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Permalink https://escholarship.org/uc/item/5wq6j8c9

Journal Ciência & Saúde Coletiva, 24(8)

ISSN 1413-8123

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Publication Date 2019

DOI 10.1590/1413-81232018248.24282017

Peer reviewed

The ban of eletronic cigarettes in Brazil: success or failure?

FREE THEMES

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> Abstract Brazil was one of the first countries in the world to ban Electronic Smoking Devices (ESDs). This ban was motivated by the lack of evidence regarding the alleged therapeutic properties and harmlessness of these products. Anvisa was criticized for this move, especially by electronic cigarette's users groups. These groups argue that prohibition prevented people's access to a product that would aid smoking cessation and be less toxic than ordinary cigarettes. Thus, the question arises as to whether this decision was successful. Available data show that ESDs have diverse formulations and some toxic substances are released at significant levels during use. Studies in animals and humans have shown a potential toxic effect, also affecting the health of passive smokers. Studies are still inconclusive regarding its use as a cessation tool. A high level of use among adolescents was observed in countries whose use was authorized. Thus, Brazil's ban prevented the population from consuming a product that has not been proven effective toward smoking cessation, with indications of significant toxicity and highly attractive to young people.

Key words *Smoking habit, Tobacco-derived products control and oversight, Tobacco products, Vapers, Vaping*

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Introduction

The National Health Surveillance Agency (Anvisa) was established by Law 9782/1999¹, and regulation, control and oversight of control products and services that pose a risk to public health (Art. 2, subsection III and Article 7 subsection XV) are among its various attributions (Art. 8). Cigarettes, cigarillos, cigars and any other fumigant products, whether or not tobacco-derived (Art. 8, § 1, subsection X) are within the scope of products subject to health surveillance.

The emergence of so-called electronic cigarettes and reports of use of these products in Brazil² led Anvisa to issue in 2009 Resolution RDC 46/2009³ prohibiting the sale and advertising of any Electronic Smoking Device (ESD) with or without nicotine throughout national territory until scientific studies and toxicological and clinical evaluations are performed, aiming at identifying its risks and alleged effectiveness in smoking cessation. In addition to the lack of scientific studies, Anvisa also considered in the ban the harmful potential of nicotine's purified extracts to human health.

Thus, Brazil was one of the first countries in the world to ban Electronic Smoking Devices (ESDs)³, popularly known as electronic cigarettes (which are actually just one of several types of known ESDs, but which in this text can be considered as synonyms).

The National Health Surveillance Agency (Anvisa) was highly criticized for this ban, especially from user groups. These groups accused (and still accuse) Anvisa of having banned a product that would aid smoking cessation and would be less toxic than ordinary cigarettes, so that this prohibition would not be reasonable from the health viewpoint, besides having no basis scientific evidence^{2,4}.

Recently, according to a personal communication from the Anvisa's General Manager of Tobacco Products, the tobacco industry joined enthusiasts to pressure Anvisa to release these products. Allegations are the same as those used over 8 years ago, that it would be a safer product and help smoking cessation.

Thus, this text aims to discuss the main aspects raised by ESD advocates and to evaluate whether regulation implemented by Anvisa is effective from the viewpoint of public health.

Methods

This paper was written by using PubMed (Medline)⁵ and SciELO⁶ databases to search for scientific articles and Google Search Engine⁷ to search for reports, legislations, stories and others documents.

We selected only full-text papers available on the Internet and published in English, Spanish or Portuguese. References were collected from March to September 2017. Papers duplicates and studies totally or partially funded by the tobacco or ESDs industry were also excluded.

In databases of scientific papers, free terms (without use of controlled vocabulary - Descriptors) were used, as a result of the different indexing processes, besides providing a greater retrieval of papers, reports and other types of publication within the criteria used. The terms Tobacco use disorder, Tobacco Smoke Pollution, Tobacco Use Cessation, Electronic Cigarettes, Tobacco Use Cessation Products, associated with the qualifiers Adverse effects, trends, health effects, composition, utilization, children, teenager, second hand smoke, epidemiology, accidents and Brazil were used.

Function, composition and toxicity of ESDs

ESDs are battery-powered electronic vaporizers⁸. Despite their various generations, the basic structure consists of a nozzle (inhalation nozzle), cartridge location or solution tank (depending on model), atomizing element, microprocessor, battery compartment and, in some cases, a LED light on the tip⁹ (Figure 1).

When using the product, the user presses a button or activates a pressure sensor by inhalation, the atomizer heats and atomizes the tank or cartridge solution. The solution is heated to temperatures between 100-250° C to generate the aerosol¹⁰, popularly called vapor¹¹. ESDs products are today in their 4th generation¹², where new technologies have been incorporated, as shown in Chart 1, even Bluetooth technology to answer phones through the equipment is available¹³. Products of all generations are currently found on the market¹².

The literature shows that e-liquids used in the ESDs are quite different in terms of chemical composition, nicotine concentration and additives used¹⁴. The literature also shows a discrepancy between the composition stated on the package and the actual composition of the prod-

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uct¹¹. About 8,000 electronic cigarette flavors have been described¹⁵.

Propylene glycol and glycerol are the major components of ESDs liquids (e-liquid). Exposure to propylene glycol can cause eye and respiratory system irritation and, in the event of chronic exposures, affect the nervous system and spleen. When heated and vaporized, it can generate pro-

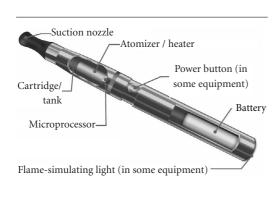


Figure 1. Parts of an Electronic Smoking Device.

pylene oxide, which is classified as 2B carcinogen by IARC^{16,17}. To date, no studies demonstrating the formation of this substance in ESDs have been identified. In the case of glycerol, the heating process would be related to the formation of acrolein, a known upper airway irritant, where some studies point to the formation of this agent in the vapor of ESDs^{16,18}.

Studies have also described that electronic cigarettes would release some toxic substances, such as formaldehyde, acrolein, acetaldehyde, propanol, nicotine, tobacco-specific nitrosamines and particulate matter, usually with much lower concentrations of these agents than those found in traditional cigarettes^{12,16,19-32}. However, Jesen et al.33 demonstrated that the new generation of electronic cigarettes in some situations (high-voltage devices) would expose e-cigs smoker to doses of formaldehyde 5 to 15 times higher than the concentrations found in common cigarettes. We must certainly consider that these studies were conducted in the laboratory and in conditions that could be difficult to reproduce in real life. In addition, the puff regime and the analytical methods used in the available studies vary widely, which makes their comparability difficult. Therefore, caution should be exercised in the analysis and comparison of these results.

Chart 1. Characteristics of ESDs.

Generation	Type of equipment	Structure	Battery (mAh)	Observations	
lst		Cin als misses	90-200	Cartridge	
	Single-use ESD	Single piece	Fixed voltage		
	D 1 1. 1. 1	Reusable battery/ Single	90-200	Cartridge	
	Rechargeable battery	-use cartridge	Fixed voltage		
	Three-piece tank	Separate battery, atomi-	90-200	Tank	
	system	zer and tank	Fixed voltage		
2nd	Reusable/replenisha-	Separate battery and	300 - 1100	Tank/ Variable vol-	
	ble ESD	tank	Variable voltage	tage	
	Reusable/replenisha-	Separate battery and	300 - 1100	Tank/ MODs (user	
			Voltage and power ba-	fills the tank with	
	ble ESD	tank	sed on battery output	solution that he can	
			300 - 1100	prepare)	
3rd	Reusable/replenisha- ble ESD	Separate battery and		- 1	
		tank	Variable voltage and	Tank	
			power		
4th			>1000	Tank/Temperature	
	Reusable/replenisha-	Separate battery and		control/ some models	
	ble ESD	tank	Variable voltage, power	are equipped with	
			and temperature	Bluetooth technology	

Source: Modified from (12).

Table 1 shows the composition of cartridges and aerosol of selected substances compared to conventional cigarettes.

In vitro and animal studies show some toxic effects and that toxicity varies depending on the flavor additives used in e-liquids. Compared with

nn 11 -	0	•	C 1 .	1 1 • 1	C 1 '	DOD 1	conventional cigarettes	
Table I	(om	naricon	of selecter	1 chemicale	s tound in	ESDe and	conventional cigarettee	
Table 1	• COIII	parison	or sciecte	a chemical	s iouna m	LODS and	conventional eigarettes	

	Matrix	Electronic cigarettes	Conventional cigarettes
Nicotine	Liquid	0 – 50 mg/ ml (composição do e-liquid)	0,8 – 2,3 mg/g
СО	Aerosol	<0.1 mg/99 puffs	10-23 mg/cigarette
Aldehydes			
Formaldehyde	Aerosol	Low voltage 3.3V – ND	3 mg/day (20-unit pack)
Acetoaldehyde	Aerosol	High voltage 5V – 14.4 +- 3.3 mg day (3 ml of fluid) / Type of vapor – More efficient deposition in the respiratory tract 0.11–1.36 µg/ 15 puffs <lq 11="" m3<="" mg="" td="" –=""><td>18-1400 μg/cigarette</td></lq>	18-1400 μg/cigarette
	Refill solution	0.10 – 15.63 mg/L	
Acrolein	Aerosol	<LQ – 4.19 µg/ 15 puffs	2.4-62 μg/cigarette (fume)
o-methyl	Aerosol	1.3 - 7.1 µg/15 puffs	ND
benzoaldehyde	11010001		112
Acetone	Aerosol	2.9 mg/m^3	50 – 550 μg/ cigarette
Tobacco-specific	nitrosamines	-	
NNN	Aerosol	0.00008–0.00043 µg/15 puffs	0.005–0.19 μg/ cigarette
	Aerosol	<ld-4.3< td=""><td></td></ld-4.3<>	
	Refill solution	0.34 – 60.08 μg/L	
NNK	Aerosol	0.00011–0.00283 µg/15 puffs	0.012–0.11 µg/cigarette
	Refill solution	0.22 – 9.84 μg/L	
NAT	Refill solution	<ld 62.19="" l<="" td="" μg="" –=""><td>0.3 – 5 μg/cigarette</td></ld>	0.3 – 5 μg/cigarette
NAB	Refill solution	<ld 11.11="" l<="" td="" μg="" –=""><td>109 – 1,033 μg/cigarette (NAB + NAT)</td></ld>	109 – 1,033 μg/cigarette (NAB + NAT)
Metals and metal	loids		
Cadmium	Refill solution	0.42 – 205 μg/L	0.5 – 1.5 μg/cigarette
Nickel	Refill solution	58.7 – 22,600 μg/L	0.078 – 5 μg/cigarette
Lead	Refill solution	4.89 – 1,970 μg/L	1.2 μg/cigarette
Chrome	Refill solution	53.9 – 2,110 μg/L	0.0002–0.5 μg/cigarette
Manganese	Refill solution	28.7 – 6,910.2 μg/L	155 – 400 μg/g
Polycyclic aromat	tic hydrocarbons	and cresol	
Cresol	Aerosol	0.16 ppm/ 38 ml puff	11-37 μg/cigarette
Anthracene	Aerosol	7 μg/ cartridge	24 μg/cigarette
Phenanthrene	Aerosol	48 μg/ cartridge	77 μg/ cigarette
Pyrene	Aerosol	36 μg/ cartridge	45–140 μg/ cigarette
Volatile organic c	ompounds		
Toluene	Aerosol	0.02 – 0.63 μg/15 puffs	8.3 – 70 μg/cigarette(fume)
p, m Xylene	Aerosol	<ld 0.2="" 15="" puffs<="" td="" µg="" –=""><td>366 μg/cigarette</td></ld>	366 μg/cigarette
Propylene Glycol	Aerosol	$1,660 - 5,525 \mu g/puff 59 - 67\% 21 - 82\%$ of the refill's composition	1 – 2 mg/ cigarette
Glycerin	Aerosol	$5 - 15 \mu g/puff 21 - 82\%$ of the refill's composition	1 – 2 mg/ cigarette

NNN - N-nitrosonornicotine; NNK - 4-(methylnitrosamin) 1 - (3- pyridyl)-1 –butanone; NAT - N-nitrosoanatabine; NAB - N-nitrosoanabasine, <LQ – Below the quantification limit; <LD – Below the detection limit; ND – Not detected.

conventional cigarettes, the effects of these emissions would be less toxic³⁴⁻³⁷.

Effects of ESDs on humans

In humans, reports from users indicated irritation in the mouth and throat, coughing, headache, dyspnea and vertigo³⁸. Another study suggests a potential carcinogenic effect of electronic cigarette emissions³⁹. There was also a significant increase in nicotine and cotinine levels in the saliva and urine of electronic cigarettes users^{20,40-42}, in some cases comparable to traditional cigarette smokers⁴⁰. Passive smokers of electronic cigarettes also had increased levels of cotinine and nicotine in urine^{43,44}. A study also suggests that e-liquids flavors can affect the rate of nicotine absorption in humans and contribute to the acceleration of increased heart rate and other subjective effects described among users⁴⁵.

One study observed acute pulmonary effects, pulmonary impedance, resistance to peripheral airflow and oxidative stress after 5 minutes of electronic cigarette use⁴⁶. Another study pointed to the reduction of forced expiratory volume⁴⁷.

Regarding the health effects in humans in the long term, there are no studies to that effect, due to the fact that they have been on the market for a relatively short time.

Other health hazards

Another relevant point of electronic cigarettes is the increasing number of cases of intoxication by accidental ingestion of their cartridges, especially among children⁴⁸. Searching for *Brazilian Toxicological Information System*⁴⁹ and news on the Internet, there were no reports of accidental intoxication by e-liquids in Brazil.

Another risk to its users and those close to them is the risk of explosion of the batteries of these devices, and there have been reports of injuries and fires caused by the explosion of ESD batteries, usually occurring while these devices were being charged^{9,50}.

Environmental Tobacco Pollution

Regarding environmental tobacco pollution, studies have shown that concentrations of toxic substances to which passive smokers are exposed is up to 10 times lower than that of conventional cigarettes. However, we should remember that these same studies pointed out that passive smokers are still exposed to toxic substances such

as nicotine 1,2 propanediol and particulate matter^{43,47,51,52}. Therefore, the use of these products in collective use environments is not recommended. since even at lower levels, toxic substances found in the emissions of these products have potential harm to health^{16,21,43,52-55} and are still a potential source of third-hand contamination⁵⁶. The concept of third-hand smoke or contamination applies when the smoker releases nicotine while exhaling smoke (or vapor), and this is impregnated on surfaces and objects, persisting for months in these environments. Because of this, reactions occurred between environmental pollutants and compounds emitted by the smoker. One of the components formed from these reactions would be the tobacco-specific nitrosamines⁵⁷.

ESDs as smoking cessation aids

Looking at the literature on electronic cigarettes as an alternative to smoking cessation, studies seem to suggest a slight increase in cessation rates among users of electronic cigarettes. However, published data are not sufficient to state that electronic cigarettes would be an effective method to stop smoking⁵⁰. Questions are also raised about the impact of these products on the cognitive behavioral approach, as they are not inducive to the self-assessment and self-monitoring experience, reinforcing the idea that it is still premature to consider these products cessation-effective⁵⁰. No study was found to evaluate the cost-effectiveness of these products in smoking cessation.

In relation to cessation, the case of England, which, based on a report commissioned by Public Health England, (agency linked to the Ministry of Health of that country), may recommend the use of electronic cigarettes as smoking cessation aid⁵⁸.

This report concludes that ESDs would be 95% less toxic than conventional cigarettes; they would be helping to reduce smoking rates among young people and could be effective in smoking cessation⁵⁸. One of the authors went further and stated that the ESDs could be: *a watershed in public health, in particular because of the reduction of the enormous health inequalities caused by smoking*⁵⁹.

However, this report was heavily criticized by an editorial in Lancet⁶⁰ for basing its main conclusion (that ESDs would be 95% less toxic than cigarettes) by ignoring the caveats made by authors of the main study⁶¹ (two studies were used, one of which is a short 4-page report to the English Parliament⁶²) which substantiated this conclusion that there was no solid evidence for assessed harm and that there was no formal criterion for the recruitment of experts, or in the words of the Lancet editor: *the opinions of a small group of individuals with no prespecified expertise in tobacco control were based on an almost total absence of evidence of harm*⁶⁰.

In addition, the editorial notes that this same study was funded by the manufacturers of ESDs⁶⁰, which raises substantial issues about conflicts of interest involving the main bibliographical reference of the English report.

Use and marketing of ESDs

Observing data on the use of electronic cigarettes in countries where the marketing of these products is released, a high degree of experimentation and use among youngsters^{16,63,64} is observed, and in some countries such as Poland and the United States, more than 1/3 of the young people have already experienced ESDs^{64,65}. Studies also show a significant frequency of double users^{64,66}. A meta-analysis published in 2017 also points out that adolescents who use ESDs are four times more likely to be at risk of smoking traditional cigarettes than those who do not use these devices⁶⁷.

In the United States, the use of electronic cigarettes, among high school students, increased from 1.5% in 2011 to 20.8% in 2018⁶⁸. Among elementary school students, the use of these products increased from 0.6% in 2011 to 4.9% in 2018⁶⁸. In short, almost 1 in 5 American high school students makes use of electronic cigarettes⁶⁸. For this reason the US government has declared that the use of electronic cigarettes among young people is an epidemy⁶⁹. The rapid growth in consumption of these products could be caused by the introduction of new products with new nicotine manipulation technologies⁷⁰.

In addition, smoking experts have stated that there is no treatment for nicotine addiction caused by this new generation of electronic cigarettes in adolescents to date⁷¹.

Data about the use of electronic cigarettes in in Brazil is very limited and indicates that 4.6% of adult smokers have tried cigarettes or used electronic cigarettes in the last 6 months (the study did not distinguish between experimentation and continuous use)⁷². Another study carried out in university students revealed that 2.7% had tried it, and 0.6% had regular use of it⁷³. No studies were found on the use of ESDs among children or adolescents in Brazil. The use of other types of ESDs in Brazil has also not been reported. The ban could explain the reduced use of these products in Brazil.

Studies on the use of ESDs in Brazil⁷²⁻⁷⁴ have shown that the prevalence of use of these products was the lowest among countries participating in the International Tobacco Control Survey (ITC), but their use in life was not so different when compared to these other countries. Another important finding of the study is that a significant fraction of smokers, independent of country or level of regulatory restriction, believed that ESDs were safer than conventional cigarettes^{72,74}.

World ESD regulations

Research conducted by the World Health Organization⁷⁵ has shown that the regulatory approach between countries is very diverse, and more than half of the countries have no regulation or at least no specific regulation exists. In Brazil, these products are classified as tobacco-derived products³.

Probably because of this regulatory diversity and the different legal and regulatory frameworks of countries, the World Health Organization does not indicate how these products should be classified but, on the other hand, understands that these products should be within the scope of the Framework Convention on Tobacco Control and which have the potential to weaken tobacco control policies if they are not effectively regulated⁷⁵⁻⁷⁷.

Although there are natural differences in the way that ESDs are regulated, the fact that these products are regulated especially in regard to the harmful potential of nicotine and its capacity to cause dependence and so as to prevent these products from interfering negatively in tobacco control policies (free environments, as a gateway for new smokers, interfere with cessation, etc.) is undisputable^{16,75-78}.

Final considerations and conclusions

More than eight years after its banning and revisiting the scientific literature in search of some new data that could lead to a possible revision of the standard, the same questions that led to the prohibition of these products still continue without a response capable of fulfilling the regulatory requirements for the release of these products in Brazil. While data suggest lower toxicity of these products than traditional cigarettes, they could not be considered harmless either. However, a question arises where we weigh a possible harm reduction: "What is the acceptable harm reduction standard of a product that simulates smoking? Considering that cigarette toxicity is so high, it is relatively easy for something to be less toxic than conventional cigarettes, but this doesn't mean that it does not pose a threat to human health".

The enormous variety of flavors, the different compositions and toxic emissions of the ESDs indicate that the regulation of these products in a possible release of sales should be carried out case by case and not broadly, without considering the different formulations, types and voltages applied. By prohibiting these products, Brazil prevented the population from consuming a product whose alleged smoking cessation assistance has not been confirmed, with indications of significant toxicity. It also prevented young people from experimenting with this product.

We can thus consider that, for the Brazilian tobacco control setting, the benefits of this ban outweighed by far and were more significant than the supposed and unproven benefits of the release of these products. Thus, we can consider that Anvisa's decision was correct and the motivation of banning these products remains valid, thus contributing to the already recognized success in its tobacco control policies.

Collaborations

ALO Silva and JC Moreira worked on conception, research, methodology and final writing.

Acknowledgements

The authors would like to thank Anvisa and Fiorruz, and would like to clarify that this paper represents solely and exclusively the opinion and thinking of the authors, based on the scientific evidence available at the time, it does not represent any Anvisa, Fiorruz, Ministry of Health and the Brazilian Government institutional policy and/or opinion.

References

- Brasil. Lei nº 9.782, de 26 de Janeiro de 1999. Define o Sistema Nacional de Vigilância Sanitária, cria a Agência Nacional de Vigilância Sanitária, e dá outras providências. [Internet]. *Diário Oficial da União* 1999; 27 Jan. [cited 2017 Jun 2]. Available from: http:// www2.camara.leg.br/legin/fed/lei/1999/lei-9782-26janeiro-1999-344896-norma-pl.html
- Brazilian Vapers [Internet]. [cited 2017 Jun 2]. Available from: http://www.brazilianvapers.com. br/2013/01
- Brasil. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada RDC nº 46, de 28 de agosto de 2009. Proíbe a comercialização, a importação e a propaganda de quaisquer dispositivos eletrônico. [Internet]. *Diário Oficial da União* 2009. [cited 2017 Jun 2]. Available from: http://portal.anvisa.gov.br/documents/10181/2718376/RDC_46_2009_COMP. pdf/2148a322-03ad-42c3-b5ba-718243bd1919
- Flávio Zarur Lucarelli. O cigarro eletrônico é pouco conhecido no Brasil e ajuda a parar de fumar [Internet]. 2013 [cited 2017 May 27]. Available from: http:// www.brazilianvapers.com.br/2013/01/cigarro-eletronico-e-pouco-conhecido-no.html
- PubMed. Home PubMed NCBI [Internet]. [cited 2017 Sep 23]. Available from: https://www.ncbi.nlm. nih.gov/pubmed/
- Scientific Electronic Library Online (SciELO) [Internet]. [cited 2016 Jul 21]. Available from: http://www. scielo.org/php/index.php
- Google [Internet]. [cited 2017 Sep 18]. Available from: https://www.google.com.br/?gws_rd=ssl
- Caponnetto P, Campagna D, Papale G, Russo C, Polosa R. The emerging phenomenon of electronic cigarettes. Expert Rev Respir Med [Internet]. 2012 Feb [cited 2017 Sep 18];6(1):63-74. Available from: http:// www.tandfonline.com/doi/full/10.1586/ers.11.92
- U.S. Fire Administration. *Electronic Cigarette Fires and Explosions* [Internet]. Emmitsburg: U.S. Department of Homeland Security's/ Federal Emergency Management Agency/U. S. Fire Administration; 2014 Oct [cited 2017 Sep 18] p. 13. Available from: https://www. usfa.fema.gov/downloads/pdf/publications/electronic_cigarettes.pdf
- Rowell TR, Tarran R. Will chronic e-cigarette use cause lung disease? *Am J Physiol - Lung Cell Mol Physiol* [Internet]. 2015 Dec 15 [cited 2017 Sep 18]; 309(12):L1398-409. Available from: http://ajplung. physiology.org/lookup/doi/10.1152/ajplung.00272. 2015
- Cheng T. Chemical evaluation of electronic cigarettes. Tob Control [Internet]. 2014 May [cited 2017 Jun 2];23(Supl. 2):ii11-7. Available from: http://tobaccocontrol.bmj.com/lookup/doi/10.1136/tobaccocontrol-2013-051482
- Farsalinos KE, Gillman IG, Hecht SS, Polosa R, Thornburg J. Analytical Assessment of e-Cigarettes: From Contents to Chemical and Particle Exposure Profiles. Amsterdam: Elsevier; 2016.

- Supersmoker Bluetooth The first ever cigarette with phone function! While you smoke an e-cigarette. *Bluetooth e-cigarette* [Internet]. [cited 2018 Sep 7]. Available from: http://www.supersmokerbluetooth.com/
- Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine Levels in Electronic Cigarettes. *Nicotine Tob Res* [Internet]. 2013 Jan 1 [cited 2017 Jun 2]; 15(1):158-66. Available from: https://academic.oup. com/ntr/article-lookup/doi/10.1093/ntr/nts103
- Zhu S-H, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control [Internet]. 2014 Jul [cited 2017 Jun 2];23(Supl. 3):iii3-9. Available from: http:// tobaccocontrol.bmj.com/lookup/doi/10.1136/tobaccocontrol-2014-051670
- Grana R, Benowitz N, Glantz SA. E-Cigarettes: A Scientific Review. *Circulation* [Internet]. 2014 May 13 [cited 2017 Sep 20];129(19):1972-86. Available from: http://circ.ahajournals.org/content/129/19/1972
- Laino T, Tuma C, Moor P, Martin E, Stolz S, Curioni A. Mechanisms of propylene glycol and triacetin pyrolysis. *J Phys Chem A* 2012; 116(18):4602-4609.
- US EPA O. Health Effects Notebook for Hazardous Air Pollutants. Acrolein [Internet]. 2016 [cited 2017 Sep 23]. Available from: https://www.epa.gov/sites/ production/files/2016-08/documents/acrolein.pdf
- Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P 3rd, Benowitz N. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* [Internet]. 2014 Mar 1 [cited 2017 Sep 20];23(2):133-139. Available from: http://tobaccocontrol.bmj.com/content/23/2/133
- McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol* [Internet].
 2012 Oct [cited 2017 Jun 2];24(12):850-7. Available from: http://www.tandfonline.com/doi/full/10.3109/ 08958378.2012.724728
- Pellegrino RM, Tinghino B, Mangiaracina G, Marani A, Vitali M, Protano C, Osborn JF, Cattaruzza MS. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). Ann Ig Med Prev E Comunita 2012; 24(4):279-288.
- 22. Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D, Schettgen T, Jörres RA, Fromme H. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health* [Internet]. 2014 Jul [cited 2017 Jun 9];217(6):628-637. Available from: http://linkinghub.elsevier.com/retrieve/pii/S14384 63913001533
- Jankowski M, Brożek G, Lawson J, Skoczyński S, Zejda JE. E-smoking: Emerging public health problem? *Int J Occup Med Environ Health* [Internet]. 2017 [cited 2017 Jun 2];30(3):329-344. Available from: http:// ijomeh.eu/E-smoking-emerging-public-health-problem-,67520,0,2.html

- 24. United States of America. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm. In: *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General* [Internet]. Centers for Disease Control and Prevention (US); 2010 [cited 2017 Sep 20]. Available from: https://www.ncbi.nlm. nih.gov/books/NBK53014/
- Hoffmann I. The changing cigarette, 1950-1995. J Toxicol Environ Health [Internet]. 1997 [cited 2016 May 16];50(4):307-364. Available from: http://www. tandfonline.com/doi/abs/10.1080/009841097160393
- Alan Rodgman, Perfetti TA. The Chemical Components of Tobacco and Tobacco Smoke. 2nd ed. Boca Raton: CRC Press; 2013.
- Arnold C. Vaping and Health: What Do We Know about E-Cigarettes? *Environ Health Perspect* [Internet]. 2014 [cited 2017 Sep 20];122(9):A244-249. Available from: http://ehp.niehs.nih.gov/122-A244
- Jefferson Fowles, Michael Bates. The Chemical Constituents in Cigarettes and Cigarette Smoke: Priorities for Harm Reduction. A Report to the New Zealand Ministry of Health [Internet]. Epidemiology and Toxicology Group ESR: Kenepuru Science Centre; 2000 Mar p. 67. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.202.6021&rep=rep1&type=pdf
- Stratton K, Shetty P, Wallace R, Bondurant S, editors.. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington: National Academies Press; 2001.
- Tayyarah R, Long GA. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. *Regul Toxicol Pharmacol* [Internet]. 2014 [cited 2017 Sep 20];70(3):704-710. Available from: http://www.sciencedirect.com/ science/article/pii/S027323 0014002505
- Bernhard D, Rossmann A, Wick G. Metals in cigarette smoke. *IUBMB Life* [Internet]. 2005;57(12):805-809. Available from: http://onlinelibrary.wiley.com/doi/ 10.1080/15216540500459667/abstract
- Hess CA, Olmedo P, Navas-Acien A, Goessler W, Cohen JE, Rule AM. E-cigarettes as a source of toxic and potentially carcinogenic metals. *Environ Res* 2017; 152:221-225.
- 33. Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden Formaldehyde in E-Cigarette Aerosols. *N Engl J Med* [Internet]. 2015 [cited 2017 Jun 9]; 372(4):392-394. Available from: http://www.nejm. org/doi/10.1056/NEJMc1413069
- 34. Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ, McIntosh S, Robinson R, Rahman I. Vapors Produced by Electronic Cigarettes and E-Juices with Flavorings Induce Toxicity, Oxidative Stress, and Inflammatory Response in Lung Epithelial Cells and in Mouse Lung. Khan MF, editor. *PLoS One* [Internet]. 2015 [cited 2017 Jun 9];10(2):e0116732. Available from: http:// dx.plos.org/10.1371/journal.pone.0116732

- Bahl V, Lin S, Xu N, Davis B, Wang Y, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod Toxicol [Internet]. 2012 [cited 2017 Jun 9];34(4):529-537. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0890623812002833
- Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of Electronic Cigarette Liquids and Aerosol for the Presence of Selected Inhalation Toxins. *Nicotine Tob Res* [Internet]. 2015 [cited 2017 Jun 9];17(2):168-174. Available from: https://academic.oup.com/ntr/ article-lookup/doi/10.1093/ntr/ntu176
- Kosmider L, Sobczak A, Prokopowicz A, Kurek J, Zaciera M, Knysak J, Smith D4, Goniewicz ML. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax* [Internet]. 2016 [cited 2017 Jun 9];71(4):376-377. Available from: http://thorax.bmj.com/lookup/doi/10.1136/tho raxjnl-2015-207895
- Polosa R, Morjaria JB, Caponnetto P, Campagna D, Russo C, Alamo A, Amaradio M, Fisichella A. Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med* [Internet]. 2014 [cited 2017 Jun 9]; 9(5):537-546. Available from: http://link.springer. com/10.1007/s11739-013-0977-z
- 39. Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, Tsui T, Aguilera JA, Advani S, Crotty Alexander LE, Brumund KT, Wang-Rodriguez J, Ongkeko WM. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. *Oral Oncol* [Internet]. 2016 [cited 2017 Jun 9];52:58-65. Available from: http://linkinghub.elsevier.com/ retrieve/pii/S1368837515003620
- Etter J-F. A longitudinal study of cotinine in longterm daily users of e-cigarettes. *Drug Alcohol Depend* [Internet]. 2016 [cited 2017 Jun 9];160:218-221. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0376871616000107
- Etter J-F, Bullen C. Saliva cotinine levels in users of electronic cigarettes. *Eur Respir J* [Internet]. 2011 [cited 2017 Jun 9];38(5):1219-1220. Available from: http://erj.ersjournals.com/cgi/doi/10.1183/0903 1936.00066011
- Etter J-F. Levels of saliva cotinine in electronic cigarette users: Cotinine in vapers. *Addiction* [Internet]. 2014 May [cited 2017 Jun 9];109(5):825-9. Available from: http://doi.wiley.com/10.1111/add.12475
- Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, Wallace Hayes A, Tsatsakis AM, Koutedakis Y. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol* [Internet]. 2013 [cited 2017 Jun 9];25(2):91-101. Available from: http://www.tandfonline.com/doi/full/10.3109/08958 378.2012.758197
- 44. Ballbè M, Martínez-Sánchez JM, Sureda X, Fu M, Pérez-Ortuño R, Pascual JA, Saltó E, Fernández E. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. *Environ Res* [Internet]. 2014 [cited 2017 Jun 9];135:76-80. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0013935114003089

- 45. St.Helen G, Dempsey DA, Havel CM, Jacob P, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend* [Internet]. 2017 Sep 1 [cited 2017 Jul 18];178:391-398. Available from: http://www. drugandalcoholdependence.com/article/S0376-8716(17)30319-8/fulltext
- 46. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term Pulmonary Effects of Using an Electronic Cigarette. *Chest* [Internet]. 2012 [cited 2017 Jun 9];141(6):1400-1406. Available from: http://linkinghub.elsevier.com/ retrieve/pii/S0012369212603274
- Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand Exposure to Vapors From Electronic Cigarettes. *Nicotine Tob Res* [Internet]. 2014 [cited 2017 Jun 9];16(6):655-662. Available from: https://academic.oup.com/ntr/article-lookup/doi/10.1093/ntr/ntt203
- Gupta S, Gandhi A, Manikonda R. Accidental nicotine liquid ingestion: emerging paediatric problem. Arch Dis Child [Internet]. 2014 [cited 2017 Jun 2];99(12):1149-1149. Available from: http://adc.bmj. com/content/99/12/1149
- Sistema Nacional de Informações Tóxico-Farmacológicas (Sinitox). Sistema Nacional de Informações Tóxico-Farmacológicas [Internet]. [cited 2017 Jun 9]. Available from: http://sinitox.icict.fiocruz.br/dados-nacionais
- 50. Martins SR. Cigarros eletrônicos: o que sabemos? Estudo sobre a composição do vapor e danos à saúde, o papel na redução de danos e no tratamento da dependência de nicotina [Internet]. Rio de Janeiro: Ministério da Saúde (MS); 2017 [cited 2017 May 19]. Available from: http://www.inca.gov.br/bvscontrolecancer/publicacoes/cigarros_eletronicos.pdf
- Geraghty P, Dabo J, Garcia-Arcos I, Cummins N, Foronjy R. Late-breaking abstract: Late-breaking abstract: E-cigarette exposure induces pathological responses that result in lung tissue destruction and airway hyper reactivity in mice. *Eur Respir J* [Internet]. 2014 [cited 2017 Jun 9];44(Supl. 58):3435. Available from: http://erj.ersjournals.com/content/44/Suppl_ 58/3435
- 52. Chorti M, Poulianiti K, Jamurtas A, Kostikas K, Tzatzarakis M, Vynias D, Koutedakis Y, Flouris A, Tsatsakis A. Effects of active and passive electronic and tobacco cigarette smoking on lung function. *Toxicol Lett* [Internet]. 2012 [cited 2017 Jun 9];211:S64. Available from: http://linkinghub.elsevier.com/retrieve/pii/S03 78427412003529
- 53. Brandon TH, Goniewicz ML, Hanna NH, Hatsukami DK, Herbst RS, Hobin JA, Ostroff JS, Shields PG, Toll BA, Tyne CA, Viswanath K, Warren GW. Electronic Nicotine Delivery Systems: A Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology. J Clin Oncol [Internet]. 2015 [cited 2017 Jul 18];33(8):952-963. Available from: http://ascopubs.org/doi/10.1200/ JCO.2014.59.4465

- Flouris AD, Poulianiti KP, Chorti MS, Jamurtas AZ, Kouretas D, Owolabi EO, Tzatzarakis MN, Tsatsakis AM, Koutedakis Y. Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxicol* [Internet]. 2012 [cited 2017 Jun 9];50(10):3600-3603. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0278691512005030
- 55. Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air* 2013; 23(1):25-31.
- Goniewicz ML, Lee L. Electronic Cigarettes Are a Source of Thirdhand Exposure to Nicotine. *Nicotine Tob Res* [Internet]. 2015 Feb;17(2):256-258. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PM C4837997/
- Ganjre AP, Sarode GS. Third hand smoke A hidden demon. Oral Oncol [Internet]. 2016 [cited 2017 Oct 30];54:e3-4. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1368837516000105
- 58. McNeill A, Brose LS, Calder R, Hitchman SC. E-cigarettes: an evidence update A report commissioned by Public Health England. [Internet]. Public Health England; 2015 [cited 2017 Sep 23] p. 113. Report No.: PHE 2015260. Available from: https://www.gov. uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_ England_FINAL.pdf
- Public Health England. E-cigarettes around 95% less harmful than tobacco estimates landmark review. [Internet]. [cited 2017 Sep 23]. Available from: https:// www.gov.uk/government/news/e-cigarettes-around-95-less-harmful-than-tobacco-estimates-landmarkreview
- Lancet T. E-cigarettes: Public Health England's evidence-based confusion. *Lancet* [Internet]. 2015 [cited 2018 Dec 20];386(9996):829. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00042-2/abstract
- 61. Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, Foulds J, Fagerstrom K, Letlape K, Milton A, Polosa R, Ramsey J, Sweanor D. Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach. *Eur Addict Res* [Internet]. 2014 [cited 2017 Oct 10];20(5):218-225. Available from: http://www. karger.com/Article/FullText/360220
- West R, Hajek P, Mcneill A, Brown J, Arnott D. Electronic cigarettes: what we know so far. London: A report to UK All Party Parliamentary Groups; 2015.
- 63. Vardavas CI, Filippidis FT, Agaku IT. Determinants and prevalence of e-cigarette use throughout the European Union: a secondary analysis of 26 566 youth and adults from 27 Countries. *Tob Control* [Internet]. 2015 [cited 2017 Jun 9];24(5):442-448. Available from: http://tobaccocontrol.bmj.com/lookup/ doi/10.1136/tobaccocontrol-2013-051394

3023

- 64. U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: a report of the Surgeon General. [Internet]. Atlanta: US Departament of Health and Human Services, Centers for Disease Control and Prevention and Health Promotion, Office on Smoking and Health; 2016 [cited 2017 Sep 27] p. 295. Report No.: NLM QV 137. Available from: http://www.cdc.gov/tobacco/data_statistics/sgr /e-cigarettes/
- 65. Goniewicz ML, Gawron M, Nadolska J, Balwicki L, Sobczak A. Rise in Electronic Cigarette Use Among Adolescents in Poland. J Adolesc Health [Internet]. 2014 [cited 2017 Jun 9];55(5):713-5. Available from: http://linkinghub.elsevier.com/retrieve/pii/S105 4139X14003103
- 66. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev 2014; (12):CD010216.
- 67. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Pediatr [Internet]. 2017 [cited 2017 Jun 28]. Available from: http://archpedi.jamanetwork.com/article.aspx-?doi=10.1001/jamapediatrics.2017.1488
- 68. Cullen KA. Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students - United States, 2011-2018. MMWR Morb Mortal Wkly Rep [Internet]. 2018 [cited 2018 Dec 19];67. Available from: https://www. cdc.gov/mmwr/volumes/67/wr/mm6745a5.htm
- 69. Surgeon General. Surgeon General's Advisory on E-cigarette Use Among Youth [Internet]. 2018 [cited 2018 Dec 21]. Available from: https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf
- 70. King BA, Gammon DG, Marynak KL, Rogers T. Electronic Cigarette Sales in the United States, 2013-2017. JAMA 2018; 320(13):1379-1380.
- 71. Hoffman J. Addicted to Vaped Nicotine, Teenagers Have No Clear Path to Quitting. The New York Times [Internet]. 2018 [cited 2019 Feb 7]; Available from: https://www.nytimes.com/2018/12/18/health/vaping-nicotine-teenagers.html
- 72. Cavalcante TM, Szklo AS, Perez CA, Thrasher JF, Szklo M, Ouimet J, Gravely S, Fong GT, Almeida LM. Conhecimento e uso de cigarros eletrônicos e percepção de risco no Brasil: resultados de um país com requisitos regulatórios rígidos. Cad Saude Publica [Internet]. 2017 [cited 2017 Oct 30];33. Available from: http://www.scielo.br/scielo.php?script=sci_abst ract&pid=S0102-311X2017001505006&lng=en&nrm=iso&tlng=pt

- 73. Oliveira WJC de, Zobiole AF, Lima CB de, Zurita RM, Flores PEM, Rodrigues LGV, Pinheiro RCA, Silva VFFRSE. Electronic cigarette awareness and use among students at the Federal University of Mato Grosso, Brazil. J Bras Pneumol [Internet]. 2018 [cited 2019 Mar 19];44(5):367-369. Available from: http:// www.scielo.br/scielo.php?script=sci_abstract&pid =S1806-37132018000500367&lng=en&nrm=iso&tlng=en
- Gravely S, Fong GT, Cummings KM, Yan M, Quah 74. ACK, Borland R, Yong HH, Hitchman SC, McNeill A, Hammond D, Thrasher JF, Willemsen MC, Seo HG, Jiang Y, Cavalcante T, Perez C, Omar M, Hummel K. Awareness, Trial, and Current Use of Electronic Cigarettes in 10 Countries: Findings from the ITC Project. Int J Environ Res Public Health [Internet]. 2014 [cited 2018 Apr 3];11(11):11691-704. Available from: http:// www.mdpi.com/1660-4601/11/11/11691
- 75. World Health Organization (WHO). Electronic nicotine delivery systems. Report - Conference of the Parties to the WHO Framework Convention on Tobacco Control. Sixth session Moscow, Russian Federation [Internet]. 2014 Oct p. 13. Report No.: FCTC/ COP/6/10 Rev.1. Available from: http://apps.who.int/ gb/fctc/PDF/cop6/FCTC_COP6_10-en.pdf
- World Health Organization (WHO). Electronic Nic-76. otine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS) - Conference of the Parties to the WHO Framework Convention on Tobacco Control. Seventh session Dheli, India [Internet]. Dheli, India; 2016 Nov [cited 2017 Sep 24] p. 11. Report No.: FCTC/COP/7/11. Available from: http://www. who.int/entity/fctc/cop/cop7/FCTC_COP_7_11_ EN.pdf?ua=1
- Grana RP, Benowitz NM, Glantz SAP. Background 77. Paper on E-cigarettes (Electronic Nicotine Delivery Systems). eScholarship [Internet]. 2013 Jan 1 [cited 2017 Sep 23]; Available from: http://escholarship.org/ uc/item/13p2b72n
- 78. Nicotine Delivery Systems [Internet]. The Tobacco Atlas. [cited 2017 Sep 23]. Available from: http://www. tobaccoatlas.org/topic/nicotine-delivery-systems/

Article submitted 24/07/2017 Approved 14/11/2017 Final version submitted 16/11/2017