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On Nicotine Delivery Devices

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ACRONYMS AND ABBREVIATIONS

AECOSAM: Spanish Agency for Consumer Affairs, Food Safety and Nutrition
BAT: British American Tobacco
CDC: United States Centers for Disease Control and Prevention
95% CI: 95% confidence interval
CNPT: National Committee for the Prevention of Tobacco Use
EC: electronic cigarettes
EDADES: Survey on Alcohol and Drugs in Spain
ENDS: electronic nicotine delivery systems
ENSP: European Network for Smoking and Tobacco Prevention
ESTUDES: Survey on Drug Use in Secondary Schools in Spain
ETS: environmental tobacco smoke
EU: European Union
EVICT: Cannabis and Tobacco Evidence
FCTC: Framework Convention on Tobacco Control
FDA: United States Food and Drug Administration
HTP: heated tobacco products
IARC: International Agency for Research on Cancer
ITP: Protocol to Eliminate Illicit Trade in Tobacco Products
JTI: Japan Tobacco International
NDD: nicotine delivery device
OR: Odds ratio
PMI: Philip Morris International
PNSD: National Drug Plan
SEDET: Spanish Society of Tobacco Experts
THC: tetrahydrocannabinol
UFP: Ultrafine particle
WHO: World Health Organization

Contents

1. DESCRIPTION OF THE PROBLEM

The emergence of new electronic smoking devices in Spain poses a serious threat to public health. The absence of regulations, or the existence of regulations that are subject to the interests of the tobacco industry (which currently owns most of these new products), threatens the public health gains made in various countries in protecting people from problems related to tobacco use – in Spain, specifically, through Act No. 28/2005 and its subsequent amendments.

This report presents a consensus, based on proven scientific evidence, on a specific type of electronic device that does not contain tobacco but does contain nicotine. These devices are more commonly known as electronic cigarettes (e-cigarettes or ECs).

1.1. DEVICE TYPES AND CHARACTERISTICS

A distinction must be made between two types of products: (1) heated tobacco products (HTPs), which, as the name suggests, contain tobacco, and (2) electronic nicotine delivery systems (ENDS) or nicotine delivery devices (NDDs), which do not contain tobacco but in most cases do dispense nicotine.

HTPs or heat-not-burn (**HNB**) tobacco products are tobacco-containing devices in which tobacco is heated to lower temperatures than in conventional cigarettes,[1] resulting in the release of an aerosol containing nicotine, other tobacco substances and additives [1]. The most widely available HTP in Spain is IQOS, whose manufacturer claims that its nicotine delivery is as good as that of conventional (or combustible) cigarettes and better than that of ECs (which is most likely true of the first three generations of ECs, but not of the fourth). Data provided by the manufacturer show that these products may help addicted adult smokers to quit smoking conventional cigarettes and reduce their exposure to harmful chemicals, but only if they switch completely to HTPs. They are promoted as less toxic or "healthier" [2], but they emit toxins at levels above those considered safe (although most at a lower rate than conventional tobacco products). On 7 July 2020, the US Food and Drug Administration (FDA) authorized the marketing of the IQOS brand as a product that significantly reduces the production of harmful chemicals, but not as a "modified risk tobacco product" as the company would have people believe. The Secretariat of the Framework Convention on Tobacco Control (FCTC) [3] and the organization Stopping Tobacco Organizations & Products (STOP) [4] have therefore warned that IQOS should not be considered a safe product. The FDA will continue to monitor the situation to ensure that tobacco use does

[1] "Conventional cigarettes" or "conventional tobacco products" are terms used to designate manufactured tobacco products, also known as traditional, classic, combustible or combusting tobacco products.

not increase among young people, and although it has approved the marketing of IQOS, it does not endorse their use. It is not considered proven that these products are less harmful to health, especially among people who have previously smoked [5].

The European Union (EU) considers HTPs "novel tobacco products" [6]. Virtually the entire public health community therefore argues that they should be regulated like tobacco in all respects. Except for one paragraph in the conclusions, there is no further mention of these products in this document, as they are not ENDS.

Table 1. Differences and similarities between ENDS and HTPs (updated by SEDET, 2019)

	Conventional cigarettes	HTPs	ENDS
Requires preheating	No	Yes (for quicker absorption)	No (yes for latest models)
Contains nicotine	Yes	Yes	Yes (generally)
Contains tobacco	Yes	Yes	No
Produces solid waste	External	Internal	Internal
Mainstream emissions	Yes	No	No
Sidestream emissions	Yes	Yes	Yes
Promoted as "healthier"	No	Yes	Yes
Leads to addiction	Yes	Yes	Yes (older models perhaps less so)
Maintains addiction	Yes	Yes	Yes
Promoted as useful for smoking cessation	—	No	Yes
Useful for smoking cessation	No	No	Insufficient evidence (in any case, not the newest models)

ENDS are nicotine delivery systems in which a liquid is heated, producing an aerosol that is inhaled by the user. The term "ENDS" encompasses products more commonly known as ECs, e-cigs, e-cigarettes, e-cigars, and e-hookahs. They are sometimes referred to as vaporizers or vaping devices, although it should be noted that vaporizers can be used to vape other substances, such as tetrahydrocannabinol (THC) and other cannabinoids, energy-boosting substances, sauces and even butter and vodka. These products do not contain tobacco and under European Directive 2014/40/EU are considered "tobacco-related products".

ECs or ENDS consist of a small tank or cartridge that is inserted into the device, which by means of an electronic system with a rechargeable battery and an atomizer, produces an aerosol when heated. This aerosol is inhaled (or "vaped") in the same way as smoke from conventional cigarettes.

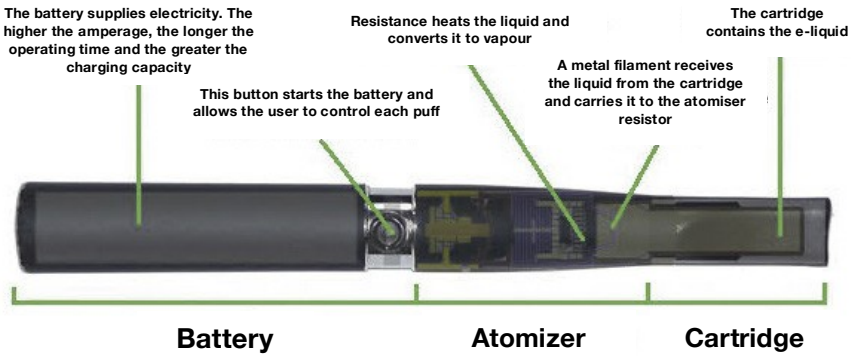


Figure 1. General structure of an electronic cigarette

Source: Castellar S, Ayesta F; Martín. F. Nuevos productos por calentamiento (ENDS & HTPs). (Tema A07). PIUFET 3.0, University of Cantabria, Santander.

There are a wide variety of products and refills on the market (Figure 1), which have evolved over time. They are generally classified by generation, although this classification scheme is not very functional (Figure 2).

Figure 2. Types of ENDS

Source: FDA. Vaporizers, E-Cigarettes, and other Electronic Nicotine Delivery Systems (ENDS). Available from: https://www.fda.gov/tobacco-products/products-ingredients-components/vaporizers-e-cigarettes-and-other-electronic-nicotine-delivery-systems-ends

Table 2. Evolution of ENDS

 **1st generation**	**Cig-a-likes.** Look like cigarettes. Also known as disposable or closed systems.
 **2nd generation**	**Vape pens.** Usually larger than cigarettes and look like fountain pens. They are also known as rechargeable e-cigarettes.
 **3rd generation**	**Box mods.** Also known as vape tanks and vapours/tanks/mods (VTMs), advanced personal vaporizers (APVs), modular units and open systems.
 **4th generation**	**Vape pods.** Require preheating. Contain nicotine salts with readily available nicotine, which makes it highly addictive.

Source: Prepared by the authors.

The aerosol produced by an e-cigarette contains a combination of chemicals (some of which are also present in conventional cigarettes), including nicotine (in most cases), propylene glycol, vegetable glycerine, polyethylene glycol, water and artificial flavourings. Over 15,500 different flavours are used in ECs, including vanilla, tobacco, menthol, chocolate, cinnamon and fruity flavours [7]. After heating, toxic substances and carcinogenic compounds (acrylaldehyde, formaldehyde, acetone and other carbonyls) are detectable in the aerosol to a lesser or the same extent as in cigarette smoke, as are various heavy metals, such as nickel, chromium and lead [8].

In the EU countries, the nicotine concentration in these devices cannot exceed 20 mg/ml, unlike in other countries such as the US, where the Juul device, for example,

has a concentration of 59 mg/ml. Devices that contain nicotine – which the vast majority do – maintain nicotine addiction. Their capacity to induce an addictive disorder depends on the ingredients included in their cartridges, their concentrations and the heating system. It is difficult to predict the level of addiction owing to the high variability in these products [9], but the evidence suggests that the most recent products – vape pods – are as addictive as conventional cigarettes. IQOS-MESH, developed by PMI (which, despite its name, is an e-cigarette) belongs to this latest generation and, like other devices in this category, needs to be preheated and is highly addictive. Evidence shows that the latest-generation products are specifically targeted at a younger population segment that is less interested in smoking conventional cigarettes but is interested in experiencing "something new" [10].

1.2. MAGNITUDE OF THE PROBLEM

Youth population. The Survey on Drug Use in Secondary Schools in Spain (ESTUDES) 2018/19 [11], which is conducted among students aged 14–18, found that 48.4% reported having used e-cigarettes at some point in their lives, a much higher percentage than the 20.1% who reported having used ECs in the previous survey in 2016/17. Prevalence at age 18 was 56.5% for boys and 47.7% for girls; 61.7% reported having used non-nicotine cigarettes, 11.3% having used nicotine cigarettes and 21.6% having used both.

Of the students who reported smoking tobacco on a daily basis, 86.8% said they had used ECs. The situation was similar among those who reported having used cannabis in the last month: 84.4% also reported having used ECs. Among those who had used ECs, only 9.7% had used them to reduce their tobacco use or to quit smoking; the percentages were about the same for both sexes.

Among students who said they had not smoked tobacco in the last 30 days, 6.4% reported having used nicotine-containing ECs. In comparison with those who had never used ECs, those who had used ECs reported a lower perception of risk associated with tobacco use (70% more – 7.9% – did not consider smoking a pack a day a significant risk) [11] and with cannabis use (130% more – 17.6% – did not consider regular cannabis use a significant risk) [11]. These two findings suggest a higher likelihood of e-cigarette initiation, which may be a gateway to nicotine, tobacco and cannabis use [8,11,12,13].

The motivations that lead young people to experiment with e-cigarettes are manifold. They include curiosity and the low perception of risk typical of their age, peer pressure and the pervasiveness of the messages spread by traditional and social media. Factors that contribute to this form of nicotine use include the ease with which ECs can be obtained via the Internet or in shops, with little regulation or control; appealing advertising by the vaping industry, both through conventional media formats and online; the variety of e-liquid flavours; and the belief that e-cigarettes are safer than conventional cigarettes [14].

E-cigarette use is greater in countries that have not restricted advertising and have mostly not regulated these devices, such as the United States [15], where EC use has been found not to be associated with a decrease in cigarette smoking among young people [16]. Although the percentage varies by country and by the regulations in place, in at least a small percentage of the youth population, ECs serve as a gateway product for subsequent use of tobacco products, including conventional cigarettes, as well as for experimentation with cannabis and its derivatives [17].

Adult population. In Spain, as in other countries, EC use in the adult population is lower than in the student population. According to the Spanish Alcohol and Drug Survey (EDADES) conducted in 2017 (previous surveys did not ask about EC use), among the Spanish population aged 15–64 years, 8.8% had used EC (with or without nicotine) at some time in their lives – 9.6% of men and 8.1% of women. The group aged 15–24 had the highest prevalence among both males and females: 15.1% and 10.9%, respectively, had used ECs at some point in their lives and 1.5% and 1.2% used them daily. Predictably, EC use is more frequent among smokers (>18%) than among those who have never smoked (2.0%) [18].

Although there is a percentage of the adult population who only use ECs, the majority are dual users who use both ECs and combustible tobacco products.

Outlook. Given the trend of prevalence of use and the promotional activities of the manufacturers of these products, it is expected that, without adequate regulation, these figures will increase, as has occurred in countries that have not really regulated these products until very recently (as in the case of the United States [19,20], which is facing an epidemic of e-cigarette use among young people and an increase in respiratory pathologies associated with the use of these devices [21,22). In Spain, although the regulations need to be enhanced, Directive 2014/40/EU has served as a containment measure.

1.3. TOBACCO INDUSTRY MARKET AND MARKETING STRATEGIES

Throughout the history of the manufacture and marketing of tobacco products, the tobacco industry has continually attempted to camouflage, conceal or even deny evidence of the harm caused by the use of its products. The industry has done so in the face of the authorities and the public through advertising strategies using appealing or exotic flavours and associating tobacco products with diverse and changing values such as glamour, freedom, sexuality, masculinity or femininity [23,24].

In addition, faced with growing understanding of the risk of tobacco products, manufacturers advertised that they had introduced improvements that made their products healthier – although they did not – such as mouthpieces, filters and less tar and nicotine, and used terms such as “natural”, “low”, “light”, “mild” to market the idea that they were less harmful. Such terms are now prohibited as misleading in the EU and other countries.

The publication of confidential internal tobacco industry documents in 1994 brought to light the deceptive strategies and tactics used by the tobacco industry to encourage people to continue smoking, including concealing the toxicity of their products and the harmful health effects of environmental tobacco smoke (ETS) from the public, manipulating product content to increase addictiveness and using advertising strategies aimed at their target audience: children and young people.

There is also evidence of the systematic use of strategies aimed at discrediting the World Health Organization (WHO) in order to thwart, hinder or reduce the impact of the various tobacco control measures that the Organization was promoting at the global level. Some of these strategies proved so effective that they led to the reduction of budgets for WHO's scientific and policy activities. Others were aimed at convincing developing countries that WHO's tobacco control programme was a "first world" agenda being carried out at the expense of the developing world. Still others sought to distort the findings of important scientific studies on tobacco and generally to discredit WHO as an institution [25].

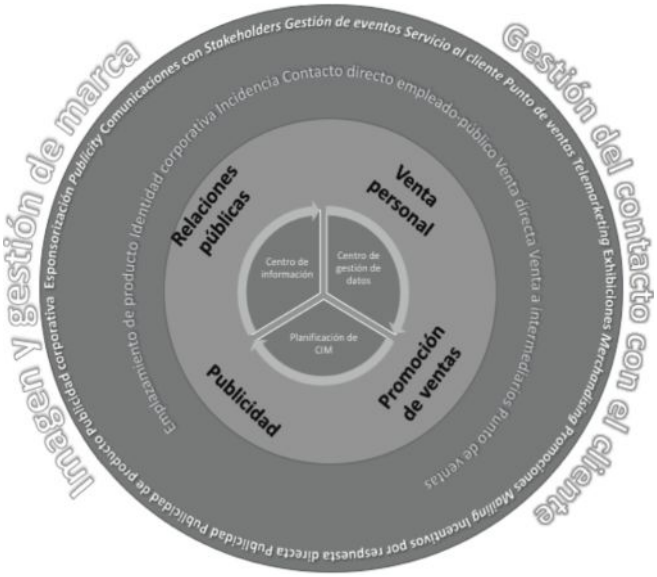
The unexpected rise in the popularity of the original e-cigarettes, which was probably linked to the increased perception of risk associated with tobacco use and the tobacco industry's loss of credibility, has forced the industry to reinvent itself, appearing to Western societies to dissociate itself from conventional cigarettes and to embrace the use of new technologies. The industry has taken over most of the EC patents and has also developed new devices, including both ENDS and HTPs. Philip Morris International, for example, has invested at least US$6 billion in developing its heated tobacco product (IQOS) and another US$12.8 billion in acquiring a 35% share of the JUUL e-cigarette. The company now reports that it is investing US$300–400 million a year in new products.

In the last decade, the market share of ECs has increased thanks to an aggressive marketing campaign utilizing themes previously used to promote conventional cigarettes (feeling and experience of freedom, good taste, romance, sociability, etc.), as well as the classic idea that ECs are a healthier option and the novel idea that they are useful for smoking cessation and that they can be used in smoke-free environments. These arguments coincide with the reasons given by both adults and young people as motivations for using ECs [26].

Big tobacco companies, with their market power, marketing intelligence and huge budgets, can afford to work with large communications agencies and thus have an impact on different target audiences by repositioning their product in the market. Through product innovation, they are using integrated marketing communication to promote new nicotine delivery devices. The new products resemble "smart" devices – like mobile phones – which in itself helps to shift the image of nicotine consumption away from cigarettes. Moreover, they come in a variety of colours and flavours and some can be recharged with a USB connector that allows the device to be plugged in to the user's computer.

By using the technique known as integrated marketing communication (Figure 3) [27], companies are reaching different target audiences, including consumers (smokers, ex-smokers and non-smokers), health professionals and nonprofit organizations and government agencies.

Figure 3. Integrated marketing communication scheme



IMC campaigns use recurring themes: focusing on the possibility of being able to smoke again in places where smoking is not allowed, presenting e-cigarettes as a less toxic or healthier alternative [28], suggesting that they can help people quit smoking, showing people with fashionable lifestyles [29] and stylish accessories [26], all in association with new technologies. The messages are along the lines of “I like the way you Blu”, “A better way to smoke”, “Vape freedom”, “No smelly smoke” or “Kyle smoked for 35 years. In 2018 he switched to Juul”, accompanied by “cool” images in clean, natural environments.

Most promotional websites claim that ECs help with smoking cessation, a claim that is also indirectly reflected in advertising campaigns for these products (e.g., the New Year’s campaign of an EC brand: “In 2020, I can do it without raiding the fridge”; “In 2020, I can do it without getting grumpy”).

The communications channels used include point-of-sale promotions (merchandising and salesforce); content marketing via social media using influencers and celebrities; outdoor advertising on MUPIs (outdoor advertising boards – the acronym comes from the French *mobilier urbain pour l’information*), bus shelters and banners; public relations at various events, sponsorship and salesforce activities, all aimed at attracting and

retaining customers. Through all these strategies, companies succeed in strengthening both their brand image and their relationships with current and potential consumers.

These marketing strategies are also supported by the continual pursuit – and sometimes bribery – of reputable legislators, politicians and clinicians, thereby cultivating a corporate image of social responsibility and apparent concern for health. Companies have even pitched proposals to WHO, claiming that promoting and using ECs will reduce the number of cigarettes smoked globally [24], something that in reality is up to them to do. All these arguments aim to reduce the perceived risks of their products, divert attention away from their addictiveness and toxicity and attempt to portray them as attractive in order to encourage their use.

2. SAFETY, TOXICITY AND HEALTH EFFECTS

As noted in the introduction, e-cigarettes vary widely in structure and composition. Their safety and toxicity most likely also vary.

Since most of the toxic effects of tobacco occur over the long term, it will not be possible to determine the comparative toxicity of these new products for at least a decade or two. While they generally result in lower exposure to most of the substances contained in conventional cigarettes, it does not necessarily follow that their toxicity is lower, as their harmful effects may occur only when a certain threshold is reached or may be linked to other substances present only in ECs.

Interpretation of the health risks of these products is complicated by the fact that 35% of the published papers on the subject suffer from serious conflicts of interest: 95.1% of studies without industry links conclude that these products are hazardous to health, whereas only 7.7% of industry-funded studies arrive at the same conclusion (OR 66.9; 95% CI: 8.1-552.9) [30].

The capacity of these products to generate toxic substances in their emissions is related to several factors, including the content of the liquid in the cartridge and the intensity and speed at which these liquids are heated. The risk of toxicity depends not only on the effects on the body of each ingredient present in the aerosol, but also on the possible interactions between them and with other environmental factors. It is also critically dependent on personal factors, such as previous or concurrent tobacco use, time spent vaping, frequency of use and intensity of inhalation [31].

2.1. INGREDIENTS

The main ingredients in EC liquids and aerosols are:

Nicotine. Nicotine is a highly addictive substance [32] present in most ECs. It produces biological effects that extend to all body systems. After administration, nicotine increases sympathetic tone, increasing myocardial oxygen demand, heart rate, blood pressure and vasoconstriction. These effects are much stronger when the nicotine is inhaled (or received intra-arterially in the case of a fetus). Although it has less impact at the population level, nicotine is a recognized co-carcinogen that promotes tumour growth [33] and metastasis, increasing angiogenesis and inhibiting apoptosis (programmed cell death); increased resistance to chemotherapeutic agents and decreased immune response have also been reported [34].

Propellants. The most commonly used substances are polyethylene glycol (PEG) and glycerol or vegetable glycerine (VG), which are often used in combination; propylene glycol (PG) is also used. These substances are also used as wetting solvents in pharmaceuticals, cosmetics, disinfectants and antifreeze and for making artificial smoke. They are used as food additives, as well (E-1520, E-422 and E-1520, respectively). It is not known how much of these substances can safely be inhaled after

heating, as they generate formaldehyde, acetaldehyde and acrolein (recognized carcinogens and pulmonary toxicants), which explains why they have been reported to cause eye, throat and respiratory tract irritation, and an increased risk of asthma in children, when used in closed spaces [5].

Glycerine has characteristics and uses similar to those of propylene glycol [31]. It is considered safe for oral consumption, but not for inhalation. Two cases of lipoid pneumonia related to EC vapour containing glycerine have been described [35], one of them in Spain, which was reported in the press [36].

When heated, propylene glycol and glycerine generate acrolein, which causes chronic pulmonary inflammation, reduced immunity, neutrophil inflammation, mucus hypersecretion and protease-mediated lung tissue damage, which are associated with the development of chronic obstructive pulmonary disease [37].

Flavourings. As noted earlier, at least 15,500 flavourings have been found to be present in various e-liquids [5]. Flavourings are used to increase the palatability of the product and to attract young people to vaping and induce those who have not yet developed a strong nicotine dependence to continue vaping. Popular flavours include fruit, cinnamon, tobacco, alcohol, coffee, chocolate, butter, caramel and mint. Thermal decomposition of some flavouring compounds generates aldehydes (carcinogens), producing levels that exceed safety standards [38]. Several studies have linked certain flavours (cinnamon and cherry, for example) and some flavouring agents (acetoin, 2,3-pentanedione and diacetyl) with higher nicotine concentrations and with vascular dysfunction and pneumonitis [39,40].

Menthol. Menthol, in addition to being a flavouring (a flavour and colour generally associated with healthy effects), produces a sensation of freshness, reduces the harshness of e-liquid smoke and suppresses the cough reflex. There is also evidence that it can lead more rapidly to addiction and that its use is associated with a lower probability of cessation. All cigarettes (and many of the new products) normally contain menthol, although those labelled as menthol cigarettes contain more of it. Since May 2020, the use of menthol in tobacco products has been banned in the European Union, but the ban does not apply to ECs. The main reason for this ban is that menthol encourages the initiation of regular use by minors.

Other substances. Other toxic substances such as carbonyls (formaldehyde, acetaldehyde, acrolein, glycidol) and nitrosamines, substances associated with carcinogenesis, have also been detected in e-cigarettes, as have non-negligible concentrations of heavy metals (lead, chromium, nickel, copper), which are associated with various neurological, cardiovascular, respiratory [41], allergic [42] and oncological [13] disorders.

Ultrafine particles. Ultrafine particles in EC aerosol transport nicotine to the pulmonary alveoli. The most problematic of these particles are those smaller than 2.5 μm ($PM_{2.5}$).

Irrespective of their composition, ultrafine particles are implicated in the genesis of acute and chronic cardiovascular pathologies [43] and pulmonary, neurodegenerative and oncological diseases [44].

2.2. TOXICITY

Based on currently available evidence, it is likely that ECs are less toxic than conventional cigarettes (which cause premature mortality among slightly more than half of those who regularly smoke them according to the manufacturer's instructions for use), but it is not clear that the reduction in toxicity is significant.

The toxicity of conventional cigarettes is tremendous, so the fact that something is "less toxic" does not in any way mean that it is not harmful to health. The toxicity of ECs is discussed below.

Oncologic pathology. Biomarkers of exposure to key carcinogens and toxins are markedly reduced among smokers of conventional cigarette who switch completely to ECs, which makes it quite likely that exclusive use of e-cigarettes is less carcinogenic than cigarette smoking. Even so, it should be remembered that cancer accounts for only one third of cigarette-related deaths and that, as noted in the previous section, certain substances classified by the International Agency for Research on Cancer (IARC) as group I carcinogens (known to be carcinogenic to humans) are present, usually at low but biologically relevant levels, in ECs [45].

Cardiovascular pathology. There is growing evidence on ECs and their capacity to increase cardiovascular risk. Several cohort studies have found an increased risk (up to twofold) of myocardial infarction. Most independent studies suggest that vaping, or using ECs, potentially damages the cardiovascular system through mechanisms of thrombosis and atherosclerosis, since EC use leads to endothelial dysfunction, increased platelet aggregability, and increased inflammatory mediators. The risk is greater among those with underlying cardiovascular disease and those who use both ECs and conventional cigarettes, although it is likely that the cardiovascular risks of exclusive EC use are less severe than those of cigarette smoking [46,47,48,49].

In the short term, not all studies have found cardiovascular changes, but it should be noted that studies with conflicts of interest are significantly less likely to identify cardiovascular effects of concern [30,50].

Respiratory effects. The respiratory tract, the aerosol's route of entry, is particularly affected by it. E-cigarette use is an independent risk factor for severe respiratory disease (increasing the risk by a factor of 1.3). Concomitant use of conventional and electronic cigarettes, the most common pattern of use, produces more harm than the use of either product alone [51]. E-cigarette use has been associated with increased bronchial reactivity, decreased defence mechanisms, increased respiratory secretions and greater alveolar cytotoxicity and necrosis.

Inflammatory diseases affecting the small airways and alveoli (lipoid pneumonia, eosinophilic pneumonia, diffuse alveolar haemorrhage, organizing pneumonia, diffuse alveolar damage, respiratory bronchiolitis, interstitial lung disease associated with respiratory bronchiolitis and hypersensitivity pneumonitis) have become increasingly frequent. Associations have also been established with increased symptomatology of chronic bronchitis, chronic cough, phlegm, exacerbation of asthma and increased susceptibility to and delayed recovery from respiratory infections [52].

EVALI syndrome or vitamin E acetate crisis. In June 2019, a series of cases of lung injury associated with vaping products began to be described in the United States. The peak incidence occurred in September, but cases were still being detected in emergency departments in early 2020. As of 18 February 2020, 2,807 persons had been hospitalized (persons from all 50 states had been admitted), 68 of whom had died [22,53,54].

The majority of the patients were previously healthy young people (two thirds were male) who had gradually, over a period of days or weeks, begun to experience fever, tachycardia, tachypnoea and hypoxemia (even in patients without respiratory symptoms at the time of presentation), accompanied by other respiratory symptoms (cough, chest pain, shortness of breath), gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea, which in some cases preceded the respiratory symptoms) and systemic symptoms (fatigue, fever, weight loss). A range of clinical and pathological diagnoses were posited, including acute lung injury and adult respiratory distress syndrome, diffuse alveolar damage, lipoid pneumonia, acute necrotizing pneumonitis, organizing pneumonitis with lipid-laden macrophages, nonspecific inflammation, hypersensitivity pneumonitis and eosinophilic pneumonia. The syndrome eventually became known as e-cigarette or vaping product use–associated lung injury (EVALI) [22].

Three months after the onset of the first cases, it began to be confirmed that tocopherol acetate (vitamin E acetate), a substance used in the dilution of cannabis, could be the main cause of the syndrome, although a recent study suggests that the possible cause is nickel-chromium alloys present in the heating elements and atomizers of some devices used by persons affected by EVALI [55].

Several conclusions can be drawn from this crisis: (1) the regulation of vape products is deficient; the incident occurred because an attempt was made to dilute THC by using a product approved for use in foods and cosmetics, but it was used in higher concentrations and subjected to higher temperatures; (2) products with no history of toxicity can be highly or mildly toxic when exposed to high temperatures or administered in high concentrations; (3) there is considerable overlap in the use of vaping products containing different substances (nicotine and cannabis, in particular); more than half of the persons affected by EVALI reported having vaped products with nicotine in addition to vaping THC; only one in six affected persons reported having vaped only nicotine products (more than 80% tested positive for cannabinoids) [56].

Poisonings and accidents. Handling of the liquid nicotine containers used to refill ECs (or other ENDS) by children and adults has led to an increase in the incidence of symptoms of poisoning, ranging from dizziness and vomiting to tachycardia, hypertension and tachypnoea. This risk is non-existent in disposable closed-system products. Nevertheless, calls to poison control centres for EC-related problems are increasing every year [26,57]. A lack of quality control on some of these devices has led to explosions that have caused burns and sometimes serious orofacial injuries (in the United States the annual number of such injuries between 2015 and 2017 has been estimated at 369–988) [58].

Effects on pregnancy. It is well known that tobacco use during pregnancy produces harmful effects, increasing the risk of miscarriage, placenta praevia, low birthweight, premature birth, perinatal mortality, cleft lip and sudden infant death syndrome [59]. Although the relationship is less clear-cut, tobacco use has also been associated with an increased risk of cognitive deficits and behavioural abnormalities, such as hyperactivity and attention deficit disorder in children of women who smoked during pregnancy [60,61]. Although there is no hard evidence of toxicity to the fetus from EC use during pregnancy, given the ingredients in ECs and their potential risk, as a precautionary measure, health authorities do not recommend their use at this stage. As established in the Rio Declaration [63]: When an activity poses a possible threat to human health or to the environment, precautionary measures should be taken, even if the effects are not well established scientifically.

Other effects on adolescent health. In addition to the health effects discussed above, EC use in the adolescent years poses additional risks. The teenage years are critical for the development of the brain, which continues to mature until the age of 21 or 22. Nicotine affects the development of the brain's reward system. Like cigarette smoking, continued use of ECs can not only lead to nicotine addiction but can also cause other drugs, such as cannabis [64], cocaine and amphetamines, to have a greater addictive impact [65,65]. Regular nicotine use can also affect the development of brain circuits that control attention and learning [39,67,68,69,70].

2.3. E-CIGARETTES AND COVID-19

The current COVID-19 pandemic, caused by SARS-CoV-2 coronavirus infection, has led to more than 27,000 deaths in Spain in less than 4 months. The main complications of the disease are respiratory and cardiovascular, and the aggressive immune response it triggers can lead to multi-organ failure.

As regards transmission and contagion of the SARS-CoV-2 virus, the most plausible routes of transmission from person to person are considered to be [71]:

1. Direct contact with secretions from infected persons: Flügge droplets of more than 5 microns, which be transmitted over a distance of up to 2 metres.

2. Indirect contact through objects or other fomites contaminated with the coronavirus (SARS-CoV-2), which can remain on surfaces from hours to days, depending on the material.

In addition, according to recent publications [72,73], the airborne route may be a long-distance transmission pathway, since droplets smaller than 5 microns in aerosols generated by infected persons may transmit the coronavirus over distances of more than the 2 metres initially estimated, as these microdroplets can remain suspended and travel in the air for several hours.

Droplets emitted by talking, coughing or sneezing are easily deposited on objects in the environment. If they contain viruses, they can be carried into people's noses, mouths or eyes when these objects are touched, thus increasing the chances of infection. For this reason, the protective measures adopted internationally have called for social distancing of at least 1.5 metres, handwashing and disinfection of fomites, and the use of masks. The confirmation of aerosols as key factors in the transmission of COVID 19 could increase the safe distance for vaping by several metres, as the current recommendation of 1.5 meters would be insufficient to prevent contagion.

People who use e-cigarettes must remove their masks and repeatedly bring the device to their mouths, as a result of which two things may happen [74]:

3. They may be exposed to virus-bearing droplets exhaled by other people.

4. They may expose people and objects in their environment to droplets exhaled when they use ECs, which travel at a higher speed than when talking, similar to what happens when someone coughs, sneezes or sings. If the user is a coronavirus carrier, these droplets can spread viruses into the environment. In addition, the EC itself becomes a contaminated fomite.

Although the health effects of EC use cannot be determined until decades after the onset of use, emerging evidence suggests that exposure to EC aerosols damages lung cells, decreases the ability to respond to infection and leads to an increased risk of cardiovascular pathology [75]. Hence, it seems prudent to assume that these devices could increase the risk of infection as a result of the repeated hand-to-mouth movement involved in their use and that EC use could also increase the risk of severe complications from COVID-19 [76,77,78].

A recent study in a young population concluded that EC users were five to seven times more likely to be infected by COVID-19 than those who did not use EC. The authors report that COVID-19 is associated with EC use and with dual use of ECs and conventional tobacco products in this group [79].

Accordingly, smoking and vaping in a public space could increase the risk of becoming infected with SARS-CoV-2 for:

1. **Persons who smoke/vape**

   a. When they remove their masks, they are not protected from other people who carry the virus.

   b. They put their mucous membranes in contact with their hands when smoking or vaping; moreover, tables, ashtrays containing cigarette butts and ECs and their components may be vectors for virus transmission.

2. **Persons in the environment of the smoker/vaper: family members and non-users**

   We cannot be sure that 2 metres is enough to ensure that the droplets emitted when using ECs do not reach other people. Second-hand and third-hand smoke or aerosol may thus become potential sources of COVID-19 contagion.

3. **Hospitality workers**

   Act No. 42/2010 on health measures to protect against tobacco use made the working environment safe for hospitality workers by ensuring that they could avoid inhaling toxic substances from tobacco smoke. Now, on terraces they are being exposed to aerosols from both conventional cigarettes and ECs and other ENDS and they also have greater exposure to potentially contaminated fomites associated with the use of such products.

4. **Hotel and restaurant managers**

   Allowing the use of ECs during a pandemic makes hotels and restaurants dangerous places, where both customers who come to enjoy leisure time and the employees who work in these establishments face a higher risk of contracting the virus. Hospitality and eating establishments would receive a quality boost by not allowing the use of any smoking or vaping devices that could increase the likelihood of infection.

The Spanish Ministry of Health [70] and various organizations (Nofumadores.org, FAECAP, QXNS, SEPAR, OMC, SESPAS, CNPT) [80,81,82] have made statements to this effect, recommending that spaces should be free from smoke and aerosols from ENDS and other forms of tobacco use.

2.4. INVOLUNTARY EXPOSURE TO AEROSOLS

Although ECs do not emit sidestream smoke, which is the smoke emanating from the lit end of a traditional cigarette, they do have mainstream emissions, which is the smoke or aerosol exhaled by the smoker into the ambient air [83,84]. The exhaled aerosol is a source of passive or involuntary exposure. ECs do not emit only water vapour, as the industry has often tried to make people believe. They contain other substances, some of which have already been identified as toxic.

The aerosols from these new products are a source of pollution from various substances, including nicotine, ultrafine particles ($PM_{2.5}$) [85], propylene glycol and glycerine heating products (formaldehyde, acetaldehyde, acrolein) and metals (lead, chromium and nickel) [6]. All of these substances are known to cause harm to health [86]; some, such as nickel, are found in higher concentrations in EC emissions than in tobacco smoke.

Levels of cotinine (a metabolite of nicotine exposure) in the saliva and urine of people who live with EC users, or are exposed in enclosed spaces, are similar to the levels found after passive exposure to conventional cigarette smoke [87,88].

Several studies report concentrations of ultrafine particles in environments where ECs are used that are much higher than the standard set by the US Environmental Protection Agency [89] and standards recommended by WHO and the European Union [90].

The evidence currently available seems to indicate that involuntary exposure is potentially harmful to health and not without risk [91,92], although further study and longer-term monitoring are needed to pinpoint the consequences of exposure.

WHO recommends that Parties to the Framework Convention on Tobacco Control (FCTC) should consider enacting legislation to ban the use of ECs, as well as conventional cigarette smoking, in enclosed spaces [92], as such spaces are where non-users are most exposed. In real-world studies, the level of fine particulate matter ($PM_{2.5}$) in EC aerosol was up to 25 times higher than the levels recommended by WHO and the European Union [90].

Another concern among scientists regarding the toxicity of ECs is that the temperatures at which the mainstream emissions emanate is not much different from those of mainstream smoke from conventional cigarettes.

2.5. ENVIRONMENTAL IMPACT OF E-CIGARETTES

In 2017, WHO published a monograph on the far-reaching impact of tobacco from an environmental perspective [93]. One section of the monograph is devoted to the products covered in this document.

At present, the major transnational tobacco companies sell mainly disposable, non-reusable “closed” system products (such as Juul, Vuse, MarkTen). While these products avoid the risk of nicotine poisoning in minors, their damage to environmental health may be significantly greater.

Most independent vaporizer and EC manufacturers market open, or reusable, systems, although recently the tobacco companies BAT and JTI have also started to market such products in the UK. However, the average lifespan of these devices is not very long and they become e-waste relatively quickly.

ECs represent an environmental threat of considerable proportions. These devices present a dual biohazard because of the large amount of residual nicotine contamination they cause and because they are contaminated e-waste [94]. Broken devices can contaminate urban and natural environments with metals, battery acid and nicotine [95]. Their plastic components can cause endocrine system disruption. Lithium-ion batteries require proper disposal to avoid environmental contamination. Electronic circuit boards require disassembly, sorting, subsequent recycling and proper disposal. These electronic wastes are very difficult to recycle. There is currently no legal way to recycle them in the US and many other countries. It is estimated that well over 60 million EC products are sold annually. Virtually none include instructions for disposal.

Article 18 of the FCTC states that all signatories “agree to have due regard to the protection of the environment and the health of persons”. The number of devices discarded annually and their environmental toxicity makes it urgent to address all dimensions of the environmental impact of this social phenomenon. This means establishing regulations on recycling schemes, without which the environmental impact of ECs may create an even bigger problem than the one currently caused by cigarette butts.

3. ANALYSIS OF POTENTIAL THERAPEUTIC USES

3.1. SMOKING CESSATION

To date, not many controlled studies of sufficient quality have been conducted on the effectiveness of e-cigarettes for smoking cessation. Most of the studies that have been conducted have been observational. This might be because only the health sector is interested in testing whether certain ECs can be useful for smoking cessation. Companies producing ECs have shown no interest in marketing their products as pharmaceuticals or in conducting the necessary controlled clinical trials. Nonetheless, as noted above, they do claim that ECs are or can be used for smoking cessation.

In principle, it makes some sense that nicotine in a form that is absorbed at a slower rate than from cigarettes could be used for smoking cessation. This is the case with nicotine replacement therapy (NRT) in its various forms. Two problems arise, however: (1) up to now, all therapies for all addictive substances have used a different route of administration from that used for the problem behaviour; using the inhalation route does not, a priori, seem the best way to change smoking behaviour; (2) the speed of nicotine absorption for the latest ECs is no slower than for cigarettes (for pharmacological reasons and because it is in the tobacco companies' interest to keep their customers permanently captive) [96,97].

Almost all longitudinal population-based studies (which have been conducted mainly in the USA and the UK) have found that EC use is not associated with increased cessation [7,26,98,99,100,101,102], which strongly suggests that the use of these products generally undermines abstinence [102]. However, in some populations their use has been found to be associated with an increased number of attempts to quit [98,103,104]. EC use is also associated with a reduction in cigarette smoking, with some smokers becoming dual users of conventional tobacco products and ECs.

The conclusion of almost all the articles addressing this issue [26,98,105] is that there is a need for well-designed trials that measure biochemically validated outcomes and adverse events, as the limitations of the existing cohort studies and clinical trials do not allow reliable conclusions to be drawn. In the same vein, the latest Cochrane review (from 2016) regarding the usefulness of e-cigarettes for smoking cessation concludes that "the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated 'low' by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) standards" [102].

Although the results are mixed, most studies comparing ECs with nicotine patches or other non-nicotine ECs as a smoking cessation aid have found no significant long-term differences [7,13,98,99,106,107].

A randomized, relatively controlled study [108] published in 2019 compared EC use with the use of NRT of the participants' choice, coupled with behavioural support, for four weeks. The study found that 18.0% of participants in the group using EC had completely abstained from conventional cigarette smoking for one year (although 80% of them were still using ECs). In comparison, the 1-year abstinence rate in the NRT group was 9.9% (and only 10% of participants were still using NRT after a year). Different conclusions can be drawn from these findings, depending on how "cessation" is defined. If cessation is considered to be quitting conventional tobacco use only while maintaining EC use (whether this constitutes cessation remains an open question, but there are some who point out that ECs do at least reduce harm), in this study EC was found to be more effective than NRT (RR: 1.83; 95% CI: 1.30–2.58). If cessation is taken to mean completely stopping cigarette smoking and other forms of nicotine use, after one year 3.6% of the group using ECs and 9.0% of the group using NRT had quit both conventional cigarettes and the treatment used, with NRT proving more effective. Those who received NRT were 2.63 times more likely (95%CI: 1.43–4.76) to achieve cessation. In any case, it is noteworthy that 82.0% of those who used ECs in this study did not quit smoking and that even the NRT success rates were below those found in a 2018 Cochrane review of specific studies of the usefulness of this pharmaceutical intervention [109].

With regard to the growing use of e-cigarettes during pregnancy, the latest Cochrane review on the subject, published in 2020, concludes that the efficacy and safety of ECs when used for smoking cessation in pregnancy is unknown [62].

Evidence on whether ECs really work for smoking or nicotine cessation is limited thus far [84]. While there is no conclusive (robust and independent) evidence on this issue, there are some data, mainly from observational studies, indicating that ECs might be effective, but at the moment this evidence is only suggestive. For this reason, the latest recommendations of WHO [7,13,92,110] and of scientific societies [106] are cautious about the usefulness of ECs for smoking cessation. In fact, ECs are not recommended as a smoking cessation method.

If at some future time ECs are shown to be useful for smoking cessation, EC manufacturers should apply for their devices to be classified as effective clinical treatments and meet the requirements set by drug regulatory agencies to be approved as such. Furthermore, their use should be monitored by various health professionals, as appropriate, as their unsupervised use has been found to be a hindrance, not an aid, to smoking cessation. If ECs are to be sold as smoking cessation aids, the current EC sales scenario will also need to change radically, as they would need to be sold in outlets licensed to sell medical devices. To date, no EC company in Spain has applied for a permit to have its products classified as a smoking cessation aid.

3.2. HARM REDUCTION

The tobacco industry has made various modifications to cigarettes over time as a strategy to change people's perception of the harm they cause (though not the actual

harm done to health). Milder blonde cigarettes, filter tips and light cigarettes have been some of the noteworthy modifications. ENDS, including e-cigarettes, heated tobacco products and others [111], are among the more recent modifications. The aim of the tobacco companies has always been to keep consumers addicted to nicotine, expand their markets (by targeting population subgroups, such as women) and attract new generations of customers in order to sustain their businesses. The strategies they have systematically used have included and continue to include: (a) direct and indirect promotion and advertising, mainly aimed at children and young people; (b) obstruction of government efforts to regulate tobacco products; and (c) manipulation of science, with the aim of sowing doubt and thus gaining time and achieving the above-mentioned aim. The oft-repeated claim that the toxicity of these products is 95% less than that of conventional cigarettes, for example, is not supported by any scientific evidence [112]: it is the result of a closed meeting, financed by the tobacco industry, following which a group of self-proclaimed experts (only some of whom were actually experts) published a paper without peer review and based on weak arguments whose conclusions would then be echoed by other media and institutions [113].

In the face of the real and potential health risks of regular EC use, as discussed above, most of the professionals working in this field consider that the precautionary principle should apply.

Harm reduction or risk reduction strategies are health strategies used to address various addictive disorders. Although they are rarely implemented at the population level (e.g., if you drink, don't drive), they are commonly applied at the individual, clinical level for high-risk individuals who have difficulties in changing their problem behaviour in the short term. Precisely for this reason, and even more so if treatment is involved, these strategies should be carried out in a healthcare setting and under the supervision of healthcare professionals using health products authorized for these uses. Individuals who are dependent on heroin, for example, receive methadone in healthcare settings; they do not buy it in tobacco shops or shopping centres.

From an individual or healthcare perspective, such a strategy might be considered on an exceptional basis for adult smokers with pathologies associated with tobacco use who have not previously been able to quit smoking through interventions carried out in healthcare settings and using methods for which there is proven scientific evidence.

If someone who meets the conditions set out in the previous paragraph comes to a professional's office seeking information or wanting to use ECs, the professional has an ethical duty to empathetically accept such requests. The next step should be to determine whether the individual adequately understands the risks of the various nicotine products and, if not (which is usually the case), the professional should endeavour to inform the person. Individuals who persist in their intention to use ECs should be told that: (1) there is no clear scientific evidence that EC use is associated with a significant reduction in the risks associated with tobacco use, so their use should not be proactively recommended; (2) EC use is a choice of the patient, who assumes

the risks of using the device and of its unpredictable side effects; (3) in all cases, the patient should be advised to use the device for a limited time (no more than 3–6 months) and should be actively warned against dual use; (4) the management of nicotine doses will have to be left up to the user, since e-cigarettes are not health products that include exact and known doses of nicotine and other components; and (5) patients should be assured that the healthcare professional remains at their disposal in the event that at some point they decide to change their problem behaviour. Healthcare professionals should not and cannot be responsible for the handling of devices that are not recognized as medical devices [114], especially when they have not been shown to be safe and are associated with a negative impact on smoking prevention, as they encourage young people to smoke and increase the potential for relapse [115].

From a public health perspective, it may at some point be deemed advisable to implement population-based tobacco harm reduction strategies. However, most professionals do not see this as justified at the present time, when the prevalence of tobacco use in the population is over 20% and many of the control measures for which there is scientific evidence of usefulness have yet to be applied (see the following section on regulation). If such strategies are eventually seen as appropriate, they would need to meet two key conditions: (1) they would be strategies controlled by public health professionals and not left to the market, and (2) they would need to be implemented in a framework aimed at denormalizing the use of tobacco and nicotine products, as advised by WHO under the FCTC, in order to avoid a decline in smoking cessation attempts and an increase in initiation of use by children and young people.

4. REGULATORY ISSUES

There are many different aspects to consider when regulating ECs or any other nicotine delivery product, starting with the electronic device itself. It is necessary to develop standard criteria regarding the disposal of their batteries, atomizers and tanks or cartridges; the composition of e-liquids and the control of the substances emitted and released from both first-hand and second-hand vaping. It is also necessary to regulate matters related to promotion and advertising, permitted areas of use, the warnings that such products must carry and how they must be presented, control of sales and taxation of e-cigarettes.

Because of the relative novelty of these products and their close association with tobacco use, as well as indirectly with medicines policies, legislation on ECs is under discussion in most countries and is continuously evolving. Big Tobacco lobbies governments to promote its interests through multiple mechanisms.

4.1. THE KEY CONCEPT IN TOBACCO CONTROL: DENORMALIZATION

The objective of public health is to make healthy behaviours the easiest behaviours to adopt. To this end, public health professionals seek to ensure that people are not

pressured – by commercial or other interests – to engage in behaviours that they will later come to regret because of the harms they entail.

The various aspects of regulation pursue a clearly defined objective: to "denormalize" and ensure that behaviours that are objectively (and according to the public's scale of values) unhealthy are not seen as normal or desirable. In contrast, the primary objective of those who promote a product is its normalization. Those who have an economic or other interest in promoting unhealthy behaviour always seek regulations that appear to be strict but do not "denormalize" the behaviour in question.

The WHO FCTC makes it clear that anything that does not take place within a "denormalizing" framework cannot really be useful. Accordingly, we need to broaden the measures aimed at controlling the nicotine dependence epidemic.

In order to achieve a denormalization of tobacco and nicotine use, all the various types of ENDS should be regulated as tobacco products. This type of uniform regulation makes it more difficult for people to start using such products, helps former smokers to avoid relapsing and facilitates smoking cessation for those who do smoke.

4.2. CURRENT REGULATORY FRAMEWORK

Regulation of ECs varies from country to country, ranging from no regulation at all to total prohibition (Japan, Brazil, Singapore, Seychelles, Uruguay and India) [116]. Some countries have introduced strict restrictions on e-cigarettes [117] and some regulate them as medicines (UK).

In Australia nicotine is classified as a "dangerous poison" and as such it is illegal to import, purchase, possess or use nicotine for vaping without a prescription, although tobacco and ECs can be sold to persons of legal age. If these products were to be approved for therapeutic use (like nicotine replacement products, which are available free of charge), the regulations would require them to be supplied only by prescription. Even then, they could not be marketed as a retail product because they are designed to resemble tobacco products.

In the US, the FDA in 2016 ruled that EC devices and e-liquids should be regulated as tobacco products and should be subject to the Agency's regulatory authority. The FDA has classified ECs as drug delivery devices and, as such, they are subject to the provisions of the Food, Drug, and Cosmetic Act (FDCA) relating to import and sale. For products that were already on the market, a premarket authorization (PMTA) must be submitted by May 2020 [118]. The FDA will evaluate various parameters, including ingredients, product characteristics and health risks, and product attractiveness to minors and non-users. Regulation is uneven across the states within the US, with 13 states equating ECs with tobacco in all respects [119]. ECs may not be used on commercial flights.

In February 2014, the European Parliament adopted a new directive (2014/40/EU), which updated the previous directive of 2001 [4]. It requires standardization and quality control of e-liquids and vaporizers, disclosure of e-liquid ingredients and child-resistant and tamper-proof protection for e-liquid packaging. Since its entry into force in May 2016, this directive has prohibited the purchase and sale of e-cigarettes to minors under the age of 18 and limited the levels of nicotine and flavouring used. The directive also limits advertising of ECs in the written press and on television and radio, but leaves the regulation of other media and of EC use in various public spaces to Member States [120]. The directive recommends that the regulation of these products should be based on a high level of public health protection.

The regulation of ECs in the UK [121] is similar to that in the EU, with some different recommendations for persons who are unsuccessful in their attempts to quit smoking. Although since 2016 the UK has had an established system for regulating ECs as drugs or drug delivery devices, all ECs currently on the market are sold as consumer products and are thus subject to the Tobacco and Related Products Regulations 2016 (a transposition of the EU directive).

In line with the EU directive, Spain has established limitations for remote sales of ENDS such as ECs and refill containers. It has also established that e-liquids may not contain more than 20 mg/ml of nicotine, that disposable cartridges or refillable tanks may not contain more than 2 ml of liquid and that refill containers may not contain more than 10 ml. In addition, it has been established that vaping liquids may not contain certain additives – such as vitamins, caffeine, taurine or others – that might suggest that the product promotes vitality or offers energy-boosting benefits or reduces health risks. The Consumer Protection Act prohibits the use of ENDS in government buildings, healthcare facilities, educational establishments (except for outdoor areas of universities and other adult educational establishments), public transport and children's playgrounds [122]. At present, throughout Spain – with the exception of the Basque Country, which classifies e-cigarettes as tobacco products – the use of ENDS in bars, nightclubs, cinemas, shopping centres or non-government workplaces is not expressly prohibited.

Unlike HTPs, for which the regulations on advertising, promotion and sponsorship are similar to those for tobacco, ENDS advertising is only prohibited on television, radio and in the written press.

In accordance with Royal Decree No. 579/2017, manufacturers and importers of ENDS and refill containers are obliged to submit, prior to marketing, information on the label and package design and the information leaflet for each brand and product type to the Ministry of Health and to the EU on the EU-CEG portal. They must also submit sales data, usage preferences and information on ingredients, adverse effects and identified health risks [123]. Although the decree does not limit the sale of ENDS to tobacconists or regulated vending machines, as is the case with conventional cigarettes, it does put them on an equal footing with conventional cigarettes with respect to the prohibition of their sale to minors, who may not be offered products that imitate the shape or characteristics of conventional cigarettes.

As noted above, the Basque Autonomous Community Addictions Act No. 1/2016 [124] establishes that the regulations applicable to conventional tobacco also apply to ENDS, both with respect to sales to minors and with respect to advertising bans and places where their use is permitted. Although other autonomous regions have the authority to adopt such regulations, they appear to be waiting for national regulations.

4.3. TAX REGULATIONS (FCTC article 6)

A well-designed tax scheme for tobacco and nicotine products is one of the key tools that can effectively contribute to prevention and control of the epidemic of nicotine dependence and its associated morbidity and mortality.

In Spain, taxes for ECs are not comparable to those for tobacco products, as ECs are not subject to excise tax. The CNPT, in line with the position taken by the National Commission for Markets and Competition [125], considers that this difference in taxation between combustible tobacco and EC products is detrimental to public health and recommends the application of specific excise taxes based on the amount of nicotine in the product, a measure that some of our neighbours in the European Union have already introduced, such as Italy and Portugal, which have rates of around €0.5/ml [126]. The aim of this tax measure is for the tax burden to be passed on in the retail price, something that will be a serious deterrent to uptake of e-cigarettes, especially among children and young people. The application of excise taxes on EC products would also help to increase control over the supply chain, resulting in stronger guarantees with respect to the safety and quality control of these products [126].

To be effective, tax equalization must be absolute — or close to absolute (85–90%) if the evidence shows a significant reduction in toxicity in some types of ENDS.

According to the Smoke Free Partnership, an organization dedicated to promoting tobacco control advocacy and policy research at the national and EU levels, the main priority for taxation of ECs is that taxes should be considered within a broader regulatory framework for these products (including product regulation, marketing, promotion and advertising, use restrictions, etc.) [127]. ECs are notified and marketed in accordance with the provisions of Article 18 of Directive 2014/40/EU on tobacco products, which extends the requirements of the tobacco directive to these products. ECs should be included in the scope of the revision of the Tobacco Tax Directive [127].

4.4. MARKETING REGULATIONS (Art. 13 of the FCTC)

The regulation of ENDS has been incomplete in terms of advertising and promotion. The large tobacco companies are taking advantage of legal loopholes concerning the use of outdoor advertising in order to create and enhance their brand image and reposition nicotine as something desirable and fashionable. To do this, in addition to the classic resources that have not yet been restricted, they are using social media, websites and influencers and celebrities, among other integrated marketing strategies.

Brands' social media and websites should be monitored to detect possible non-compliance. It is also important, as in the case of HTPs (such as IQOS), which are regulated like conventional tobacco products, to monitor their advertising and promotional activities. Examples of non-compliance by tobacco companies are being found in press releases, public relations activities and/or sponsorship of events. These companies insist that they are only promoting the technology, which has no use other than for the consumption of tobacco-related products.

It is very important to standardize advertising restrictions for both classic tobacco products and new products, mainly because the aim of all advertising is to normalize a behaviour and because the main target – though not the only one – of the ENDS business is the child and youth population, which is the population that offers the best prospects for the future (something that those in the business will of course deny, despite all the evidence to the contrary).

4.5. OTHER REGULATORY CONSIDERATIONS

According to the manifesto on the EC epidemic published by the European Network for Smoking and Tobacco Prevention (ENSP) [128], of which CNPT is a member, together with 67 other members from 34 European countries, it is not in the interest of public health to replace a very harmful product like conventional cigarettes with potentially less harmful, but still harmful and addictive, products such as e-cigarettes. In order to avoid the renormalization of smoking, ENSP recommends the following in relation to the regulation of ECs:

1. a general ban on advertising
2. a total ban on e-cigarette use in all public places where smoking is not allowed
3. A complete prohibition on flavours to limit vaping uptake by children and young people
4. A restriction on e-cigarette sales to minors
5. Comprehensive price regulation
6. The application of the Protocol to Eliminate Illicit Trade in Tobacco Products to the EC

Along the same lines, the 2018 **Madrid Declaration for Health and the Advancement of Tobacco Regulation in Spain** [129] proposes to apply the current regulation on smoke-free spaces to all related products (ECs and herbal smoking products). The aim is twofold: on the one hand, to avoid the passive toxicity that these products can cause and, on the other, to denormalize their use public places.

The aim of a broader regulatory framework for these products should therefore be to reduce the use of all tobacco products, while at the same time discouraging the use of EC products, in particular by young people and non-smokers. The regulatory and fiscal

regime needed to achieve this objective is likely to differ from country to country, owing to differences in the challenges faced, policy environments, levels of FCTC implementation, and the potential market impact of these products for the most commonly used tobacco products. Strengthening FCTC implementation remains the highest priority in terms of comprehensive policies to reduce the burden of tobacco use.

Below, we highlight the importance of bringing regulations into line with Articles 8, 9 and 18 of the FCTC:

Art. 8 of the FCTC. Involuntary exposure of the non-smoking population to the toxic contents of the aerosols emitted by ENDS may, in principle, be less harmful than exposure to conventional cigarette smoke, but evidence shows that it is not harmless. Preventing such involuntary exposure should therefore be a fundamental objective, in keeping with the precautionary principle. In addition to protecting the non-smoking population, restrictions on smoking in enclosed or semi-enclosed places also help to denormalize the various forms of use.

When the smoke or vapour produced by the earlier ECs or tanks is compared with that of more recent models, it is evident that, because of the various additives used, the latter is much more transparent, a change that is aimed at reducing the perception of toxicity on the part of those who inhale these aerosols (actively or passively).

Art. 9 of the FCTC. If the main aim of ENDS is to get smokers to stop smoking and switch to these new products, it makes no sense to allow the use of colours and flavours in the new products (or in cigarettes). What people who are dependent need is nicotine. Most of the flavours (sweet, fruity) and colours (flashy, eye-catching) are aimed first at attracting the attention and then overcoming the resistance (this is what an addictive disorder is at its core) of those who have never been smokers and of those who have never considered becoming smokers.

Art. 18 of the FCTC. Another important matter still to be regulated concerns the environmental pollution caused by ENDS. The Euromonitor market research group [41] estimates that 55 million people will be using ENDS by 2021. In addition to the impact of aerosol emissions, this will lead to a large accumulation of plastic and electronic waste (including batteries, plastic cartridges with toxic content, heavy metals, mercury and battery acid) which in turn will call for the establishment of regulated recycling schemes; otherwise, the environmental impact of ECs could be even greater than that of cigarette butts.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1. CONCLUSIONS

The Spanish health authorities have already addressed this issue on several occasions: the Interterritorial Council of the National Health System issued a document in February 2018 recommending against the use of ECs or other ENDS [92]; in January 2019 the Ministry of Health, Consumer Affairs and Social Welfare published a technical report on these new products [5]; and in October 2019 the Ministry released an information note on the action taken in response to the alert issued in the United States in connection with the use of ECs. Nevertheless, CNPT considers it urgent to better regulate the threat posed to tobacco prevention and control by the proliferation of these new products.

The tobacco epidemic is evolving towards dual use of tobacco and other related products, such as ENDS (especially e-cigarettes) and HTPs. As professionals, we need to be alert to this situation and take action in the interest of public health based on reliable, proven information.

These new products are having a negative impact on efforts to control the tobacco epidemic, as their promotion, in most cases, discourages cessation of tobacco use, and they are being promoted mainly among younger age groups with the aim of introducing them to nicotine use and addiction.

According to the manifesto on the EC epidemic [128] of the European Network for Smoking Prevention (ENSP), of which CNPT is a member, it is not in the interest of public health to replace a very harmful product like conventional cigarettes with potentially less, but still harmful and addictive, products such as e-cigarettes.

The aim of a broader regulatory framework for these products should be to reduce the use of all tobacco products, while discouraging or disincentivizing the use of new products (ENDS, HTPs, etc.), in particular by young people and non-smokers.

Although the potential toxicity of ECs is not yet known because, as with tobacco, their harmful effects are delayed, scientific evidence shows that they are by no means harmless. They are likely to be less toxic than conventional cigarettes, but it is not clear that the reduction in toxicity is significant [97]. ECs should be regulated on the basis of the precautionary principle, in the light of the available evidence and pending studies showing long-term effects. To date, the use of ECs for medical purposes cannot be envisaged, as their manufacturers have never applied to the Spanish drug regulatory agency for authorization to market them as a pharmaceutical product.

The tobacco industry, rather than being part of the solution, is part of the problem. Throughout its history, it has used numerous tricks and strategies to circumvent tobacco control measures. It has now expanded these strategies based on a deeper understanding of marketing in order to position its new products in the market and promote their use, attempting to clean up the industry's image and cultivate an aura of

healthiness, which is frequently reminiscent of the early strategies employed by the tobacco companies. The current "influencers" and the new advertising methods based on integrated marketing communication are conveying to young people and to people who wish to quit smoking a false belief in the harmlessness of ECs, which could be a major setback to the control of the tobacco epidemic.

It is clear that many of the control measures that could be implemented have not yet been applied in Spain, but it is even clearer that many of them have not been applied to the new products. HTPs are tobacco products and should be regulated as such. There is no doubt about that, although there are a few legal loopholes. Most tobacco control professionals believe that, for the sake of public health, ENDS should be regulated in the same way as tobacco.

5.2. PROPOSALS

In line with the Madrid Declaration of June 2018 [129], the following measures are proposed:

- **Increase the tax levied** on new products and devices, including ENDS, to the same or almost the same amount as the tax on tobacco products.
- **Restrict all advertising**, direct and indirect, promotion and sponsorship of these devices in the same way that tobacco advertising is restricted. Likewise, restrict advertising and promotion, even subliminal, on social media and by celebrities and influencers on the Internet, in films and on television, and hold the media accountable for the content they disseminate.
- **Expand and standardize smoke-free policies** applicable to ECs and other types of ENDS in all enclosed public spaces and in open environments where minors may be present.
- **Monitor ENDS use** and its implications for concomitant use of other drugs, especially smoked drugs such as tobacco and cannabis.
- **Restrict the use of flavourings and colourings as much as possible**, as their use is primarily aimed at attracting non-users.
- **Continue to control sales to minors** of devices, liquids and paraphernalia associated with ENDS, whether through retail outlets, the Internet or cannabis grow shops where cannabinoid-containing vaping liquids are sold.
- **Highlight the importance of the role models** provided by parents, education and health professionals, politicians and important public figures in society (sports stars, artists, influencers, etc.).
- **Promote programmes to prevent the use of addictive substances** – especially those that have become most normalized in our society, such as nicotine, cannabis and alcohol – in educational establishments, including the promotion of homes free of polluting emissions resulting from the use of addictive substances.
- **Increase social awareness**, helping the public to acquire a risk perception that reflects the reality of inhaled drugs such as nicotine and cannabis.

- **Regulate the recycling of ENDS waste**.
- **Encourage support** from healthcare providers to facilitate cessation for people with established nicotine dependence, irrespective of the product used.
- **Apply the Protocol to Eliminate Illicit Trade in Tobacco Products** (ITP) to ENDS.
- **Introduce plain packaging** for all tobacco products (a measure of proven effectiveness) and to the extent possible for all novel products, including ENDS.

These proposals can be summed up in the following **recommendations**:

1. **Legally equate** ENDS with tobacco products in terms of use, sale and purchase, labelling, emission-free spaces, advertising, promotion, sponsorship and taxation.

2. **Promote strategies aimed at providing evidence-based information** on ENDS – without conflicts of interest – by health and education professionals and the media.

3. **Reduce the use of and exposure to aerosol from these devices** in the general population and in particular among young people and pregnant women.

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