

E-cigarettes and urologic health: a collaborative review of toxicology, epidemiology, and potential risks

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49 **Abstract**

50 **Context:** Use of electronic cigarettes (ECs) is on the rise in most high income countries.

51 Smoking conventional cigarettes is a known risk factor for urological malignancy incidence,
52 progression and mortality as well as for other urological health indicators. The potential
53 impact of EC use on urological health is therefore of clinical interest to the urology
54 community.

55 **Objective:** To review the available data on current EC use including potential benefits in
56 urological patients, potential issues linked to toxicology of EC constituents and how this
57 might translate into urological health risks.

58 **Evidence Acquisition:** A Medline search was carried out in August 2016 for studies reporting
59 urological health outcomes and EC use. Snowballing techniques were also used to identify
60 relevant studies from recent systematic reviews. A narrative synthesis of data around EC
61 health outcomes, toxicology, potential use in smoking cessation and health policy was
62 carried out.

63 **Evidence synthesis:** We found no studies to date that have been specifically designed to
64 assess prospectively urological health risks, even in an observational setting. Generating
65 such data would be an important contribution to the debate on the role of ECs in public
66 health and clinical practice. There is evidence from a recent Cochrane review of RCTs that
67 ECs can support smoking cessation. There are emerging data around potentially harmful
68 components of ECs such as tobacco-specific nitrosamines, polyaromatic hydrocarbons and
69 heavy metals could be linked to possible urological health risks.

70 **Conclusions:** ECs might be a useful tool to encourage conventional cigarette smoking
71 cessation. However, data collection around EC specific impact on urological health is needed
72 to clarify the possible patient benefit, outcomes and adverse events.

73 **Patient summary:** Whilst ECs might help some people to stop smoking, their overall impact
74 on urological health is not clear.

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97 **1. Introduction**

98 Tobacco smoking is an established cause of bladder and kidney cancer (50% and 20% of
99 incident cases, respectively [1]). For people who smoke, there are clear benefits of quitting.
100 For people who don't smoke, or would never have started smoking in the absence of EC,
101 there are potential risks. As such, it is important for urologists and urological health
102 researchers to understand the possible implications of EC use in urology patients.[2]

103

104 *1.1 What are e-cigarettes?*

105 Electronic cigarettes (ECs) are battery-powered devices that all work by heating a liquid ('e-
106 liquid') to create an aerosol that is then inhaled. The aerosol produced is more commonly
107 referred to as vapour, and the use of the device as 'vaping'. Some are designed to resemble
108 traditional cigarettes ('cigalikes' or first generation products), whereas newer generation
109 (tank systems) are modular and can be personalised. The cigalike devices are closed systems
110 and are, generally, not refillable. They may be made for single use (i.e. disposable) or they
111 can have a rechargeable battery and replaceable cartridges that contain the heating coil (or
112 atomizer) and liquid. The newer generation products are generally greater in size and
113 consist of a high capacity lithium battery, sometimes with variable power, an atomizer, and
114 a tank that the user fills with liquid. The atomizer is usually manually activated, which gives
115 greater control over vapour production than the automated systems. Most people start out
116 using a cigalike device, but regular vapers generally use tank system ECs [3].

117

118 There are three main components of the e-liquid; propylene glycol or glycerol or a mix of
119 these, nicotine, and flavouring. The propylene glycol/glycerol mix is important for user
120 satisfaction (e.g. a high propylene glycol content gives a greater 'throat hit'), but may also

121 be important for nicotine delivery.[4] Nicotine concentrations vary from 0 to 36mg/ml, with
122 18mg/ml being the most commonly used.[5, 6] However the European Tobacco Products
123 Directive, which came into effect on 20 May 2016, now limits the concentration to a
124 maximum of 20mg/ml. The directive also restricts the volume of bottles of e-liquid to 10ml
125 and volume of EC tanks to 2ml, as well as a number of other measures including restrictions
126 on advertising and promotions and packaging and labelling requirements. EC liquid (e-liquid)
127 is available in numerous flavours, which are important for user satisfaction. In Great Britain,
128 the most commonly used flavour by current vapers is tobacco, followed by fruit and
129 mint/menthol flavours.[3] The flavours used are considered safe for oral ingestion, but the
130 effects of heating these and then inhaling them are unknown. Some flavours appear to be
131 more cytotoxic than others (e.g. strawberry [7] and cinnamon [8]) and associated with
132 increased risk of respiratory disease (e.g. diacetyl, [9] which gives a buttery flavour).

133

134 Heating nicotine-containing e-liquid produces nicotine-containing vapour; however, the
135 association between the concentration of nicotine in the e-liquid and in vapour is
136 inconsistent. Other factors such as heating of the liquid, voltage and amperage resistance,
137 and how the user inhales on the EC also have a role to play. ECs also do not deliver as much
138 nicotine on a puff by puff basis as standard cigarettes.[10] Therefore, vapers typically take
139 longer puffs than with standard cigarettes (e.g. a mean of 2.4 seconds for conventional
140 cigarettes versus 4.3 seconds for ECs).[11]

141

142 *1.2. Epidemiology/demographics around EC use*

143 Since being introduced, the prevalence of EC use has seen a relatively rapid increase in
144 many high-income countries from which national longitudinal data are available, notably

145 North American and European countries. For example, the prevalence of ever-use among
146 individuals aged ≥ 15 years in 27 states of the European Union increased from 7.2% in 2012
147 to 11.9% in 2014 (Table 1).[12] On average, 15.3% of ever e-cigarette users became current
148 users in 2014. The greatest increases in the European Union occurred in Malta (5.5%
149 increase), Ireland (5.1%), Sweden (4.5%), and France (4.3%). In that survey, the lowest
150 prevalence in 2014 was reported from Portugal (5.7%), whereas the prevalence was 10% or
151 more in 15 countries, with the highest prevalence in France (21.3%).[12] Experimenting and
152 ever use of ECs is generally common among youth,[13] but in Europe, prevalence of regular
153 EC use is much higher in older adults who smoke. In 2014, prevalence of ever EC use in
154 individuals aged ≥ 15 years in the United Kingdom was 15.5%, and approximately one
155 quarter of them transitioned to current users.[12] Among adolescents aged 11–18 years in
156 Great Britain, prevalence of ever use of ECs in 2014 was 8.2%, while it was 1.7% for monthly
157 or more use.[14]

158

159 On the other hand, prevalence of more regular use is higher in youth than older adults in
160 North America. In 2013, 8.5% and 1.8% of Canadians reported ever and current (past 30-
161 day) use of ECs, respectively.[15] The highest prevalence of current use was in age 20–24
162 (3.9%), followed by age 15–19 (2.6%).[15] In the United States, the prevalence of current
163 use among individuals aged ≥ 18 years in 2013–2014 was 3.3%.[16] However, there has been
164 a substantial increase in ECs use among high-school students in the United States, with
165 current use prevalence increasing from 1.5% in 2011 to 16.0% in 2015.[17] The recent US
166 Surgeon General's report warned that in 2014, current use of ECs by young adults 18–24
167 years of age surpassed that of adults 25 years of age and older. The report points to

168 potentially harmful constituents of ECs: particularly nicotine which can lead to addiction and
169 can harm the developing adolescent brain.[18]

170

171 Information on EC use at the national level from countries in other regions is limited. In a
172 survey of Chinese adults (age 15–65 years) in Hong Kong in 2014, the prevalence of ever EC
173 use was 2.3%.[19] Among individuals aged ≥ 15 years in New Zealand in 2014, 13.1% had
174 ever used ECs and only 0.8% were current users. The highest prevalence of current use was
175 in age 22–44 years (1.2%), followed by age ≥ 45 (0.7%).[20] Prevalence of ever and current
176 use of ECs among students aged 13–18 years in South Korea in 2011 was 9.4% and 1.4%,
177 respectively.[21] Since 2011, questions on ECs use have been added to the Global Adult
178 Tobacco Survey (GATS), which is a nationally representative household survey of individuals
179 aged ≥ 15 years in a number of countries.[22] The prevalence of current EC use in four
180 countries with available data was 0.3% in Indonesia and 0.8% in Malaysia in 2011 and 0.9%
181 in Qatar and 1.9% in Greece in 2013.[22] It should be noted that due to rapid changes in
182 prevalence of EC use in some countries, prevalence of use across countries, especially
183 among youth, may not be comparable using results of surveys conducted in different years.

184

185 EC use has the potential to help smokers to quit cigarette smoking or reduce smoking
186 intensity.[23] However, one of the primary concerns of EC use is the maintenance of
187 tobacco use in current smokers (without any substantial decrease in smoking intensity), re-
188 initiation in former smokers, and in particular, nicotine dependence in adolescents,[24–28]
189 as EC user adolescents may show a higher intention to smoke traditional cigarettes.[25, 27]
190 However, in many countries, the rate of EC use by never-smokers or smoking initiation
191 following EC use has been relatively low, although there might be some variations across

192 countries. In a survey conducted in 2014 in the European Union, initiation of tobacco use by
193 using ECs was reported by 0.8% of participants who had used any tobacco product. Use of
194 nicotine-containing EC among never smokers was low (1.3%), with 0.09% reporting daily
195 use.[29] The prevalence of current EC use among never-smokers in 2013 was 0.3% in
196 Canada [15] and 1.4% in the United States.[26] Among adolescents, EC use at least monthly
197 was reported by only 0.2% of adolescents aged 11–18 years in Great Britain in 2014.[14]
198 Among middle and high school students in the United States in 2011–2013, prevalence of
199 current EC use was 0.3% among never smokers.[24] Prevalence of ever and current use of
200 ECs only (no other tobacco products) in age 13–18 years in South Korea in 2011 was 1.4%
201 and 1.1%, respectively.[21] Despite low rates of ECs use among never smoker adolescents,
202 this group could include a substantial number of children, as generally prevalence of
203 tobacco smoking in this age group is low. For example, the group of never smoker students
204 that were current ECs users (0.3% of never smokers) in the United States in 2013 included
205 263,000 children.[24]

206

207

208 **2. Evidence acquisition**

209 In order to identify any eligible trials addressing EC use and urological health outcomes, a search of
210 the electronic databases MEDLINE was carried out from inception to August 2016. MEDLINE search
211 terms were (e-cigarette or electronic-cigarette) AND (bladder or prostate or kidney or urol*). In
212 addition to database searches, recent systematic reviews of EC use were hand searched for any
213 potentially eligible trials. To add context to the any available trials data, evidence around smoking
214 cessation, available toxicology data and health policy around EC regulations are presented in this
215 review. Quality appraisal was done subjectively according to expertise and clinical judgement of the

216 authors. Given that EC use and urological outcomes is an emerging clinical issue with a fragmentary
217 evidence base and involves rapidly evolving technologies, a narrative synthesis of these data was
218 undertaken.[30]

219

220 **3. Evidence synthesis**

221 *3.1 Current urological health outcomes and trials of EC use*

222 We found no published clinical studies, which are *a priori* designed to evaluate the impact of
223 ECs on urological health outcomes. We were able to find only one published protocol for a
224 prospective observational study that will document hospitalizations and adverse events that
225 could report urological health outcomes (although not specifically designed to do this).[31]

226

227 *3.2 Toxicity data and potential urological health impacts from ECs*

228 ECs were introduced into the US and UK markets in 2007 [32] and so their long-term health
229 risks are not yet clear. Reducing the use of conventional cigarettes has numerous obvious
230 health benefits including links to incidence and progression of urological malignancies [33]
231 and complications after primary treatment for urological cancer.[34] EC operation does not
232 involve combustion and so no smoke or other harmful combustion products, such as tar and
233 carbon monoxide, are formed. Reduced excretion of tobacco-specific nitrosamines and
234 other carcinogens has been found in the urine of vapers compared with smokers. [35, 36]
235 ECs are thought to be much safer for long-term health by the public than traditional tobacco
236 cigarettes.[37] It is however, important to recognise that these devices are not entirely
237 benign. Due to the nature and components of these devices, ECs have a diverse hazard
238 profile. Operation of EC at high temperatures can generate relatively high levels of

239 aldehydes [38, 39], which have carcinogenic potential. However vapers naturally avoid this,
240 as it creates an unpleasant taste (commonly known as a 'dry puff')[39, 40]. A recent
241 systematic review highlighted adverse events linked between EC use and the respiratory,
242 gastrointestinal, cardiovascular, neurological and immune system; serious leg burns due to
243 exposure of the battery; serious oral burns, lacerations and fractures from an account of an
244 EC 'explosion'; both accidental and intentional nicotine overdoses (suicide attempts).[41]

245

246 Data regarding the constituents of ECs is evolving in the literature. Levels of each
247 component can be varied (e.g. Allen et al (2016) describe over 7000 flavours[42]) and there
248 is heterogeneity amongst manufacturers.[43] For example, nicotine levels were seen to vary
249 from 0 mg/ml to 87 mg/ml across studies, and there were reported deviations from the
250 device label of ingredients of up to 100%.[43] Furthermore, there is inconsistency in the
251 delivery of chemicals within each puff from the same device or brand. This may be due to
252 subtle differences in the size of particulate matter within each refill solution and the
253 delivery system that is used.

254

255 A recent review describes chemical profiles of EC solutions, cartridges, aerosols and
256 environmental emissions.[43] Whilst ECs are designed to be devoid of tar, some ECs have
257 been found to contain carcinogens such as tobacco-specific nitrosamines and formaldehyde.
258 Other constituents such as polyaromatic hydrocarbons and heavy metals are known to
259 cause cancer, and nicotine itself is thought by some to pose a urological cancer risk. [44, 45]
260 For instance, polycyclic aromatic hydrocarbons (International Agency for Research on
261 Cancer (IARC), Group 1 (human carcinogen)[46]), which has been associated with bladder
262 cancer.[47] EC have also been found to contain certain heavy metals, such as lead.[48] Lead

263 exposure has been linked to increased kidney cancer risk. [49, 50] The concentration of lead
264 in EC aerosol is variable but has been suggested in at least one analysis to be comparable to
265 that found in conventional cigarettes.[51] Other heavy metals in EC such as cadmium, nickel
266 and chromium are possible carcinogens (IARC 2b). Nickel, in particular, has been recorded at
267 levels present in ECs that are much higher than conventional cigarettes. [51] Although these
268 heavy metals are linked to an increase cancer risk, they have not yet been linked to
269 urological malignancies.[49] Cresol, which has been found in aerosols from EC cartridges is
270 also found in creosote, a suspect bladder carcinogen.[47]

271

272 In addition, in vitro data has demonstrated that EC vapour exposure, independent of
273 nicotine content induces increased cell death. In both normal epithelial cells and cancer cell
274 lines (head and neck squamous cell carcinoma) treated with nicotine free and nicotine-
275 containing vapour, up to a threefold increase in DNA double strand breaks has been
276 reported.[52] Nicotine is also negatively correlated with total sperm motility due to
277 metabolic breakdown products cotinine and trans-3'-hydroxycotinine levels in seminal
278 fluid.[53] Furthermore, cadmium (found in ECs) is associated with low sperm density.[54]
279 Preliminary evidence from a murine model has reported exposure to EC refill liquid can alter
280 anti-oxidant defence and induce histopathological changes reflecting renal collecting duct
281 cell apoptosis.[55]

282

283 Whilst there is a theoretic potential for adverse urological health outcomes from the use of
284 ECs it should be stressed that robust data are currently absent to offer a convincing
285 argument for either side of the debate. A recent systematic review of the health
286 consequences of vaping/ECs highlighted frequent methodological problems with available

287 studies, problematic authorship conflicts of interest, small cohort size, selection bias,
288 conflicting results and a paucity of long-term follow-up data.[48]

289

290 *3.3 Can ECs help stop tobacco smoking?*

291 The literature on the role ECs play in smoking cessation is growing very slowly, and the
292 messages are somewhat mixed. This section summarizes the current evidence from a range
293 of different study designs and levels of evidence.

294

295

296 *3.3.1 Prospective cohort studies*

297 Five studies, with long-term outcomes, have looked at the use of ECs in people who were
298 not ready to quit smoking. One followed 40 smokers over two years and reported that 13%
299 achieved at least six months of CO validated abstinence from conventional cigarettes and
300 28% had achieved a sustained $\geq 50\%$ reduction from baseline cigarette consumption.[56, 57]

301 The second tested the same approach with 14 smokers with schizophrenia and reported
302 14% 30-day CO validated abstinence rates at one-year.[58] The third followed a group of 34
303 smokers for 8 months after discharge from hospital.[59] Over half (53%) reported no longer
304 smoking. In the fourth, 50 smokers were provided with a second-generation device with
305 9mg/ml concentration of e-liquid. At 6 month follow-up 36% were biochemically validated
306 7-day point prevalence abstainers.[60] The fifth cohort study followed 71 smokers who
307 purchased an EC from a vape shop. One year after their purchase 41% reported that they
308 had not smoked at all for at least the last 30 days.[61]

309

310 Data are now being reported by the UK stop smoking services. A London-based stop
311 smoking service offered 100 clients, all of whom wanted to quit smoking, a choice of a first
312 or second generation EC.[62] In total, 67 accepted the offer and of these 45 (65%) were
313 recorded as biochemically validated abstainers at the end of treatment (4-weeks post-quit
314 date). The results from this study closely reflect the UK Stop Smoking Service monitoring
315 data from over 450,000 people that made a quit attempt, where 4-week self-reported quit
316 rates were 66% among people who used ECs (n=2221), compared to 48% among people
317 who used combination NRT (n=135,719).

318

319 Although there are data to support ECs as a potential aid to smoking cessation in the
320 general population, it is important to note that in those already diagnosed with cancer,
321 there is less certainty. Prospective cohort data from a major US cancer treatment centre
322 reported that significantly higher percentage of EC users were highly nicotine dependent
323 when compared with nonusers and were twice as likely to be smoking at the time of follow-
324 up as nonusers.[63]

325

326 *3.3.2 Randomised controlled trials*

327 To date only three randomised controlled trials that have examined the effects of EC in
328 helping people stop smoking have been published. One examined their use in people who
329 wanted to quit,[64] and two in those who did not.[65, 66] In a study of people who wanted
330 to quit from New Zealand [64], the investigators compared nicotine-containing ECs (n=289),
331 with 21mg nicotine patches (n=295), and with non-nicotine ECs (placebo ECs, n=73).

332 Participants were provided with a referral to telephone quitline but with no face-to-face

333 contact. In this minimal support context, there were no significant differences in validated
334 continuous abstinence at six months (7.3% nicotine EC, 5.8% nicotine patch, and 4.1% non-
335 nicotine EC). These findings were similar to an Italian study comparing EC use (two different
336 doses for 12 weeks) to non-nicotine ECs in 300 smokers who were not intending to quit. [65]
337 Biochemically validated six-month abstinence rates (at one-year follow-up) were not
338 significantly different; 13%, 9% and 4% in the three groups, respectively. Both of these
339 pioneering trials were underpowered and used first generation EC products with poor
340 nicotine delivery. These ECs often malfunctioned and neither is now available on the
341 market.

342

343 The third trial [66], from Belgium, randomised 48 smokers who did not want to quit to use
344 an EC (a tank system) or no intervention. At 8-week follow-up, 34% of those given an EC to
345 use had quit smoking compared to none in control group. From week 8, all participants
346 were provided with an EC and followed up at 8 months. Among this cohort 19% of early EC
347 users and 25% of the late starters (the control group) had stopped smoking. The results
348 from this study are difficult to interpret because of the small sample size and design.

349

350 *3.3.3 Systematic reviews*

351 There are now 16 published systematic reviews on ECs for smoking cessation. A recently
352 updated Cochrane review found that ECs with nicotine helped smokers quit for at least 6
353 months compared with no nicotine ECs (RR= 2.29, 95% CI: 1.05-4.96; 9% vs. 4%). [67] The
354 authors of the review gave these findings a 'low' confidence rating using GRADE standards,
355 not because of poor quality studies, but because there are only two studies. Crucially, the
356 'low' judgement also means that further research is very likely to have an important impact

357 on our confidence in the estimate of effect and is likely to change the estimate. The addition
358 of more trials to this review will further strengthen the conclusions made. Other systematic
359 reviews draw similar conclusions to the Cochrane review (e.g.[68, 69]), unsurprisingly
360 because they include the same studies. The review and meta-analysis by Kalkohern and
361 Glantz [70] came to the opposite conclusion (that EC use is associated with significantly
362 lower odds of achieving abstinence; OR 0.72; 95% CI: 0.57-0.91). The data in this review
363 included reports of many small surveys and cohort studies (all with serious limitations)
364 rendering the findings of this meta-analysis difficult to interpret.

365

366 Given that ECs now deliver nicotine to the user in similar quantities as NRT and even
367 cigarettes, there is little reason to doubt they could help people stop smoking. Some
368 estimates of the numbers who have stopped using ECs have been made. For example,
369 Farsalinos estimated 6.1 million European ever EC users have stopped smoking.[71] In
370 England this figure is thought to be around 0.56 million. Further research and monitoring
371 will strengthen confidence in these findings.[72]

372

373

374 *3.4 European health policy and ECs*

375 The use of ECs for smoking reduction or cessation is influenced by a range of factors that
376 extend beyond the safety and efficacy of these devices. Regulation also affects their use, in
377 particular policies that may result in changes to the price, availability or promotion of the
378 products.[73] The global context for EC regulation is highly variable.[74] In many countries
379 such as Argentina, Brazil, Indonesia, and Singapore, the import, distribution and sale of ECs
380 is banned. Other countries such as New Zealand, South Africa and Switzerland have

381 implemented a two tier system where ECs themselves and nicotine-free cartridges or e-
382 liquid can be sold sale of but nicotine-containing refills or e-liquid are prohibited. Other
383 countries permit their import and sale but certain restrictions on age of sale or marketing
384 are in place. Policies have evolved as use has become more prevalent and governments
385 have responded to a range of concerns often about youth uptake, addictiveness or safety.
386 Ironically, many jurisdictions now have more restrictive regulation on ECs than tobacco
387 products.

388 In the European Union (EU), EC use is prevalent and countries have taken a range of
389 approaches to regulation.[29] From May 2016 the revised EU Tobacco Products Directive
390 (TPD) was implemented and article 20 of the Directive applies to ECs and refill containers
391 that do not have a medicinal license.[75] Only one device, E-Voke (manufactured by British
392 American Tobacco) has been granted a medicinal license but is not yet available on
393 prescription or as an over the counter medication.[76] The EU TPD requires manufacturers
394 and importers of ECs to comply with a notification process that involves providing data on:
395 ingredients and emissions; nicotine delivery and uptake; health and addictive effects; the
396 product components and production process; and a declaration on safety and quality when
397 used as intended. It is anticipated that this process will remove some products from the
398 market that can't meet these requirements.

399

400 The TPD also places a limit on nicotine concentration with devices that do not have a
401 medicinal license limited to 20mg/ml and refill containers up to a maximum volume of 10ml.
402 The basis for this requirement is contested and some concerns have been expressed about
403 this limit in terms of delivering nicotine to smokers who are highly dependent.[77] ECs must
404 also be secure in terms of leakage and breakage, be child and tamper proof and contain a

405 leaflet with warnings, instructions and further information. Packaging must contain a
406 warning label about nicotine being a highly addictive substance and promotional elements
407 on packaging are also subject to regulation. Some forms of marketing are also restricted
408 under the TPD including the prohibition of all cross border advertising and sponsorship
409 although other forms of marketing such as billboards and point of sale are at the discretion
410 of member states. Finally, annual submissions on products are required to be submitted to
411 governments and a system for collecting information on adverse effects on health must be
412 in place. Other policy issues such as age of sale, use in public places and the regulation of
413 flavours are the responsibility of national governments.

414

415 **4. Discussion**

416 We were not able to find any clinical studies with prospective outcomes assessing EC use
417 and urological outcomes. We have presented data around toxicology of compounds found
418 in EC constituents and how this might impact urological health, but these must be viewed as
419 hypothesis generating and treated with caution. As such the use and potential outcomes
420 associated with EC use in urological patient populations is still to be determined. Some
421 international studies, such as the International Tobacco Control Survey,[78] are already
422 providing useful data allowing comparisons of the prevalence of EC use in adults and young
423 people, impact on smoking cessation, and harm perceptions to be examined across
424 countries. In the UK, Cancer Research UK and Public Health England have established the UK
425 Electronic Cigarette Research forum (UKECRF) which brings together researchers from a
426 range of disciplines three times a year to build new collaborations and pursue studies that
427 aim to address research gaps. The forum also produces a monthly evidence bulletin
428 summarising new studies. Networks of this type are needed in other countries to develop

429 high quality proposals for EC research and generate evidence to inform policy and practice
430 in this rapidly developing field. More research on patterns of tobacco use after e-cigarettes
431 use, in particular among youth, is needed.[79] Also, little information is available on
432 prevalence of use of nicotine-containing and non-nicotine e-cigarettes. Appropriate
433 regulations are needed to protect non-smokers especially adolescents, whilst granting
434 access to smokers to support cessation. In terms of urological health outcomes specifically,
435 data around vapour emission quantities and compositions would be helpful and to work
436 towards validated and standardised contents of ECs. This is an important public health
437 question because EC have been popularised as an aid to smoking cessation, particularly
438 among teenagers. Given the long latency of most cancers, it may take at least 15 years of
439 follow up to identify urological cancer risk among EC users. Analysis of the urine of EC users
440 for compounds such as nitrosamines, aldehydes, lead, arsenic, nickel, chromium and how
441 these are associated with the development of urological malignancies over time would also
442 be a valuable addition to the knowledge base. There is also the challenge of differentiating
443 between conventional cigarette and EC induced health problems, given that most EC users
444 also smoke conventional cigarettes. In this regard, methodologically robust prospective
445 studies looking at urological malignancies in EC users would be valuable data to add to this
446 debate.

447

448 **Figure Legends:**

449 Table 1: Selected representative prevalences of e-cigarette use

450

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452

453 **Author contributions:** The views expressed here may not represent those of the authors'
454 organizations.

455 Liam Bourke had full access to all the data in the study and takes responsibility for the
456 integrity of the data and the accuracy of the analysis.

457 **Study concept and design:** Bourke, Catto

458 **Acquisition of data:** Bourke, Bauld, Bullen, Cumberbatch, Giovannucci, Islami, McRobbie,
459 Silverman and Catto.

460 **Analysis and interpretation of data:** Bourke, Bauld, Bullen, Cumberbatch, Giovannucci,
461 Islami, McRobbie, Silverman and Catto.

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476 **Table 1.**

Reference; country, year	Age, no. of participants	Prevalence		
		E-cigarette use	Overall, %	Never tobacco smokers, %
Filippidis et al. [12];* European Union (27 countries), 2012–2014	≥15 years 2012: 26,751 2014: 26,792	Ever use, 2012 Ever use, 2014 Transition of ever to current users	7.2 11.9 15.3 (F 14.2; M 17.7)	
Eastwood et al. [14]; Great Britain, 2013–2014	11–18 years 2013: 2,062 2014: 1,952	< monthly, 2013 Monthly or more, 2013 < monthly, 2014 Monthly or more, 2014	3.7 0.9 † 6.5 1.7 †	0.6 0.1 1.5 0.2
Hu et al. [16]; USA, 2013–2014	≥18 years 75,233	Every or some days All 18–24 years 25–44 45–64 ≥ 65 Every/some days or rarely	3.3 (F 2.8, M 4.0) 5.5 4.4 2.8 0.9 6.6 (F 7.9, M 5.5)	
Czoli et al. [15]; Canada, 2013	≥15 years ~2.5 million	Use in the past 30 days All 15–19 years 25–44 45–64 ≥ 45 Ever use	1.8 (F 1.8, M 1.8) 2.6 (F 2.1, M 3.0) 3.9 (F 3.5, M 4.3) 2.4 (F NR, M 3.0) 1.0 (F 1.2, M 0.8) 8.5 (F 8.1, M 8.9)	0.5 (F 0.5, M 0.5) 3.6 (F 3.4, M 3.9)
Singh et al. [17]; USA, 2011–2015	Middle or high school students 2011: 18,866 2015: 17,711	Use in the past 30 days High school, 2015 Middle school, 2015 High school, 2011 Middle school, 2011	16.0 (F 12.8, M 19.0) 5.3 (F 4.8, M 5.9) 1.5 0.6	
Jiang et al. [19]; Hong Kong, 2014	15–65 years 809	Ever use All 15–29 years 30–49 50–65	2.3 (F 1.3, M 3.6) 5.2 1.8 1.0	1.0
Li et al. [20]; New Zealand, 2014	≥15 years 2,594	Monthly or more All 15–17 years 18–24 25–44 ≥ 45 Ever use	0.8 (F 1.0, M 0.5) 0.0 0.2 1.2 0.7 13.1 (F 12.8, M 13.7)	0.1
Lee et al. [21]; South Korea, 2011	13–18 years (students) 75,643	Use in the past 30 days All students Grade 7 8 9 10 11 12 Ever use	4.7 (F 1.8, M 7.8) 2.0 3.3 4.7 7.1 6.0 6.2 9.4	0.6
Palipudi et al. [22]; Greece, Indonesia, Malaysia, and Qatar, 2011–2013	≥15 years Greece (9,357), Indonesia (8,303), Malaysia	Current use ** Greece All 15–24 years 25–44	1.9 (F 1.8, M 7.8) 0.0 2.8	1.1 ¶

Reference; country, year	Age, no. of participants	Prevalence			
		E-cigarette use	Overall, %	Never tobacco smokers, %	
	(4,244), Qatar (8,389)	45–64	2.7		
		≥ 65	0.8		
		Indonesia			
		All	0.3 (F 1.8, M 7.8)	0.0 ¶	
		15–24 years	0.2		
		25–44	0.3		
		45–64	0.3		
		≥ 65	0.0		
		Malaysia			
		All	0.8 (F 1.8, M 7.8)	0.1 ¶	
		15–24 years	4.4		
		25–44	5.0		
		45–64	0.0		
		≥ 65	0.0		
		Qatar			
		All	0.9 (F 1.8, M 7.8)	0.2 ¶	
		15–24 years	0.5		
25–44	1.0				
45–64	1.3				
≥ 65	0.0				
Bunnell et al. [24]; USA, 2011–2013	Middle or high school students 61,932	Use in the past 30 days Ever use		0.3 0.9	

477 F, female; M, male; NR, not-reported.

478 * Prevalences for individual countries are also presented in the article.

479 ** Those who responded “daily or less than daily” to the question “Do you currently use e-
480 cigarettes on a daily basis, less than daily, or not at all?”

481 † Males were 2.5-times more likely to be monthly or more users than females.

482 ¶ Among those with no current tobacco smoking.

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503 **References**

504

- 505 [1] Purdue MP, Silverman DT. Clearing the Air: Summarizing the Smoking-related
506 Relative Risks of Bladder and Kidney Cancer. *Eur Urol.* 2016;70:467-8.
- 507 [2] Yeh JS, Bullen C, Glantz SA. CLINICAL DECISIONS. E-Cigarettes and Smoking
508 Cessation. *N Engl J Med.* 2016;374:2172-4.
- 509 [3] Health AoSa. ASH Fact Sheet on the use of electronic cigarettes among adults in
510 Great Britain. London, UK: ASH UK; 2015.
- 511 [4] Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and
512 cardiovascular function in comparison with regular cigarettes. *Regulatory toxicology
513 and pharmacology: RTP.* 2014.
- 514 [5] Etter J-F, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and
515 perceived efficacy. *Addiction.* 2011;106:2017-28.
- 516 [6] Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: an
517 online survey of electronic cigarette users. *Addiction.* 2013;108:1115-25.
- 518 [7] Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly
519 affect inhalation toxicity of aerosol generated from electronic nicotine delivery
520 systems (ENDS). *Tob Control.* 2016.
- 521 [8] Behar RZ, Luo W, Lin SC, Wang Y, Valle J, Pankow JF, et al. Distribution,
522 quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and
523 aerosols. *Tob Control.* 2016.
- 524 [9] Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL. Clinical
525 bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med.*
526 2002;347:330-8.
- 527 [10] Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes,
528 its release in vapour and its consistency across batches: regulatory implications.
529 *Addiction.* 2014;109:500-7.
- 530 [11] Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery
531 systems (ENDS) from YouTube videos. *Tobacco Control.* 2013;22:103-6.
- 532 [12] Filippidis FT, Lavery AA, Gerovasili V, Vardavas CI. Two-year trends and
533 predictors of e-cigarette use in 27 European Union member states. *Tobacco control.*
534 2016.
- 535 [13] Vardavas CI, Filippidis FT, Agaku IT. Determinants and prevalence of e-
536 cigarette use throughout the European Union: a secondary analysis of 26 566 youth
537 and adults from 27 Countries. *Tobacco control.* 2015;24:442-8.
- 538 [14] Eastwood B, Dockrell MJ, Arnott D, Britton J, Cheeseman H, Jarvis MJ, et al.
539 Electronic cigarette use in young people in Great Britain 2013-2014. *Public Health.*
540 2015;129:1150-6.
- 541 [15] Czoli CD, Reid JL, Rynard VL, Hammond D. Tobacco Use in Canada: Patterns
542 and Trends, 2015 Edition. Special Supplement: E-cigarettes in Canada. Waterloo,
543 Canada: Propel Centre for Population Health Impact, University of Waterloo.
- 544 [16] Hu SS, Neff L, Agaku IT, Cox S, Day HR, Holder-Hayes E, et al. Tobacco
545 Product Use Among Adults - United States, 2013-2014. *MMWR Morb Mortal Wkly
546 Rep.* 2016;65:685-91.
- 547 [17] Singh T, Arrazola RA, Corey CG, Husten CG, Neff LJ, Homa DM, et al. Tobacco
548 Use Among Middle and High School Students--United States, 2011-2015. *MMWR
549 Morb Mortal Wkly Rep.* 2016;65:361-7.
- 550 [18] E-cigarette use among youth and young adults: a report of the Surgeon General.
551 Accessed 09/12/16 at <http://e->

552 cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf.
553 2016.

554 [19] Jiang N, Chen J, Wang MP, McGhee SM, Kwong AC, Lai VW, et al. Electronic
555 cigarette awareness and use among adults in Hong Kong. *Addict Behav.*
556 2016;52:34-8.

557 [20] Li J, Newcombe R, Walton D. The prevalence, correlates and reasons for using
558 electronic cigarettes among New Zealand adults. *Addict Behav.* 2015;45:245-51.

559 [21] Lee S, Grana RA, Glantz SA. Electronic cigarette use among Korean
560 adolescents: a cross-sectional study of market penetration, dual use, and
561 relationship to quit attempts and former smoking. *J Adolesc Health.* 2014;54:684-90.

562 [22] Palipudi KM, Mbulo L, Morton J, Mbulo L, Bunnell R, Blutcher-Nelson G, et al.
563 Awareness and Current Use of Electronic Cigarettes in Indonesia, Malaysia, Qatar,
564 and Greece: Findings From 2011-2013 Global Adult Tobacco Surveys. *Nicotine &*
565 *tobacco research : official journal of the Society for Research on Nicotine and*
566 *Tobacco.* 2016;18:501-7.

567 [23] Beard E, West R, Michie S, Brown J. Association between electronic cigarette
568 use and changes in quit attempts, success of quit attempts, use of smoking
569 cessation pharmacotherapy, and use of stop smoking services in England: time
570 series analysis of population trends. *BMJ.* 2016;354:i4645.

571 [24] Bunnell RE, Agaku IT, Arrazola RA, Apelberg BJ, Caraballo RS, Corey CG, et
572 al. Intentions to smoke cigarettes among never-smoking US middle and high school
573 electronic cigarette users: National Youth Tobacco Survey, 2011-2013. *Nicotine &*
574 *tobacco research : official journal of the Society for Research on Nicotine and*
575 *Tobacco.* 2015;17:228-35.

576 [25] Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, et
577 al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco
578 Product Smoking in Early Adolescence. *JAMA.* 2015;314:700-7.

579 [26] McMillen RC, Gottlieb MA, Shaefer RM, Winickoff JP, Klein JD. Trends in
580 Electronic Cigarette Use Among U.S. Adults: Use is Increasing in Both Smokers and
581 Nonsmokers. *Nicotine & tobacco research : official journal of the Society for*
582 *Research on Nicotine and Tobacco.* 2015;17:1195-202.

583 [27] Wang MP, Ho SY, Leung LT, Lam TH. Electronic cigarette use and its
584 association with smoking in Hong Kong Chinese adolescents. *Addict Behav.*
585 2015;50:124-7.

586 [28] Barrington-Trimis JL, Urman R, Leventhal AM, Gauderman WJ, Cruz TB,
587 Gilreath TD, et al. E-cigarettes, Cigarettes, and the Prevalence of Adolescent
588 Tobacco Use. *Pediatrics.* 2016;138.

589 [29] Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in
590 the European Union: analysis of a representative sample of 27 460 Europeans from
591 28 countries. *Addiction.* 2016.

592 [30] The Editors. Reviews: making sense of an often tangled skein of evidence.
593 *Annals of internal medicine.* 2005;142:1019-20.

594 [31] Manzoli L, La Vecchia C, Flacco ME, Capasso L, Simonetti V, Boccia S, et al.
595 Multicentric cohort study on the long-term efficacy and safety of electronic cigarettes:
596 study design and methodology. *BMC public health.* 2013;13:883.

597 [32] Orellana-Barrios MA, Payne D, Mulkey Z, Nugent K. Electronic Cigarettes-A
598 Narrative Review for Clinicians. *The American journal of medicine.* 2015;128:674-81.

599 [33] Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco
600 Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and
601 Meta-analysis of Incidence and Mortality Risks. *Eur Urol.* 2015;70(3):458-66.

602 [34] Byun DJ, Cohn MR, Patel SN, Donin NM, Sosnowski R, Bjurlin MA. The Effect
603 of Smoking on 30-Day Complications Following Radical Prostatectomy. *Clin*
604 *Genitourin Cancer*. 2016.

605 [35] Kotandeniya D, Carmella SG, Pillsbury ME, Hecht SS. Combined analysis of N'-
606 nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in the urine of
607 cigarette smokers and e-cigarette users. *Journal of chromatography B, Analytical*
608 *technologies in the biomedical and life sciences*. 2015;1007:121-6.

609 [36] Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, Ransom BWS,
610 et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette
611 users versus cigarette smokers. *Nicotine & Tobacco Research: Official Journal of the*
612 *Society for Research on Nicotine and Tobacco*. 2015;17:704-9.

613 [37] Martinez-Sanchez JM, Fu M, Martin-Sanchez JC, Ballbe M, Salto E, Fernandez
614 E. Perception of electronic cigarettes in the general population: does their usefulness
615 outweigh their risks? *BMJ open*. 2015;5:e009218.

616 [38] Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde
617 in e-cigarette aerosols. *The New England Journal of Medicine*. 2015;372:392-4.

618 [39] Farsalinos KE, Voudris V, Poulas K. E-cigarettes generate high levels of
619 aldehydes only in 'dry puff' conditions. *Addiction*. 2015;110:1352-6.

620 [40] Nitzkin JL, Farsalinos K, Siegel M. More on hidden formaldehyde in e-cigarette
621 aerosols. *The New England Journal of Medicine*. 2015;372:1575.

622 [41] Hua M, Talbot P. Potential health effects of electronic cigarettes: A systematic
623 review of case reports. *Prev Med Rep*. 2016;4:169-78.

624 [42] Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH, et
625 al. Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a
626 Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes.
627 *Environmental health perspectives*. 2016;124:733-9.

628 [43] Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control*. 2014;23
629 *Suppl 2*:ii11-7.

630 [44] Cumberbatch MG, Cox A, Teare D, Catto JW. Contemporary Occupational
631 Carcinogen Exposure and Bladder Cancer: A Systematic Review and Meta-analysis.
632 *JAMA Oncol*. 2015;1:1282-90.

633 [45] Yuge K, Kikuchi E, Hagiwara M, Yasumizu Y, Tanaka N, Kosaka T, et al.
634 Nicotine Induces Tumor Growth and Chemoresistance through Activation of the
635 PI3K/Akt/mTOR Pathway in Bladder Cancer. *Mol Cancer Ther*. 2015;14:2112-20.

636 [46] Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. A
637 review of human carcinogens--Part F: chemical agents and related occupations.
638 *Lancet Oncol*. 2009;10:1143-4.

639 [47] Silverman DT; Devesa SS; Moore LE; Rothman N. Bladder Cancer. In:
640 Schottenfeld D, Fraumeni JF Jr. eds. *Cancer Epidemiology and Prevention*. 3rd Ed.
641 New York: Oxford University Press.2006.

642 [48] Pisinger C, Dossing M. A systematic review of health effects of electronic
643 cigarettes. *Prev Med*. 2014;69:248-60.

644 [49] Boffetta P, Fontana L, Stewart P, Zaridze D, Szeszenia-Dabrowska N, Janout V,
645 et al. Occupational exposure to arsenic, cadmium, chromium, lead and nickel, and
646 renal cell carcinoma: a case-control study from Central and Eastern Europe.
647 *Occupational and environmental medicine*. 2011;68:723-8.

648 [50] Liao LM, Friesen MC, Xiang YB, Cai H, Koh DH, Ji BT, et al. Occupational Lead
649 Exposure and Associations with Selected Cancers: The Shanghai Men's and
650 Women's Health Study Cohorts. *Environmental health perspectives*. 2016;124:97-
651 103.

652 [51] Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles
653 including nanoparticles are present in electronic cigarette cartomizer fluid and
654 aerosol. *PloS one*. 2013;8:e57987.

655 [52] Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, et al. Electronic
656 cigarettes induce DNA strand breaks and cell death independently of nicotine in cell
657 lines. *Oral Oncol*. 2016;52:58-65.

658 [53] Pacifici R, Altieri I, Gandini L, Lenzi A, Pichini S, Rosa M, et al. Nicotine,
659 cotinine, and trans-3-hydroxycotinine levels in seminal plasma of smokers: effects on
660 sperm parameters. *Ther Drug Monit*. 1993;15:358-63.

661 [54] Saaranen M, Kantola M, Saarikoski S, Vanha-Perttula T. Human seminal
662 plasma cadmium: comparison with fertility and smoking habits. *Andrologia*.
663 1989;21:140-5.

664 [55] Golli NE, Jrad-Lamine A, Neffati H, Dkhili H, Rahali D, Dallagi Y, et al. Impact of
665 e-cigarette refill liquid exposure on rat kidney. *Regul Toxicol Pharmacol*.
666 2016;77:109-16.

667 [56] Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect
668 of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and
669 cessation: a prospective 6-month pilot study. *BMC public health*. 2011;11:786.

670 [57] Polosa R, Morjaria JB, Caponnetto P, Campagna D, Russo C, Alamo A, et al.
671 Effectiveness and tolerability of electronic cigarette in real-life: a 24-month
672 prospective observational study. *Internal and emergency medicine*. 2013:[Epub
673 ahead of print].

674 [58] Caponnetto P, Auditore R, Russo C, Cappello GC, Polosa R. Impact of an
675 electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a
676 prospective 12-month pilot study. *International journal of environmental research and
677 public health*. 2013;10:446-61.

678 [59] Pacifici R, Pichini S, Graziano S, Pellegrini M, Massaro G, Beatrice F.
679 Successful Nicotine Intake in Medical Assisted Use of E-Cigarettes: A Pilot Study.
680 *International journal of environmental research and public health*. 2015;12:7638-46.

681 [60] Polosa R, Caponnetto P, Maglia M, Morjaria JB, Russo C. Success rates with
682 nicotine personal vaporizers: a prospective 6-month pilot study of smokers not
683 intending to quit. *BMC public health*. 2014;14:1159.

684 [61] Polosa R, Caponnetto P, Cibella F, Le-Houezec J. Quit and smoking reduction
685 rates in vape shop consumers: a prospective 12-month survey. *International journal
686 of environmental research and public health*. 2015;12:3428-38.

687 [62] Hajek P, Corbin L, Ladmore D, Spearing E. Adding E-Cigarettes to Specialist
688 Stop-Smoking Treatment: City of London Pilot Project. *Journal of Addiction
689 Research & Therapy*. 2015;6:244.

690 [63] Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette
691 use among patients with cancer: characteristics of electronic cigarette users and
692 their smoking cessation outcomes. *Cancer*. 2014;120:3527-35.

693 [64] Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al.
694 Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*.
695 2013;382:1629-37.

696 [65] Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, et al.
697 Efficiency and Safety of an eLectronic cigAReTte (ECLAT) as Tobacco Cigarettes
698 Substitute: A Prospective 12-Month Randomized Control Design Study. *PloS one*.
699 2013;8:e66317.

700 [66] Adriaens K, Van Gucht D, Declerck P, Baeyens F. Effectiveness of the
701 Electronic Cigarette: An Eight-Week Flemish Study with Six-Month Follow-up on

702 Smoking Reduction, Craving and Experienced Benefits and Complaints.
703 International journal of environmental research and public health. 2014;11:11220-48.
704 [67] Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P.
705 Electronic cigarettes for smoking cessation. The Cochrane Database of Systematic
706 Reviews. 2016:CD010216.
707 [68] Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L. E-cigarettes
708 and smoking cessation: evidence from a systematic review and meta-analysis. PLoS
709 one. 2015;10:e0122544.
710 [69] Khoudigian S, Devji T, Lytvyn L, Campbell K, Hopkins R, O'Reilly D. The
711 efficacy and short-term effects of electronic cigarettes as a method for smoking
712 cessation: a systematic review and a meta-analysis. International Journal of Public
713 Health. 2016;61:257-67.
714 [70] Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and
715 clinical settings: a systematic review and meta-analysis. The Lancet Respiratory
716 Medicine. 2016;4:116-28.
717 [71] Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in
718 the European Union: analysis of a representative sample of 27 460 Europeans from
719 28 countries. Addiction (Abingdon, England). 2016.
720 [72] West R, Shahab L, Brown J. Estimating the population impact of e-cigarettes on
721 smoking cessation in England. Addiction. 2016;111:1118-9.
722 [73] Royal College of Physicians. Nicotine without smoke: Tobacco harm reduction
723 Accessed 01/09/16 at [https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-](https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0)
724 [smoke-tobacco-harm-reduction-0](https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0).
725 [74] Rose A, Fillion KB, Eisenberg MJ, Franck C. Electronic cigarettes: A comparison
726 of national regulatory approaches. Can J Public Health. 2015;106:e450-3.
727 [75] European Commission. European Union (2016) EU Tobacco Directive. Revision
728 of the Tobacco Products Directive. Accessed 01/09/16 at
729 http://ec.europa.eu/health/tobacco/products/revision/index_en.htm
730 [76] Medicines and Healthcare Products Regulatory Agency. e-Voke 10mg electronic
731 inhaler, PL42601/0003 e-Voke 15mg electronic inhaler PL42601/004. Accessed
732 01/09/16 at
733 [http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con475307.p](http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con475307.pdf)
734 [df](http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con475307.pdf).
735 [77] Munafo M. What a drag. New Sci. 2016;229:28-9.
736 [78] Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong HH, et
737 al. Electronic nicotine delivery systems: international tobacco control four-country
738 survey. American journal of preventive medicine. 2013;44:207-15.
739 [79] Etter JF, Bullen C, Flouris AD, Laugesen M, Eissenberg T. Electronic nicotine
740 delivery systems: a research agenda. Tob Control. 2011;20:243-8.

741