

THE EU-COMMISSION'S SCHEER PRELIMINARY OPINION ON E-CIGARETTES



Our Response

On September 23rd, the working group on e-cigarettes of the European Commission's Scientific Committees on health, Environmental and Emerging Risks (known as SCHEER) released its preliminary opinion on electronic cigarettes for public consultation.

The most striking point about this report is the lack of any comparison between e-cigarette use and smoking. This is a worrying omission given that e-cigarettes are designed for adult smokers and are likely to be 95% less harmful than combustible cigarettes, according to Public Health England. We hereby provide our input to the Committee along these lines as part of the public consultation.

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Contents



Scientific Opinion #3	2
Assessment of Health Risks #6.5	3
Consumer behaviour related to exposure assessment #6.5.1	4
Exposure assessment #6.5.2	5
Hazard identification of most relevant compounds #6.5.3	6
Human evidence for health impacts of electronic cigarettes #6.5.4	7
Risk Assessment #6.5.5	8
Role in the initiation of smoking (particularly focusing on young people) #6.6	9
Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use #6.7	10

Scientific Opinion | #3



#Line	
n/a	It is striking that throughout the report, the Committee fails to make any meaningful attempt to compare the risk of e-cigarette use to the risks of smoking. Given that, according to the Commission's own data, less than 5% of e-cigarette users are never smokers, this would seem the obvious reference point when considering the risks associated with e-cigarette use.
	The report should be reframed completely with reference to the risks of e-cigarettes as compared to the risks of smoking combustible cigarettes.
	A good example of how this can be done is <u>Nutt et al (2014)</u> , which systematically compares the risks of routine use of a wide range of nicotine containing products:
	"Cigarettes are the nicotine product causing by far the most harm to users and others in the world today. Attempts to switch to non-combusted sources of nicotine should be encouraged as the harms from these products are much lower."
P 12 L 42	The hazard assessment reviews the hazard profiles of a number of substances that might be found in electronic cigarette aerosol. However, it does not compare these hazards to those found in cigarette smoke in order to take a view on the relative risk for each category of product. A wealth of data is available on this subject.
P 13 L 19	SCHEER notes the risk of nicotine poisoning and later (p40) states that 60mg of nicotine is fatal for humans. This estimate was based on erroneous self-experiments performed in the mid of the 19th century and was been corrected to 0.5-1 g several years ago <u>(Mayer, 2014)</u> .
P 16 L 27	Stagnating or rising smoking prevalence among youth would warrant concern and should be the main indicator of a "gateway effect". Simply put, were vaping leading more young people to smoke, then we would see a higher prevalence of smoking among young people develop as the e-cigarette came to prominence.
	However, in the past decade, smoking rates among youth have continuously decreased at unprecedented high rates in virtually all EU Member States.
	<u>Data from the OECD</u> shows that smoking among 15-16 year olds has fallen significantly in most EU countries between 2007 and 2015, the period in which e-cigarettes were introduced onto the EU market; and <u>data from the</u> <u>German Government (</u> attached) also shows a significant fall in youth smoking rates in that jurisdiction.
P 18 L 41	The conclusion of the Committee does not take into account all of the available evidence. In addition to RCTs and cohort studies, survey data are important in measuring the effect of electronic cigarettes.
	<u>Farsalinos (2016)</u> surveyed 27.460 EU citizens from the then 28 Member States. The study concluded that E-cigarette use in the European Union appears to be largely confined to current or former smokers, while current use and nicotine use by people who have never smoked is rare. More than one-third of current e-cigarette users polled reported smoking cessation and reduction.
	Observational studies should also have been considered by the Committee in respect of this question. <u>Jackson et al (2019)</u> , for instance, concluded that "use of e-cigarettes and varenicline are associated with higher abstinence rates following a quit attempt".
	Population data can also be used to determine the rate at which e-cigarettes lead to smoking cessation. For instance, <u>Zhu et al (2017)</u> concluded that "The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level".

Assessment of Health Risks | #6.5



#Line	
D 47	The Committee reports that some users experience irritation and cough, citing Polosa (2011). In fact, this study is careful to point out that these minor AEs "decreased substantially" by week 24.
P 47 L 13 - 16	From week 4 to 24 the occurrence of minor AEs decreased in every reported measure: throat irritation (23.4 to 14.8%); mouth irritation (20.6 to 7.4%); dry cough (32.4 to 11.1%). Most importantly, there were zero serious Adverse Events reported in Polosa et al. Polosa and colleagues also draw attention to the fact that side effects most commonly reported in trials for drugs for nicotine dependence are totally absent.
P 49 L 2	All of the citations are in vitro studies in which there was no combustible cigarette control and which used EC aerosol exposure that wasn't relevant to human use. This led <u>Li Volti et al (2018)</u> to say of such studies:
- 20	"The present study does not replicate normal conditions of use and lacks standardized protocols for E-cigarette aerosol exposure and dosimetry. To this regard, animal studies and in vitro systems often include chronic, high- dose exposures and do not approximate the type of exposure from human vaping, thus leading to extreme overestimation of toxicological effects"
P 49 L 2	Again, the review here fails to consider the health impact on smokers with chronic lung conditions. As <u>Polosa</u> (2016), in a study of COPD patients who smoke, found:
- 2	"A marked reduction in cigarette consumption was observed in ECs users. A significant reduction in COPD exacerbations was reported in the COPD EC user group, their mean (\pm SD) decreasing from 2.3 (\pm 1) at baseline to 1.8 (\pm 1; p = 0.002) and 1.4 (\pm 0.9; p < 0.001) at F/up1 and F/up2 respectively. A significant reduction in COPD exacerbations was also observed in ECs users who also smoked conventional cigarettes (i.e. 'dual users'). COPD symptoms and ability to perform physical activities improved statistically in the EC group at both visits, with no change in the control group."
P 51 L 27 - 57	Current evidence unequivocally demonstrates that the air concentrations of potential toxicants are far below various internationally accepted thresholds after unrestricted vaping in closed rooms; and, of course, significantly lower than that emitted from cigarettes. We attach six papers that the Committee should consider and believe that this section should be revised in line with the evidence.
	<u>McAuley, T. R et al (2012)</u> O'Connell, G. et al (2015) Logue, J. M. et al (2017) Liu, J. et al (2017) van Drooge, B. L. et al (2019) Schober, W. et al (2019)
	Shearston et al (2019) is not evidence that ECs cause secondhand exposure; it is a protocol for a study which has not yet reported any findings.
P 52 L 5 - 10	Diez-Izquierdo (2018) is a review in which the only in-home (natural setting) test showed no significant differences in nicotine levels on surfaces in the homes of ENDS users compared to non-smokers/non-ENDS users.
P 55 L 7 - 13	SCHEER states that the "weight of evidence concerning effects of second-hand exposure of children and adolescents cannot be established as there exists a complete paucity of evidence regarding the acute and long term effects on cardiovascular and other health outcomes in this group."
	While true, the same statement would apply to the vapor of heated cooking pots or the odor of perfume. This is because there is no rationale for investigating the effects of emissions lacking significant amounts of potentially harmful substances on health outcomes. This context and perspective is important when framing the lack of evidence.

Consumer behaviour related to exposure assessment | #6.5.1



#Line	
P 26 L 27	Only data from the United States - where the market is regulated in an entirely different way - are provided. Moreover, the data provided is not up to date. The most recent <u>(2020) NYTS data</u> showed that 1.8 million fewer young people use e-cigarettes. Youth smoking rates in the US are at record lows.
- 47	Comparative studies looking at the US and European countries confirm that reliance on data from the US is not a rational way to look at prevalence in Europe. <u>Hammond et al (2020)</u> undertook a cohort study examining rates of vaping and smoking among youths aged 16 to 19 years in the United States, Canada, and England from 2017 to 2019.
	The study shows that smoking prevalence among UK youth and young adults decreased even further from 2018 to 2019, even as vaping prevalence slightly increased.
	Again, the report fails to consider what has happened to youth smoking rates during this period, continuing in its error of failing to take account of cigarettes in the discussion around e-cigarettes.

Exposure assessment | #6.5.2



#Line	
P 28 - 29	SCHEER extensively discusses the number and size of particles emitted by e-cigarettes without mentioning that they are liquid droplets, like the particles in fog or the aerosol emitted by metered-dose inhalers prescribed to patients with asthma or other restrictive lung diseases.
	In contrast to the solid particles in tobacco smoke, which cause long-term inflammatory processes in the lung, liquid droplets dissolve upon contact with tissue. Their size determines the site of deposition (oral cavity, upper airways, or lung) but is otherwise irrelevant.
	SCHEER lists every substance that has ever been detected in e-liquids or aerosols, regardless of their concentrations or their impact on human health. The committee's reference to Klager et al., who reported that 60 % of tested liquids contained diacetyl or acetoin, was conducted in the United States and is not relevant to the European Union where the use of such substances is prohibited by current legislation.
	Other potentially harmful compounds listed in this section are reactive oxygen species, tobacco-specific nitrosamines, and metals. The concentration of free radicals in e-cigarette aerosols is about 10-fold lower than in tobacco smoke <u>(Bitzer et al, (2020)</u>). Tobacco-specific nitrosamines are hardly detectable <u>(Goniewicz et al (2014)</u>), and the concentrations of metals are far below internationally accepted thresholds <u>(Farsalinos et al (2018)</u>).
P 32 L 1	The data in table 3 shows only the levels of the identified substances in e-cigarette aerosol. However, this data lacks context or meaning when not read in conjunction with the requisite data for combustible cigarettes.
- 20	RIVM has collected significant data on these points, and it is surprising that this is not considered relevant.
P 37 L 4 - 12	This flaw in the Committee's approach - comparing the risks of e-cigarettes with the risk of no use rather than with use of cigarettes - is evident in its conclusions on p37. These conclusions completely fail to identify the relative risk with cigarette smoking as a critical factor when considering its risk assessment protocol.
P 40	It is stated that 60 mg of nicotine is fatal for humans. The 60-mg estimate, which would implicate nicotine toxicity comparable to that of the deadly poison cyanide, was based on erroneous self-experiments performed in the mid of the 19th century and has been corrected to 0.5 - 1 g several years ago, as per <u>Mayer (2014)</u> .

Hazard identification of most relevant compounds | #6.5.3



#Line	
P 39 L 34 - 45	The cited paper by Khlystov and Samburova does not represent the current science. Dr Konstantinos Farsalinos, a prominent researcher of e-cigarettes, <u>wrote a letter to the editor of the journal</u> pointing out some of the issues with this manuscript. The paper is not consistent with other similar studies and should not be used as a basis for the SCHEER report. We attach a number of studies that are more representative of the current consensus:
	<u>Conklin et at (2018)</u> and <u>Farsalinos et al (2018)</u> both found small or zero increases in aldehyde content compared with non-flavoured e-cigarette liquid; these studies should be cited.
	It should be noted in this context that <u>according to the WHO</u> , ambient air contains between 10 and 200 μg/m3 of formaldehyde.
P 40 L 19 - 30	The report discusses the cancerogenic potential of nicotine based on the presence of N-nitrosamines in trace amounts in tobacco-derived nicotine preparations, including those used in the pharmaceutical industry for the manufacture of nicotine replacement therapies.
	As e-cigarettes are made using pharmaceutical grade nicotine, these compounds are barely detectable in e-cigarette liquids. <u>Belushkin et al (2020)</u> , for example, tested a wide range of e-cigarettes, all of which contained negligible levels of nitrosamines.
P 40 - 41 L 33	<u>Flora et al (2015)</u> provides guidance on how to compare permissible exposure limits to e-vapor product yields. We attach the study "Characterization of potential impurities and degradation products in electronic cigarette formulations and aerosols" and the equation used by the research team.
- 16	Burstyn (2013) is listed among the citations but does not appear in the text of the report. This study made an early assessment of e-cigarette toxic exposures relative to 'total limit values' (TLV) for occupational health exposures. Burstyn concluded:
	"The vast majority of predicted exposures are <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was possible."
	We suggest that a section be added to 6.5.3 that addresses how one might convert exposure limits into a daily exposure amount to facilitate a comparison with permissible exposure limits. Absent this, exposure limits have no context or meaning.
P 41 L 34 - 43	The Committee has chosen to comment on the use of flavours to make products attractive in this section, despite it being focused on the potential health hazards, indicating that the Committee considers the appeal of e-cigarettes to be a hazard in and of itself.
	In this respect, the Committee could, in the interests of balance, consider how the existence of an attractive alternative to smoking can be of public health benefit in a Europe where 26% smoke and 700,000 die from smoking related disease annually.
	In this context, it is worth noting within the report the potential unintended consequences of seeking to make e-cigarettes less attractive. This is discussed at length by the <u>Royal College of Physicians (2016)</u> who conclude:
	"if [a risk averse] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking"

Human evidence for health impacts of electronic cigarettes | #6.5.4



#Line	
P 47 L 18 - 25	The Committee cites Palamidas as reporting increases in Heart Rate (HR) after acute 1 hour ad libitum use of an unknown ENDS device containing 11 mg nicotine. Contrary to these results, Cossio et al performed a study of 16 healthy smoking naive participants and reported that there was no significant increase in heart rate (HR) or blood pressure (BP) after acute use of either a 0% or 5.4% nicotine ENDS product.
	In other studies which have reported increased in HR after acute usage, it was noted that these increases were smaller in comparison to those induced by use of combustible cigarettes (Franzen et al 2018; Szołtysek-Bołdys et al 2014; Yan and D'Ruiz 2015).
	One study found that ENDS users had to use the product for 6x longer to approach the increases in HR and BP observed after smoking one conventional cigarette (Vlachopoulos et al 2016).These acute changes in BP and HR have been shown to be attributed solely to nicotine (Antoniewicz et al 2019; Chaumont et al 2018).
P 47 L 29	The statement that "the most consistent evidence regarding the effect of electronic cigarettes on human health concerns cardiovascular diseases" is based on the European Heart Network's opinion. However, large clinical studies show that the moderate acute effects of nicotine on heart rate and blood pressure are not associated with increased cardiovascular risk.
	<u>Mills et al (2014)</u> found "no clear evidence of harm" when they examined the cardiovascular effect of a variety of nicotine replacement therapies; since the nicotine used in e-cigarettes is of the same grade (as specified in the European Pharmacopeia) there is no reason to suspect that the nicotine contained in e-cigarettes has a different effect. <u>Benowitz et al (2018)</u> reported findings along similar lines when reviewing the cardiovascular effects of nicotine replacement therapies.
P 48 L 10 - 47	This section, which reviews the potential cardiovascular risks of nicotine use, focuses on the cardiovascular effects of nicotine. However, the long term epidemiological data on nicotine use without smoke - for example through the use of licensed nicotine replacement therapies (which have been on the European market for many decades) - do not indicate that such use results in serious health effects.
	In line 10, for instance, attention is drawn to Vlachopoulos et al (2016) on the effects of electronic cigarette use on arterial stiffness, which concludes that e-cigarette use can contribute to aortic stiffness. The same authors <u>undertook a similar study on caffeine</u> which came to similar conclusions on the effects of caffeine on aortic stiffness.
	However, this does not mean that there is a clear link between nicotine use and cardiovascular diseases due to routine use of either nicotine or caffeine <u>(see Wilson and Bloom, 2016)</u> .
	The Committee fails to acknowledge that the relevant marker for cardiovascular risks is what happens to the cardiovascular system when smokers switch to e-cigarettes. <u>George et al (2019)</u> examined this in their paper "Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes". The conclusion is clear: that smokers (and in particular female smokers) "demonstrate significant improvement in vascular health within 1 month of switching from TC to EC".
P 51 L 27 - 55	The studies that are cited in this section of the Committee's report are completely unrelated to electronic cigarettes. In fact, they relate only to the exposure that is foreseeable from combustible cigarettes, meaning that the data is of no value in this context. It is surprising that the Committee has chosen to use data related to the exposure to cigarette smoke in its conclusion about emissions from electronic cigarettes.

Risk Assessment | #6.5.5



#Line	
n/a	It is striking that no serious attempt to compare the risk of e-cigarette use to smoking is undertaken in the review. Given that the target market is adult smokers, this comparison is necessary to understand the potential benefits of e-cigarettes for that part of the population.
	The failure to do so constitutes a divergence from the principles contained on p38 of the SCHEER guidance on Weight of Evidence (2018) to which the report is supposed to adhere. That guidance notes that "problem formulation should be purpose oriented and conducted with the correct understanding of the relevant questions". It is difficult to understand why the report does not consider the comparison of harm from e-cigarettes with combustible tobacco as a relevant question given the obvious relationship between the two.
n/a	<u>McNeil et al (2018)</u> is cited in relation to the lack of evidence for specific harms from particular flavouring substances. However, the key finding of PHE, that e-cigarette use is likely to be around 95% safer than smoking cigarettes, is omitted. This finding, from a well respected public health body, should be taken into account as part of the narrative report and given weight in the scientific opinion, where currently it is not.
	We attach the <u>2015 PHE evidence review</u> where this was first announced and note that the 2018 report cited upholds this estimate:
	"stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously."
P57 L28	Referring to "smokers of electronic cigarettes" is incorrect since e-cigarettes do not combust. Moreover, it is contradictory to the statement of the Committee on terminology (page 19; lines 47-55).
P 59 L 23 - 40	Stephens et al (2018) is cited in order to substantiate the source and scale of any potential carcinogenic risks from electronic cigarette. However, the report completely ignores the central objective of this study, made clear in its title:
	"Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke"
	The central finding of this study is that e-cigarette users are typically exposed to 0.4% of the lifetime cancer risk of smokers, but this finding does not seem to have been considered in the SCHEER report despite the committee having read the study. It is clearly relevant to the risk assessment and should be included in the narrative as well as considered in the scientific opinion.
P 60 - 61 L 55	The risks of irritative damage to the respiratory tract are not placed in the context of the comparable risks associated with smoking. This leads the SCHEER to characterise a risk that applies to never-smoking users who, according to Eurobarometer data, make up a tiny fraction of total users of e-cigarettes in Europe.
- 13	A number of studies show that for smokers, there is significant benefit to the respiratory system in those who switch to e-cigarette use.
	<u>Polosa (2014)</u> undertook an examination of asthmatics who had switched - either completely or partially - to e-cigarette use from smoking. The study concluded:
	"Overall there were significant improvements in spirometry data, asthma control and AHRNo severe adverse events were noted. This small retrospective study indicates that regular use of e-cigs to substitute smoking is associated with objective and subjective improvements in asthma outcomes. Considering that e-cig use is reportedly less harmful than conventional smoking and can lead to reduced cigarette consumption with subsequent improvements in asthma outcomes, this study shows that e-cigs can be a valid option for asthmatic patients who cannot quit smoking by other methods."

Role in the initiation of smoking particularly focusing on young people) | #6.6



#Line	
P 62 L 48	A number of reviews are used to justify the conclusion that there is strong evidence for a gateway effect. The Committee accepts that much of the evidence is from the US, and therefore not directly applicable in the context of the European Union.
	However, the committee fails to consider smoking rates among young people in the United States. This is problematic given the stated objective of this section of the report: namely to ascertain whether e-cigarette use among young people is likely to lead to them taking up smoking. If e-cigarettes were prividing a gateway to cigarettes, as the committee suggests is evidenced, then US government data would show greatly increased smoking rates in line with the growing popularity of e-cigarettes.
	However, US data shows that smoking among young people has actually fallen sharply since e-cigarettes were introduced to the market. <u>Data from the US CDC</u> (attached) shows that from 2013-2015 (during the period where e-cigarettes became popular) experimentation with cigarettes fell from 41.1% to 32.3%; and regular smoking fell from 5.6% to 3.4%. The data from 2019 showed that these numbers remained stable - with 32% having experimented with smoking. If e-cigarettes are a gateway to cigarette smoking in the US, then why is youth smoking falling so significantly there?
P 67 L 26	While the studies noted in this section tend to find that those young people who use e-cigarettes are also likely to use cigarettes at some point, none consider why this might be, simply assuming that if both are used by the same subject then one led to the other. Recent evidence from the US - where the majority of the studies SCHEER has reviewed originate - indicates that the relationship might not be so straightforward in its causality.
	<u>Selya et al (2020)</u> , attached, undertook a secondary review of the "monitoring the Future" dataset, encompassing 12.421 8th and 10th grade students. The analysis found that e-cigarette use "does not appear to be associated with current, continued smokingfailing to support claims that e-cigarettes have a causal effect on concurrent conventional smoking among youth".
	This study was published after the report from the committee was put to consultation; and given its highly authoritative source of data, It would be appropriate for the Committee to reconsider its conclusions in light of this new evidence.
P 69 L 34 - 441	As the report notes, the Eurobarometer data looks at experimentation with e-cigarettes among those aged 15-24, which is an odd age range to review. In the majority of EU Member States, the legal smoking age is 18, meaning that 70% of the ages contained in the sample can legally smoke.
	Since only 3% of those surveyed in Eurobarometer never smoked before using an e-cigarette, the report should consider the possibility that the majority of those in the 15-24 age group who have tried e-cigarettes are doing so for the right reason: as legal age smokers looking for a less harmful alternative to smoking.
n/a	National data from Member States and other countries where TPD is in force can also be used to consider relevant trends. <u>Irish Government data from 2019</u> (attached) show smoking rates in the country have fallen from 23% in 2015 to 17% in 2019; concurrent with a rise in e-cigarette use from 3-5%. Less than 1% of non-smokers use e-cigarettes, according to the data.

Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use | #6.7



#Line	
n/a	National data from Member States and other countries where TPD is in force can also be used to consider relevant trends. <u>Irish Government data from 2019</u> (attached) show smoking rates in the country have fallen from 23% in 2015 to 17% in 2019; concurrent with a rise in e-cigarette use from 3-5%. Less than 1% of non-smokers use e-cigarettes, according to the data.
P 70 L 36	The Committee notes the use of electronic cigarettes as a cessation aid across the EU varies significantly across the Member States and the UK; citing the UK as having the highest rate of e-cigarette use in this context.
- 41	It would help the report achieve its stated objective if it were to consider this in light of data on smoking rates across the Member States. In this regard, the UK - which has the highest level of e-cigarette use - has seen the largest fall in smoking prevalence according to Eurobarometer. In the UK, prevalence of cigarette smoking fell from 22% (2015) to 17% (2017).
P 71 L 1 - 17	As has been correctly identified by the Committee, two randomized controlled trials have been published comparing the efficacy of e-cigarette use and nicotine replacement therapies (NRT). Both studies showed e-cigarettes to deliver significantly higher cessation rates than NRT, while the latter is approved for a quit indication based on a randomized control trial.
	As two RCTs have shown conclusively that e-cigarettes are effective in smoking cessation, it seems absurd for the committee to conclude in the opinion taken in the scientific opinion, that the weight of evidence for smoking cessation is weak (P 19 L 1-2). The current evidence as reviewed by the committee is that e-cigarettes are associated with greater levels of cessation than nicotine replacement therapies.
P 70 L 45	A new Cochrane review has been published following the opening of this consultation. <u>Hartmann-Boyce (2020)</u> concludes:
	"More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy"
P 71 L19 - 28	The message from the UK Public Health authorities (2020) has been significantly at odds with that in the United States. For completeness, the <u>view of Public Health England</u> should be considered as per their latest evidence update:
	"data from stop smoking services in England suggests that when a vaping product is used in a quit attempt, either alone or with licensed medication, success rates are comparable to, if not higher than, licensed medication alone"
	It seems odd to quote US authorities without quoting those from the UK.
n/a	No consideration is given to the impact of non-traditional flavours on smoking cessation. There is data to suggest that use of non tobacco flavours and smoking cessation are correlated. These studies are attached.
	Farsalinos et al found that dual users (those who both smoke and vape) were more likely to be using tobacco flavours (53%) than former smokers (43.1%); while former smokers preferred sweet (63.9%) and fruit (71.7%) flavoured e-cigarettes.
	Russell et al surveyed 22.411 US e-cigarette users, the majority of whom had given up smoking entirely. Results indicated that adults who had completely switched from smoking cigarettes to using e-cigarettes in the past 5 years are increasingly likely to have initiated e-cigarette use with products not flavored to taste like tobacco.