevitable, but not necessarily hazardous.

5.2.3 These much lower levels of toxins in ENDS vapour become evident in studies of smokers who switch completely to ENDS use, and in whom significant reductions in exposure to volatile organic compounds, nitrosamines and carbon monoxide have been documented along with improved self-reported health [39]. Switching to ENDS while abstaining from smoking has also been shown to normalise lung function and improve respiratory symptoms [40], and to contribute to a reduction in blood pressure in smokers with elevated systolic blood pressure [41].

5.3 Paragraph 9 states that nicotine can have adverse effects on foetal development, may contribute to cardiovascular disease, and may function as a tumour promoter. However, it is important to acknowledge that the effects of nicotine alone are likely to be substantially less than those of continued tobacco smoking; it also remains far from certain that the reported adverse effects of nicotine do translate into significant morbidity or mortality.

5.4.1 Evidence reviews of harm to the developing foetus cited in paragraph 9 refer almost exclusively to animal studies [42, 43] and hence are of questionable validity to human development. The citation to a study demonstrating harm to the human foetus *in vivo* refers to cognitive changes arising from attempts to quit smoking, not developmental change [44], whilst other human study data suggesting increased risks of cognitive impairment, ADHD and other mental health problems in children of mothers who smoke reflect the effects of tobacco smoking, and the multiple confounders involved with smoking, rather than nicotine alone [45-47]. The extent of any adverse effect of nicotine exposure *in utero* or during adolescence in humans, therefore, remain uncertain [5,48]. A recent Cochrane review suggests that use of medicinal nicotine by pregnant women who smoke has no negative effects on birth outcomes [49]; and a randomised trial of use of nicotine in pregnancy has demonstrated that children born to smokers who used NRT during pregnancy were more likely to have healthy developmental outcomes than children of smokers who received a placebo [50]. Paragraph 9 concludes that the evidence is sufficient to warn children and adolescents, pregnant women and women of reproductive age against using ENDS and nicotine, and we agree that it is prudent to warn all non-smoking pregnant women and young people to avoid all nicotine use. However those who are already smokers would be well advised to use ENDS instead of tobacco, while young people who elect, against this advice, to begin to experiment with nicotine would be best advised to experiment with ENDS rather than tobacco. A wide coalition of UK health organisations has recently endorsed the use of ENDS as a substitute for smoking in pregnancy [51].

5.4.2 Whilst experimental models may provide data suggesting that nicotine has actions that could promote or accelerate cardiovascular disease, evidence on NRT use in man demonstrates that in practice these concerns do not translate into an increased risk of disease [4, 52, 53]. Experimental studies in rodents have demonstrated that exposure to

nicotine can increase the growth of experimental tumours [54], but the nicotine doses involved are extremely high and the relevance of these experimental models to human cancer is far from clear. Evidence from studies of long-term use of NRTs in man have confirmed no evidence that nicotine causes cancer [4, 55]; the International Agency for Research on Cancer (IACR) has not classified nicotine as carcinogen [56]; and a recent substantive review concluded that there is '*inadequate evidence to conclude that nicotine per se does or does not cause or modulate carcinogenesis in humans*' [57]. Consequently, there is no evidence that exposure to the nicotine levels sustained by ENDS users causes or promotes cancer.

5.5 Flavours are used widely in ENDS liquids. Many of the flavours used are known to be safe when ingested, but this is not necessarily the case when heated and inhaled. *In vitro* studies indicate that there is wide variation in the cellular toxicity of the various flavours, and that toxicity varies greatly by the product type used [58]. We agree with the statement in paragraph 10 that the health effects of these additives are not well defined, and we recognise grounds for concern that inhalation of some compounds found in flavoured vapour may pose appreciable health risks, and particularly for lung disease. The 2016 report by the Royal College of Physicians reviewed the available evidence on carcinogens, oxidants and other toxins detected in e-cigarette vapour and concluded that their presence may increase the risks of lung cancer, COPD, cardiovascular and other smoking-related diseases, but that the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms [5]. The report also pointed out that these risks arise primarily from contaminants and components generated by vaporisation, which should be amenable to reduction through technological and purity improvements [5].

5.6 Paragraph 11 acknowledges that ENDS are likely to be less hazardous than cigarettes, but argues that no quantitative estimate of this difference currently has scientific credibility. We agree that precise quantification is difficult, and highly dependent on product and e-liquid constituent characteristics, but disagree that the likely order of magnitude cannot be estimated. Given that nicotine itself accounts for little if any of the health effects of tobacco use, and that use of NRT has not been found to be associated with significant long term health harms, the hazards of ENDS use arise entirely from other constituents of vapour: and the range of constituents, and the concentrations of almost all of them, are far less than those generated by combustion of tobacco. Both Public Health England and the Royal College of Physicians have reviewed the evidence on the likely magnitude of the risk to health posed by ENDS and reached very similar conclusions: Public Health England estimated the risk at 5% of that of tobacco smoking, and the Royal College of Physicians that the risk was unlikely to exceed 5% [5, 59]. As ENDS quality standards are implemented, this relative risk may fall.

5.6.1 Whatever the true extent of the reduction in risk realised by smokers who switch to ENDS, it is important that public health messages are consistent in emphasising the reduced risk of ENDS relative to tobacco. In Britain, only 15% of adults correctly think that ENDS are a lot less harmful than smoking, while 25% believe they are as harmful or more harmful [13]. In the United States, only 5.3% of adults think, correctly, that ENDS are very much less harmful than smoking, while 37.5% think incorrectly that there is no difference in risk or that e-cigarettes are more harmful [60].

5.6.2 The danger of such misperceptions is that smokers will not appreciate the benefits of switching and so continue to smoke. If physicians or public health practitioners do not understand relative risks then there is a danger that they will give poor advice and do harm as a result. To address this problem of misperception of risk, the Royal College of Physicians proposes the following carefully worded statement that reflects a degree of uncertainty, but aims to align risk perceptions more closely to the current understanding of science:

"Although it is not possible to precisely quantify the long-term health risks associated with e-cigarettes, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure".

(Section 5.5 page 87)

We believe this remains the best most realistic formulation at present, and that it errs on the side of caution.

5.6.3 Paragraph 11 goes on to assert that modelling studies suggest that a relative hazard three times lower than that of tobacco is necessary to achieve a net population benefit. This is not true. Levy et al (cited in paragraph 11 as evidence supporting this statement) actually conclude that:

"a large proportion of VNP initiation leading directly to more cigarette smoking by otherwise never smokers or an increase in the magnitude of harms from VNPs relative to cigarettes (or both) would be required before a tipping point is reached where harms begin to exceed benefits at the population level" [15].

Professor Levy has expressed concern about his work being used by WHO in this way. He states:

"I am troubled by the WHO statement that my model indicates "for there to be a potential population-wide net health benefit from ENDS/ENNDS at present usage rates, these products would need to be at least three times "safer" than cigarettes." My model only looked at a single cohort at an age where individuals were likely to initiate smoking and did not consider smokers in later cohorts where e-cigarettes have the potential to increase cessation from cigarettes. Consequently, additional benefits may accrue when including e-cigarette use by later cohorts. Further, I did not consider e-cigarette risks at 1/3 the risk of cigarettes, because I do not consider that such a high level of risk is plausible given current evidence".

The Kalkhoran study [61] does model relative risks of ENDS relative to smoking of 0.25 and 0.5. However the estimates of costs to society in this study are highly dependent on numerous assumptions made about effects of ENDS on smoking, for which no supporting evidence is presented. The risk threshold of 'at least three times safer' in paragraph 11 thus has no validity and rests on misunderstandings of these modelling papers.

5.7 We agree with the statement in paragraph 12 that it is important to elucidate the risks of ENDS, and that comparisons only with tobacco smoke are insufficient. Comparisons with tobacco smoke elucidate the risk of ENDS relative to smoking; whilst comparisons with ambient air, and context from safe occupational exposure limits, elucidate risks relative to non-use. Both are necessary to the estimation of population harm from ENDS use, and demonstrate that while not free from hazard, ENDS are substantially less hazardous than tobacco cigarettes [62].

6. HEALTH RISKS TO BYSTANDERS FROM EXPOSURE TO EXHALED AEROSOL FROM ENDS USERS

Original text:

13. *A recent systematic review of the health risks from passive exposure to exhaled aerosol from ENDS/ENNDS users - or second-hand aerosol (SHA) - concluded that "the absolute impact from passive exposure to electronic cigarette vapour has the potential to lead to adverse health effects." A WHO-commissioned review found that while there are a limited*

number of studies in this area, it can be concluded that SHA is a new air contamination source for particulate matter, which includes fine and ultrafine particles, as well as 1,2-propanediol, some VOCs, some heavy metals, and nicotine.

14. *The levels of some metals such as nickel and chromium are higher in SHA from ENDS than in second-hand smoke (SHS) and certainly background air. Compared to air background levels, PM 1.0 and PM 2.5 in SHA are between 14 and 40 times, and between 6 and 86 times higher respectively. In addition, nicotine in SHA has been found between 10 and 115 times higher than in background air levels, acetaldehyde between two and eight times higher, and formaldehyde about 20% higher. Except for heavy metals, these compounds are generally found at lower concentrations than those found in SHS. At present, the magnitude of health risks from higher than background levels of these compounds and elements are empirically unknown.*
15. *While some argue that exposure to SHA is unlikely to cause significant health risks, they concede that SHA can be deleterious to bystanders with some respiratory pre-conditions. It is nevertheless reasonable to assume that the increased concentration of toxicants from SHA over background levels poses an increased risk for the health of all bystanders.*

Response:

6.1 Paragraphs 13 and 14 conclude that second-hand aerosol is a new source of air contamination with a range of particles and substances, including fine and ultrafine particles, 1,2-propanediol, some VOCs, some heavy metals, and nicotine. The systematic review cited in the WHO report [63] did not identify actual health risks because it referred primarily to the presence of, and not the level of exposure to, constituents of vapour. Any risk assessment analysis requires, by definition, the evaluation of exposure levels before determining any potential health effects.

6.2 Emission of fine and ultrafine particles has been cited as evidence of environmental contamination by ENDS. Compared to background levels in air, PM_{1.0} and PM_{2.5} in SHA are between 14 and 40 times, and between 6 and 86 times higher respectively [64]. However, more than 99.9% of this aerosol, if generated from glycerol-based liquids, is composed of glycerol and water, and 0.05% composed of nicotine [64]. This particulate matter is unlikely to represent a significant risk to health.

6.3 Levels of nicotine in ambient air in a room where ENDS vapour is being generated have been estimated at between 0.6 and 4.6 µg/m³ with a third generation ENDS device [65], and at 0.82 to 6.23 µg/m³ when generated by a machine [66]; this latter study probably overestimates nicotine emissions since the absorption of nicotine when a person inhales is not taken into consideration. Average salivary cotinine levels in non-smokers exposed to ENDS users at home for at least 2 hours per day have been recorded in one study to be extremely low, at 0.19 ng/ml, though higher than those (0.07 ng/ml) observed in unexposed control subjects [67]. This compares to levels of about 300 ng/mL in users of ENDS and in smokers [68].

6.4 Total carbonyls in exhaled air from ENDS have been shown to be similar to those in control exhaled breaths or room air blanks [64]. On the contrary, tobacco smoking led to a significant increase in exhaled carbonyl levels [64]. The presence of carbonyls is normal in exhaled breath and in room air, reflecting the pervasive nature of carbonyls in indoor environments [69, 70].

6.5 Metal emissions are expected to be generated by the heating process involved in creating ENDS vapour. However in a study assaying arsenic, barium, cadmium, chromium, cobalt, copper, lead, manganese, nickel, rubidium, strontium and zinc in the aerosol of 12 ENDS products [32] only three metals (cadmium, lead and nickel) were found at levels above the limit of quantification, and in all cases at very low levels [32]. These metals were also detected in blank samples and in emissions from a pharmaceutical nicotine inhaler, raising the possibility that environmental air was the source. Another study found detectable levels of aluminium, barium,

chromium, copper, iron, lead, manganese, nickel, strontium, tin, titanium, zinc and zirconium in electronic cigarette aerosol from a first-generation ENDS product [37]. A risk assessment analysis of the findings of these two studies has estimated average daily exposure from the 13 electronic cigarette products analysed was 2.6- to 387-fold lower than US Permitted Daily Exposure (PDE) limits, 325-fold lower than Minimal Risk Levels (MRLs) and 514-fold lower than Recommended Exposure Limits (RELs) [38]. One of the 13 products was found, when used at the extreme of maximum daily use, to generate levels of cadmium exposure 10% higher than the PDE for cadmium [38]. These findings indicate that metal emissions are unlikely to represent serious health hazards.

6.6 Formaldehyde is an abundant chemical that is exhaled by healthy (non-smoking, non-vaping) humans [71]. In a study in which a smoker in an 8m³ space took six inhalations over 5 minutes from three ENDS at 15 minute intervals, a gradual increase in ambient formaldehyde levels that was not influenced by ENDS use was demonstrated [72]. Smoking a conventional cigarette in the same space then generated very high levels [72]. Estimated exposure to formaldehyde from active consumption of 600 puffs of electronic cigarette under realistic conditions is around 678 µg/day [36], around one third of the daily exposure sustained from breathing air containing formaldehyde at the WHO upper acceptable limit of 80 ppb (100 µg/m³) [73]. This results in a daily exposure of 2000 µg/day, assuming an average ventilation rate of 20 m³/day. Passive exposure of others to formaldehyde is thus expected to have negligible health effects. Similar findings apply for acetaldehyde, an endogenous metabolite detected in the exhaled breath of healthy volunteers at levels ranging from 0.2 to 0.6 nmol/l (i.e. 8.81-26.43 µg/m³) [74]. Acetaldehyde levels increase minimally relative to background levels (from 9.0 µg/m³ to 12.4 µg/m³) after ENDS use [29] and remaining well below the EU Indoor Air Quality guideline for acetaldehyde of 200 µg/m³ [75].

6.7 Paragraph 15 argues that it is '*nevertheless reasonable to assume that the increased concentration of toxicants from SHA over background levels poses an increased risk for the health of all bystanders*'. The quantitative evidence above indicates that if any health risk arising from exposure exists, it is likely to be negligible.

7. ABILITY OF ENDS TO AID SMOKERS TO QUIT SMOKING

Original text:

16. *The scientific evidence regarding the effectiveness of ENDS/ENNDS as a smoking cessation aid is scant and of low certainty, making it difficult to draw credible inferences. A 2014 review based on two randomized clinical trials (RCTs) concluded that although the analyzed ENDS had a similar, although low, efficacy for quitting smoking, the overall quality of the evidence was low. The WHO-commissioned review reached similar conclusions about the RCTs' quality of evidence and efficacy.*
17. *Longitudinal studies are more abundant and better reflect "real world" conditions of use than RCTs, but present more methodological concerns. Two reviews of these studies suggest that the use of ENDS may reduce the chances of quitting smoking. However, the evidence is of very low certainty. Although most longitudinal studies found no cessation benefit or a diminished cessation benefit associated with use of ENDS, a few studies found that the use of third generation ENDS under specific conditions of frequency of use may have cessation benefits. This needs to be further explored before reaching any final conclusions. In summary, given the scarcity and low quality of scientific evidence, it cannot be determined whether ENDS may help most smokers to quit or prevent them from doing so.*

Response:

7.1 Paragraphs 16 and 17 conclude that the evidence on the effectiveness of ENDS in helping

smokers to quit is scarce, and of low quality; and draw attention to studies suggesting that ENDS use either has little effect, or reduces, the likelihood of quitting. Paragraph 17 acknowledges that third generation devices may be more effective as cessation aids, but concludes that it cannot be determined whether ENDS help smokers to quit.

7.2 This is incorrect for several reasons. First, the UK MHRA has ruled that any product that delivers nicotine sufficiently to achieve blood levels similar to those of established Nicotine Replacement Therapy (NRT) products are effective cessation therapies. It is therefore inconceivable that ENDS that deliver nicotine in line with this ruling will be anything other than effective in this respect. We know that NRT is effective. The latest Cochrane review on this topic draws evidence from 150 trials involving over 50,000 participants and concludes that NRT use increases the likelihood of successful quitting. The effectiveness of NRT is attributable directly to the delivery of nicotine to the user. For ENDS therefore, the NRT evidence is relevant as it suggests that smokers will need to use sufficient doses of ENDS and with sufficient frequency for ENDS to be effective.

7.3 The systematic review of ENDS effectiveness cited in the WHO report [76] identified only two randomised controlled trials of ENDS in smoking cessation, and concluded that the products tested, both of which were first generation devices with poor nicotine delivery [77, 78], increased the likelihood of quitting by a ratio of 2.29, and to a similar degree to that achieved by single product NRT. This finding is thus entirely consistent with expectation. A recent update to this review [79] found no additional randomised trials, though several are currently in progress. A randomized trial that did not meet inclusion criteria for this review found that a second-generation e-cigarette substantially increased smoking cessation rates after 2 months (34% vs 0% for a control group receiving no e-cigarette) [80].

7.4 A recent review of observational studies reached a very different conclusion, that ENDS use undermines quitting [81]. This, however, was the result of an artefact of including studies that only followed smokers who were not helped by ENDS use [82], in contrast, studies that ask about the use of quitting aids at the last quit attempt show that ENDS use is associated with quitting success [83-86]. Evidence from across the European Union and within the UK indicates that large numbers of smokers have quit with the help of ENDS. Cessation rates among people using ENDS in conjunction with behavioural support provided by the English NHS Stop Smoking Services are achieving higher quit rates than those using NRT plus behavioural support [87]. A cohort study from the USA has recently demonstrated that dual users of tobacco and ENDS are more likely to quit smoking [88].

7.5 Most importantly, vaping is now starting to have population level effects. In Europe [89] and the UK [90], a large number of smokers have quit with the help of ENDS. Many would have stopped even if ENDS were not available, but changes in ENDS use have been positively associated with success rates of quit attempts [86]. The latest data from the UK show that up to now, in a population where 8.8 million people continue to smoke, some 800,000 smokers switched successfully to vaping while another 650,000 who smoked and vaped have now stopped both [91]. Policies that the WHO paper recommends would prevent such beneficial developments.

7.6 First principles, randomised trials, observational data from studies that exclude selection bias and population trend data are thus consistent in demonstrating that ENDS are effective cessation aids. There is no credible evidence that ENDS use inhibits smoking cessation.

8. ABILITY OF ENDS TO INITIATE YOUTH IN NICOTINE USE AND SMOKING

Original text:

18. WHO commissioned a review of the data on the prevalence and trends of ENDS/ENNDS use among people of 20 years of age or less. The review identified a total of 27 studies that

used probability sampling from very few countries. The age range of respondents varied across studies, as did the prevalence of ENDS/ENNDS use reported across jurisdictions. From 2013 to 2015, current use among non-smokers is around 2%, although in jurisdictions like Florida, USA and Poland it was 13% and 19%, respectively. Current use among smokers is around 17%, with Florida (44.8% in the 11-14 age range and 51.7% in the 15-18 age range) and Poland (57.4%) showing much higher prevalence.

- 19. Trend data of young people's current use of ENDS/ENNDS from probability sample surveys are only available from three countries: the USA, Poland and Italy. In Italy, current use of ENDS/ENNDS among smokers and non-smokers is very low and is not increasing. England presents a similar situation, although available trend data is not based on probability samples. The USA and Poland both show a rapid increase in the current use of ENDS/ENNDS. Use among non-smoking youth in Florida, USA and Poland has increased by a factor of five and eight respectively in three years, to reach a prevalence of 6.9% and 13% in these jurisdictions.*
- 20. The trend data show that there are two groups of countries. In one, the prevalence of ENDS/ENNDS use is low and is not increasing significantly; in the other, which includes the largest market in the world (the USA), prevalence is rapidly increasing. There is considerable debate about whether in these countries the increase in ENDS/ENNDS use among young non-smokers is a precursor to smoking. Existing longitudinal studies indicate that ENDS/ENNDS use by minors who have never smoked at least doubles their chance of starting to smoke. It is not clear whether the association of ENDS/ENNDS use and smoking is because their use leads to smoking, or because young ENDS/ENNDS users and smokers share similar social and behavioural characteristics, rendering them susceptible to the use of nicotine.*

Response:

8.1 Paragraphs 18-20 refer to studies reporting ever and current use of ENDS by children and young people included in an (as yet) unpublished review commissioned by the WHO and limited to 27 studies using probability sampling. The report is said to conclude that there are two evident patterns of use among young people in different countries: one in which use is low and stable; the other in which ENDS use is rising rapidly.

8.2 There are many more than 27 studies of the use of ENDS amongst representative samples of young people. It is not clear why the WHO authors have chosen to select only those involving probability sampling, and wrong to exclude other valid studies from discussion in this section.

8.3 We agree that experimentation with ENDS among young people is rising in some countries, but most surveys assess only 'ever use', which includes just one puff on an ENDS, ever; and 'current use', which is defined as use at least once in the past 30 days. The latter definition categorises recent experimental users as current users: the reality is, however, that most use in adolescents is experimental and short-lived. Surveys therefore need to assess whether regular use is occurring, and examine this by smoking status. In studies that have done this, the findings are consistent: they show that experimentation (ever use) among young people in some countries is common, but that use at least weekly remains low overall and is concentrated in young people who already smoke. Regular use in never smokers remains very rare in any survey that has measured this. Professor Ken Warner, writing in the American Journal of Preventive Medicine, examines data from the Monitoring the Future survey of older teenagers in American High Schools [92]. Unlike some American surveys it is possible to establish the frequency of e-cigarette use (not just recent, i.e. past 30-day use) from this survey. He identified that non-smoking high school students were extremely unlikely to ever use e-cigarettes, and amongst those that did, most had only ever used them on 1-2 of the past 30 days. Current smokers were far more likely to regularly use e-cigarettes. In addition, there is some evidence that many adolescents who use e-cigarettes use liquids that do not contain nicotine, i.e. ENDS [93].

8.4 The main area for concern is whether young people who have never smoked, and who in the absence of ENDS would not have become smokers, are becoming ENDS users; but here the evidence is very limited indeed. An analysis of UK surveys provides an illustrative example [94]. We reviewed four nationally representative cross-sectional surveys conducted in the same year, 2014, in each part of the United Kingdom [94]: a survey of youth across the UK [95], youth across Great Britain [96], young people in Scotland [97], and young people in Wales [98]. Although the age range between surveys differed slightly the findings were remarkably consistent. Around 12% of teenagers had ever tried an ENDS in that year, but a much smaller proportion (varying from 0.4% in Scotland to 2% in the UK wide survey) had used an ENDS more than monthly, and very few (1% UK, 0.7% in the Great Britain sample) more than weekly. Among teenagers who had never smoked tobacco, rates of ever trying an ENDS were also low, at between 2 and 5% [94]. Importantly, three of these surveys found no evidence at all of never smoking young people regularly using ENDS [95-97]. The fourth, a large survey in Wales of 9,055 11-16 year olds, identified just 54 never smoking young people who reported using ENDS at least monthly [98]. What these UK data show is the importance of assessing frequency of use, not just asking about experimentation at any time or experimentation recently. This is particularly important amongst never smokers. The WHO report does not acknowledge this, and does not cite the studies that include this important measurement.

8.5 Trend data on ENDS use (paragraph 19) also need to assess regular rather than experimental use, and to be interpreted in relation to trends in tobacco smoking. Data from across the US, for example, show that smoking rates are at an all-time low and that ENDS use among non-smoking youth is rare [92]. The Florida figures should be put in this overall context.

8.6 There are few longitudinal studies, but those available show an association between ever use of ENDS and smoking at follow up, though the numbers of young people in these surveys who used an ENDS but did not smoke at baseline, and who went on to become smokers, is extremely low. This association does not, however, provide evidence of a causal association between ENDS use and smoking, since the findings may arise from common liability to use of both products and the fact that the measures focus on experimentation and trial rather than regular use of either ENDS or tobacco. Existing longitudinal studies, therefore, do not provide evidence that ENDS use in young people leads to smoking. To illustrate, it is worth looking more closely at two of the four longitudinal studies cited in the WHO briefing [99, 100] (though similar points apply to the other two [101, 102]).

The first study [99] involved 2,530 14 year olds in California. None of the teenagers had tried any combustible tobacco product at baseline, but 222 had tried ENDS (with the measure being ever use). These teens were followed up one year later when one in four of the ever ENDS users had tried at least one puff of a tobacco cigarette, compared to just under one in 10 of the non-smokers who had not tried an ENDS at baseline. These numbers are very small, but more importantly the measures are very weak. Trying an END once or twice, and then trying a tobacco cigarette (the measure was a puff in the last six months) does not demonstrate that young people will become regular users of either product, and provides no evidence that the *cause* of the subsequent smoking was the prior ENDS use. The second study had a smaller sample, 694 12-26 year olds. These were all non-smokers, and just 16 had tried an ENDS (again, 'ever use'). One year later, just over one in three of those who had tried an ENDS had taken at least one puff of a tobacco cigarette compared with one in ten of those who had never tried ENDS. So more teenagers who had tried ENDS than not had puffed on a real cigarette one year later. But this was still just six young people, and as in the first study, there was no measure of regular use. These studies thus provide no basis for concern about a 'gateway effect'.

8.7 While experimentation with ENDS among young people has been rising, smoking rates in developed countries have been consistently falling [97, 103]. There is no evidence that use of ENDS is contributing to a stalling or reduction in the rate of decline in youth smoking, and in the US, the country from which many of the alarming headlines about ENDS use and smoking in youth

emerge, rates of cigarette smoking in young people have dropped in recent years at a more rapid rate than in the past [104-106].

8.8 ENDS use may have benefits for young people who smoke if these devices help them quit, now or in the longer term. The analysis of youth data in the WHO report does not acknowledge this, and does not highlight that existing surveys can fail to examine ENDS use by smoking status, instead reporting overall prevalence. The WHO report also fails to acknowledge the possibility that by offering an alternative to the tobacco cigarettes favoured by older people, ENDS may be helping to denormalise smoking among the young.

9. ENDS MARKETING

Original text:

21. *Promotion: There is insufficient research or surveillance on how and to what extent ENDS/ENNDS manufacturers are promoting their products in the main country markets. Existing data indicates that spending on ENDS/ENNDS advertising has been increasing since 2012; that marketing uses diverse channels - point-of-sale, audiovisual and print mass media and online; and that promotional approaches vary by type of manufacturer. An unquantified amount of advertising uses deceptive health claims and its targeting includes youth and incites rebellion against smoke-free policies. There are also concerns that some companies are using or might use ENDS/ENNDS advertising to promote smoking, advertently or unintentionally.*
22. *Price: The limited empirical research on the topic shows that:*
 - a. *ENDS/ENNDS sales and prices have a strong inverse relation;*
 - b. *ENDS/ENNDS and cigarettes are substitutes, with higher cigarette prices being associated with increased ENDS/ENNDS sales. Therefore, differential tax policies based on product type could lead to substitution between different types of ENDS/ENNDS and between ENDS/ENNDS and cigarettes;*
 - c. *Existing initial costs for a rechargeable ENDS/ENNDS devices and costs of disposable ENDS/ENNDS are generally higher than those of cigarettes.*
23. *Product characteristics: Flavour is one of several significant product appeal factors that influences people's willingness to try ENDS. Certain flavours, such as fruit and confectionary or candy-like aromas, appeal to children, younger never-smokers and young ENDS/ENNDS beginner and may therefore play a role in motivating experimentation among them. In 2009, one company declared that they would halt flavour sales to discourage underage use although years later they reversed their decision. Flavours also seem to play a role among adults and experienced ENDS/ENNDS users in helping migration away from tobacco. Flavoured ENDS/ENNDS may be, therefore, one of several product features that appeal to taste predilections, while also suggesting a level of safety and building user image.*
24. *Product placement: Internet sales, as opposed to those in retail stores, accounted for one-third of the worldwide market in 2014. In three regions - Asia Pacific, Australasia and Latin America - Internet sales accounted for the largest share of the market (70%, 85% and 94%, respectively).*

9.1 Paragraph 21 summarises the diversity of ENDS promotion and highlights concerns that some promotions use deceptive health claims, or target young people, incite rebellion against smoke-free policies, and either intentionally or unintentionally promoting smoking.

9.2 However, inspection of the cited evidence indicates that the health claims made for these products include reduced harm relative to tobacco cigarettes [107-109], which is in fact true;

that ENDS help smokers to quit [107-109], which is true; and that ENDS do not emit second-hand smoke [107], which is also true. The cited source of evidence of incitement to rebel against smoke-free policies is an analysis of news coverage that notes that people may vape where smoking is not permitted [110]. There is nothing in this paper to suggest that ENDS advertising encourages rebellious smokers *to smoke* where smoking is not permitted (i.e. a rebellion): and even any rebellion claim rests on untested speculations by the authors.

9.3 While we agree that advertising targeted at non-nicotine users, particularly children, is counterproductive to public health; and would oppose any advertising that intentionally or otherwise promoted smoking, we argue that advertising that promotes harm reduction and smoking cessation to smokers has the potential to be beneficial to public health. That ENDS companies are promoting their products as a means to quit or reduce harm is therefore probably a good thing; and as ENDS users are almost exclusively smokers, the paper should recognize that ENDS promotion could be a factor in reducing cigarette sales and converting smokers from smoking to vaping - which is beneficial to public health. Likewise, restraints on ENDS promotion could have the unintended effect of increasing smoking. There are examples of poor ENDS advertising, just as there are for every product. However, experience in the UK with a Code of Practice [111, 112] showed that complaints fell to very low levels once it was clear what the rules are.

9.4 We agree with the analysis of price elasticity and the market equilibrium between ENDS and tobacco cigarettes, which demonstrates the importance of maintaining a price advantage for ENDS, and particularly of not applying tobacco taxes to the ENDS category. This is one of the few sections of the WHO report that recognises that ENDS and cigarettes are substitutes and that their demand profiles therefore interact. That insight should be extended to the section on promotion - if there is a cross elasticity of demand for the product, then one would expect a cross elasticity in promotional expenditure - in other words, if the logic of the section on price is applied to the section on promotion, increased promotion of ENDS should lead to decreased demand for cigarettes.

9.5 Paragraph 22 addresses the role of flavours in ENDS, highlighting their potential to appeal to children and young people and to smokers, and speculates that flavours may therefore appeal to taste predilections while also suggesting safety. However, some of the cited evidence in relation to children and young people is misrepresented. All of the participants in the Czoli study [113] were aged 16 or over, and most were smokers. The Ford study [95] was conducted by the University of Stirling, including Professor Bauld who is a contributor to this commentary. The WHO report does not make clear that the Ford study simply reported teenagers' *beliefs* about marketing, not their behavioural responses to marketing, as the WHO report claims. Only 2% of participants in this study were regular ENDS users, and all were smokers.

The Ambrose study [114] surveyed young people already using ENDS and asks what they like about them: nearly all (81.5%) answer affirmatively to the statement "Because they come in flavours I like". This is a statement of the obvious for existing consumers; it does not establish a general appeal to youth or non-smokers. In addition to flavour, participants widely cited reduced harm and quitting as reasons to use ENDS. The Vasiljevic study [115] concluded that "*In an experimental study, we found no evidence that exposing English children aged 11-16 years to adverts for candy-like flavoured and non-flavoured e-cigarettes increased the low appeal of smoking tobacco, the low appeal of using e-cigarettes, or low susceptibility to tobacco smoking*". The WHO report fails to report the findings of one of the few experiments conducted with both teenagers and adults on their interest in and preferences for ENDS flavours [116]. The survey concluded that interest in ENDS flavours was very low among teenagers (0.41 on a 10-point scale); those most affected by flavour were adult ENDS users.

9.6 Paragraph 23 does acknowledge the potential importance of flavours in encouraging and sustaining ENDS substitution by smokers. In the UK, over 60% of ENDS users choose a non-tobacco

flavour [13], and recent qualitative data indicate that non-tobacco flavours are also popular among ENDS users in the USA [117]. Flavours are important in enabling smokers to switch to ENDS use.

9.7 Paragraph 24 concludes that internet sales account for a substantial part of the ENDS market. This is inevitable for a product that is evolving so rapidly, and particularly so for countries where *de facto* prohibitions on conventional retailing are in place.

10. COMMERCIAL INTERESTS

Original text:

26. *The engagement of TTCs in the marketing of ENDS/ENNDS is a major threat to tobacco control. There are concerns that TTCs are marketing ENDS/ENNDS in order to:*
- a. minimize the threat to tobacco sales by promoting ENDS as a complement rather than an alternative to tobacco, or controlling technological innovations that would prevent improvements in their efficacy as an aid to cessation;*
 - b. promote smoking through ENDS/ENNDS advertising, and promotion to adults and children;*
 - c. assert potential benefits of ENDS/ENNDS - and, in the near future, nicotine inhaler technology - as an excuse to engage with and influence policymakers, scientists and advocates in tobacco control with a view to undermining the WHO FCTC, while at the same time building credibility in corporate social responsibility initiatives.*
27. *A growing concern is the extent to which research on the topic has links to commercial and other vested interests of the ENDS/ENNDS industry, including the tobacco industry, and its allies. In a review of 105 studies analysing the composition of liquids and emissions, 30% had authors that had received funding from ENDS/ENNDS interests - including the tobacco industry.*

10.1 The WHO report misconstrues the ENDS market, the role of transnational tobacco companies (TTCs) in this market, and undervalues the potential effect of a disruptive technology such as ENDS to the commercial viability of the traditional cigarette business. The references cited in the report point out how regulations, such as those the WHO seeks, actually help the cigarette companies. Yet in its section on regulatory options, WHO appears entirely unaware of how its regulatory proposals may provide the tobacco industry with a twin advantage: (1) slowing down the disruption of the cigarette market; (2) shaping the e-cigarette market to suit the ENDS business model favoured by the TTCs.

10.2 We agree that the engagement of TTCs in the ENDS market is a cause for concern, for the reasons given in paragraph 26, and it is important that WHO policy prevents these outcomes. For this reason it is important that ENDS suppliers can promote their products as a complete substitute for, not a complement to, tobacco cigarettes; and can continue to innovate and improve the performance of ENDS and other novel nicotine devices to improve their competitiveness with cigarettes. Regulatory approaches that inhibit these processes therefore play to TTC interests. We agree that promotion of smoking should be prevented, and support measures to prevent advertising to children, or imagery that translates from ENDS to tobacco, as has been successfully achieved in the UK. TTC engagement with policy to undermine the FCTC can be prevented by applying the measures contained in FCTC Article 5.3 [5].

10.3 Unless aided by regulation that kills the open systems business, competition and market forces will prevent TTCs from controlling options for smokers. The commercial reality is that the cigarette trade faces an existential threat from ENDS, and some TTC are trying to compete in this market to avoid becoming yet another company that, like Kodak, were forced quickly from

market domination to irrelevance by a new and disruptive technology. TTCs are now being forced to develop and promote reduced harm products to survive. It is vital that regulatory approaches sustain the disruptive competition that is forcing this change.

10.4 Paragraph 27 refers to commercial and other vested interests among researchers. All areas of medicine interact with commercial interests, and those working in the treatment of nicotine addiction necessarily have to interact with suppliers of nicotine and other smoking cessation therapies and substitutes. As with links with the pharmaceutical industry in other areas of medicine, prohibition of those links will retard much research and development. The key thing is that all such interests are openly and consistently declared, and managed appropriately [118].

11. REGULATORY OPTIONS

Original text:

28. The following is a non-exhaustive list of options that Parties might consider in accordance with their national law, in order to achieve the ENDS/ENNDS objectives set out in the COP 6 decision on ENDS/ENNDS.

29. Objective: prevent the initiation of ENDS/ENNDS by non-smokers and youth with special attention to vulnerable groups. Although the debate about whether the use of ENDS/ENNDS is a gateway to smoking is unresolved, preventing this eventuality requires making the initiation and persistence of smoking as difficult as possible. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options:

- a. Banning the sale and distribution of ENDS/ENNDS to minors;*
- b. Banning the possession of ENDS/ENNDS by minors;*
- c. Banning or restricting advertising, promotion and sponsorship of ENDS/ENNDS (see FCTC/COP/6/10 Rev.1);*
- d. Taxing ENDS/ENNDS at a level that makes the devices and e-liquids unaffordable to minors in order to deter its use in this age group*
- e. Banning or restricting the use of flavours that appeal to minors;*
- f. Regulating places, density and channels of sales; and*
- g. Taking measures to combat illicit trade in ENDS/ENNDS.*

30. Objective: minimize as far as possible potential health risks to ENDS/ENNDS users and protect non-users from exposure to their emissions.

- a. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options to minimize health risks to users:*
- i. Testing heated and inhaled flavourants used in the e-liquids for safety, and banning or restricting the amount of those found to be of serious toxicological concern such as diacetyl, acetyl propionyl, cinnamaldehydes or benzaldehyde;*
 - ii. Requiring the use of ingredients that are not a risk to health and are, when allowed, of the highest purity;*
 - iii. Regulating electrical and fire safety standards of ENDS/ENNDS devices;*
 - iv. Regulating the need for manufacturers to disclose product content to government;*
 - v. Regulating appropriate labelling of devices and e-liquids;*
 - vi. Requiring manufacturers to monitor and report adverse effects; and*
 - vii. Providing for the removal of products that do not comply with regulations.*

- b. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options to minimize health risks to non-users:*

- i. Prohibiting by law the use of ENDS/ENNDS in indoor spaces or at least where smoking is not permitted;
- ii. Requiring health warnings about potential health risks deriving from their use. Health warnings may additionally inform the public about the addictive nature of nicotine in ENDS; and
- iii. Reducing the risk of accidental acute nicotine intoxication by a) requiring tamper-evident/child resistant packaging for e-liquids and leak-proof containers for devices and e-liquids and b) limiting the nicotine concentration and total nicotine amount in devices and e-liquids.

31. Objective: prevention of unproven health claims being made about ENDS/ENNDS. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options:

- a. Prohibiting implicit or explicit claims about the effectiveness of ENDS/ENNDS as smoking cessation aids unless a specialized governmental agency has approved them;
- b. Prohibiting implicit or explicit claims that ENDS/ENNDS are innocuous or that ENDS are not addictive; and
- c. Prohibiting implicit or explicit claims about the comparative safety or addictiveness of ENDS/ENNDS with respect to any product unless these have been approved by a specialized governmental agency.

32. Objective: protect tobacco control activities from all commercial and other vested interests related to ENDS/ENNDS, including interests of the tobacco industry. Parties, including those that have banned the importation, sale, and distribution of ENDS/ENNDS, may consider the following options:

- a. Raising awareness about potential industry interference with Parties' tobacco control policies;
- b. Establishing measures to limit interactions with the industry and to ensure transparency in those interactions that do take place;
- c. Rejecting partnerships with the industry;
- d. Taking measures to prevent conflicts of interest for government officials and employees;
- e. Requiring that information provided by the industry be transparent and accurate;
- f. Banning activities described as "socially responsible" by the industry, including but not limited to activities described as "corporate social responsibility";
- g. Refusing to give preferential treatment to industry; and
- h. Treating State-owned industry in the same way as any other industry."

11.1 This section of the WHO report presents a menu of regulatory options to prevent initiation of ENDS use by non-smokers; minimise health risks; prevent unproven health claims; and protect tobacco control from commercial and vested interests. This section is written from a perspective that more regulation is needed to achieve these objectives: there is however no consideration as to whether other objectives are also important, and how regulation might, by addressing the WHO objectives, act against the wider public health interest.

11.2 The key objective of tobacco control, and the FCTC, is prevent harm to health from tobacco use (see para 1.2 above). The purpose of regulation should be to achieve this aim. Since ENDS offer smokers a means to escape from dependence on smoking tobacco it is essential that new regulation encourages, rather than discourages, use of ENDS and innovation to make products more effective and affordable [5]. The WHO report does not appear to consider the extent to which the proposed regulatory options might reduce the appeal and effectiveness of ENDS and other novel nicotine devices, and thereby perpetuate, rather than reduce, smoking.

11.3 Each paragraph in this section implicitly endorses or 'normalises' the regulatory option of ENDS prohibition by stating that "*Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options*". WHO should not be endorsing

prohibition: it is unethical to deny smokers lower risk options than cigarettes [5]; rather, WHO should be encouraging countries with explicit or *de facto* prohibitions to reconsider, as is currently happening in Australia and New Zealand.

11.4 The section is devoid of policy analysis: the proposals are made without assessment of effectiveness or cost-effectiveness. The text does not recognise that there are trade-offs to be made between different objectives - for example between reducing smoking and reducing nicotine use; encouraging adults to switch to ENDS while preventing youth uptake; reducing youth uptake among teenagers who would otherwise never smoke and encouraging teenagers who smoke to switch to ENDS.

11.5 There is no assessment of unintended consequences, in this or any other section of the WHO paper. The Royal College of Physicians explains the risks of poorly designed or excessive policy interventions in its 2016 report [5], thus:

“A risk-averse, precautionary approach to e-cigarette regulation can be proposed as a means of minimising the risk of avoidable harm, eg exposure to toxins in e-cigarette vapour, renormalisation, gateway progression to smoking, or other real or potential risks. However, if this approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.” (Section 12.10 page 187)

The WHO report should, but does not, acknowledge this dilemma, and weigh up the relative merits of different courses of action. Almost every policy listed could easily have the effect of protecting the incumbent cigarette trade, and promote smoking rather than vaping, for the following reasons, listed point-by-point in relation to paragraphs 29 and 30:

Bans on sales to minors: WHO does not acknowledge two U.S. studies suggesting that where sales of ENDS to under-18s were prohibited, smoking *increased* in relative terms [119, 120].

Banning possession by minors: There are few places that make under-age possession of *cigarettes* an offence. The responsibility is usually imposed on adults not to make sales to minors. Banning possession would be an especially damaging idea if the young people were using ENDS as an alternative to smoking, and may even have been given them by a concerned parent or adult to try.

Banning or restricting advertising: Making ENDS less visible to young people may lead to additional teenage smoking and have the effect of protecting the cigarette trade from competition. ENDS manufacturers need to build appeal and communicate innovation to smokers. To the extent that WHO's policies prevent that, they would be providing regulatory protection for the cigarette trade.

Taxing ENDS: The proposal for differential taxation is welcome (and recognises a harm reduction potential). As a practical matter, governments have to balance three aspects of tax policy: (1) public health goals; (2) revenue raising; (3) cost of tax administration. Given the diversity of ENDS suppliers and products, and consequent high cost of administration, and the public health imperative of the FCTC, the best approximation for an appropriate excise duty for ENDS is zero. There is no case for adding any tax above that of general sales or value added taxes.

Banning flavours that appeal to minors: There is very little to suggest that a particular class of flavours appeal disproportionately to young non-users or that this is a *causal* factor in taking up vaping, rather than simply an expression of preference once a decision

to try ENDS has been made. There are two potential unintended consequences not recognised by WHO in making this proposal. First, that most experienced adults use flavours other than tobacco flavour and the proposals risk compromising the appeal to adults, again protecting the cigarette trade by reducing the rate of switching or increasing the rate of relapse from ENDS use to smoking. Second, that such a policy is incapable of distinguishing between: (1) young smokers (for whom ENDS are a much less dangerous alternative); (2) young never-smokers who would otherwise progress to smoking in the absence of ENDS; (3) young never smokers who would not progress to smoking in the absence of ENDS. It is only this third category who might benefit from this policy and unless they progressed from ENDS to smoking any harm is likely to be low. The first two, however, may be harmed by this policy. WHO does not appreciate this complexity or recognise it as risk in its policy proposal.

Regulating places and density of sales outlets: Measures to reduce accessibility of ENDS are a regulatory protection of the cigarettes trade. There is no justification for this measure and it is only just under discussion for the far more harmful tobacco products.

Taking measures to combat illicit trade in ENDS: Unjustified prohibition, excessive taxation, product limitations, or excessively burdensome regulation are the most likely cause of illicit trade. Illicit trade in ENDS is an unintended consequence of bad policies intervening in individuals' efforts to take control of their health using a new technology. The solution is not to have the bad policies to start with.

Banning or restricting certain ingredients: This is a rational policy in the case of ingredients known to be carcinogenic, mutagenic, repro-toxic or respiratory sensitisers. However, the WHO should not be proposing a list of named chemicals without supporting evidence, risk assessment or threshold guidance. It is also important to balance potentially minor health risks with effects on product appeal that encourages users to switch from smoking to vaping, thereby avoiding much larger exposures from smoking.

Setting standards for ENDS and e-liquids: Section 35.a. (ii-vii) list good practice in standard setting, and it would be welcome if WHO supported the development of ISO and other standards [22]. The approach of technical standard setting is far superior to other approaches, such as setting *ad hoc* standards in primary legislation as with the EU Tobacco Product Directive, establishing an onerous authorisation process that will destroy much of the market as with the U.S. FDA's deeming rule.

Prohibiting by law the use of ENDS in indoor spaces or at least where smoking is not permitted: There is no justification for using the law to override the preferences of the owners or managers of indoor spaces unless a material risk to bystanders or workers has been identified, which it has not [121]. As well as an unjustified imposition on property owners' rights to determine their own vaping policy, there are at least two possible unintended consequences. First, that it will promote relapse to smoking. Second, that it reduces the appeal of vaping relative to smoking, and hence protect the cigarette trade.

Health warnings: It is unclear what evidence-based health warnings could be placed on ENDS. It would be better to provide meaningful risk-communications to consumers encouraging ENDS use as an alternative to smoking. For example, "*No nicotine product is completely safe, but this product presents substantially lower risks to health than cigarettes*". The option of presenting realistic risk communication has not been considered or proposed by WHO.

Using child resistant packaging for nicotine liquids: There is near universal agreement with this measure. WHO could have done better by recommending a single standard, for example ISO 8317.

Limiting nicotine strength and container size: There is no evidence that limiting strengths or container size is an effective strategy for reducing toxic exposures, and scientists have challenged proposals for such policies [122]. In addition, limitations on strengths can have negative unintended consequences - for example they may make ENDS less helpful for more heavily dependent smokers, make it harder for novice users to get through the period of learning when they first switch from tobacco, and reduce the scope for innovation. Reducing the size of containers means more containers for a given consumption. It is unclear what this achieves, other than increased waste and pollution. Other potentially hazardous liquids, for example household bleach, are not controlled by reducing container size. The correct approach is to rely on child-resistant containers, hazard warnings and advice on how to store containers and to respond to accidental exposures. Excessive restrictions of this nature may have the unintended effect of boosting black market trade in high strength liquids and therefore increase the risks.

11.6 We agree with the proposal in paragraph 31 that vendors should not be able to make therapeutic claims about ENDS unless subject to medical authorisation, or make false or misleading statements on the health risks or any other aspect of ENDS. However, authorities should not prevent vendors making statements about their products that are true and do not mislead. That right should be governed by consumer protection legislation that applies to all products, for example, UK Trade Descriptions Act 1968, Chapter 29 [123]. It is important that any measures in this area are confined to vendors and not applied generally to consumers, reviewers, scientists, think-tanks and other interested parties.

11.7 There should be a professional requirement to ensure that statements on the health hazards and benefits of ENDS by health professionals and organisations are also true and do not mislead. Negligent statements or advice by trusted professionals can be as harmful as and more widespread than medical malpractice if they have the effect of preventing people trying low-risk products and continuing to smoke.

11.8 The recommended policies on protecting tobacco control activities from commercial and other vested interests listed under paragraph 32 uncritically extend the provisions of FCTC Article 5.3 and related guidance to makers of ENDS, including those with no tobacco industry connections. No rationale is given for treating these companies this way. The history of deceit, distorting science and inappropriate interference in tobacco control policy does not apply to these companies. ENDS companies may be positive for health by providing a harm-reduction alternative to smoking. Because of the potential for unintended consequences arising from poorly conceived interventions in the ENDS market (as discussed above), all Parties should be open to contact with ENDS manufacturers and vendors. Finally, it should be noted that other commercial interests, notably the pharmaceutical industry, do actively 'interfere' in tobacco control and ENDS regulation to pursue their own commercial interests, but they are not listed here.

12. ACTION BY THE CONFERENCE OF THE PARTIES

Original text:

33. *The COP is invited to note this report and provide further guidance.*

Response:

12.1 We invite the COP to read this critique in parallel with the original WHO report, and particularly in relation to Article 3 of the Framework Convention on Tobacco Control.

12.2 Our conclusion, like that of Public Health England [59] and the Royal College of Physicians [5], is that ENDS have the potential dramatically to reduce the harm sustained by tobacco smokers.

12.3 We recognise that the long term risks of ENDS are not known, and although likely to be small, are also likely to exceed those arising from long-term NRT use, or complete cessation of nicotine.

12.4 However, these risks are likely to be dramatically lower than those of smoking.

12.5 All smokers should therefore be advised to quit smoking as quickly as possible, but those who are not ready or able to quit should be encouraged, as strongly as possible, to switch to other reduced hazard nicotine products, including ENDS.

12.6 Health professionals and organisations should communicate clear messages on the relative benefits of ENDS as a source of nicotine for smokers, and avoid creating false perceptions of risk.

12.7 We agree that the emergence of ENDS presents risks to public health, particularly in the form of use by persons who were not or would not have become smokers.

12.8 We therefore support the application of proportionate regulation to ensure reasonable product standards, and to prevent promotion of ENDS to children. We advise against regulation that unnecessarily renders ENDS less affordable or available to smokers, or stifles innovation.

12.9 We argue that flavours are important to many users of ENDS, and that while some appear attractive to children, it would be wrong to prohibit the use of flavours.

12.10 There is no evidence that ENDS emissions are harmful to bystanders, and hence no health grounds on which to prohibit use where smoking is not allowed.

12.11 The involvement of the tobacco industry in the ENDS market should not be used as an argument against the use of ENDS: problems arising from tobacco industry involvement can be prevented through application of measures designed for this purpose laid out in Article 5.3 of the Framework Convention on Tobacco Control.

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