Konstantinos Farsalinos, MD, MPH

Research Associate

University of Patras, Greece

University of West Attica, Greece

Tel: +306977454837

Email: kfarsalinos@gmail.com

April 23, 2024

Subject. Submission for Spain's Draft Royal Decree amending Draft Decree 579/2017.

Introduction – About me

I am writing this letter to present the case for tobacco harm reduction considering the planned amendments in the legislation of Spain which are expected to include new regulations on tobacco harm reduction products.

I am a physician, public health expert and researcher on tobacco harm reduction, focusing on nicotine products such as electronic cigarettes and heated tobacco products. Since 2012, I have published more than 100 studies in international scientific journals, and have presented in more than 70 international conferences. My research has covered all relevant areas of tobacco harm reduction, including product safety, efficacy as smoking substitutes, clinical studies, population surveys (including analyses of the Eurobarometer and large US adult and youth population surveys), patterns of nicotine product use and policy evaluation and recommendations. I was the handling editor and one of the authors of the first scientific book on electronic cigarettes published by Elsevier USA in 2016, author of a book chapter for a German book (two editions) about electronic cigarettes and author of a chapter in a textbook of toxicology. In November 2019, I was declared as a Highly Cited Researcher 2019 by Web

of Science. This is a list of 6200 scientists (out of a total of 9 million researchers analyzed) who had the highest scientific impact worldwide in the past decade (2008-2018). I have with no commercial or other vested interests in tobacco, tobacco harm reduction or the pharmaceutical industry and I do not work or provide services for any commercial entity. My CV is available here and my published studies are available on PubMed.

The current situation in Spain

It is concerning that even today, after many years of extensive research, there is a lot of misunderstanding, misinformation, and misinterpretation of science concerning tobacco harm reduction and non-combustible nicotine products. Unfortunately, this has created confusion among regulators and the politicians, and there is a risk of creating unbalanced regulations that could have adverse public health effects. The phenomenon of misconceptions and misinterpretation has been largely evident in Spain where, in 2014, a whole campaign was launched based on the argument that glycerin in electronic cigarettes causes lipoid pneumonia and will harm users. However, this argument was biologically implausible since glycerin is an alcohol (a polyol) and not a lipid; thus, it cannot cause lipoid pneumonia.

The public health authorities in Spain have largely rejected the concept of tobacco harm reduction, unlike other countries such as the UK, New Zealand, Greece and Sweden which have been more supportive. The planned amendments, although vaguely defined until now, are expected to introduce further restrictions on harm reduction products.

Safety/risk profile of harm reduction products

To understand the safety/risk profile of any product it is important to look at the totality of evidence rather than focus on isolated studies. For example the first review of the evidence on

electronic cigarette safety included 114 references of published studies [1] while Public Health England included 415 references in their 2018 report [2], which is annually updated. Similar reviews examining the totality of evidence exist for heated tobacco products [3], while nicotine pouches represent the cleanest form of non-tobacco nicotine product, similar to pharmaceutical nicotine replacement therapies.

When reviewing the evidence from hundreds of published studies, there is no doubt today that electronic cigarettes and heated tobacco products are by far less harmful than smoking. It is crucial to emphasize that in the case of electronic cigarettes the level of risk reduction is estimated to be at least 95% (and probably more) compared to smoking [2], while some heated tobacco products have received authorization from regulatory authorities in the United States (and recently in Greece) to be marketed with "reduced exposure" information, meaning that using these products instead of smoking results in substantially reduced exposure to toxic chemicals [4].

There are many reasons for the difference in the risk profile of tobacco harm reduction products.

1. **There is no combustion in electronic cigarettes, heated tobacco products and nicotine pouches.** Nicotine pouches are oral products that do not involve any heating, while the rest heat liquid or tobacco in order to generate aerosol that the user inhales. This means that carcinogenic combustion products, which are produced due to the combustion of organic matter (tobacco) in tobacco cigarettes at temperatures that exceed 800^{o}C, are totally absent in these products. Trace amounts of thermal decomposition products from the far lower (compared to smoking) temperatures of heating are emitted, which in some cases result in lower daily exposure than breathing clean indoor air [5,6]. In a clinical

setting, vapers were found to have biomarkers of toxin exposure similar to former smokers using pharmaceutical nicotine replacement therapies or to non-smokers who did not use any other nicotine product, which were of course by far lower compared to smokers [7-9]. From a risk perspective, **it is totally inappropriate and without any scientific basis to classify electronic cigarettes, heated tobacco products and nicotine pouches in the same category as tobacco cigarettes and apply similarly restrictive regulations, since the lack of combustion means that there is no smoke produced from these products.**

2. **Ingredients in electronic cigarette liquids have a long history of safety and have been approved for human consumption through ingestion.** Glycerol and propylene glycol, the main ingredients representing > 90% of the e-liquid ingredients are non-toxic, non-carcinogenic and approved for human use in 1959 and 1982, respectively [10]. They are used in food, medications (even intravenous medications) and cosmetics for decades. All flavorings used in e-liquids are approved food flavorings. These currently represent the best options as ingredients for electronic cigarettes, acknowledging that the route of intake is different from their original intended use [10]. Nicotine use is also not associated with elevated cancer risk and is not considered a major risk factor for cardiovascular disease, despite the transient (but of no prognostic value) short-term effects on heart rate and blood pressure. The evidence on the safety profile of nicotine concerning cardiovascular and cancer risk comes from long-term epidemiological studies among snus users and is compelling [11-15].

3. **Dual use of tobacco cigarettes and harm reduction products is a normal and expected phase in the transition towards smoking abstinence and is NOT associated with higher risk compared to smoking.** Dual use is an acceptable transition period that also happens when smokers use approved nicotine replacement therapies or oral smoking cessation medications. In fact, nicotine replacement therapies have been approved by the UK MHRA as long-term complete or **partial** substitutes for smoking. Studies have shown that many dual users can effectively reduce smoking consumption, which will reduce future risk. Two studies reported that dual users of tobacco cigarettes and electronic cigarettes did not have higher level of toxin exposure compared to smokers who consumed the same amount of cigarettes [7,9]. Thus, even adding harm reduction product use to smoking is not increasing toxin exposure and may very well reduce harmful exposure by substituting part of their tobacco cigarette consumption with a lower risk source of nicotine intake. Of course, complete smoking abstinence is the ideal goal and is expected to maximize the reduction in health risk. Therefore, dual users should be encouraged to completely quit smoking. However, it will be harmful for health if a smoker who has substantially reduced cigarette consumption with the use of harm reduction products is convinced to stop dual use because the smoker will most likely relapse back to previous smoking patterns and cigarette consumption. Finally, dual use is not an argument against use of a harm reduction strategy considering that medications for smoking cessation are not only initiated through dual use but, more importantly, end-up becoming exclusive smokers (i.e. fail to quit) in the majority of cases.

4. **Nicotine is not carcinogenic and is generally of minimal risk.** Electronic cigarettes and nicotine pouches contain nicotine of pharmaceutical purity, similar to approved nicotine replacement therapies. Nicotine replacement therapies have been approved from the US

FDA and the UK MHRA for long term (even life-long) use if needed by a smoker to reduce or quit smoking and avoid relapse; this is relevant to nicotine pouches which, in reality, represent a commercial form of a nicotine replacement therapy. Contrary to popular belief, nicotine does not contribute significantly to smoking-related disease. **Nicotine is not a carcinogen.** In fact, a review of the chemistry of nicotine-containing harm reduction products (electronic cigarettes and heated tobacco products) found that **the lifetime cancer risk is reduced by 97.6% to 99.6% compared to smoking** [16], while nicotine pouches have a risk (if any) similar to nicotine replacement therapies. This represents a tremendous benefit. For diseases other than cancer, nicotine has minimal (if any) effect on the initiation and propagation of atherosclerosis and heart disease [17]. Few years ago, a landmark study found that smokers who switch from smoking to electronic cigarette use show improvements in arterial function in just 4 weeks after making the switch [18]. Importantly, the same improvement was observed in those use nicotine-containing and nicotine-free electronic cigarettes. It is known since the 1970s that "*smokers smoke for nicotine but die from the tar*" [19]. Nicotine may be necessary for smokers in order to quit the harmful use of combustible tobacco cigarettes by transitioning to substantially less harmful nicotine products. Such a transition is expected to result in substantial health benefits, as long as smokers become aware that nicotine is not the reason for smoking-related disease and premature death.

In conclusion, there is no doubt that all tobacco harm reduction products are vastly less harmful than smoking. Tobacco harm reduction product that needs to be actively endorsed by authorities and regulators as a smoking substitute. Based on currently available evidence, clinicians, healthcare providers and regulators should actively encourage smokers to switch to harm reduction products if they are unwilling and

unable to quit by themselves or with currently approved medications, since there are no other options for these people.

Tobacco harm reduction and smoking cessation

To reduce health risk, it is essential that harm reduction products are successful in substituting for smoking, and today there is compelling evidence on their smoking cessation potential. A large number of studies have examined reported reasons for regular, frequent and sustained use among the population as well as the association between harm reduction products, mainly electronic cigarettes, and smoking status in population studies and in clinical trials.

1. **The vast majority of regular electronic cigarette and heated tobacco product users are current or former smokers.** This is clear evidence that electronic cigarettes are appealing predominantly to people with a positive smoking history. In the European Union, 92.7% of current electronic cigarette users are current or former smokers [20]. Similar findings have been observed elsewhere as well as in specific European Union member states. In the US, data from the CDC National Health Interview Survey show that 90.9% of daily electronic cigarette users are current or former smokers [21]. In Greece, 98.5% of current electronic cigarette users were current or former smokers [22]. In the UK, 93.9% of current electronic cigarette users are current or former smokers [23]. Similar findings were observed when analyzing heated tobacco product use [24].

2. **Population studies have found strong associations between electronic cigarette use and having quit smoking, while cigarette sales were reduced at an accelerated rate after the introduction of heated tobacco products.** In the US, current daily electronic

cigarette users had > 3 times higher odds of having quit smoking compared to never electronic cigarette users [25,26]. In Greece, current daily electronic cigarette users had almost 11 times higher odds of having quit smoking compared to never electronic cigarette users [27]. In the European Union, current daily electronic cigarette users had 3-5 times higher odds of having quit smoking compared to never-users of electronic cigarettes [28]. In the US, it was found that the substantial increase in electronic cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level [29]. The authors emphasized that this was the first statistically significant increase observed in population smoking cessation among US adults in nearly a quarter of a century.

3. **Clinical trials have shown that electronic cigarettes are more effective than approved nicotine replacement therapies in smoking cessation.** A study examined smoking cessation at 1 year and identified that twice more smokers managed to quit when using electronic cigarettes than when using pharmaceutical nicotine products [30]. Another study found that among pregnant smoking women, electronic cigarettes were twice more effective than nicotine replacement therapies for smoking cessation [31]. Importantly, their safety for use in pregnancy was similar to that of nicotine patches. A Cochrane systematic review of the literature, analyzing 88 clinical studies, reported that there is high certainty evidence that quit rates were higher in people randomized to nicotine-containing electronic cigarettes than in those randomized to pharmaceutical nicotine replacement therapy products [32].

4. **Heated tobacco products have largely displaced tobacco cigarettes.** Japan was the first country where heated tobacco products were introduced, in late 2015. An analysis of the trends in tobacco cigarette sales in Japan from 2011 to 2019 found that domestic cigarette sales in Japan declined at an accelerated pace since 2016 following the introduction of these products into the Japanese national marketplace [33]. An overall reduction in total sales of heated and combustible tobacco products was observed, but the decline in tobacco cigarette sales since the introduction of heated tobacco products into the market was 5-fold higher compared to the trend before they were marketed. Another study reported that per capita cigarette sales were increasing at a rate of 0.10 to 0.14 (depending on statistical approach) per month before the introduction of heated tobacco in Japan but declined at a rate of 0.63 to 0.66 cigarettes per month after heated tobacco products became available [34]. It has been reported that tobacco cigarette sales in Japan have been reduced from 180 billion cigarettes in 2015 (just before heated tobacco products became available) to less than 100 billion in 2022.

In conclusion, currently available evidence strongly supports the potential of tobacco harm reduction products, particularly electronic cigarettes, in helping smokers quit. This is particularly important for smokers unable or unwilling to quit with currently approved medications. It is well-established that approved smoking cessation medications have limited success (approximately 7% long-term success rate for nicotine replacement therapies and 20-25% for oral medications), are not popular among smokers and have a significant cost to the government and the tax payers due to the healthcare resources needed. Tobacco harm reduction products represent additional, self-funded by the smoker, smoking cessation aids that should be actively endorsed when medications fail or are not an acceptable option. **Their smoking cessation potential can be translated into a substantial reduction in health risk**

among those who successfully switch from smoking to harm reduction product use, as long as a balanced and appropriate regulation is implemented in order to provide smokers the opportunity to make the switch. This is not simply a subjective theoretical approach. There is the real world example of Sweden, the only smoke-free country in Europe. Sweden has managed to become smoke-free only because of the adoption by the population of a harm reduction product, snus. Not only has Sweden eliminated smoking, particularly among men, but it has also experienced tremendous population health benefits, having by far lower death rates from tobacco related lung cancer, cancer in other organs and cardiovascular disease compared with the rest of the EU.

Flavors in electronic cigarettes

Globally, there is a heated debate concerning the availability of flavors in electronic cigarettes. Spain appears to consider introducing restrictions in flavor availability for electronic cigarettes. Some argue that such measures are necessary since non-tobacco flavors are marketed in order to attract youth. However, this is not the case.

1. **Adult users, particularly former smokers, also use multiple and, in most cases, predominantly non-tobacco flavors.** There is a lot of evidence from cross-sectional surveys that non-tobacco flavors, particularly fruit, sweet, and dessert flavors, are very popular among adult vapers, especially those who have managed to quit smoking with the help of electronic cigarettes. In fact, variability of flavors is crucial in order for adult smokers to choose the appropriate product to substitute for smoking, and they are important in their efforts to quit and to avoid relapse back to smoking [35-37]. The same studies have also showed a clear transition from tobacco to non-tobacco flavors over time, which may represent an opportunity to prevent relapse to smoking by moving further

away from the experience and flavor that resembles tobacco cigarettes. Characteristically, a US study following-up 383 adult vapers for 5 years identified that preference to tobacco flavors was reduced by almost 50% while preference for chocolate, candy and other sweet flavors almost doubled [38]. Importantly, 98.2% of these vapers were more than one flavor on a regular basis, with tobacco being the preferred flavor for only 11.2% of them.

2. **Flavors in electronic cigarettes can play an important role in smoking cessation.** Vapers choose products based on self-preference and satisfaction. It is important that products are appealing and pleasant for smokers in order to serve as effective smoking substitutes. Former-smoking electronic cigarette users report that switching between flavors within the same day is common and that regular use of multiple e-liquid flavors was associated with significantly higher odds of having quit smoking, with fruit and sweet flavors being the most popular choices among established long-term vapers [35]. A longitudinal study examining factors associated with past 30-day abstinence from cigarette smoking among people buying an electronic cigarette, found that non-tobacco flavors users were 30% more likely to report smoking abstinence compared to those using tobacco flavor [39]. Data from the 2018–2019 Tobacco Use Supplement-Current Population Survey (TUS-CPS) survey showed that smokers who used electronic cigarettes with nontobacco flavors were more likely to make a quit attempt and to successfully quit compared to those exclusively using non-flavored or tobacco-flavored electronic cigarettes [40]. An analysis of the waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) Study focusing on young adults reported that electronic cigarette users with one and multiple non-tobacco/non-menthol flavors were more likely to have reduced or quit smoking over the past year compared to non-electronic cigarette users [41]. Another analysis of waves 1 to 4 of the PATH survey found that vaping non-

tobacco flavors was no more associated with youth smoking initiation than vaping tobacco flavors but was associated with increased adult smoking cessation [42]. A study following-up 886 dual users for 2 years (from 2016 to 2018) reported that use of fruit and other sweet flavored e-liquids is positively related to smokers' transition away from cigarettes compared to users of tobacco flavors [43]. Finally, a recent systematic review concluded that the availability of a variety of flavors in electronic cigarettes is one of two main factors in electronic cigarettes appeal among adult smokers, and might facilitate complete substitution for cigarettes [44].

3. **Flavors are not the main reason for electronic cigarette use among youth, while youth are mainly experimenting with use.** Analysis of the 2019 National Youth Tobacco Survey, performed in the United States by the CDC, showed that flavors were only the third most popular reason for trying electronic cigarettes [45]. Even among youth, current smokers were more than 11 times more likely to report current electronic cigarette use compared with adolescents who were not current smokers [46,47]. Frequent electronic cigarette use was reported by less than 1% of never-smoking adolescents [47]. Similar findings were reported from the Monitoring the Future Survey in the US [48]. Frequent-smoking youth were 17 times more likely to be current electronic cigarette users compared to never-smoking youth [49]. This clearly shows that regular/frequent electronic cigarette use is mainly confined to smoking youth. Additionally, another study concluded that the data from the CDC NYTS do not support claims of a new epidemic of nicotine addiction stemming from the use of electronic cigarettes [50]. Among current electronic cigarette users who had never tried tobacco products, responses consistently pointed to minimal dependence. An analysis of several surveys across Great Britain, Scotland and Wales consistently found that most electronic cigarette use by youth is

experimentation and does not turn into regular use, while levels of regular use among young people who have never smoked remained very low [51]. It is important to note that restrictions of flavors may have the unintended consequence of increasing tobacco cigarette use. Data from the United States suggest that there are increased smoking rates among adolescents in states with stricter regulation compared to those with less strict regulations on electronic cigarettes [52,53]. Finally, considering that flavors in electronic cigarettes are mainly derived from the food industry, restrictions are expected to result in the creation of a black market, which would very likely approach vulnerable population groups such as youth.

4. **The claims about a gateway-to-smoking effect of electronic cigarettes (or other harm reduction products) among youth has been rejected by the unprecedented decline in smoking rates, which are down to historically low levels during the growing popularity of electronic cigarettes.** While this has been the main argument for implementing strict regulations, official CDC data show that during the period of growing electronic cigarette popularity and (largely experimental) use, the smoking rates have been declined at a much faster rate compared to previously, and the US is now experiencing a smoke-free generation among youth. Specifically, among middle school students in the US, the current smoking rate declined from 4.3% in 2011 to 1.1% in 2023, while among high school students the rate went down from 15.8% in 2011 to 1.9% in 2023 (data from the US CDC). In reality, the next generation of adult Americans will be a smoke-free generation. This dramatic decline in smoking rates was not found to be undermined by the growing popularity of e-cigarettes after 2013; instead, a more rapid decline was observed during that period [54]. These findings once again completely reject

the “gateway theory”, proving once again that the common liability model is more appropriate to explain such behaviors.

In conclusion, any regulation on electronic cigarette flavors should consider the balance between protecting from unintended use by some population subgroups (e.g. by adolescents or never smokers) and avoiding adverse effects and potential harm to other subgroups (e.g. by preventing smokers from switching to electronic cigarettes in a harm reduction approach to quitting smoking). The data suggest that an overly-restrictive regulation, such as banning the sales of specific flavor groups (especially fruit and dessert/pastry/bakery or other sweet flavors), will have unintended consequences, preventing smokers from switching to electronic cigarette use and/or increasing the relapse rate among former smokers who have managed to quit with the help of electronic cigarettes. Such restrictions will simply make the products less appealing to smokers. Due to the harm reduction potential and related health benefits of switching from smoking to electronic cigarette use, any regulatory decisions are substantially more complex than the past decisions to ban flavors in tobacco cigarettes. An oversimplified approach based on the argument of the past ban on tobacco cigarette flavors cannot be applicable in the case of electronic cigarettes (or other harm reduction products) since, unlike tobacco cigarettes which do not provide any benefits but only cause harm, electronic cigarettes have strong public health prospects by acting as substitutes for smoking. This applies not only to flavors but to the overall regulatory framework concerning availability, variability, accessibility, education and communication about electronic cigarettes. Furthermore, banning flavors will likely result in the development of an uncontrolled and unregulated black market, which will approach youth since the latter represent a vulnerable population group, and create unnecessary risks due to questionable

product quality and ingredients. In reality, a ban on flavors will protect none but will harm many, particularly smokers and former smokers.

Recommended regulatory framework for tobacco harm reduction products

For tobacco harm reduction to be an effective public health strategy, the future regulatory environment in Spain needs to be needs to be improved and be based on evidence. **Regulation should clearly differentiate harm reduction products from tobacco cigarettes, and consider these products as a valuable tool and an ally in smoking control.**

The principles that should be followed to change the current regulatory framework are:

1. **Regulation should be clearly based on the risk-proportionate principle.** This represents the only proper approach and has been commonly applied to the regulation of any product. Evidence on risk determines the levels of restrictions that need to be implemented. As presented above, there is compelling and undisputed evidence on the very low risk of tobacco harm reduction products, especially when compared with the devastating effects of smoking.

2. **Regulation should be realistic, ensure product availability and accessibility, and allow for innovation and rapid adoption of technological evolution.** It would make little sense to create a regulation that would be expensive or difficult to implement and comply. Additionally, flavor restrictions will limit accessibility, variability and appeal for adult smokers. This would result in the elimination of a large proportion of currently-available tobacco harm reduction products, which incentivizes the creation of an

uncontrolled black market. Both consequences will end-up in indirectly protecting the status quo, which is a nicotine market consisting mostly of tobacco cigarettes. Additionally, no quality standards can be expected from back market products. As for youth, they will in fact be specifically targeted by the black market since they represent a vulnerable population group. Rapid technological evolution has resulted in improvement in performance, efficacy and safety of tobacco harm reduction products. Innovation should be encouraged. Currently available products are safer and more effective as smoking substitutes than the products available few years ago because of using better materials, having better functional characteristics and providing a better experience for smokers. Thus, recent products are more effective in alleviating smoking and nicotine cravings. Hurdles to the availability and accessibility of tobacco harm reduction products are unintentionally protecting tobacco cigarette sales. Characteristically, the decision of some countries to ban the sales of nicotine pouches, products that are similar to pharmaceutical nicotine replacement therapies and are, thus, associated with the most minimal of risks, creates the irrational reality of allowing the legal sales and access to the most lethal nicotine-containing product (tobacco cigarettes) while banning the least harmful product (pouches).

3. **Regulation should ensure that tobacco harm reduction product marketing is not banned but is carefully regulated in order to target smokers only.** The regulation should of course maintain the ban on the sales of these products to people younger than 18 years old. Heavy fines and other consequences should be adopted for those violating the ban. A prohibitive regulatory framework on marketing to adults will, however, prevent smokers from being educated and informed about the potential of tobacco harm reduction products to reduce their health risk when used as smoking substitutes.

4. **Regulation should create a competitive advantage for tobacco harm reduction products compared to tobacco cigarettes.** Unfortunately, tobacco cigarettes are very cheap to produce and generate substantial profits for the industry. Tobacco harm reduction products are innovative technological products; thus, they are by definition more expensive to produce than tobacco cigarettes. Regulation should ensure that smokers are motivated to switch to lower-risk nicotine products and completely quit smoking. Product cost is a major motive for smokers to try and use alternative to smoking products. Therefore, any taxation policy, which ideally should not include any excise tax, should ensure that they remain substantially cheaper than tobacco cigarettes. In fact, it would ironic to implement additional taxation to tobacco harm reduction products as a measure to deter use, since they represent the biggest competitor to tobacco cigarettes today and they are used as smoking substitutes. A recent study in the US found that taxing electronic cigarettes results in an increase in tobacco cigarette sales [55]. Certainly this is not the intention of the Spanish government. Additionally, smokers should have easier access to harm reduction products than to tobacco cigarettes. A regulated and, thus, carefully controlled marketing strategy for these products is essential in order to target, inform and educate smokers about the existence and value of such alternative-to-smoking products in improving their health. Additionally, products should contain enough nicotine; otherwise, consumer will simply continue to smoke in order to obtain the nicotine they need. High nicotine levels and variability of flavors were found to be the two major determinants of the attractiveness of electronic cigarettes among adult smokers, while non-tobacco flavors have been found to promote smoking cessation. Similar associations are expected with other harm reduction products.

5. **Regulation should classify tobacco harm reduction products as consumer products with specific rules and restrictions.** The success of these products as smoking substitutes is based on their use as consumer products rather than a therapeutic intervention. They are used according to smokers' preferences and needs, while choice also depends on personal taste and preference. This can only be ensured through a regulatory framework of characterizing these products as consumer products with the restrictions mentioned above, but with a clear differentiation between these products and tobacco cigarettes.

6. **Regulation should introduce reduced-risk labeling or, at least, reduced exposure messages in tobacco harm reduction products.** The main incentive for smokers to quit is to reduce health risks. The current environment is characterized by gross misinformation and misperceptions among the population, especially smokers, about the relative risk of harm reduction products compared to smoking. Most smokers wrongly believe that these products are equally or even more harmful than smoking. This is unacceptable and harmful for public health. A possible future intention to introduce negative messages in packaging and labelling, such as plain packaging and graphical or text health warnings, is expected to deteriorate the level of misinformation and misperceptions. Instead, regulatory authorities should consider adding messages that clearly differentiate these products from tobacco cigarettes and present the reduced risk potential for cancer and other disease conditions. This is a simple display of honesty and would represent messaging that is fully supported by current scientific knowledge. There is already evidence that inappropriate health warnings may inadvertently deter smokers from initiating use and substituting their tobacco smoking for electronic cigarettes use [56], while a message that electronic cigarettes are much less harmful than smoking

encourage more smokers to switch without resulting in increased uptake among non-smokers [57]. It is also ironic that regulatory authorities in Greece and in the US (FDA) have approved a reduced exposure claim for heated tobacco products, while the Spanish government would consider introducing warnings about harm from these products. The latter would represent a clear message to smokers than all nicotine product are of equal risk, a message that would clearly discourage them of attempting to quit smoking through the use of these products. **Instead, a message about reduced risk or reduced exposure from tobacco harm reduction product use compared to smoking is evidence-based and represents the truth that citizens in Spain (particularly smokers) are entitled to know.**

An outline of recommendations for an appropriate regulatory framework is provided in a table at the end of this document.

Conclusions

Smoking is the most important, preventable risk factor for cancer, cardiovascular and respiratory disease. **Currently available evidence is compelling in supporting the vastly lower risk potential of tobacco harm reduction products compared to tobacco cigarettes, the efficacy of these products as smoking substitutes and the large benefits expected in the health of smokers who switch to the use of these products.** This scientific reality should be translated into proper regulatory decisions.

Spanish citizens are entitled to appropriate information about the availability and the benefit of switching from smoking to harm reduction products. These products represent an opportunity for tremendous public health benefits. It should be reminded that public health is

about preventing disease and premature death, while judging behaviors (i.e. nicotine use) represents a moralistic approach with little relevance to public health.

The endorsement of harm reduction products as part of a comprehensive smoking control strategy, complementing all other smoking control measures, is reasonable, essential and evidence-based, and it is expected to have a significant positive public health impact in Spain.

I remain at your disposal and I would be glad to provide further insight and perhaps participate in meetings where I could present further evidence on the prospects of tobacco harm reduction products in reducing smoking-related disease and death and comments on specific articles of the new legislation, once announced in detail.

Note. A table and references are provided in the following pages.

With respect,

Konstantinos Farsalinos, MD, MPH

Table. Proposals for a regulatory framework on electronic cigarettes as a tobacco harm reduction strategy.

Regulatory rules	Rationale - evidence	Benefit
Classification		
Different classification for harm reduction products vs. tobacco cigarettes.	Electronic cigarettes and nicotine pouches do not contain any tobacco, while no harm reduction product produces smoke. Nicotine has minimal adverse health effects and is not carcinogenic. The lack of combustion is a main determinant of the risk difference between tobacco cigarettes and harm reduction products.	It will be easier for smokers to understand the difference in function, characteristics and risk between the products.
Different restrictions on harm reduction products vs. smoking.	Restrictions should be based on a risk continuum and be evidence-based. For example, while banning smoking in closed public places is scientifically justified, current evidence suggests no substantial health harm from second-hand exposure to harm reduction products.	Smokers will better understand the difference in risk between products, and might be more motivated to quit by switching to harm reduction product use.
Product quality		
Reasonable quality standards for harm reduction products.	While harm reduction product do not involve combustion, this cannot justify the liberal use of any compound without considering known and potential risks. Standards should be reasonable and easy to comply, to avoid creating a monopoly (e.g. by big tobacco companies).	Ensure product quality for consumers, further minimize potential risks. The current European Union model of setting quality standards is a good example, and there is no reason to apply further restrictions that would limit variability and/or increase product cost.

Registration of all products through a transparent and rapid process that allows innovation.	As for any consumer product, regulation needs to clearly record the products that are available to consumers. The process will ensure compliance with all other regulatory decisions. Prevent unnecessary delays in introducing new innovations.	Avoid the creation of a "black market" and the marketing of products with questionable quality. Ensure that any new knowledge or information about risks will be addressed while technological improvements in safety and performance enter the market rapidly.
Availability, accessibility and promotion		
Regulated (but not banned) marketing that targets smokers only.	Harm reduction products are intended to be used as smoking substitutes and not as a new "trendy" habit for everyone to adopt. Smokers need to be informed about the availability of these products and their potential benefits when substituting for tobacco cigarettes. Deliver a clear message that the best approach is for people to quit smoking without using any alternative product, but harm reduction products are definitely an option for those unable to quit. Harm reduction products should supplement (not substitute) all other tobacco control efforts.	Ensure that harm reduction products are appealing to smokers only and are not attractive to non-smokers. Allow smokers to make informed decisions about their health. Provide an additional option for smokers unable or unwilling to quit by themselves or with currently-approved methods. Endorsing tobacco harm reduction as an acceptable tool and an ally in smoking control.
Ban on the sales to youth (< 18 years old)	Ensure minimal access of youth to harm reduction products.	Prevent harm reduction products from being a new "trend" among youth.
Increased accessibility of harm reduction products.	While tobacco cigarettes are available everywhere and are easily accessible, sales points for harm reduction products, particularly electronic cigarettes are limited. Online sales improve accessibility to a harm reduction product. Any restrictions will unintentionally protect the sales of the most accessible and available product (i.e. tobacco cigarettes).	Accessibility to harm reduction products must be facilitated for smokers. Accessibility to tobacco cigarettes should be limited.

Packaging/labeling warnings on harm reduction products should be confined to the dependence potential of nicotine. Messages about reduced risk or reduced exposure from harm reduction product use compared to smoking should be added.	Health warnings are scientifically justified for tobacco cigarettes (and other combustible products). There is no scientific evidence on the introduction of warnings about health risks from harm reduction products. A warning about the dependence potential of nicotine is justified. Messages about risk reduction from harm reduction products compared to tobacco cigarettes are based on overwhelming currently-available evidence.	Smokers will better understand the risk difference between products. People who do not want to develop dependence on nicotine will be warned against the use of nicotine-containing products. Smokers should and need to know the truth that harm reduction products are expected to substantially reduce health risks compared to smoking.
Substantially reduced or (preferably) no taxation for harm reduction products.	Financial incentives should be used to convince more people to switch from tobacco cigarettes to harm reduction products.	Reduced price will allow more smokers to afford harm reduction products.
Research on innovation and monitoring of use		
Facilitation of innovation and introduction of new products, including local production.	Product innovation over time has created safer and more effective and satisfying products for smokers. Product variability is needed because choice is based on self-preference. Local production will likely reduce product cost.	Better-performing products that smokers like to use can increase smoking substitution rates. Safer products will further minimize potential risks. Reduced product cost will enhance the accessibility of more smokers to harm reduction products and provide additional motivation to switch.

References

1. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf. 2014 Apr;5(2):67-86. doi: 10.1177/2042098614524430.
2. Public Health England. Evidence review of e-cigarettes and heated tobacco products. 2018. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf
3. Tattan-Birch H, Hartmann-Boyce J, Kock L, Simonavicius E, Brose L, Jackson S, Shahab L, Brown J. Heated tobacco products for smoking cessation and reducing smoking prevalence. Cochrane Database Syst Rev. 2022 Jan 6;1(1):CD013790. doi: 10.1002/14651858.CD013790.pub2.
4. FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information
5. Farsalinos KE, Voudris V. Do flavouring compounds contribute to aldehyde emissions in e-cigarettes? Food Chem Toxicol. 2018 May;115:212-217. doi: 10.1016/j.fct.2018.02.059.
6. Farsalinos KE, Kistler KA, Pennington A, Spyrou A, Kouretas D, Gillman G. Aldehyde levels in e-cigarette aerosol: Findings from a replication study and from use of a new-generation device. Food Chem Toxicol. 2018 Jan;111:64-70. doi: 10.1016/j.fct.2017.11.002.
7. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. Ann Intern Med. 2017 Mar 21;166(6):390-400. doi: 10.7326/M16-1107.
8. Akiyama Y, Sherwood N. Systematic review of biomarker findings from clinical studies of electronic cigarettes and heated tobacco products. Toxicol Rep. 2021 Jan 27;8:282-294. doi: 10.1016/j.toxrep.2021.01.014. PMID: 33552927; PMCID: PMC7850959.
9. Stokes AC, Xie W, Wilson AE, Yang H, Orimoloye OA, Harlow AF, Fetterman JL, DeFilippis AP, Benjamin EJ, Robertson RM, Bhatnagar A, Hamburg NM, Blaha MJ. Association of Cigarette and Electronic Cigarette Use Patterns With Levels of Inflammatory

and Oxidative Stress Biomarkers Among US Adults: Population Assessment of Tobacco and Health Study. Circulation. 2021 Feb 23;143(8):869-871. doi: 10.1161/CIRCULATIONAHA.120.051551.

10. Farsalinos K, Gillman GI, Hecht SS, Polosa R, Thornburn J. Analytical Assessment of e-Cigarettes. From Contents to Chemical and Particle Exposure Profiles. Elsevier, 2017. ISBN: 978-0-12-811241-0.
11. Araghi M, Galanti MR, Lundberg M, Liu Z, Ye W, Lager A, Engström G, Alfredsson L, Knutsson A, Norberg M, Wennberg P, Lagerros YT, Bellocco R, Pedersen NL, Östergren PO, Magnusson C. No association between moist oral snuff (snus) use and oral cancer: pooled analysis of nine prospective observational studies. Scand J Public Health. 2021 Dec;49(8):833-840. doi: 10.1177/1403494820919572.
12. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Engström G, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Pedersen NL, Trolle Lagerros Y, Ostergren PO, Magnusson C. Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival. J Intern Med. 2014 Jul;276(1):87-95. doi: 10.1111/joim.12219.
13. Lee PN. Summary of the epidemiological evidence relating snus to health. Regul Toxicol Pharmacol. 2011 Mar;59(2):197-214. doi: 10.1016/j.yrtph.2010.12.002.
14. Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. BMC Med. 2009 Jul 29;7:36. doi: 10.1186/1741-7015-7-36.
15. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Nilsson P, Pedersen N, Trolle Lagerros Y, Ostergren PO, Magnusson C. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. Eur J Epidemiol. 2012 Oct;27(10):771-9. doi: 10.1007/s10654-012-9704-8.
16. Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 2017 Aug 4. pii: tobaccocontrol-2017-053808. doi: 10.1136/tobaccocontrol-2017-053808.
17. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004 May 19;43(10):1731-7.

18. George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, Donnan PT, Khan F, Lang CC. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. J Am Coll Cardiol. 2019 Nov 13. pii: S0735-1097(19)38193-8. doi: 10.1016/j.jacc.2019.09.067.
19. Russell MA. Low-tar medium-nicotine cigarettes: a new approach to safer smoking. Br Med J. 1976 Jun 12;1(6023):1430–1433.
20. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. Addiction. 2016 Nov;111(11):2032-2040. doi: 10.1111/add.13506.
21. Farsalinos KE, Polosa R, Cibella F, Niaura R. Is e-cigarette use associated with coronary heart disease and myocardial infarction? Insights from the 2016 and 2017 National Health Interview Surveys. Ther Adv Chronic Dis. 2019 Sep 27;10:2040622319877741. doi: 10.1177/2040622319877741.
22. Farsalinos KE, Siakas G, Poulas K, Voudris V, Merakou K, Barbouni A. Electronic cigarette use in Greece: an analysis of a representative population sample in Attica prefecture. Harm Reduct J. 2018 Apr 13;15(1):20. doi: 10.1186/s12954-018-0229-7.
23. ASH UK. Use of e-cigarettes (vaporisers) among adults in Great Britain. Available at: https://ash.org.uk/wp-content/uploads/2019/09/Use-of-e-cigarettes-among-adults-2019.pdf.
24. Panagiotakos DB, Georgoulis M, Kapetanstrataki M, Behrakis P. Prevalence, patterns, and determinants of electronic cigarette and heated tobacco product use in Greece: A cross-sectional survey. Hellenic J Cardiol. 2023 Mar-Apr;70:10-18. doi: 10.1016/j.hjc.2023.01.002.
25. Farsalinos K, Niaura R. E-cigarettes and smoking cessation in the United States according to frequency of e-cigarette use and quitting duration: analysis of the 2016 and 2017 National Health Interview Surveys. Nicotine Tob Res. 2019 Feb 15. pii: ntz025. doi: 10.1093/ntr/ntz025.
26. Giovenco DP, Delnevo CD. Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. Addict Behav. 2018 Jan;76:129-134. doi: 10.1016/j.addbeh.2017.08.002. Epub 2017 Aug 3.
27. Farsalinos K, Siakas G, Poulas K, Voudris V, Merakou K, Barbouni A. E-cigarette use is strongly associated with recent smoking cessation: an analysis of a representative population

sample in Greece. Intern Emerg Med. 2019 Sep;14(6):835-842. doi: 10.1007/s11739-018-02023-x.

28. Farsalinos K, Barbouni A. Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13057 Europeans from 28 countries. Tob Control. 2020 Feb 3. pii: tobaccocontrol-2019-055190. doi: 10.1136/tobaccocontrol-2019-055190.
29. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ. 2017 Jul 26;358:j3262. doi: 10.1136/bmj.j3262.
30. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med. 2019 Feb 14;380(7):629-637. doi: 10.1056/NEJMoa1808779.
31. Hajek P, Przulj D, Pesola F, Griffiths C, Walton R, McRobbie H, Coleman T, Lewis S, Whitemore R, Clark M, Ussher M, Sinclair L, Seager E, Cooper S, Bauld L, Naughton F, Sasieni P, Manyonda I, Myers Smith K. Electronic cigarettes versus nicotine patches for smoking cessation in pregnancy: a randomized controlled trial. Nat Med. 2022 May;28(5):958-964. doi: 10.1038/s41591-022-01808-0.
32. Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Livingstone-Banks J, Morris T, Hartmann-Boyce J. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2024 Jan 8;1(1):CD010216. doi: 10.1002/14651858.CD010216.pub8.
33. Cummings KM, Nahhas GJ, Sweanor DT. What Is Accounting for the Rapid Decline in Cigarette Sales in Japan? Int J Environ Res Public Health. 2020 May 20;17(10):3570. doi: 10.3390/ijerph17103570.
34. Stoklosa M, Cahn Z, Liber A, Nargis N, Drope J. Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. Tob Control. 2020 Jul;29(4):381-387. doi: 10.1136/tobaccocontrol-2019-054998.
35. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. Int J Environ Res Public Health. 2013 Dec 17;10(12):7272-82. doi: 10.3390/ijerph10127272.

36. Farsalinos K, Russel C, Lagoumintzis G, Poulas K. Patterns of flavored e-cigarette use among adults vapers in the United States: an internet survey. Submitted to the FDA docket No. FDA-2017-N-6565. Available at: https://www.regulations.gov/document?D=FDA-2017-N-6565-22941.

37. Russell C, McKeganey N, Dickson T, Nides M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. Harm Reduct J. 2018;15(1):33.

38. Du P, Bascom R, Fan T, Sinharoy A, Yingst J, Mondal P, Foulds J. Changes in Flavor Preference in a Cohort of Long-Term Electronic Cigarette Users. Ann Am Thorac Soc. 2020 May;17(5):573-581. doi: 10.1513/AnnalsATS.201906-472OC.

39. Russell C, Haseen F, McKeganey N. Factors associated with past 30-day abstinence from cigarette smoking in adult established smokers who used a JUUL vaporizer for 6 months. Harm Reduct J. 2019 Nov 7;16(1):59. doi: 10.1186/s12954-019-0331-5.

40. Mok Y, Jeon J, Levy DT, Meza R. Associations Between E-cigarette Use and E-cigarette Flavors With Cigarette Smoking Quit Attempts and Quit Success: Evidence From a U.S. Large, Nationally Representative 2018-2019 Survey. Nicotine Tob Res. 2023 Feb 9;25(3):541-552. doi: 10.1093/ntr/ntac241.

41. Chen JC. Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation-A Large National Study among Young Adult Smokers. Subst Use Misuse. 2018 Oct 15;53(12):2017-2031. doi: 10.1080/10826084.2018.1455704.

42. Friedman AS, Xu S. Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation. JAMA Netw Open. 2020 Jun 1;3(6):e203826. doi: 10.1001/jamanetworkopen.2020.3826.

43. Li L, Borland R, Cummings KM, Fong GT, Gravely S, Smith DM, Goniewicz ML, O'Connor RJ, Thompson ME, McNeill A. How Does the Use of Flavored Nicotine Vaping Products Relate to Progression Toward Quitting Smoking? Findings From the 2016 and 2018 ITC 4CV Surveys. Nicotine Tob Res. 2021 Aug 18;23(9):1490-1497. doi: 10.1093/ntr/ntab033.

44. Gades MS, Alcheva A, Riegelman AL, Hatsukami DK. The Role of Nicotine and Flavor in the Abuse Potential and Appeal of Electronic Cigarettes for Adult Current and Former Cigarette and Electronic Cigarette Users: A Systematic Review. Nicotine Tob Res. 2022 Aug 6;24(9):1332-1343. doi: 10.1093/ntr/ntac073.
45. US CDC. Youth and Tobacco Use. 2019, November 8. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm
46. Villanti AC, Pearson JL, Glasser AM, Johnson AL, Collins LK, Niaura RS, Abrams DB. Frequency of youth e-cigarette and tobacco use patterns in the U.S.: Measurement precision is critical to inform public health. Nicotine Tob Res. 2017;19(11):1345-1350. doi: 10.1093/ntr/ntw388.
47. Farsalinos K, Tomaselli V, Polosa R. Frequency of Use and Smoking Status of U.S. Adolescent E-Cigarette Users in 2015. Am J Prev Med. 2018 Jun;54(6):814-820. doi: 10.1016/j.amepre.2018.03.003.
48. Warner KE. Frequency of E-Cigarette Use and Cigarette Smoking by American Students in 2014. Am J Prev Med. 2016;51:179-184.
49. Farsalinos K, Barbouni A, Niaura R. Changes from 2017 to 2018 in e-cigarette use and in ever marijuana use with e-cigarettes among US adolescents: analysis of the National Youth Tobacco Survey. Addiction. 2021 Jan;116(1):139-149. doi: 10.1111/add.15162.
50. West R, Brown J, Jarvis M. Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey reveal about high school e-cigarette use in the USA? (Preprint). Qeios 2019;ID: 745076.3. doi. 10.32388/745076.3.
51. Bauld L, MacKintosh AM, Eastwood B, Ford A, Moore G, Dockrell M, Arnott D, Cheeseman H, McNeill A. Young People's Use of E-Cigarettes across the United Kingdom: Findings from Five Surveys 2015-2017. Int J Environ Res Public Health. 2017 Aug 29;14(9). pii: E973. doi: 10.3390/ijerph14090973.
52. Friedman AS. How does electronic cigarette access affect adolescent smoking? J. Health Econ. 2015;44:300–8. doi. 10.1016/j.jhealeco.2015.10.003.
53. Pesko MF, Hughes JM, Faisal FS. The influence of electronic cigarette age purchasing restrictions on adolescent tobacco and marijuana use. Prev Med. 2016;87:207-212. doi: 10.1016/j.ypmed.2016.02.001.

54. Delnevo CD, Villanti AC. Dramatic Reductions in Cigarette Smoking Prevalence among High School Youth from 1991 to 2022 Unlikely to Have Been Undermined by E-Cigarettes. Int J Environ Res Public Health. 2023 Sep 30;20(19):6866. doi: 10.3390/ijerph20196866.
55. Chad D. Cotti, Charles J. Courtemanche, Johanna Catherine Maclean, Erik T. Nesson, Michael F. Pesko, Nathan Tefft. The Effects of E-Cigarette Taxes on E-Cigarette Prices and Tobacco Product Sales: Evidence from Retail Panel Data. The National Bureau of Economic Research. NBER Working Paper No. 26724. January 2020. Available at: https://www.nber.org/papers/w26724.
56. Kimber C, Frings D, Cox S, Albery IP, Dawkins L. Communicating the relative health risks of E-cigarettes: An online experimental study exploring the effects of a comparative health message versus the EU nicotine addiction warnings on smokers' and non-smokers' risk perceptions and behavioural intentions. Addict Behav. 2020 Feb;101:106177. doi: 10.1016/j.addbeh.2019.106177.
57. Kimber C, Frings D, Cox S, Albery I, Dawkins L. The effects of the European e-cigarette health warnings and comparative health messages on non-smokers' and smokers' risk perceptions and behavioural intentions. BMC Public Health. 2018 Nov 14;18(1):1259. doi: 10.1186/s12889-018-6161-7.