Report of the Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) on the safety of use of electronic cigarettes

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Abstract

The Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) has assessed the health risks associated with electronic cigarettes. The assessment concludes that the safety of electronic cigarettes is uncertain. The types of cigarettes, the amount of ingredients in the vaporised liquid, and the substance that is released, differ greatly. The long-term health effects are unknown. The short-term effects include mouth and throat inflammation, nausea, vomiting and coughing. Propylene glycol, glycerine, nicotine, flavouring, carcinogens, heavy metals and other chemicals have been found in the vapour that is released when "vaping". There are no long-term studies that demonstrate that e-cigarettes are effective in treating tobacco addiction, or chronic toxicity studies in rodents to learn the long-term effects of exposure due to the use of electronic cigarettes. The in vitro studies on the effects of electronic cigarette smoking on cell cycle regulation, oxidative and mitochondrial stress and DNA damage associated with the cells of human airways would be of great use to evaluate the health risks. Epidemiological data on the adverse health effects of electronic cigarettes is also needed, especially on the most vulnerable population. On the other hand, the transposition of the European regulation regarding the manufacture, presentation and sale of tobacco products is currently underway.

Key words

Electronic cigarettes (e-cigarettes), cartridges, tank, refill containers, nicotine, propylene glycol, vaping.

Note: The term "vaping" is really an Anglicism, but given its extensive use in magazines and the media, it has been used to facilitate the readers' understanding of this report.

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1. Introduction

The Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) presents this report, mainly aimed at assessing the safety of using e-cigarettes, mainly with regard to the contents of their cartridges: nicotine, propylene glycol, glycerine and other additives. The influence of the vaporising system on the creation of vapour produced by these devices is assessed.

Amongst many others, the following databases were consulted, specified for their relevance: PubMed-Medline, SciFinder, ScienceDirect and Web of Knowledge and the 2014 report by the General Directorate of Public Health, Quality and Innovation of the Ministry of Health, Social Services and Equality (MSSSI), was also taken into account. This report did not analyse the electronic component.

This report was approved in the meeting of the Scientific Committee of AECOSAN held on 20 April 2016. The report was sent for its consideration and observation to the General Directorate of Public Health, Quality and Innovation of the Ministry of Health, Social Services and Equality. For this reason, this report was submitted for review in view of considerations arising from the Smoking Prevention Unit, which reports to the aforementioned General Directorate. This review was carried out on 13 July 2016.

1.1 Reference terms

The Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) consulted the Scientific Committee about whether or not e-cigarettes pose a risk to health through "vaping", which involves inhaling water vapour along with nicotine, propylene glycol, and flavouring, amongst other products. We wanted to ascertain what level of nicotine is inhaled and, lastly, what adverse effects the formation of vapour generated could have on third parties. Other matters to bear in mind are the conditions of use, since they have a direct or indirect effect on the health of e-cigarette users.

2. Recognised uses and sociological framework

With the aim of analysing the health risks of the consumption of a product, such as that which occupies us, some aspects that go beyond the intrinsic characteristics of the product must be considered, since they affect their consumption conditions, and therefore, their effects on health. Risk is a function of the danger of the product itself and its exposure. This exposure may be voluntary or involuntary. The exposure is determined by environmental (place where the product is consumed) and personal factors (product consumption habits, perceptions about it and its danger, and attitudes, amongst others), which influence the intensity and frequency of the act of consumption, in this case, the act of vaping inherent to the use of e-cigarettes. As such, the circumstances that affect this vaping act must be taken into account to better assess the risk of the product.

As confirmed in the study by Grana and Ling (2014) on the perception and consumption of e-cigarettes, these types of products are advertised on television, the internet and print media as

a healthier alternative to smoking tobacco cigarettes, as a useful method for stopping smoking and reducing the consumption of cigarettes, and also as a way of circumventing anti-smoking laws by allowing users to smoke in any public place. It has been verified that the perceptions of consumers about the risk and the benefits, as well as the decisions to use e-cigarettes, are very much influenced by the way in which they are marketed and due to the existence of very aggressive advertising. Analysing the websites of sales of e-cigarette brands in 2012, Grana and Ling (2014) found that the most important messages were that the products are healthier (95%), cheaper (93%), and cleaner (95%) than conventional cigarettes; other advantages, according to the advertisements, were the possibility of vaping in any public place (88%), and using them in places subject to smoke-free policies (71%); that they don't create smoke for third parties (76%), and they associate the consumption of these e-cigarettes with the idea that they are more modern (Grana y Ling, 2014). These healthier properties, in accordance with advertising, were reinforced by text and images with representations of videos of doctors present on 22% of websites. Direct or indirect statements about stopping tobacco smoking were found in 64% of advertising claims. In short, the advertising states that e-cigarettes only create an "inoffensive water vapour".

Against the benefits claimed in the marketing, there is a wide consensus that there is a lack of scientific evidence to support these supposed benefits. (Ministry of Health, Social Services and Equality, 2014).

Moreover, the individual risks or their benefits and the assessment of the total impact of these products occur in the context of a wide availability of the product, but also of the dual use of e-cigarettes and conventional cigarettes. The data show that e-cigarettes are not always used to replace traditional tobacco cigarettes (Grana et al., 2014), (Ministry of Health, Social Services and Equality, 2014).

In the Spanish context, 40% of a sample of 736 people believe that e-cigarettes have a harmful effect on users and 27% believe that they also negatively affect people who are exposed passively. In this same study, a majority believe that these cigarettes are useful for smoking less, rather than for stopping smoking (Martínez-Sánchez et al., 2015).

Although the data are limited, it is evident that the air emissions produced by e-cigarettes are not simply "harmless water vapour", as is often claimed, and they may be a source of pollution in enclosed spaces. The introduction of e-cigarettes in clean air environments may cause damage to the population if the use of the product reinforces the act of vaping as socially acceptable or if the use undermines the benefits of smoke-free policies.

Given that the advertising of these products highlights their "good qualities", we may be witnessing a case of misleading advertising, with the aim of stimulating their consumption instead of that of conventional tobacco cigarettes. This circumstance was taken into account in the recent Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products, which includes e-cigarettes in their sphere of application, as well as the draft Royal Decree that incorporates it into the Spanish legal system and that is currently being processed.

The user's belief that e-cigarettes are less harmful leads to a greater intensity of vaping than in the case of the conventional smoker and it increases exposure to risk because of the increase both in the frequency and the intensity of vaping. The advertising of this product promotes this situation, and although there is a lack of studies in Spain about habits and perceptions of e-cigarette users, the existing data suggest the need to control the advertising and labelling information, in order to provide consumers with true, comprehensible and complete information and avoid an erroneous perception about the use of the product and its consequences.

3. Definition and characterisation of the product

Directive 2014/40/EU defines electronic cigarettes as "products that can be used for consumption of nicotine-containing vapour via a mouth piece, or any component of that product, including a cartridge, a tank and the device without cartridge or tank. Electronic cigarettes can be disposable or refillable by means of a refill container and a tank, or rechargeable with single use cartridges".

Electronic cigarettes (also called e-cigarettes are referred to in Spanish legislation as "devices that allow the release of nicotine". E-cigarettes are designed to simulate and replace traditional tobacco cigarette consumption. Their design may imitate cigarettes or have a completely different appearance that does not in any ways resemble tobacco cigarettes (such as pens, USB sticks, etc.), as occurs with many of the most modern devices.

E-cigarettes mainly consist of three parts 1) an inhaler, 2) an atomising device and 3) a battery. Many e-cigarettes also have an indicator light at the end of the cigarette, which simulates the light of a conventional tobacco cigarette when it is inhaled.

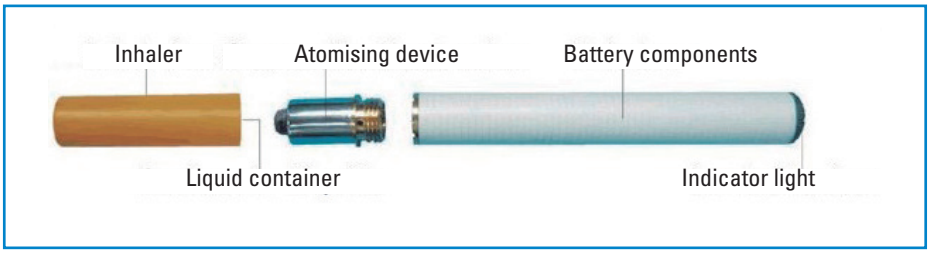

Figure 1. Parts of an electronic cigarette.

The inhaler consists of a cartridge or a replacement part that contains a solution, the main ingredients of which include, as well as nicotine (there are devices in which it is not present), a wetting agent such as propylene glycol or water, with or without the addition of glycerine and various flavourings. The atomising device consists of a resistor that heats up to between 40 and 65ºC and can reach higher temperatures in third generation atomisers (Yamin et al., 2010). When a user "vapes" with this type of electronic cigarette, a sensor detects the flow of air, the indicator light comes on and the atomiser starts to work. The latter heats up the liquid contained in the cartridge, evaporating it. The vapour formed is that which is inhaled, with there not being a sidestream of smoke.

There are currently three types of device on the market: 1) The abovementioned "first generation" devices, which imitate the size and appearance of conventional tobacco cigarettes and they are generally disposable.

2) "Second generation e-cigarettes" that have atomisers with the possibility of the user filling them up with commercial fluids. They have a better battery and the ability to change the atomiser head, while the body is maintained, thus reducing the cost of the transaction. 3) "Third generation" devices, also called "Mods" due to their extensive modification possibilities, contain large capacity lithium batteries with integrated circuits that allow users to modify the power of the atomiser to achieve greater temperatures, fill with commercial liquids and prepare their own mixtures (Farsalinos et al., 2014).

The main active ingredients found in the labelling of e-cigarettes are, in addition to nicotine and propylene glycol, glycerine and various flavourings.

The US Food and Drug Administration (FDA) indicates that these cigarettes contain substances that have toxic behaviour in this use, such as diethylene glycol (antifreeze) or carcinogenic compounds such as nitrosamines (FDA, 2009).

4. Safety

The safety criteria for these products depend on many factors (WHO, 2014). The differences in the battery voltages and circuit systems may lead to a considerable variability with respect to the capability of the products to heat up the solution and transform it into vapour and, therefore, they can affect the administration of nicotine and other active ingredients and contribute to the formation of toxic substances in the emissions.

Also, the behaviour of consumers may affect the absorption of nicotine; this is the case for the duration of the vaping, the extent of inhalation and the frequency of use. However, while in a conventional tobacco cigarette a quicker and deeper vape increases the administration of nicotine, in e-cigarettes it may decrease due to the design, in order to cool down the heating device.

In addition to the differences between manufacturers, some consumers modify the products in order to alter the administration of nicotine and other abused substances. The products vary greatly with regard to the ease with which they can be modified and filled with substances other than nicotine solutions.

As such, the toxicity of e-cigarettes varies depending on the design and type of cigarette, the quality and concentration of active compounds present in the vaping liquid, the characterisation of the vapour, the method of manufacture, and the quality control used by the manufacturer.

4.1 Danger of the chemical substances

It is difficult to carry out a priori a comprehensive assessment of the danger of active chemical substances or components, since there are currently no specific regulations for e-cigarettes governing the contents of nicotine and other toxic products. The recent Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws,

regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products, and the draft Royal Decree that incorporates it into the Spanish legal system, currently being processed, will contribute to establishing a specific regulatory framework for these products.

If we firstly consider the ingredients declared on the labels, leaving aside nicotine for a more comprehensive approach, we must highlight that some of them, such as propylene glycol, glycerine and some flavourings have been approved for use in foods at certain concentrations, but this does not indicate, in other uses, that they are safe to be repeatedly vaped.

– **Propylene glycol**: or propane-1,2-diol, is an excellent solvent for many organic chemical solubles that are insoluble in water. It is a clear, colourless, slightly viscous liquid that is fully miscible with water. It is used, among other applications, as a wetting agent in pharmaceutical products, in conventional cigarettes, in cosmetics and in disinfectants. It is also used as a food additive (E-1520), as an antifreeze product and to make artificial smoke.

The FDA has determined that propylene glycol is "Generally Recognized As Safe" (GRAS) for use in cosmetics and medications. According to the 1994 OSHA Hazard Communication Standard; 29 CFR Part 1910.1200, contact of the product with the eyes may cause mild irritation and redness. Prolonged or repeated contact may cause dermatitis and irritation in the respiratory tracts, amongst other effects. It is recommended to avoid direct contact with the skin and eyes and vapour mists (BASF-Safety Data Sheet 1,2-PROPYLENE GLYCOL USP. Version: 2.0 (30054515/SDS_COS_US/ES). Date reviewed: 2015/02/19). Although the US Environmental Protection Agency (EPA) has determined that it is not necessary to establish a threshold limit value (TLV) of exposure to propylene glycol in work environments, the American Industrial Hygiene Association recommends maximum exposure of eight hours for a total vapour concentration of 50ppm or mg/m^3.

Despite the fact that its use has been approved and considered safe for oral consumption, the values may be completely different for inhalation. Some studies have shown short-term toxic effects associated with exposure to this product in enclosed spaces, related to irritation of the eyes, throat and airways (Wieslander et al, 2001; Moline et al., 2000). The irritation of these pathways involves a particularly high risk in people with related diseases. In the long term, the exposure to propylene glycol has been associated with an increased risk of asthma in children (Choi et al., 2010).

Glycerine: or 1,2,3-propanetriol, is a trialcohol of characteristics and uses that are similar to propylene glycol. It is also considered safe for oral consumption but that does not imply that it is for inhalation. In fact, two cases of lipoid pneumonia have been reported related to the vapour combined with glycerine of electronic cigarettes (McCauley et al., 2012), one of them in Spain was published in the press (Tardón, 2014).

Moreover, with regard to carcinogenic substances, such as those mentioned above, the FDA found in e-cigarettes detectable amounts of substances that are carcinogenic and toxic to humans that were not declared, such as diethylene glycol, N-nitrosamines and specific impurities

of tobacco that are potentially harmful (anabasine, myosmine, and b-nicotyrine) (Goniewicz et al., 2013).

Diethylene glycol is a toxic substance included as propellant, also used as an antifreeze agent in cars. Other authors have also found small amounts of nitrosamines in the liquids of e-cigarettes, along with formaldehyde, acetaldehyde and acrolein in different e-cigarettes. Formaldehyde and acrolein probably form through the combustion of glycerine. Acrolein can be absorbed and a product of its breakdown has been found in the urine of e-cigarette users, however, to a lesser extent than after smoking conventional cigarettes (DKFZ, 2013).

The French Consumer Affairs Institute analysed samples from e-cigarettes and also found carcinogenic substances (Institut National de la Consommation, 2013) amongst them, nickel, in concentrations higher than in the smoke of traditional tobacco, (Williams et al., 2013). The presence of particles was also determined in the vapour produced by the e-cigarettes whose range of magnitude is similar to that of conventional tobacco cigarettes, with ultrafine particles predominating (diameter 100-200nm) compared with those of a greater size detected in the smoke of cigarettes. However, the levels generated are lower than in conventional tobacco cigarettes (Schripp et al., 2013).

A study by Williams et al (2013) assessed whether the inhalation liquid and the resulting vapour contained trace metals derived from the components of the e-cigarette, identifying tiny particles both in the liquid of the cartridge and in the vapour. The vapour contained particles (size >1µm) of tin, silver, iron, nickel, aluminium and silicate compounds, and nanoparticles (size of 100nm) of tin, chrome and nickel, from the filament and other metallic parts and from fibreglass used in the devices. The concentrations of nine to eleven metals analysed in the vapour were equal to or greater than those corresponding ones in the smoke of the conventional tobacco cigarette. Many of the elements identified in the vapour may cause respiratory diseases and some are cytotoxic. These authors conclude that the presence of metallic particles and silicates in the vapour shows the need to improve quality and control in design and production, as well as carry out studies to assess the potential impact of the vapour of e-cigarettes on the health of users and non-smokers exposed passively.

The potential cytotoxicity of some liquids for e-cigarettes has raised concerns about the risk of pregnant women who use these devices or are exposed to their vapours (Bahl et al., 2012). Cytotoxicity has also been related with concentration and the number of flavouring compounds used in the vaping liquid, and it was found that there are an enormous variety of flavours (fruits, mint, caramel, etc.). Likewise, in the opinion of the World Health Organization, flavours similar to those of sweets may attract young people to try e-cigarettes and facilitate the development of tobacco smoking (WHO, 2007).

The available studies show that, in general, vapour contains carcinogenic compounds and other toxic substances found in tobacco smoke but at average levels of 1 to 2 orders of magnitude lower than traditional tobacco smoke, but greater than that of a nicotine inhaler, used as a medication-device to stop smoking. In certain cases, it has been observed that the nickel of some of these carcinogenic agents, among them formaldehyde and other toxic substance such

as acrolein, is as high as that of the smoke produced by some cigarettes (WHO 2010). As such, we cannot exclude the possibility that the use of e-cigarettes may increase the risk of cancer or other diseases, even if the toxic substances are present in small amounts.

Lastly, for *nicotine*, in the following paragraph we consider specifically the identification and characterisation of the danger of this compound, and we will subsequently analyse exposure and the characterisation of the risk.

4.2 Identification and characterisation of the danger of nicotine

Nicotine or 3-[2-(N-methylpyrrolidinyl)] pyridine, is an alkaloid found naturally in tobacco, mainly in its leaves. The toxic and addictive characteristics of this alkaloid determine a known danger; it has negative effects on the central nervous system, endocrine system, cardiovascular system, musculoskeletal system, respiratory system, gastrointestinal tract, metabolism in general and on the development of the foetus. These effects logically potentially develop when using e-cigarettes that contain nicotine. As such, it has been shown that its use increases the heart rate (Vansickel et al., 2013). Blood levels of nicotine increase when e-cigarettes that contain nicotine are used and, although these products appear to release it more slowly and in lower levels than conventional tobacco products, it is possible that experienced consumers may generate compensatory inhalation mechanisms to increase the release of nicotine, as indicated above. The pharmacological effects of nicotine at the brain level are related to the generation of dependence. Ex-smokers who use e-cigarettes and those who consume both products possibly maintain their nicotine dependence (WHO, 2012).

4.3 Exposure

In this section, exposure to nicotine through e-cigarette vaping is assessed as well as the involuntary exposure in the environment. The risk resulting from skin contact is also considered, mainly during refilling and the accidental intake of the refill liquid by children.

Nicotine concentrations in e-cigarette liquids can vary between 0 and 26mg/ml, they may even contain more than 36mg/ml, according to the preferences of users.

Exposure to large amounts of nicotine is highly toxic, and may be lethal. Nicotine is easily absorbed through the mucosa and the skin, while its bioavailability through the mouth is low.

There are currently discrepancies when toxicity values are established for nicotine. As such, most pharmacology treatises, databases and safety data sheets on the product set the lethal dose for adults at between 30 and 60mg/person (Mayer, 2014). The 60mg would correspond to an oral DL_{50} of around 0.8mg/kg, a dose that is considerably lower than the values determined in the laboratory, which are in a range from 3.3 (mice) to over 50mg/kg (rats) (Hayes, 1982).

Recently, some authors (Mayer, 2014) have established higher toxicity values. It has been demonstrated that the lowest limit of lethal plasma levels of nicotine for there to be clinical intoxication is 4mg/L of plasma. Considering an oral bioavailability of 20% and assuming linear pharmacokinetics, the intake of a 60mg/person dose, the amount that some cartridges may have, and which would correspond approximately with the smoking of 60 conventional tobacco

cigarettes, would provide a plasma nicotine concentration of 0.18mg/L, which is a concentration at least 20 times lower than minimum lethal plasma levels. The same cannot be ensured for higher concentrations, which also exist, and other presentations. For these calculations, it was considered that whenever a tobacco cigarette is smoked, approximately 1mg of nicotine is captured (0.7mg according to the labelling of the tobacco cigarette packs for an average of 8 inhalations/cigarette).

Furthermore, it is considered that the lowest limit that causes mortality from nicotine intake in adults is 510-1000mg, which would correspond to an oral DL_{50} value of 6.5-13mg/kg b.w. (lethal dose of a substance that is fatal for half of the animals tested). These values were confirmed in dogs, which have a similar response to nicotine as humans (Mayer, 2014).

With regard to the risk of the nicotine content in e-cigarettes compared to the values of conventional tobacco cigarettes, both the data found in the references and those presented to this Research and Quality Control Centre Committee (CICC in its Spanish acronym) [internal report of the INC-CICC (2011)]*, show very low levels of concentration in comparison with those of conventional tobacco cigarettes.

In this latest report (INC-CICC, 2011) the quantitative analysis of nicotine indicates that the amounts found in vapour produced when the cigarette is inhaled is 0.15-1.91mg/cartridge or e-cigarette. Sixty samples of 3 different brands were analysed.

These INC-CICC 2011 report data are high values, if compared with the maximum values permitted by the regulation in force for conventional cigarettes (<1mg of nicotine according to the labels on boxes (R.D. 1079/2002 of 18 October), but they are not so much since a cartridge or refill of an e-cigarette is equivalent, in the experimental conditions employed, to several conventional tobacco cigarettes.

In the abovementioned report of the CICC within the National Consumer Affairs Institute (INC-CICC, 2011), currently CICC-AECOSAN, it is observed that a conventional cigarette requires an average of 8 inhalations to be fully consumed. To fully consume an e-cigarette cartridge or refill, with the smoking machine used and in the experimental conditions reported, a greater number of inhalations is required, which, when extrapolated, would correspond to a greater number of conventional tobacco cigarettes.

Specifically, in this report, brand no. 1 requires 360 inhalations/cartridge, brand no. 2 requires 220 inhalations/cartridge and brand no. 3, 100 inhalations/cartridge, which correspond to 45, 25 and 12.5 conventional cigarettes respectively if we use as a reference an average of 8 inhalations per cigarette. Taking into consideration the foregoing list of the number of inhalations/cartridge and the number of cigarettes equivalent to a cartridge, the abovementioned nicotine levels of 0.15-1.91mg/cartridge or e-cigarette would be equivalent to values of between 0.003 and 0.153mg/conventional tobacco cigarette.

In any case, it must be borne in mind that the method, under ISO 4387:2000 reference, that is used for determining the content of nicotine and other substances in vapour involves the use of a smoking machine designed for conventional tobacco cigarettes and analytical methods of gas chromatography and mass spectrometry, accredited by ENAC (National Accreditation

Entity) in the CICC, which use, as a matrix, tobacco smoke from conventional cigarettes and not vapour produced after the heating of a resistor, characteristics that are specific to these kinds of e-cigarettes. As such, the data obtained are a result of direct "extrapolation" and must be assessed with caution.

The tables below show the results of INC-CICC report (2011).

No. cigarettes/day	1	5	10	15	20	25	30	35	40	45	50	55	60
mg. nicotine/day	0,8	4	8	12	16	20	24	28	32	35	40	44	48

ml. vaped/day	mg/ml of nicotine in a cartridge																			
	36	**30**	**28**	**26**	**24**	**22**	**20**	**18**	**16**	**14**	**12**	**10**	**9**	**7**	**6**	**5**	**4**	**3**	**2**	**1**
1	45	38	35	33	30	28	25	23	20	18	15	13	11	9	8	6	5	4	3	1
1.5	68	56	53	49	45	41	38	34	30	26	23	19	17	13	11	9	8	6	4	2
2	90	75	70	65	60	55	50	45	40	35	30	25	23	18	15	13	10	8	5	3
2.5	113	94	88	81	75	69	63	56	50	44	38	31	28	22	19	16	13	9	6	3
3	135	113	105	98	90	83	75	68	60	53	45	38	34	26	23	19	15	11	8	4
3.5	158	131	123	114	105	96	88	79	70	61	53	44	39	31	26	22	18	13	9	4
4	180	150	140	130	120	110	100	90	80	70	60	50	45	35	30	25	20	15	10	5
4.5	203	169	158	146	135	124	113	101	90	79	68	56	51	39	34	28	23	17	11	6
5	225	188	175	163	150	138	125	113	100	88	75	63	56	44	38	31	25	19	13	6
5.5	248	206	193	179	165	151	138	124	110	96	83	69	62	48	42	34	28	21	14	7
6	270	225	210	195	180	165	150	135	120	105	90	75	68	53	45	38	30	23	15	8
6.5	293	244	228	211	195	179	163	146	130	114	98	81	73	57	49	41	33	24	16	8
7	315	263	245	228	210	193	175	158	140	123	105	88	79	61	53	44	35	26	18	9
7.5	338	281	263	244	225	206	188	169	150	131	113	94	84	66	56	47	38	28	19	9
8	360	300	280	260	240	220	200	180	160	140	120	100	90	70	60	50	40	30	20	10
8.5	383	319	298	276	255	234	213	191	170	149	128	106	96	74	64	53	43	32	21	11
9	405	338	315	293	270	248	225	203	180	158	135	113	101	79	68	56	45	34	23	11
9.5	428	356	333	309	285	261	238	214	190	166	143	119	107	83	71	59	48	36	24	12
10	450	375	350	325	300	275	250	225	200	175	150	125	113	88	75	63	50	38	25	13

The millilitres that can be "vaped" per day are expressed in the left column and the mg/ml of nicotine contained in the cartridge are expressed in the upper row. The column/row value intersection, using the equivalences described above, shows the total number of conventional cigarettes equivalent to ml vaped per day.

* Internal INC-CICC report (2011). Data not published.

Efforts are currently being made to fine-tune a vaping machine for these types of e-cigarettes.

It is necessary to consider that, although compared with conventional tobacco cigarettes, e-cigarettes provide a greater amount of nicotine/vape, the problem associated with the risk of the latter is that they can be "vaped" for an indefinite period of time, while a conventional tobacco cigarette, after a series of inhalations (an average of 8), runs out.

Therefore, in accordance with the concentration of nicotine of each cartridge, its total volume and the number of vapes, a high nicotine plasma content could be reached in a less controllable and toxic manner.

Moreover, it is necessary to also consider the potential risks resulting from indirect exposure of smokers to the vapour emitted by e-cigarettes (nicotine and some toxic substance) into indoor air and particularly public places in which their use is not prohibited. There are few studies assessing passive exposure to the emissions produced by these devices. Furthermore, in some cases, they were carried out using exposure conditions not in line with real conditions. The vapours emitted, as has already been mentioned, can contain nicotine and other chemical substances that are altered during the heating process, resulting in emissions from other potentially toxic components, such as aldehydes, polycyclic aromatic hydrocarbons and metals (Kuschner et al., 2011). These circumstances make it necessary to consider a new manner of exposure, which must also be adequately assessed.

The fact that the vapours exhaled contain average levels of some toxic substances, nicotine and ultrafine particles in the air that are lower than emissions from conventional tobacco cigarettes does not mean that these levels are acceptable for those around them who are involuntarily exposed (Czogala et al., 2014; McAuley et al., 2012).

Furthermore, it is unclear if these lower levels in vapour exhaled are translated into lower exposure. As was demonstrated in the case of nicotine where, despite the lower levels achieved compared to those of traditional tobacco smoke emitted, the vapours exhaled from e-cigarettes result in similar levels of absorption, as reflected in the nicotine values detected in plasma (Flouris et al., 2013). This fact is also corroborated with certain exposure biomarkers, such as cotinine, which is the main metabolite of nicotine and, as such, its presence in urine, saliva or blood is used as a specific exposure biomarker (active or passive) of tobacco smoke. When the passive exposure to the vapour of e-cigarettes versus conventional cigarettes has been studied, measuring both the levels of nicotine in the air and cotinine in urine and saliva, it has been observed that, although the nicotine concentration is higher in spaces where conventional tobacco cigarettes are smoked than for e-cigarettes, the cotinine concentrations in saliva and urine are similar for both types of cigarettes (Ballbè et al., 2014).

It is interesting to highlight the list of effects observed after direct exposure to e-cigarettes or vapours from these cigarettes indirectly, which have been detailed in the literature (Callahan-Lyon, 2014):

- Dry mouth, throat irritation and a dry cough at the start of their use, decreasing with prolonged use

- There is no change in heart rate, carbon monoxide levels or the plasma nicotine level
- Decreased nitric oxide exhaled, and an increased breathing rate, similar to the use of traditional tobacco cigarettes
- There is no change in the normal blood count
- There is no change in lung function
- There is no change in heart function (measured by echocardiogram)
- There is no change in inflammatory markers.

Exposure through skin contact with e-cigarette liquids must also be considered, particularly if they contain nicotine, due to its high absorption through the skin.

Lastly, it is necessary to bear in mind the risk through accidental intake of e-cigarette liquids by small children, which can be particularly attractive due to their smells and flavours. The most common presentation of e-cigarette refill liquid is a 5mL vial, which, for an average nicotine concentration of 20mg/ml results in an amount of 100mg/vial, very far below the abovementioned lower limit of lethal plasma levels in adults. However, this concentration may pose a risk to children in the event of an accidental intake of the refill liquid, taking into account the toxicity of nicotine (Cameron et al., 2013; Bassett et. al., 2014).

4.4 Characterisation of the risk

For the purposes of health risks, we must consider, on one hand the electronic component of the cigarette, on which few studies have been carried out and which is not the subject of this report, and the content of substances and mixtures inside the cartridge, on the other hand.

With the data available to date, it is very difficult to accurately assess the health risks. We must bear in mind that very few e-cigarettes of those currently on the market have undergone a toxicological evaluation. Furthermore, there is no scientific consensus on the appropriate studies that must be carried out for the purposes of evaluating the health risk.

We must add to these limitations the no less important and abovementioned fact that there is, as yet, no smoking machine for vaping in accordance with the characteristics of these cigarettes that considers, among other factors, the type of matrix to be analysed, the particles generated and the potential transformation of some compounds into others following the heating, in order to, once achieved, obtain data that is more in line with the real situation and define the regulations to be applied.

For the purposes of this scientific report, we have considered the risk involved in inhaling from vaping the liquid contained in the cartridge, the exposure to non-smokers and the highest risk population (infants, children, pregnant women, the elderly and people with different kinds of diseases, amongst others), to the vapour generated by these types of cigarettes and the possibility of accidental intake, particularly by children, following the breaking of the cartridge or the addition to these cigarettes.

The safety of e-cigarettes has not been tested based on the available documentation. Due to its content of nicotine and other toxic substances, e-cigarettes may pose a risk to smokers and

must not be used in environments with a high-risk population. They are an entry route to smoking for young people.

There may be variations in the nicotine content. Various studies have highlighted the significant differences (up to 90%) between the nicotine concentration determined in the e-cigarette liquid and that declared on the label, with nicotine even being detected in liquid marketed as being "nicotine-free" (Goniewicz et al., 2013). Furthermore, as indicated, there is a wide variability in the amount of nicotine and other substances provided by vaping in accordance with the characteristics of the cigarettes and the vaping conditions.

Likewise, we must consider non-smokers' risk to indirect exposure, particularly in high-risk populations, to vapours emitted by e-cigarettes (nicotine and some toxic substances) as passive smokers in enclosed spaces (Callahan-Lyon, 2014).

Nicotine is absorbed easily by the skin and, therefore, it must not enter into direct contact with the liquid of e-cigarettes that contain it.

The accidental intake of the refill solution of e-cigarettes by children poses a serious risk to their health with regard to the toxicity and concentration of nicotine in these liquids, which may reach the lower limit of lethal plasma levels indicated. Therefore, it is important to maximise the security precautions in their presentation and the storage of the liquids that contain nicotine, in order to keep them out of the reach of children. Both e-cigarettes and refill containers must have safety seals for children.

For future risk assessments, it is important to consider, in addition to the abovementioned exposure biomarkers, the risk of diseases, morbidity and mortality, when comparing different classes of tobacco product between users and non-users of tobacco and, in any case, the assessment of the long-term adverse effects on potential cell damage (modifications to the cell cycle, oxidative stress, DNA mutations, etc.) of the cells of the mucosa and of the airways.

The main shortcoming is the lack of epidemiological data, on one hand, in the long term on the effects to the health of those who use e-cigarettes and, on the other hand, on the effects of total exposure. The belief that e-cigarettes are a safer alternative to traditional tobacco cigarettes has not yet been validated scientifically and the marketing aimed at young people is of particular concern. Various administration systems available on the market allow the user to manually adjust the voltage and the nicotine levels, which introduces, as we have already mentioned, even more variables into the evaluation of the risk to health.

5. Regulatory framework

5.1 Applicable regulations

Law 28/2005 of 26 December, on health measures with regard to smoking and regulating the sale, supply, consumption and advertising of tobacco products, does not regard electronic cigarettes as "tobacco products" since it reserves this designation for "[products] intended to be smoked, inhaled, sucked or chewed, constituted, even in part, by tobacco" (Article 2.1 letter a). However, since the reform of Law 28/2005 of 26 December, carried out by Law 3/2014 of 27 March, electronic cigarettes are considered to be "devices capable of releasing nicotine" (this

expression is defined in Article 2.1, letter f, of Law 28/2005 of December 26, as "a product, or any of its components, including cartridges and the device without cartridge, that can be used for the consumption of vapour that may include nicotine through a mouth piece"). Since the entry into force of the aforementioned reform, the twelfth and thirteenth Additional Provisions of that provision limit the places of use (or consumption) and sale of these devices, and restrict their advertising.

In relation to its content, e-cigarettes must comply with the following national provisions and those of the European Union on mixtures:

- Royal Decree 363/1995 of 10 March, approving the Regulation on the notification of new substances and the classification, packaging and labelling of hazardous substances;
- Royal Decree 255/2003 of 28 February, approving the Regulation on the classification, packaging and labelling of hazardous preparations;
- Royal Decree 717/2010 of 28 May, amending Royal Decree 363/1995 of 10 March, approving the Regulation on the classification, packaging and labelling of hazardous preparations, and Royal Decree 255/2003 of 28 February, approving the Regulation on the classification, packaging and labelling of hazardous preparations;
- Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006;
- Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

We should highlight, in relation to Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, that Article 52 provides for the possibility of Member States individually adopting provisional measures, when they have justified reasons, to consider that a substance or mixture, although complying with that provided for in Regulations, poses a serious risk to human health or to the environment. The Commission must be notified of these measures so that, within a period of 60 days, it may authorise them or order their revocation.

Under that provision, the Netherlands has adopted a provisional measure consisting of obliging producers to incorporate safety for children into e-cigarettes and refill containers. This requirement goes beyond that provided for in Regulation (EC) No 1272/2008 of the European Parliament and of the Council. The Commission authorised this measure, after it was notified by the Netherlands, through the Implementing Decision (EU) 2015/744 of 8 May 2015. This is a temporary authorisation that will remain in force until the Member State approves the measures transposing Directive 2014/40/EU of the European Parliament and of the Council, or the period for this transposition expires (19 May 2016), since this Directive establishes a similar measure in Article 20.

- In terms of labelling, Additional Provision 12a of Law 28/2005 of 26 December, declares Article 3, sections 2 and 3, as applicable to devices capable of releasing nicotine and similar products. Article 3, section 2, establishes that "the packaging of tobacco products shall include an express reference to the prohibition of their sale to individuals under 18 years of age". The use, in the provision, of the expression "tobacco products" has raised questions about its applicability to devices capable of releasing nicotine.
- The specific regulation on labelling established in Royal Decree 1079/2002 of 18 October, regulating the maximum contents of nicotine, tar and carbon monoxide in cigarettes, the labelling of tobacco products, and the measures relating to the ingredients and naming of tobacco products, amended by Royal Decree 639/2010 of 14 May, only applies to tobacco products. As such, e-cigarettes are outside its sphere of application, and, in the absence of other specific regulations, the labelling of the latter shall be governed by that provided for in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on mixtures, and in Royal Decree 1468/1988 of 2 December, approving the Regulation on the labelling, presentation and advertising of industrial products intended for their direct sale to consumers and users.

5.2 Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 and its transposition to Spanish Law

(This directive is currently in the transposition process)

Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 establishes harmonisation standards at a European Union scale on "the placing on the market and the labelling of certain products, which are related to tobacco products, namely electronic cigarettes and refill containers" (Article 1, letter f) provided that the latter products are subject to an authorisation requirement under Directive 2001/83/EC relating to medicinal products or the requirements established in Directive 93/42/EEC concerning medical devices (Article 20, section 2).

In particular, the Directive regulates in detail, in Article 20, aspects of e-cigarettes and refill containers relating to their placing on the market, composition, information that must accompany the product, labelling and advertising. It likewise imposes on manufacturers and importers the obligation to prepare certain information and make it available to the public authorities.

With regard to the placing on the market, the Directive obliges manufacturers and importers of e-cigarettes and refill containers to notify the competent authorities of the Member States 6 months in advance, of all the products they intend to place on the market. The notification must include the information detailed in the Directive, including "the toxicological data on the ingredients and emissions of the product, including those subjected to heating, mentioning, in particular, their effects on the health of consumers and bearing in mind, amongst other things, their potential addictive effect".

In relation to the composition of refill containers, the Directive devotes special attention to regulating the ingredient of nicotine. It also prohibits the liquid containing nicotine from containing the following additives:

- Vitamins and other additives that create the impression that a tobacco product brings health benefits or reduces health risks;
- Caffeine and taurine and other stimulant additives and compounds associated with energy and vitality;
- Additives with colouring properties during combustion;
- Additives with CMR properties without combustion.

The presence of glycerine or propylene glycol cartridges is not regulated.

Likewise, the Directive establishes that "Member States shall ensure that […] only ingredients of high purity are used in the manufacture of the nicotine-containing liquid" and that "except for nicotine, only ingredients are used in the nicotine-containing liquid that do not pose a risk to human health in heated or unheated form".

The Directive leaves Member States the responsibility to adopt standards on flavours (see consideration No 47 of the Directive) and invites them, when regulating the placing on the market of flavoured products, to be very aware of the attractive potential of these products for young people and non-smokers. It also reminds them that any prohibitions of these flavoured products must be justified and communicated in accordance with Directive 98/34/EC of the European Parliament and of the Council of 22 June 1998 laying down a procedure for the provision of information in the field of technical standards and regulations".

Article 20, section 4 of the Directive establishes the obligation of Member States to ensure that e-cigarettes display sufficient and adequate information about their safe use, with the objective of protecting human health and safety, contain adequate health warnings and do not include any element or characteristic that may lead to a mistake.

Specifically, Member States shall ensure that the e-cigarette and refill container packaging units include a leaflet with information instructions on the following aspects:

- use and storage, including the warning that the product is not recommended for consumption by young people and non-smokers;
- contraindications;
- warnings to specific risk groups;
- potential adverse effects;
- addiction and toxicity;
- contact data of the manufacturer or importer and an individual or legal person in the Union;

Likewise, Member States must ensure that packaging units and all external packaging of e-cigarettes refill containers include certain information on the ingredients and carry one of the two health warnings outlined in the Directive on the presence of nicotine in the product.

Neither does the Directive harmonise the standards on smoke-free environments, nor on national purchase and sale or advertising provisions, or on brand extension, nor does it introduce an age limit for e-cigarettes or refill containers.

Article 20, section 6, authorises Member States to prohibit cross-border distance selling of

e-cigarettes and refill containers to consumers. Member States that do not prohibit such sales shall require retailers to register them before the authorities of the Member State in which the establishment is located and before the Member State of residence of the potential client, as well as to have a system that allows them to verify the age of the consumer who makes the purchase. Lastly, recently, Commission Implementing Decision (EU) 2016/586 of 14 April 2016 on technical standards for the refill mechanism of electronic cigarettes was approved.

Conclusions

Electronic cigarettes have health risks.

1. In the short term, adverse effects similar to those associated with tobacco smoke have been observed: inflammation of the mouth and throat, nausea, vomiting and coughing.
2. For the major components in the liquids of the e-cigarette cartridges, propylene glycol and glycerine, despite being considered safe and approved for consumption in dietary terms, their safety has not been demonstrated for the repeated inhalation at the temperatures reached in electronic devices. Other substances contained in the liquid of cartridges that are, *per se*, non-toxic, may be toxic in smoked vapour, they may even generate other substances, not yet detected, produced by their breaking down after the heating and that could be toxic.
3. Flavouring agents, carcinogenic substances, heavy metals and other chemical products were detected in the liquid of e-cigarette cartridges. Some of these substances are potentially dangerous or toxic when they are vaped, after they are heated up.
4 Substances not identified in the labelling or that appear in a different amount to that reported have been demonstrated, which proves that there are deficient quality systems in production that, as a result, generate greater health risks resulting from their use.
5. The vapour released into the environment contains, amongst other products, propylene glycol, nicotine and carcinogenic substances that pollute enclosed spaces with the resulting risks due to passive exposure for vulnerable high-risk populations (infants, children, pregnant women, the elderly and pathologies of different kinds).
6. Bearing in mind that there is no specific e-cigarette smoking machine that allows the assessment of nicotine concentrations, the focus of the extrapolation of data obtained using a conventional smoking machine and for a small sample, appear to indicate that the average inhalation content of this alkaloid in e-cigarettes is 10 times lower than the maximum content permitted for conventional tobacco cigarettes.
7. The nicotine plasma concentration obtained after the vaping of these cigarettes is very far below that of the lowest limit of lethal plasma levels for nicotine in humans.
8. Nicotine concentration varies from some cartridges to others and may be highly toxic if the liquid is ingested directly. This generates a serious risk for health in the case of an accidental intake by the infant population, and could be increased by the absence of safety warnings that will provide information about the risk for children and the advisability of keeping the product out of their reach; and due to the fact that e-cigarettes or their refill containers, may

lack the corresponding safety seal for children. Likewise, the refill mechanisms pose a risk through skin contact or the accidental intake of the aforementioned liquids.

9. The effectiveness of e-cigarettes as an aid to quit smoking has not been demonstrated. They may reduce the desire to smoke and other symptoms characteristic of quitting, but some smokers may temporarily switch from tobacco consumption to these products without stopping smoking completely.
10. E-cigarettes could potentially act as a maintainer of nicotine addiction, or an invitation to nicotine addiction, particularly amongst the younger population.
11. Exposure to risk increases with e-cigarette user habits because the frequency of vaping increases along with its intensity.
12. Misleading advertising on e-cigarettes and its consequences for health is likely to encourage consumption of this product, despite its effective health risks.
13. Compliance with the provisions set out in Directive 2014/40/EU ensures a much higher level of safety for consumers in these devices. This safety level shall be consolidated in the transposition of the Directive to the Spanish legal system. The proposal for this transposition was prepared by the MSSSI.

Recommendations

Based on the available studies, in order to be able to adequately assess the risk to health due to the use of e-cigarettes, different public and private actors must:

1. Carry out more studies to determine the composition, quality control measures in the manufacturing, amount and characteristics of the chemical compounds included in the cartridges.
2. Define the method of vapour production, the potential products to replace nicotine, the biomarkers and parameters that allow us to study the feasibility of mucosa cells and airways (changes in the cell cycle, damage to the DNA, oxidative stress, etc.) that are in contact with the vapour produced by vaping.
3. Develop long-term studies that show if the use of these cigarettes is effective or not for treating tobacco addiction, and for knowing the chronic effects of a toxicological kind of exposure to e-cigarettes.
4. Carry out epidemiological studies that take into account the effects on health of the use of e-cigarettes, particularly for high-risk populations (infants, children, pregnant women, the elderly and different kinds of diseases).
5. Conduct tests on smoking machines that allow results to be obtained that are more in line with the vaping method specific to this product.
6. Carry out studies on the effect of glycerine and propylene glycol consumption by inhalation and, in accordance with their results, adapt the regulations.
7. Gain more knowledge, through studies, about the effects of differences in voltage and circuit systems on the administration of the different ingredients and the possibility of a formation of new toxic substances.

8. Implement better monitoring of e-cigarette advertising in order to avoid misleading, incomplete or ambiguous information.

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