Common arguments criticizing electronic cigarettes in terms of use and safety, and science-based response

Note: this is an internal report by Dr Farsalinos' research team. The purpose is to provide a common, consistent and science-based response to arguments commonly presented in the news media or by public health (mostly tobacco control) authorities criticizing electronic cigarettes. The main points addressed in this report are: passive exposure ("passive vaping"), flavors availability, gateway-to-smoking theory and classification of electronic cigarettes as medicinal or tobacco products.

1. Passive exposure to electronic cigarette use

One of the main arguments and criticism against electronic cigarettes refers to passive (second-hand) exposure to the aerosol of electronic cigarettes. This argument is totally irrelevant to second-hand smoking exposure, and is not backed by any evidence.

Several studies have addressed the chemicals emitted in the environment as a result of electronic cigarette use that would result to exposure to bystanders. Electronic cigarettes are a group of device designed and marketed as an healthier substitute to conventional cigarettes. Studies published in recent years, have shown a strong and significant reduction in terms of toxin emissions compared to tobacco cigarette smoke, and some of these studies were dedicated in determining the impact of "passive vaping" on the environment. The question "Does e-cigarette cause passive vaping?" appeared for the first time on Indoor Air in 2013 (T. Schripp et al.) [1]. Researchers analyzed the emission of a smoker in an experimental chamber of $8m^3$ (which is considered a very small room), comparing it to the emission of a vaper. This was one of the first studies on this aspect, and showed that toxic emissions from electronic cigarette use are minimal to non-existent, expecting to result in no harm to bystanders. Characteristically, most chemicals found in this study were flavoring compounds. A lot of discussion about this study concentrated on the presence of formaldehyde, with many authorities considering it proof of bystander exposure to toxic chemicals. However, all these reports failed to recognize the basic conclusion of the study authors, which reported that formaldehyde was not released from the electronic cigarette but was emitted from the exhaled breath of the volunteer, due to endogenous production of formaldehyde in humans. The graph provided by the authors explains perfectly their argument: formaldehyde levels started to

elevate **before** the volunteer initiated electronic cigarette use. Even after using the electronic cigarette with 3 different liquids, the levels were still rising at the same rate as previously, while after smoing 1 tobacco cigarette there was a large and sudden elevation of formaldehyde levels to more than 100ppb (Figure 1). Therefore, in terms of formaldehyde exposure, the levels are similar to just sitting in the same room with another person.

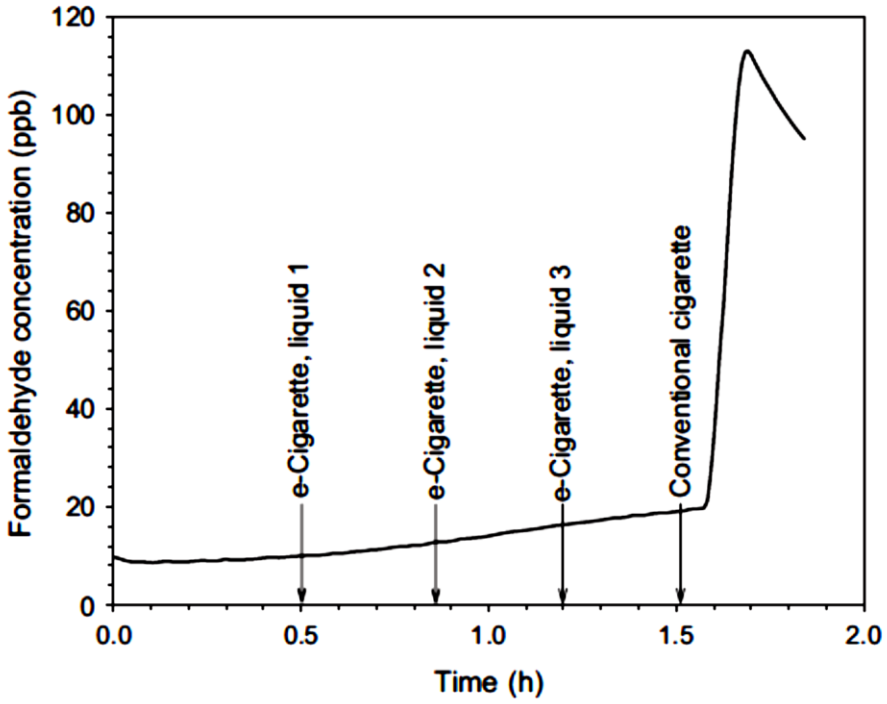

Figure 1. *Formaldehyde levels in an 8m^3 chamber before and after using electronic cigarette with 3 different liquids, and after smoking one tobacco cigarette. Reproduced from reference 1.*

Unfortunately, despite the fact that the authors proved and presented these reassuring data, they presented a conclusion that passive vaping is a reality, which led many to confuse passive vaping with passive smoking.

Another, more realistic, study was conducted in Italy by Romagna et al. [2]. Five smokers and 5 vapers were asked to smoke or vape in a 60 m^3, for 5 hours, in 2 separate sessions on separate days. Continuous air sampling of the room was performed during each session, before and after smoking and vaping, and samples were analyzed and compared. A strong methodological advantage of this study was that the air of the room was analyzed BEFORE using electronic or tobacco cigarettes, making sure that the background levels of toxins were measured and no false positive results would be reported. The study showed a significant difference in environmental toxic contaminants between electronic cigarette and tobacco cigarette use. In reality, traces of glycerol were found, which are expected to be harmless. They also measured Volatile Organic Carbon (VOC) emissions continuously, and they found that, to reach the maximum level of VOC after 5 hours of vaping, smokers just need 11 minutes of smoking. Nicotine, although present in the liquids used during the experiment, was not detected in the environment during the vaping session. Additionally, Polycyclic Aromatic Hydrocarbons PAHs) and acrolein were not detected in the air. The authors concluded that, based on their results and on official data about urban pollution, it would be safer to stay in a closed room with a vaper, than walking in the center of a big city with traffic congestion..

Another recent study, analyzed the levels of a large number of pollutant in an office room with moderate ventilation, during the presence of 3 vapers [3]. Three different brands of electronic cigarettes were tested under the same conditions. Authors, found a mild

elevation in PAHs from the baseline; however, a major disadvantage of this study was that they decided to measure the baseline levels on a DIFFERENT DAY and not before every experimental session. This is a basic methodological mistake. It would be expected that control environmental conditions would be evaluated by the researchers just before (but on the same day of) using the electronic and tobacco cigarettes, with all participants present inside the room. Instead, researchers chose to evaluate control conditions on a separate day. Moreover, they did not clarify whether the participants were present inside the room during the control measurements. These are important limitations. Studies have shown that there is a significant day-to-day variation in environmental levels of PAHs [4]. It is well-established that PAHs are formed during combustion, which does not occur with normal e-cigarette use. Therefore, it cannot be excluded that any difference in PAHs levels was due to the expected day-to-day changes in environmental levels rather than to emissions from e-cigarettes. This mistake led to the erroneous finding that using a nicotine-free liquid results in reduction of PAHs in the air, which of course is biologically implausible and shows that it was just the result of lower background levels of PAHs before electronic cigarette use was initiated. In agreement with previous studies, the authors found no modification in levels of carbon monoxide, carbon dioxide, formaldehyde, benzene, acrolein and acetone. Authors concluded that "analysis of indoor air quality, during gaping sessions, showed that e-cigarettes are not emission-free" unfortunately the authors, missed the opportunity to quantify their concern, and for this, it would be useful to make a comparison with regular tobacco smoke.

Both the first and the third study raised the issue of particulate matter (PM). This is another confusing and scientifically irrelevant argument. All studies evaluating PM and

its effects on health are performed evaluating PM from combustion processes (such as environmental pollution and cigarette smoke particles. It should be clarified that such composition is entirely different from that of particles emitted from electronic cigarettes. Currently there is no evidence that electronic cigarette aerosol particles represent a risk factor for cardiovascular or lung disease. We should not forget that the smallest particles are emitted from boiling water [5], which cannot in any way imply that inhaling water vapor can have any adverse health effects.

A recent study measured salivary and urinary cotinine levels of non-smokers, who lived in the same house with a vaper [6]. Authors, found that passive vaping results in nicotine absorption. However, there are two important aspects that need to be determined. First, nicotine absorption (even from cigarette smoke exposure) is not associated with any adverse health effects. Secondly, nicotine is obtained from other sources such as vegetables (aubergines, tomatoes, potatoes, etc) [7]. Cotinine level detected, were extremely low (0.24 ng/mL) which is more than 600-1200 time lower than the levels of cotinine normally detected in a smoker (300ng/mL). The same research group found that in smokers of 15 cigarettes/day had cotinine levels of 146ng/mL [8]. Since cotinine is directly associated with the total amount of daily nicotine intake, and assuming that smokers of 15 cigarettes per day get 15mg of nicotine and show 146ng/ml cotinine levels, we can calculate that passive vaping leads to daily nicotine intake of 0.025mg. This is also confirmed by studies showing that injecting 0.5mg of nicotine intravenously would produce plasma cotinine levels of 5ng/mL (thus, 0.024ng/mL come from 0.025mg of nicotine) [9,10]. Such a level is not only harmless but has absolutely no biological effect [11], even according to the strictest regulatory definitions.

A study by Czogala et al. further confirms the above-mentioned findings. Researchers evaluated electronic cigarette-related exposure of bystanders to toxic tobacco-specific combustion products, carbon monoxide and nicotine. They found that they were exposed to nicotine at minute quantities (3.3μg/m^3) but no exposure to combustion products or carbon monoxide was found.

In a study published in October 2014, researchers evaluated the exhaled breath of smokers and electronic cigarette users for the presence of toxic chemicals [12]. Exhaled aerosols were collected following the use of two leading U.S. commercial electronic cigarettes (e-cigarettes) and a conventional cigarette by human subjects and analyzed for phenolics, carbonyls, water, glycerin and nicotine using a vacuum-assisted filter pad capture system. Exhaled breath blanks were determined for each subject prior to each product use and aerosol collection session. Distribution and mass balance of exhaled e-cigarette aerosol composition was greater than 99.9% water and glycerin, and a small amount (<0.06%) of nicotine. Total phenolic content in exhaled e-cigarette aerosol was not distinguishable from exhaled breath blanks, while total phenolics in exhaled cigarette smoke were significantly greater than in exhaled e-cigarette aerosol and exhaled breaths, averaging 66 μg/session (range from 36 to 117 μg/session). The total carbonyls in exhaled e-cigarette aerosols were also not distinguishable from exhaled breaths or room air blanks. Total carbonyls in exhaled cigarette smoke was significantly greater than in exhaled e-cigarette aerosols, exhaled breath and room air blanks, averaging 242 μg/session (range from 136 to 352 μg/session). These results indicate that exhaled e-cigarette aerosol does not increase bystander exposure for phenolics and carbonyls above the levels observed in exhaled breaths of air.

The result of the above mentioned studies unanimously show that exposure of bystanders to the aerosol of electronic cigarettes is basically harmless. Unfortunately, regulators seem to suggest a ban on electronic cigarette use in public places based on visual aspects (emitted vapor which resembles tobacco cigarette smoke). However, this is both unscientific and questionable legally and ethically. Any regulation should be based on scientific evidence. Moreover, applying to electronic cigarettes the same rules and regulations as tobacco cigarettes provides a misleading message to smokers that they are of equal harm potential, which will further discourage them from using a significantly less harmful alternative to cigarettes.

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2. Electronic cigarette liquid flavors

There is a lot of criticism concerning flavors availability in electronic cigarette liquids. The main arguments are that flavors are marketed to attract youngsters and produce a

new generation of nicotine addicts. This argument has been raised without evaluating the current scientific evidence and it is based on speculations, theoretical risks and precautionary measures which are not justified and will only cause harm without averting any danger.

First of all, taste and smell are inherent human sensations, and there is a physiological link between these senses and pleasure. This is applied to adults and not only to youngsters. There is extensive research on the effects of flavors in reducing nicotine withdrawal symptoms. Several studies evaluating the effects of chewing gum on nicotine withdrawal have found that flavored gum was by far more successful in promoting smoking abstinence compared to unflavored gum. Cohen et al. compared the effects of three flavored gums to a No Gum Control during 48-hour cessation periods for dependent smokers [1]. Forty-nine smokers participated in three experimental conditions (peppermint, vanilla, and baked apple cardamom flavored gum) as well as a No Gum Control across four weeks while abstaining from smoking for 48-hours each week. Compared to the No Gum Control, participants in the Gum conditions reported lower levels of anxiety, dysphoria, and tension. **Vanilla and baked apple cardamom** flavored gum resulted in lower levels of negative affect while peppermint flavored gum was not different from the No Gum Control.

Cortez-Garland et al. examined independently the acts of chewing and the flavor component, as well as the combination of the two, on smoking abstinence [2]. Twenty-four dependent cigarette smokers participated in three experimental conditions (e.g., a flavorless gum base, flavor strips, and flavored chewing gum) as well as a no product control across four weeks while abstaining from smoking for 24 h each week. A

significant difference in withdrawal severity was reported by participants across conditions. Follow-up analyses revealed that the flavored gum condition yielded significantly lower withdrawal scores than the flavorless gum base and no product control conditions. These findings indicate that chewing gum appears useful in lessening the severity of nicotine withdrawal symptoms over a 24-hour period of nicotine abstinence and that flavor plays a major role in this.

Such findings are justified based on neuroscience experiments which have shown that participants who were asked to chew gum flavored with peppermint and lemon reported feeling more refreshed and comfortable after they had been chewing the flavored gum compared to chewing an unflavored gum base [3]. Therefore, it is expected that electronic cigarette liquids should contain flavors in order to be more effective as smoking substitutes. Currently, there is only one study evaluating the effects of flavors on electronic cigarette use experience and smoking craving [4]. The study evaluated the responses of 4,618 participants, with 4,515 reporting their smoking status at the time of the study. The vast majority (91.1%) were former smokers, while current smokers had reduced smoking consumption from 20 to 4 cigarettes per day. Both subgroups had a median smoking history of 22 years and had been using ECs for 12 months. On average they were using three different types of liquid flavors on a regular basis, with former smokers switching between flavors more frequently compared to current smokers; 69.2% of the former subgroup reported doing so on a daily basis or within the day. Fruit flavors were more popular at the time of participation, while tobacco flavors were more popular at initiation of EC use. On a scale from 1 (not at all important) to 5 (extremely important) participants answered that variability of flavors was "very important" (score = 4) in their

effort to reduce or quit smoking. The majority reported that restricting variability will make ECs less enjoyable and more boring, while 48.5% mentioned that it would increase craving for cigarettes and 39.7% said that it would have been less likely for them to reduce or quit smoking. The number of flavors used was independently associated with smoking cessation. The study results clearly show that flavors are marketed in order to satisfy vapers' demand. They appear to contribute to both perceived pleasure and the effort to reduce cigarette consumption or quit smoking. The pattern of changing preferences from tobacco to other types of flavors may be a way to distract them from the tobacco flavor in order to reduce smoking craving; alternatively, it could indicate that they just don't need the tobacco flavor any more, but feel the desire to experiment with and enjoy new flavors. In some cases, tobacco flavor may even become unpleasant, especially in those who have completely quit smoking. The improvement in olfactory and gustatory senses in these people can lead to both more pleasure perceived from different flavors and an aversion to tobacco flavor (in a similar way that it is unpleasant for a non-smoker); the latter has been reported in EC consumers' forums (http://www.e-cigarette-forum.com/forum/polls/209041-do-you-vape-tobacco-flavors.html). Such a phenomenon may contribute to lower relapse to smoking and may prevent the EC from being a gateway to smoking; however, this should be specifically studied before making any conclusions. Finally, the issue of taste buds "tolerance", which is anecdotally mentioned by vapers, was reported by almost half of the sample as a reason to switch between flavors, although it is most probably a type of olfactory rather than gustatory tolerance. Therefore, the availability of a large variety of flavors is perfectly justified based on the demand and need of established vapers.

Although the fact that flavors are important for existing electronic cigarette users provides sufficient explanation for their current marketing, it does not exclude the possibility that they may also attract youngsters or non-smokers. However, currently available evidence indicates that regular use of electronic cigarettes by non-smoking adults or youngsters is very limited [5-7]; thus, any restriction of flavors for the reason of protecting youngsters is currently not substantiated by evidence and no public health benefit would be derived. On the contrary, such a measure could have a negative impact and cause harm in current vapers, who are reporting that they enjoy flavors and that restrictions would make smoking reduction or cessation more difficult and would increase cigarette craving. Therefore, it would be more realistic and valuable to promote restrictions to the use of electronic cigarettes by youngsters and to properly inform the public that electronic cigarettes should be used only by smokers as a method to reduce cigarette consumption or completely substitute smoking. Additionally, there is an important ethical dilemma, which our group presented in a recent publication: should a product, which is probably beneficial for a part of the population (smokers), be restricted (which could result in reduced efficacy as a smoking substitute) because some other parts of the population (non-smokers) decide to ***voluntarily*** adopt its use and expose themselves to a new (even minor) risk? Measures such as proper education, regulation of advertising and prohibition of promotion and sales to non-smoking youth could effectively ensure that electronic cigarettes will not be used by non-smokers without restricting their potential to substitute smoking.

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3. The gateway-to-smoking theory

One of the main arguments presented by regulators and the tobacco control movement is the gateway-to-smoking theory. According to this, electronic cigarettes may renormalize smoking and may result in adoption of their use by non-smokers and subsequent switching to tobacco cigarette use. We characterize this argument as “theoretical” and “speculative”, since there is no evidence that such an effect is currently happening.

Firstly, there is no report of a single non-smoker initiating electronic cigarette use and subsequently becoming a smoker. Moreover, even if this was observed, it cannot be substantiated that the cause for tobacco cigarette use is previous use of electronic cigarettes; it may just show the predisposition of an individual to use such products. The population effect of electronic cigarettes use does not depend solely on the number of non-smokers who adopt their use but on the net result of people quitting smoking

compared to non-smokers who initate electronic cigarette use. E.g., if for every 50 smokers who stop smoking by electronic cigarette use we observe 10 non-smokers who initiate electronic cigarette use, the net public health benefit is substantially positive. In any case, the rate of adoption of electronic cigarette use by non-smokers is extremely small, and is by a large margin outweighed by the benefits observed in smokers.

The analysis of the 2011 and 2012 National Youth Tobacco Survey (NYTS) by the CDC [1] and by Duntra and Glantz [2] reported a "dramatic" elevation of electronic cigarette use by adolescents. The word "dramatic" obviously does not represent the truth. First of all, we should distinguish use by smokers from that of non-smokers. It is expected to be beneficial for smoking adolescents to use electronic cigarettes because that could result in smoking reduction or cessation. A major methodological problem and limitation of these studies is that "current electronic cigarette use" was defined as "use, even one puff, in the past 30 days". This is erroneous and cannot be considered regular current use. Even for use in past 30 days, such a pattern cannot result to nicotine dependence and will not have any adverse health implications. Despite that limitation, it is interesting to evaluate the findings of these studies. According to the NYTS data, ever electronic cigarette use w 6.4% in 2012, while for current electronic cigarette use the prevalence was 1% and 2% respectively. Concerning non-smokers, in 2012, only 1.6% were ever users and 0.5% were current users. This represents minimal use by non-smoking youngsters. It should be emphasized that the elevation in electronic cigarette experimentation and use was accompanied by a substantial **decline** in tobacco cigarette use.

Dutra and Glantz mis-presented and misinterpreted the findings by reporting that electronic cigarette use did not discourage and probably encourages smoking. Their

conclusions are not justified by the data presented, simply because in a cross-sectional study the observed relationship between e-cigarette use and higher and more sustained levels of smoking does not imply causation. Moreover, such studies do not take into account other population characteristics which may play a crucial role when determining potential causation. Of note, although the authors acknowledge this limitation in the text, they end up drawing a conclusion that is misleading the public into thinking that e-cigarettes are leading to smoking initiation and addiction among adolescents. Therefore, the finding that most electronic cigarette users are smokers is a positive findings, because it shows that they are used by the intended population. The methodological problems of the analysis were presented in a letter to the editor published by JAMA Pediatrics [3]. Specifically, the methodology of Dutra and Glantz was so obscure that when it was applied to nicotine replacement therapies and smoking cessation programs, we found that such medications and programs would "not discourage, but probably encourage, smoking".

Another study by the Glantz group in South Korean adolescents was used to justify an argument that *"We are witnessing the beginning of a new phase of the nicotine epidemic and a new route to nicotine addiction for kids…"* caused by electronic cigarette use [4]. This statement is grossly exaggerating and inaccurate. According to the published results, 85.5% of 13 year-old and 66.5% of 18 year-old students had never used tobacco or e-cigarette. In 18 year-old students, 16.9% were smoking cigarettes while 5.9% were using e-cigarettes; 85% of them (5% of total population) where dual users. So, only 0.9% of 18 year-old students was using e-cigarettes alone. From the total population, **only 0.6% of those who were not smoking tobacco cigarettes** were using electronic cigarettes.

Smokers were 66.5 times more likely to use electronic cigarettes compared to never-smokers. Former smokers were 7 times more likely to be electronic cigarette users (this probably explains that a significant proportion of the 0.6% of electronic cigarette users were former smokers), and were 8 times more likely to have used an electronic cigarette in the past (compared to never smokers). The results show that electronic cigarettes are almost exclusively used by smokers, which is the intended and targeted population.

In conclusion, the issue of electronic cigarettes being a gateway to smoking is non-existent. Although monitoring of use should continue, there is no evidence to justify any restrictions to electronic cigarette use and availability, besides implementing a sales ban to youngsters. However, it should be considered that such a measure will prevent young smokers from accessing electronic cigarettes as a less harmful alternative which could lead to smoking cessation.

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4. Classification of electronic cigarettes as medications

It is commonly mentioned that electronic cigarettes are unregulated and not approved by medicinal authorities (such as Health Canada, FDA etc). However, there is no need and no basis to characterize the quantity or the effects of any product based on whether it is classified as a medication or not. Moreover, such a classification would be arbitrary and irrelevant if a product is not used as a medications. All studies evaluating patterns of electronic cigarette use have shown that electronic cigarettes are not used as medications; therefore, such a classification is not appropriate.

The usual definition of a medicinal product is (a) when a product is used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic

action, or to making a medical diagnosis, or (b) when a product is presented as having properties for treating or preventing disease in human beings.

There are many daily activities and products which exert physiological functions. For example, water intake induces significant hormonal and metabolic changes to the human organism, such as interference with the production of aldosterone and anti-diuretic hormone and elevation of urine output by the kidneys. Salt intake has several metabolic and hormonal effects as well as effects in the regulatory system of the volume status and in kidney function. Coffee, other common beverages and energy drinks also have physiological effects on the human body (in fact, some of these products may have effects very similar to smoking). Eating and physical activity (even mild activity such as walking) have significant physiological effects (such as elevation of heart rate and blood pressure and changes in hormonal status). Smoking tobacco cigarettes or using any other form of tobacco (hookah, chewable tobacco, snus) also has physiological effects on the human body. In general, every daily activity of humans has significant effects and induces changes to the human organism. It is irrational to accept that physiological alterations in the human body are produced only by medications, since none of the above-mentioned products or activities is medicinal by nature or by definition. Therefore, in order for a substance to be considered as medicinal product by function, it should exert physiological effects above or more intense from what is expected from common daily activities and the use of common products.

Smoking substitution is a welcomed effect of electronic cigarette use. In fact, this is the only reason why part of the public health community supports and endorses e-cigarette use by smokers. However, it cannot be supported that such an effect automatically

characterizes electronic cigarettes as having physiologic functions above or more intense from what is expected from common products and hence would warrant classifying them as medicines. In the same way, if people are willing and able to substitute red meat with vegetables (which is beneficial to health and may lead to several physiologic changes in the human body, such as improvement in cholesterol levels or treatment of obesity) it would be awkward to support the view that vegetables should be considered medications. People making such claims seem to have misunderstood the main concept of tobacco harm reduction. It is a strategy of providing products that are used in order to provide pleasure to the users, and substitute the experience and pleasure perceived from smoking (which is the most harmful form of nicotine intake) with that of using an alternative product (which is less harmful). Such products are not used in the form of medications, although they result in partial or complete substitution of smoking [1]. The expressions "smoking cessation" and "smoking substitution" are basically identical. As scientists, we are unwilling to enter to the "legal word game" of characterizing electronic cigarettes as smoking cessation or smoking substitution products. Since many scientists supporting the role of electronic cigarettes are also clinicians, being in very close contact with smoking patients, the end-result is the same irrespective of the words used: stopping the use of tobacco cigarettes by substituting them with a less harmful alternative. Unfortunately, legal definitions have created more confusion rather than making things clear.

Liquids used in electronic cigarettes may contain nicotine. Nicotine in these products comes from tobacco leaves and is not produced synthetically. Although synthetic production of nicotine is feasible, to the best of our knowledge no companies currently use synthetically-produced nicotine because it is significantly more expensive

than extracting it from tobacco. The chemical molecule of nicotine in electronic cigarette cartridges is identical to the nicotine present in tobacco leaves. The only process that takes place is the removal of impurities and other chemicals present in tobacco leaves, which means that a cleaner form of nicotine is prepared. Additionally, nicotine is present in other plants, such as eggplants (aubergine), cauliflower, tomatoes and potatoes. Nicotine present in electronic cigarettes is identical in nature and molecular composition to the nicotine present in tobacco cigarettes and in other food products, making it contradictory from a legal perspective to define it as a medication in one case (electronic cigarette) and a consumer product in the other case (tobacco). Moreover, nicotine is a natural substance and its use existed before being classified as a medication; the latter was done in order to facilitate the production of nicotine replacement therapies by pharmaceutical companies.

Another important characteristic of medicinal nicotine products is that their purpose is to gradually eliminate nicotine use. Instead of treating, electronic cigarettes maintain and satisfy the consumer's liking for and/or dependence to nicotine; the advantage of using electronic instead of tobacco cigarettes is solely attributed to receiving nicotine from a less harmful product, by avoiding the products of combustion and the toxins released in tobacco smoke. This cannot be a reason to justify characterization as a medicinal product, in the same way that low-fat milk is not considered a medicinal product just because it is less harmful compared to full-fat milk. Another difference is that medicinal smoking cessation products are not made with the purpose of providing pleasure to the user. Thus, smoking substitution with the use of tobacco harm reduction products such as electronic cigarettes should not be considered a medicinal intervention. In fact, the medicinal

regulation, if applied to these products, would likely contribute to their failure as smoking substitutes, due to requirements for specific and uniform dosing and consistent absorption. In the case of nicotine intake, a major characteristic is that the user self-titrates (self-adjusts) the intensity and patterns of use according to self-perceived pleasure and saturation (satisfying nicotine needs). In the case of tobacco cigarettes, all smokers have their own unique way of using nicotine, and this is satisfied by adjusting the intensity and frequency of smoking according to self-demand. The uniform dosing and absorption characteristics are potential reasons for the failure of medicinal nicotine products in smoking cessation, and such requirements would deprive electronic cigarette users from the ability to self-adjust their use based on their personal preference. Products like e-cigarettes provide satisfaction to the user; that is why they are preferred by part of the smoking population instead of medications, and this justifies the availability of a variety of devices and flavors.

The “risk” of applying medicinal regulation is that electronic cigarettes will be transformed into another form of pharmaceutical nicotine inhaler; currently there is no need for such a product and it will not be accepted in the same way as electronic cigarettes are currently accepted by consumers. Additionally, strict medicinal regulation will give electronic cigarettes a disadvantage compared to the main competitor, which is the tobacco cigarette, by making them less accessible and more difficult to use. The cost of performing the extensive testing required by medicinal regulation will reduce the range of products available and will make them more expensive [2]. Additionally, it will negatively affect the evolution and development of new products, which is currently very fast but will be significantly hindered due to the time and resources needed to perform all

required tests. Moreover, there is the risk that electronic cigarettes will be monopolized by the large tobacco companies who have the funds to make medicines licensing applications [3].

Concerning regulation as a tobacco product, the main argument is that nicotine is derived from the tobacco plant. However, there are many problems with such an approach. First of all, there is no rationale (or scientific basis) to classify them as tobacco products: it makes no more sense to argue that nicotine is a tobacco product than to argue that biodiesel is a vegetable product because it is derived from plants. Electronic cigarettes do not contain any tobacco and do not involve combustion. The visual aspect (emitting visible aerosol which resembles tobacco cigarette smoke) is not different from water resembling vodka or other colorless alcoholic drinks. Additionally, regulation as a tobacco product carries the risk of misinforming and deceiving smokers that the risks associated with electronic cigarette use would be similar to those of smoking tobacco. The result would be unnecessary applications of restrictive measures; this will provide a competitive advantage to tobacco cigarettes, with smokers being discouraged from switching to a less harmful alternative based on misinformation. Currently available evidence overwhelmingly supports the lower risk potential of electronic cigarettes [4], and this should be properly communicated to the smokers. Although it is tempting for regulators to integrate electronic cigarettes into an already-established tobacco products regulation, this would be inappropriate, disproportionate and misleading. The main criterion for regulation should be to serve public health in the most efficient way rather than to make the work of the regulators easier.

The argument that electronic cigarettes are not absolutely safe is erroneous. It is our ethical obligation to provide smokers with a less harmful alternative, rather than punishing them for the inability of medical science to develop very effective smoking cessation medications. The key issue is to understand the risk-benefit ratio rather than the absolute risk. This is also the main principle behind every consumer product, but also in medicinal regulation; there is no medication without side effects or contraindications, however they are approved for use because the risk-benefit profile is favorable. Moreover, the frequently heard argument about the lack of long-term studies, although true, cannot justify a request for restrictions on e-cigarette use. Even for medications, which may be used for years in some cases (e.g. anti-hypertensives), no regulatory agency is asking for long-term safety data before being approved for use. Post market monitoring is applied in these cases, and we support the same for electronic cigarettes. Regulation is needed in order to promote the quality and safety of the products; however, there are other regulatory pathways by which this can be ensured. Making a separate regulation devoted to electronic cigarettes may be the most appropriate way to handle this issue. There is a need for specific testing on liquids and vapor, unique for electronic cigarettes. There are already-established standards of purity for liquid ingredients, such as the United States and the European Pharmacopoeia, which should be followed. Testing should be cost-effective and take into account that electronic cigarettes are harm reduction consumer products, substituting combustible tobacco products which have well-known devastating health effects. Therefore, there is no need to prove that they are absolutely safe. Through testing and research, products will become more effective as smoking substitutes and at the same time any potential harm will be minimized.

Moreover, regulation should be flexible-enough to address the evolution of new, more efficient products and to maintain the current variability. Finally, rules concerning marketing promotion should be carefully designed in order to educate the public that electronic cigarettes are not a new lifestyle product for everyone to adopt (as was the case of promoting tobacco cigarettes in previous decades) but are developed for the smokers who cannot or do not want to quit with currently approved medications and are now provided with the opportunity to use a less harmful alternative.

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