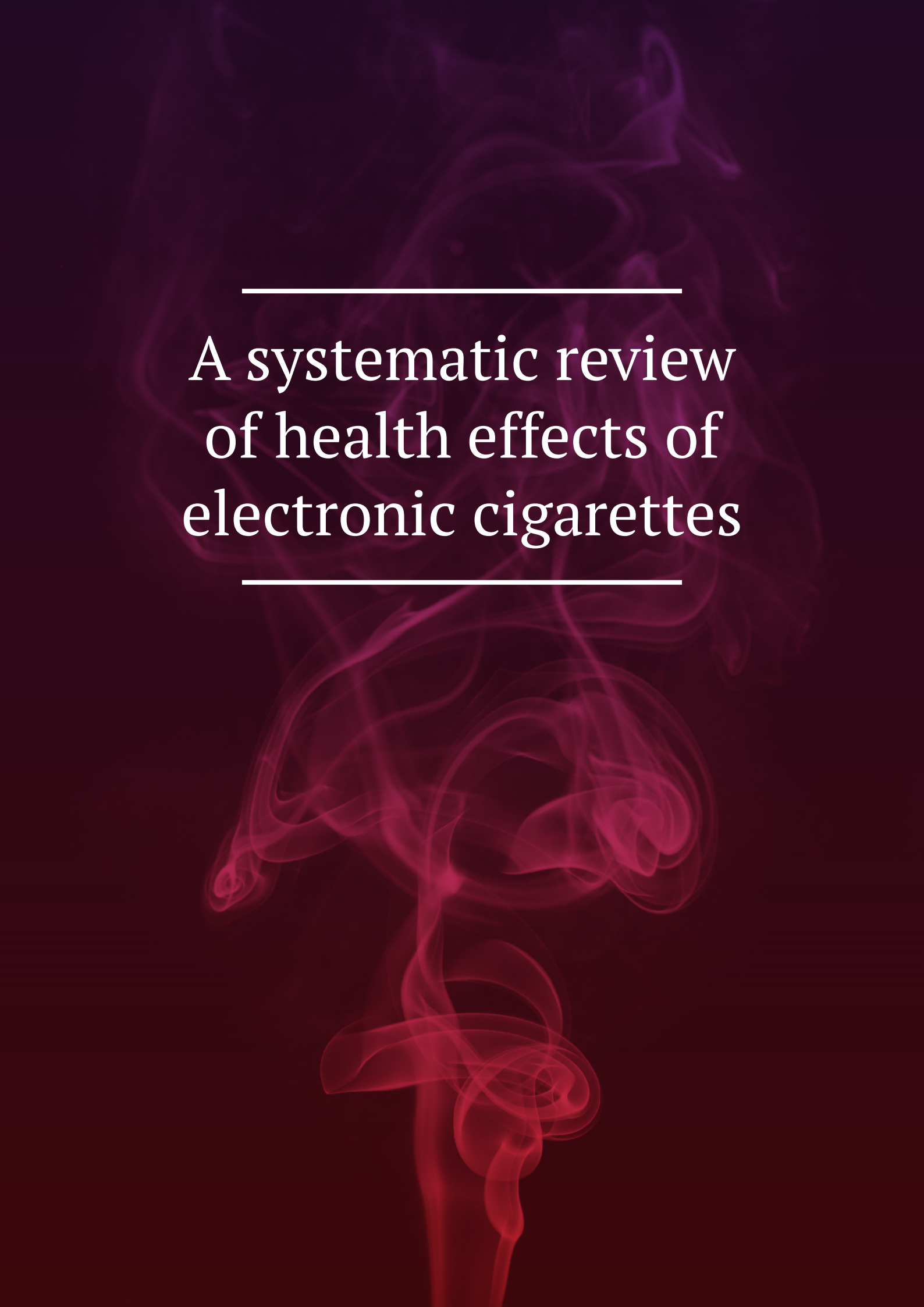

A systematic review of health effects of electronic cigarettes

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Ethical approval

Not required.

Contents

Boxes

Abbreviations

FeNO	fractional exhaled nitric oxide
NNK	nicotine-derived nitrosamine ketone
NNN	N-nitrosonornicotine
PAHs	polyaromatic hydrocarbons/polycyclic aromatic hydrocarbons
PM	particulate matter
$PM_{2.5}$	particulate matter less than 2.5 micrometres in diameter
TSNAs	tobacco-specific nitrosamines
VOC	volatile organic compound
WHO	World Health Organization

1. Methods

1.1 Search

A search was carried out in PubMed, EMBASE and CINAHL (Annex 1).

Keywords were "electronic cigarette" or "e-cigarette" or "electrically heated cigarette" or "ENDS and cigarette" or "electronic nicotine delivery system" or "electronic nicotine delivery device" or "e-liquid". The search was performed several times to update the evidence (Annex 1).

1.2 Exclusion criteria

Recommendations, expert statements, reviews, technical reports and other non-original papers were excluded, as were papers on smoking cessation, abuse liability, nicotine levels, withdrawal symptoms, poisonings (intentional and unintentional), prevalence, attitudes and beliefs.

1.3 Eligibility criteria

Original articles or abstracts on electronic cigarettes (or e-cigarettes) of any topic relevant to health, published before 26 November 2015, were considered eligible. Additionally, a few studies published after that date, found accidentally, have been included. We included studies in any language except a paper in Japanese by Ohta et al. *(1)* that we assumed to be the same paper as that by Uchiyama et al. *(2)*. Almost all studies were peer-reviewed. A few risk modelling studies have been included as they are based on original findings and typically are presented for decision-makers or the media.

1.4 Study selection

The first part of the search was performed by two authors – Charlotta Pisinger (CP) and Dr Med. Martin Døssing – who both read and discussed the articles *(3)*. The second updated search was performed by CP only.

First we screened the titles. After reading the abstract, papers that did not report a health-related topic were rejected. Agreement of the authors was necessary to exclude a paper (first review). Papers on adverse events were included even if the main focus of

the article was, for example, smoking cessation. Then, we excluded duplicates and papers describing the same study population or did not report original data. Full documents were obtained for the final inclusion. Additionally, we looked through the reference lists of the articles for missed papers and we investigated reports for overlooked papers. Finally, we included grey literature that we found accidentally or that others sent to us.

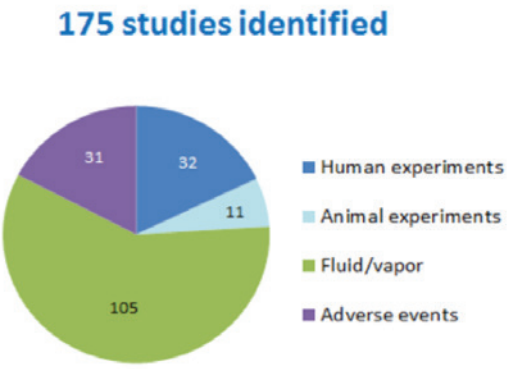
We investigated all papers for conflict of interest, funding and workplace of authors. If in doubt, we contacted the authors and asked about funding and conflict of interest or searched the Internet.

2. Overview of the studies

2.1 Topics

We identified 175 studies – 99 more than in Pisinger and Døssing *(3)* – the majority (n=105) of these investigating the content of e-cigarette fluid and vapour and/or performing experiments with cells, exposing them to e-cigarette fluid, vapour or extract of vapour. Thirty-one studies reported on adverse events, 32 were human experimental studies and 11 were animal experimental studies. Four papers investigated effects on both cells and animals *(4–7)*. These papers are described in both sections but they only count as one paper.

Figure 1. Categorization of 175 studies identified



2.2 Conflicts of interest

In 34% of the studies the authors had stated a conflict of interest or described funding, or reviewers found a non-declared conflict of interest (for details, see footnotes in Tables 1 to 4 and Annexes 2 to 5). Most of the studies with conflict of interest were funded or otherwise supported by manufacturers of e-cigarettes, but many authors had also been consultants for manufacturers of medicinal smoking cessation therapy or received research grants from them. In several cases – for example, when an author had previously received lecture fees, research grants or travel expenses from a manufacturer *(e.g. 8–10)* no major influence on the actual study is expected. However, it is important

to note that in recent years the tobacco industry, a manufacturer of e-cigarettes, has published 17 out of the 60 studies with conflict of interest (28%), primarily studies investigating content of fluid. History has shown that we should be very careful in trusting results of studies influenced by the tobacco industry *(11–13)*. Therefore, in-text citations for these studies are marked with an asterisk (*) to alert the reader. Studies funded by ecigarette manufacturers or performed in collaboration with the ecigarette industry are labelled with a chevron (^).

3. Presentation of results

3.1 Content of fluid and vapour

(See Table 1 for overview of studies; for details see Annex 2.)

General findings. Most studies have used conventional cigarettes as reference and investigated presence or concentrations of substances that are known to be harmful in conventional cigarettes. Some of the studies performed in vitro experiments with cells exposed to fluid or vapour, for example to test for cytotoxicity or viral defence. These studies are also mentioned in this section. Many studies found that the product labels did not show the ingredients (e.g. flavours, solvent, nicotine) or that the declaration did not correspond with the concentrations found (e.g. of nicotine).

Glycols.[1] These are the major components in e-cigarettes. High amounts of propylene glycol (also called 1,2-propandiol) and glycerine were found in studies testing for these substances *(8, 14–16, 17*, 18, 19, 20*, 21, 22)*.

Nicotine.[2] Several studies found a large variability in nicotine concentrations across brands, labels, cartridges and refill fluids *(14, 15, 22–32)*, while others found smaller variability *(24, 33, 34, 35*, 36)*. "Nicotine-free" products were found to contain nicotine *(14, 15, 25, 31, 37)*, sometimes in high concentrations, while others found that nicotine content corresponded to labels on the bottles *(8, 16, 38^)*. There were also differences across countries *(24)*. Two studies found the concentration of nicotine in e-cigarette vapour to be much lower than in tobacco smoke *(20*, 39)*. A study found that in products labelled with strength of nicotine ("low", "medium" or "high"), the actual nicotine concentration varied greatly across brands and could be 3 times higher in one product compared to another with the same strength *(40)*.

Particles. There is no safe level of particulates. Smaller particulate matter less than 2.5 micrometres in diameter ($PM_{2.5}$) is particularly harmful *(41)*. Particle pollution can

1 Regarding potential health consequences, see section 3.7.

2 Regarding potential health consequences, see section 3.7.

increase the risk of heart disease, lung cancer and asthma attacks and can interfere with the growth and work of the lungs. One study found that e-cigarette liquids generate many nanoparticles, up to 3000 times more than found in ambient air *(42)*. Some studies found that e-cigarettes and conventional cigarettes produce aerosols with comparable particle sizes *(43, 44*, 45)* with fine and ultrafine particles in vapour *(18)*, but one study found particles from e-cigarettes much smaller *(46*)* and another much bigger *(47)* than in tobacco smoke.

A study showed that the vapour size distribution alters in the human lung and leads to exhalation of smaller particles *(19)*. Regarding particle concentration, two studies found extremely high doses deposited in a human lung model *(48, 49)*; one found it to be double of the dose from tobacco smoke *(49)*, two studies found it to be the same as in tobacco smoke *(43, 44*)*, while three found the concentration to be lower, up to an order of magnitudes lower, than in tobacco smoke *(18, 39, 50)*, and one study found that conventional cigarettes produce more particles initially, but particle counts converge to a level comparable to the condensed vapour *(45)*. A simulation model found that e-cigarette droplets tend to grow larger in maximum size than conventional cigarette particles in the typically highly humid environment of the respiratory system *(51*)*. Two "real-life" condition studies found that vaping e-cigarettes with nicotine showed only marginal particulate matter production in indoor air, while it was much higher after vaping e-cigarettes without nicotine *(30, 52)*. The half-life of vapour was found to be very short – measured in seconds – due to rapid evaporation *(47)*. A study also showed that deposited aerosol mass varied greatly from repeat experiments with all tested products *(53*)*.

Metals. The heavy metals cadmium, mercury, lead and arsenic appear in the World Health Organization list of 10 chemicals of major public concern due to potential toxicity *(54)*. A study found that concentrations of lead and chromium in vapour were within the range of conventional cigarettes, while nickel was up to 100 times higher than in conventional cigarettes *(55)*, and one puff of e-cigarette vapour contained numerous metal particles, mainly tin, silver, nickel and aluminium *(55)*. One study found more than 6 times higher content of copper in vapour than in conventional cigarette smoke *(56)*, another found lead content in e-cigarette liquids to be in the same order as in conventional cigarettes *(57)*, and a third found concentrations of cadmium, lead, nickel and arsenic considerably lower than in tobacco smoke but chromium concentrations comparable to smoke *(22)*. Tin, chromium and nickel were found as nanoparticles. A "real-life" study showed a twofold increase of aluminium in indoor air after vaping *(30)*. One study found cadmium, nickel and lead in almost all vapours of 12 brands but the amounts of toxic metals were low, comparable with amounts contained in a nicotine inhaler (nicotine replacement therapy) *(9)*. Another study compared the levels of metals in these studies *(9, 55)* with regulatory standards and concluded that the levels of metals are unlikely to generate significant adverse health effects for smokers switching to ecigarette use *(58)*. Finally, some studies found metals at lower limits than detection in fluid *(38^)* and vapour *(20*)*, and trace quantities of mercury in vapour *(46*)* and of metals in indoor air *(59*)*.

Tobacco-specific nitrosamines (TSNAs). These are probably the most important compounds associated with negative health effects in tobacco cigarettes, due to a combination of abundance and strong carcinogenicity *(60, 61)*. N-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK) are classified as IARC group 1 carcinogens.[3]

Some studies found high maximum concentrations of total TSNAs in the vapour of most *(9)* or almost all fluids *(62)*. One study found that the concentrations of carcinogenic TSNAs were up to 400 times lower in vapour than in smoke but that vapour concentrations of TSNAs are sufficiently high in some cases to give an elevated risk of tumour development *(22)*. Other studies found that carcinogenic TSNAs were present in vapour at lower levels than tobacco smoke *(50)*, and that TSNAs were present in all samples but the levels of TSNAs and nitrate in e-cigarette liquids were one to two orders of magnitude lower compared to tobacco products *(35*)*. Other studies found trace levels of TSNAs *(20*, 63, 64*, 65*, 66)*, or of TSNAs not present *(16, 59*)*. Some studies detected TSNAs with no or weak carcinogenic effect or no TSNAs in the fluid *(8, 14, 30, 32, 40)*.

Box 1 summarizes the findings on the identified content of fluids and vapour (glycols, nicotine, particles, metals, TSNAs).[4]

Box 1. Identified content of fluids and vapour: glycols, nicotine, particles, metals, TSNAs

Glycols are the major components:

- high amounts of propylene glycol and glycerine

Nicotine. Several studies found a large variability in nicotine concentrations across brands, labels, cartridges, refill fluids – others found smaller variability

Particles. Many studies find particles in vapour:

- particle size: conflicting results:
  - fine and ultrafine particles
  - nanoparticles
  - comparable particle sizes as in tobacco smoke
  - much smaller particles than in tobacco smoke
  - much bigger particles than in tobacco smoke
  - alters in the human lung and leads to exhalation of smaller particles
- particle count: conflicting results:
  - up to 3000 times more nanoparticles than ambient air
  - double the dose from tobacco smoke
  - same as in tobacco smoke

3 Classification of the International Agency for Research on Cancer: http://monographs.iarc.fr/ENG/Classification/.

4 In general, studies with severe conflicts of interest have findings indicating little or no harm to health.

– up to an order of magnitudes lower than in smoke – tobacco smoke produce more particles initially, but particle counts converge to a level comparable to the condensed vapour – marginal particulate matter production in indoor air after vaping of product with nicotine, while it was much higher after vaping without nicotine
Metals. Lead, chromium, tin, silver, nickel, copper, aluminium, cadmium and mercury identified in several studies: • presence: conflicting results: – found in almost all vapours – found as nanoparticles • concentrations: conflicting results: – up to 100 times higher than in conventional cigarettes – 6 times higher content in vapour than in smoke – within the range of conventional cigarettes/in smoke – comparable with amounts contained in a nicotine inhaler – trace quantity – considerably lower than in smoke – at lower limits than detection
Tobacco-specific nitrosamines (TSNAs). Total TSNAs, carcinogenic TSNAs and TSNAs with weak carcinogenic effect identified: • presence: conflicting results: – all samples – most/almost all samples – not present • concentrations: conflicting results: – high maximum concentrations – lower levels than tobacco smoke – trace level – one to two orders of magnitude lower compared to tobacco products – up to 400 times lower in vapour than in smoke

Carbonyls. These are potential human carcinogens and toxicants *(67)*. In one study, formaldehyde (carcinogenic, group 1), acetaldehyde (possibly carcinogenic, group 2B) and acrolein (toxic and a strong irritant to the skin, eyes and nasal passages) were detected in the vapours of almost all e-cigarettes *(2, 9, 68)*; in another study, formaldehyde was detected in all the > 40 samples *(66)*. A study found five carbonyl compounds in the refill solutions, including formaldehyde, acetaldehyde acetone, propionic aldehyde and butyraldehyde. Acetone was found in many samples at relatively high concentrations *(40)*. Also, a study on flavoured e-liquids found that totals of flavour chemicals were high in general, and the concentrations of some flavour chemicals were sufficiently high to be of toxicological concern due to high aldehyde levels *(69)*. A study found that some samples had extremely high concentrations of

carbonyls *(2)*. High levels of carbonyls were found to be produced even in e-cigarettes without nicotine *(68)*. A study found that the concentration of formaldehyde can be up to 3 times higher in e-cigarette vapour than in tobacco smoke *(22)*. In this study, two apparently identical vaporizers made by the same manufacturer and filled with the same e-liquid yielded formaldehyde concentrations in vapour that differed by a factor of > 25, indicating that the concentration of formaldehyde in vapour depends on the vaporizer *(22)*. Another study found exposure to formaldehyde comparable with smoking *(9)*, as was also the case with vapour from high-voltage devices *(10)*. A study also found high levels of "hidden formaldehyde" (formaldehyde-releasing agents) by use of high-voltage devices; formaldehyde hemiacetal was estimated to be 5 times as high as in conventional cigarette smoke *(70)*. However, a paper concluded that even a low-voltage e-cigarette device can obtain the power of a high-voltage device with different ohmic values, with risk of dissemination of formaldehyde *(71)*. The highest levels of carbonyls were observed in vapours generated from propylene glycol-based solutions *(10)* or in the second half of a vaping period, indicating overheating of wires *(37)*. Direct dripping of e-liquid due to high temperatures attained in the atomizer may also expose users to increased volatile aldehyde levels relative to conventional e-cigarettes and even relative to conventional cigarettes, for a given nicotine yield *(72)*. One study concluded that most carbonyls were detected at low concentrations in vapour, with the exception of acetone, formaldehyde and acetaldehyde *(50)*. In a study, sucrose was found in all samples of e-liquids – this may be a source of aldehydes *(73)*. Formaldehyde, acetaldehyde and acrolein were also found in vapour in other studies *(22, 66)*, in comparison with conventional cigarettes at concentrations approximately 1/10 *(65*)* and 1/100 or less of those in smoke *(20*, 28)*. One study found acrolein in vapour at a level comparable to mainstream cigar smoke *(74)*, while other studies found acrolein in vapour at low levels *(22, 38^)*, and acetaldehyde *(38^)* and formaldehyde at low levels *(38^, 64*)*. The same author presented similar findings in another study, but in a newer version of the same abstract, acetaldehyde and acrolein were not mentioned *(46*)*. Formaldehyde, acetaldehyde, acrolein and siloxanes were found in the aerosol profiles in another study; however, these compounds were never present in the liquids in this study *(75)*. On the other hand, acetaldehyde and formaldehyde were detected in liquids in most samples in another study, at trace levels *(35*)*. Formaldehyde was detected above the limit of quantification in indoor air, but was almost similar to background levels *(76*)*. Finally, one study found that the release of formaldehyde was below the limit of detection *(19)*. It is possible to reduce the levels of harmful substances: a study found that after a revised formulation the levels of acetaldehyde and acrolein decreased, or were not measurable *(77)*.

Volatile organic compounds (VOCs). Long-term exposure to high levels of VOCs increases the risk of cancer and of damage to the liver, kidney and central nervous system *(78)*. A study found 11 VOCs among the 15 VOCs analysed, among them benzene (carcinogenic, group 1), styrene and ethylbenzene (group 2B carcinogens), and toluene *(40)*. Other studies also identified toluene *(39)* and p,m-xylene in almost all vapours *(9)*. It is possible to reduce the levels of harmful substances: a study found that after a revised

formulation the levels of benzene decreased, or were not measurable *(77)*. Benzene, toluene and 2,5-dimethylfuran were also found in vapers' exhaled breath – but smokers had a much higher burden of VOCs than vapers *(79)*. A study investigating fluid, vapour and aerosol found that all of the types of e-cigarette samples generally contained little or none of most of the target VOCs, except for acetic acid *(80)*. In other studies, the concentrations were below the level of detection or quantification or existed at trace levels only in fluid *(50)* and vapour *(20*)*.

Hydrocarbons and polycyclic aromatic hydrocarbons (PAHs). Several PAH compounds, such as benzo(a)pyrene (carcinogenic, group 1), are classified as probable human carcinogens *(81)*. A study found that PAHs in indoor air increased by 20% after vaping *(30)*, and another study found high amounts of hydrocarbons in several products from one brand, in particular alpha-pinene and beta-pinene, probably present in the flavours *(66)*. On the other hand, other studies found either no PAHs in fluid *(14, 16)*, or that most PAHs were below detection level *(50, 64*)* or as traces only *(40, 65*)*, in vapour *(20*)* and indoor air *(59*)*.

Phenols. Phenol is highly irritating to the skin, eyes and mucous membranes after acute inhalation or dermal exposures, and is toxic via oral exposure *(82)*. A study found five phenolic compounds in refill solutions, with total concentrations below 5 micrograms per gram (µg/g); levels differed dramatically among brands. No direct relationships were found between the levels of nicotine and the level of phenols, implying that phenolic compounds might originate from similar ingredients within the materials used by particular brands, such as flavours, rather than from the nicotine source per se *(40)*. It is possible to reduce the levels of harmful substances: a study found that after a revised formulation the levels of cresols decreased, or were not measurable *(77)*. In one study, total phenols were found to be present at levels 1200 times lower in all ecigarette liquids than in conventional cigarette smoke *(35*)*, and phenols were found at trace levels in vapour in another study *(20*)*. An experimental study found that content of total phenols in exhaled e-cigarette aerosols was not distinguishable from content in exhaled breath blanks *(17*)*.

Other measures. A recent toxicity assessment based on 42 samples (15 brands) concluded that none of the products were totally free from potentially toxic compounds and that a minority of liquids, especially those with flavourings, showed particularly high ranges of chemicals, causing concerns about their potential toxicity in case of chronic oral exposure *(66)*. Other studies found that half of the liquids analysed contained up to 5 times the maximum amount of impurities specified in the European Pharmacopoeia *(8)*, and that a number of the tested products contained tobacco alkaloids at concentrations that exceeded United States Pharmacopeia limits for impurities in nicotine used in pharmaceutical and food products *(29)*.

A study tested for several of the above-mentioned harmful and potentially harmful substances but a further 150 substances were detected, many of them flavourants *(22)*.

Diacetyl, a flavourant associated with respiratory disease ("popcorn lung") when inhaled, and acetyl propionyl were found in a large proportion of sweet-flavoured e-cigarette liquids, with many of them exposing users to "higher-than-safety" levels *(22, 83, 84)*.

The highly toxic diethylene glycol was found in trace amounts in two studies *(22, 32)* but not in other studies *(8, 28)*. One study found potentially harmful additives, such as coumarin *(37)*. Products advertised as containing tadalafil contained amino-tadalafil *(25, 31)*. Products advertised as containing rimonabant contained rimonabant plus an oxidative impurity of rimonabant *(25)*. One study found significant amounts of silicate beads in the aerosol *(55)*. Most nicotine-containing e-cigarettes have a basic pH > 9, which seems to influence the doses of nicotine delivered *(85)*. One study found solanesol, one of the major trisesquiterpenoid alcohols in tobacco, demonstrating that tobacco-related impurities are relevant when evaluating refill solutions *(40)*.

Primary aromatic amines were found at trace levels only in vapour *(20*)*. Tobacco industry studies with risk assessment models have been performed *(86*, 87*)*.

Problems regarding refilling process. Fluids in cartridge reservoirs leak out of most brands and there are difficulties in assembling and disassembling e-cigarettes without coming into skin contact with the refill liquid *(88)*.

Box 2 summarizes the findings on the identified content of fluids and vapour (glycols, nicotine, particles, metals, TSNAs).[5]

Box 2. Identified content of fluids and vapour: carbonyls, VOCs, hydrocarbons and PAHs, other measures

Carbonyls. Potential human carcinogens formaldehyde, acetaldehyde and acrolein detected in several studies:

- presence: conflicting results:
  - all the > 40 samples
  - almost all samples
  - not found
- concentration: conflicting results:
  - extremely high concentrations
  - high levels of carbonyls produced even in e-cigarettes without nicotine
  - 3 times higher in vapour than in tobacco
  - level comparable to mainstream cigar smoke
  - approximately 1/10 of those in smoke
  - 100/1 or less of those in smoke
  - low/trace levels

5 In general, studies with severe conflicts of interest have findings indicating little or no harm to health.

- almost similar to background level
- below the limit of detection

- special conditions with high concentrations:
  - e-cigarettes with flavours
  - vaporizer type
  - vapour from high-voltage devices
  - propylene glycol-based solution
  - second half of a vaping period (overheating)
  - direct dripping (overheating)

Volatile organic compounds (VOCs). Harmful substances as benzene (carcinogenic), toluene and 2,5-dimethylfuran (potentially neurotoxic) were identified:

- presence: conflicting results:
  - in almost all vapours
  - in little/none
  - Found in the aerosol but not in liquid
- concentrations:
  - smokers had much higher burden of VOCs
  - below the level of detection/quantification or trace level only

Hydrocarbons and polycyclic aromatic hydrocarbons (PAHs). These include benzo(a)pyrene, a probable human carcinogen:

- presence: conflicting results:
  - no PAHs
  - in several products from one brand, in particular alpha-pinene and beta-pinene, probably present in the flavours
- concentration: conflicting results:
  - high amounts of hydrocarbons
  - most PAHs were below detection level or as traces only

Other measures

- none of the products were totally free of potentially toxic compounds
- half of the liquids analysed contained up to 5 times the maximum amount of impurities specified in the European Pharmacopoeia
- diacetyl and acetyl propionyl, chemicals associated with respiratory disease when inhaled, were found in a large proportion of sweet-flavoured liquids at "higher-than-safety" levels
- primary aromatic amines (suspected carcinogenic) were found at trace levels
- phenols present at trace levels
- potentially harmful additives such as coumarin identified
- significant amounts of silicate beads in the aerosol

3.2 Experiments with cells exposed to fluid, vapour or vapour extract: in vitro studies

(See Table 1 for overview of studies; for details see Annex 2.)

Cytotoxicity. Several studies have found e-cigarettes to be cytotoxic. An in vitro study demonstrated that menthol additives have a harmful effect on human periodontal ligament fibroblasts, causing a highly significant reduction of cell migration *(89)*. One study found that several samples were highly cytotoxic to human embryonic and mouse neural stem cells, and cytotoxicity was due to flavours. Cinnamon had a strong cytotoxic effect *(90)*, a finding that was supported by another study, though a less strong effect was found on cardiomyoblasts *(91)*. The latter study also found that that cytotoxicity was mainly observed in samples where tobacco leaves were used in production, and all vapour extracts were significantly less cytotoxic compared to conventional cigarette smoke extract *(91)*. Findings from another study indicated that e-cigarette fluids induced early and late apoptosis, with a major extent in nicotine-treated samples, but present anyway in the samples treated with nicotine-free fluids *(92)*. E-fluid containing tin particles was found to be cytotoxic on human pulmonary fibroblasts *(55)*. A study on human lung epithelial cells found toxicological effects of both ecigarette vapour and the pure carrier substances; cell viability was approximately 5 times higher than in cells exposed to conventional cigarette smoke *(93)*. Another study found that both e-cigarette and conventional cigarette smoke extracts reduced human alveolar cell proliferation, though conventional cigarette smoke exhibited effects at lower concentrations *(4)*. However, other studies found that vapour from only one out of 21 ecigarette fluids had cytotoxic effects on cultured murine fibroblasts *(94^)*, that the tested ecigarette was not cytotoxic *(95*)*, and that conventional cigarettes had significantly higher cytotoxicity *(94^, 95*, 96, 97)*. Finally, one study concluded that e-cigarette liquids and vapour do not produce any meaningful toxic effects in four widely applied in vitro test systems, in which the conventional cigarette smoke preparations are markedly cytotoxic and genotoxic *(98)*.

Inflammation/oxidative stress. Many studies have found stress and inflammation in cells exposed to e-cigarettes. A recent study has shown that e-cigarette vapour exposure leads to aggresome formation via proteostasis and autophagy impairment and serves as a mechanism to induce inflammatory oxidative stress, apoptosis, and senescence that can be ameliorated by an autophagy inducer. Thus, it suggests the mechanisms by which e-cigarette exposure can potentially induce chronic obstructive pulmonary disease *(99)*. Other studies found that vapours induce the release of cytokines and pro-inflammatory mediators *(96)*, and e-cigarette components exhibit oxidants and reactive oxygen species reactivity similar to used conventional cigarette filters, and oxidants and free radicals in e-cigarette aerosols were similar to oxidant reactivity in conventional cigarette smoke *(56)*. Findings from another study indicated that e-cigarette fluids induce oxidative stress, with a major extent in nicotine-treated samples, but present anyway in the samples treated with nicotine-free fluids *(92)*. This is in concordance with a study of Kupffer cells exposed to e-cigarette vapour

extract showing inflammatory response, oxidative stress production and cytokine release, comparable to conventional cigarette exposure *(100)*, and a study using human, rat and mice bronchial and lung endothelial and lung-derived microvascular cells that concluded that soluble components of e-cigarettes, including nicotine, cause dose-dependent loss of lung endothelial barrier function, which is associated with oxidative stress and brisk inflammation *(7)*. A study using human innate immune cells found that e-cigarette exposure causes an inflammatory response from neutrophils and macrophages, and that the effects were similar to those caused by conventional cigarettes *(101)*. Other studies found that e-cigarette inhalation has an impact on cellular oxidative stress, redox imbalance and lung inflammation *(5)*. The latter study also showed that nicotine was probably not a sole contributing factor in increased oxidants and reactive oxygen species reactivity, and that that the state of the heating element after activation affects the generation of oxidants and reactive oxygen species *(5)*. "Dripping" e-liquids to produce e-cigarette vapour delivers a larger dose of oxidants and reactive oxygen species to consumers and there are at least two possible sources of oxidants and reactive oxygen species released from ecigarettes: from activation of the heating element, and from the process of vaporizing e-liquids *(5)*. A study using human lung epithelial cells found that oxidative stress was approximately 5 times lower than in cells exposed to conventional cigarette smoke *(93)*, and another study suggested that the intestinal epithelium inflammatory response is not altered by exposure to vapour from ecigarettes *(102)*. A study using young healthy human airway epithelial cells showed that e-cigarette fluid promotes pro-inflammatory cytokine IL-6 production and human rhinovirus infection *(103)*. Human lung fibroblasts exposed to e-cigarette liquid showed cell stress and other phenotypic abnormalities that were further exacerbated by nicotine *(5)*, and vacuolization and cell enlargement following treatment with 5% e-liquid containing nicotine was most similar to fibroblasts treated with 1% conventional cigarette smoke extract *(5)*.

Other findings. Human bronchial cells that contained mutations found in smokers at risk of lung cancer were grown in a culture medium that had been exposed to vapour. The researchers found that cells exposed to high-nicotine vapour showed a similar pattern of gene expression to those exposed to tobacco smoke *(104)*. A study in human embryonic stem cells also showed dysregulation of gene expression indicating a negative effect of ecigarette use on heart development *(6)*. Another study found that at biologically relevant doses, vaporized e-liquids induced increased DNA strand breaks and cell death, and decreased clonogenic survival in both normal epithelial and head and neck squamous cell carcinoma cell lines independently of nicotine content *(105)*. Exposure to e-cigarette vapour also decreased the expression of cardiac transcription factors in cardiac progenitor cells, suggesting a persistent delay in differentiation *(6)*. Also, in definitive human cardiomyocytes there was a reduced expression of sarcomeric genes. E-cigarette fluid exposure had immediate and profound adverse effects on the metabolomic state of primary human bronchial epithelial cells similar to those seen with conventional cigarette smoke condensate *(106)*.

A study showed that platelet aggregation was enhanced when platelets were exposed to ecigarette vapour extract, and for the formulations with the highest concentration of nicotine, this enhancement mirrored the effects of mainstream and sidestream tobacco smoke extracts *(107)*. Also, platelets were more likely to participate in coagulation-based reactions, suggesting an enhancement of the coagulation cascade, indicating increased risk of cardiovascular disease *(107)*.

Box 3 summarizes the effects observed in experiments with cells: in vitro studies (cytotoxicity, inflammation/oxidative stress, other findings).[6]

Box 3. Effects observed in experiments with cells (in vitro studies)

Cytotoxicity. Several studies have found e-cigarettes to be cytotoxic:

- compared with tobacco smoke:
  - cell viability approximately 5 times higher than in cells exposed to smoke
  - conventional cigarettes had significantly higher cytotoxicity
- cytotoxicity found to be due to flavours in several studies
- highly significant reduction of cell migration
- no meaningful cytotoxic or genotoxic effects

Oxidative stress and inflammation. Many studies have found oxidative stress and inflammation in cells:

- compared with tobacco smoke:
  - most studies: comparable to conventional cigarette exposure
  - one study: oxidative stress approximately 5 times lower than when exposed to smoke
  - one study: intestinal epithelium inflammatory response not altered by exposure
- aggresome formation via proteostasis/autophagy impairment
- release of cytokines and pro-inflammatory mediators
- promotes pro-inflammatory cytokine IL-6 production
- the state of heating element affects generation of oxidants/reactive oxygen species
- more in nicotine-treated samples but also present in nicotine-free fluids
- "dripping" method delivers a larger dose of oxidants/reactive oxygen species

Other findings:

- a similar pattern of gene expression to cells exposed to tobacco smoke
- increased DNA strand breaks and cell death, and decreased clonogenic survival in both normal epithelial and head and neck squamous cell carcinoma cell lines
- dysregulation of gene expression indicating a negative effect on heart development
- immediate and profound adverse effects on the metabolomic state, similar to those seen with smoke condensate
- enhanced platelet aggregation, platelets more likely to participate in coagulation-based reactions
- promotes human rhinovirus infection
- dose-dependent loss of lung endothelial barrier function

6 In general, studies with severe conflicts of interest have findings indicating little or no harm to health.

3.3 Human experimental studies

(See Table 2 for overview of studies; for details see Annex 3.)

General findings. Most studies included smokers as volunteers and compared with a reference, mostly own-brand conventional cigarettes. All experimental studies report short-term exposure only, typically a few minutes of exposure to vapour.

Adverse events. These were very similar to those reported in studies reporting adverse events (Annex 3). There was low reporting of adverse events in regular users who were e-cigarette naive before study start, with the most frequent being light-headedness, throat irritation, dizziness and cough *(108^, 109, 110^)*.

Pulmonary system. A single session of e-cigarette use in e-cigarette naive smokers, approximating nicotine exposure of one conventional cigarette, induced significant inhibition of cough reflex sensitivity, probably due to nicotine *(111)*. Other studies in e-cigarette naive smokers found increased airway resistance *(112–114)* and a concomitant decrease in specific airway conductance *(113)*, and an increase in impedance and overall peripheral airway resistance *(114)*, effects that are reminiscent of those seen with tobacco smoking. Also, the same particle dose was received as with smoking and vaping *(112)*. Two studies found immediate reductions in exhaled nitric oxide, similar to smoking *(112, 114)*, and increased fractional exhaled nitric oxide (FeNO) *(30)*, while another study found a decrease in FeNO *(115)*. A study including both healthy volunteers and patients with asthma and chronic obstructive pulmonary disease also showed that 10 minutes of vaping caused immediate significant airway obstruction *(116)*, which is in contrast to a retrospective review finding objective and subjective improvements in asthma outcomes *(117)*. A study found that short-term vaping by e-cigarette naive users of flavoured e-cigarettes resulted in significant decrease in flow when 75% of forced vital capacity had been exhaled *(118)*. Another study found that short-term usage was associated with increased flow resistance, even though spirometry-assessed lung function was deemed normal *(119)*. Passive, but not active, vaping of one e-cigarette resulted in short-term lung obstruction, indicating insufficient inhalation by e-cigarette naive smokers *(119)*. The last study found that short-term vaping of e-cigarettes generated non-significant decrease in lung function, approximately half of what was seen in smoking *(120)*.

Cardiovascular system. Some studies in e-cigarette naive smokers found that short-term vaping resulted in increased heart rate *(115, 121–125, 126*)*, an elevation in diastolic blood pressure *(121–123, 127)* comparable to the increase caused by smoking *(126*)*, and a decrease in oxygen saturation *(115)*. Other studies found no increase in heart rate *(110^, 128, 129)* or in blood pressure *(110^)*, but an increase in oxygen saturation *(110^)*. One study found no negative effect on elasticity and stiffness of ascending aorta *(130)*. Active and passive vaping in e-cigarette naive smokers did not influence the complete blood count *(131)*. One study using experienced e-cigarette users found no effect on cardiac function *(127)*. One small study suggests

that nicotine, when inhaled via e-cigarette, does not impair the cerebral pressure–flow relationship *(132)*.

Cognitive function. Two studies found improved time-based but not event-based prospective memory *(133^)* and improved nicotine withdrawal impaired concentration/memory *(134^)*; these improvements were associated with cessation of conventional cigarette smoking.

Toxicity. Urinary toxicant and carcinogen metabolites were found to be significantly lower in current e-cigarette users than in conventional cigarette smokers, but a few e-cigarette users had higher-than-expected levels of total NNAL (metabolites of the tobacco-specific nitrosamine and lung carcinogen); lower than in smokers but higher than when exposed to second-hand smoking *(135)*. Studies also found a metabolite of the pyrolysis product acrolein in urine, after vaping e-cigarettes with nicotine *(30, 136)*. The latter found that in dual users e-cigarette use significantly reduced exposure to carbon monoxide and acrolein because of a significant reduction in conventional cigarette intake *(136)*. Another study found benzene, toluene and 2,5-dimethylfuran in vapers' exhaled breath, but smokers had a much higher burden of VOCs than vapers *(79)*. An experimental study with experienced vapers found that e-cigarettes produce high levels of formaldehyde, acetaldehyde and acrolein only in dry puff conditions (the levels were increased by 30 to 250 times), in which the liquid overheats, causing a strong unpleasant taste; authors assume that vapers will avoid dry puff conditions *(137)*.

Other. A marker of oxidative stress in exhaled breath was found to be significantly increased by vaping but less than by smoking *(138)*.

Box 4 summarizes the effects observed in human experimental studies (adverse effects, toxicity, pulmonary system, cardiovascular system, other findings).[7]

Box 4. Effects observed in human experimental studies

Adverse events. Mild:

- most frequent: light-headedness, throat irritation, dizziness, cough

Toxicity. Toxicants and carcinogen metabolites found in urine of vapers:

- concentrations:
  - significantly lower than in smokers
  - high concentration of NNAL (carcinogenic) found in some vapers
  - high formaldehyde, acetaldehyde, acrolein only in dry puff conditions
- vapers' exhaled breath: benzene, toluene and 2,5-dimethylfuran (harmful substances) identified
- smokers had much higher burden of VOCs than vapers

7 In general, studies with severe conflicts of interest have findings indicating little or no harm to health.

Pulmonary system. Effects reminiscent of those seen with tobacco smoking: • increased airway resistance, decrease in specific airway conductance, increase in impedance and overall peripheral airway resistance • lung function: – non-significant decrease in lung function, approximately half of effect of smoking – normal but increased flow resistance • both healthy volunteers and patients with asthma and chronic obstructive pulmonary disease: immediate significant airway obstruction • same particle dose received in airways as with smoking • significant inhibition of reflex sensitivity • reduction in exhaled nitric oxide • fractional exhaled nitric oxide: – increased – decreased
Cardiovascular system: conflicting results on haemodynamic effect: increased heart rate, elevation in diastolic blood pressure, decrease in oxygen saturation no increase in heart rate or in blood pressure but an increase in oxygen saturation no negative effect on elasticity and stiffness of ascending aorta no effect on cardiac function
Other findings: significantly increased marker of oxidative stress in exhaled breath improved time-based but not event-based prospective memory improved nicotine withdrawal impaired concentration/memory

3.4 Animal experimental studies

(See Table 3 for overview of studies; for details see Annex 4.)

General findings. The longest time of exposure in animal studies was four months *(139)*. One study exposed animals for seven weeks *(140)*, one during pregnancy and two weeks after *(141)*, and another for four weeks *(142)* – otherwise it was short-term exposure only.

The long-term exposure study showed that exposure to e-cigarette vapour for five hours per day caused asthma and emphysema in mice *(139)*. A study showed that mice treated intratracheally with e-cigarette fluid had increased infiltration of inflammatory cells, aggravated asthmatic airway inflammation and airway hyperresponsiveness, and stimulated the production of cytokines and ovalbumin-specific IgE production *(143)*. This is in concordance with a study showing that exposure of mice to e-cigarette vapour increased pro-inflammatory cytokines and diminished lung glutathione levels, which are critical in maintaining cellular redox balance *(5)*. Other murine studies also demonstrated that ecigarette exposure resulted in increased oxidative stress

and moderate inflammation *(7, 144)* and impaired pulmonary antimicrobial defences, significantly impaired pulmonary bacterial clearance, and – in response to influenza A virus infection – increased lung viral titers and enhanced virus-induced illness and mortality *(144)*. This is also in concordance with a study finding that e-cigarettes inhibit the expression of a host defence molecule against human rhinovirus infection in mice *(103)*. Rats exposed to e-cigarette vapour developed hyperplasia and metaplasia in the larynx more frequently than non-exposed animals but the difference was non-significant, most probably due to very small study size *(142)*. Another mice study found that second-hand exposure to e-cigarette vapour induced addiction-related neurochemical, physiological and behavioural alterations *(140)*, and a mice study found increased levels of activity when exposed to vapour containing nicotine during late prenatal and early postnatal life – indicating that nicotine exposure from e-cigarette may cause persistent behavioural changes *(140)*. Exposure to e-cigarette vapour – with or without nicotine – during the neonatal period resulted in a small negative impact on the weight of mice, and exposure to e-cigarette with nicotine caused diminished alveolar cell proliferation and a modest impairment in postnatal lung growth *(145)*. In zebrafish, exposure to e-cigarette vapour extract resulted in broad, dose-dependent developmental defects coupled with severe heart malformation, pericardial oedema and reduced heart function *(6)*. On the other hand, a mice study showed that despite higher exposure conditions, e-cigarettes exhibited less toxic effects on lungs of experimental animals after short-term exposure *(4)*.

Box 5 summarizes the effects observed in animal experimental studies.

Box 5. Effects observed in animal experimental studies

Effects observed in animal experimental studies are summarized as follows:

- increased infiltration of inflammatory cells and pro-inflammatory cytokines
- increased oxidative stress and moderate inflammation
- asthmatic airway inflammation and airway hyperresponsiveness
- impaired pulmonary antimicrobial defences
- enhanced virus-induced illness and mortality
- asthma and emphysema
- hyperplasia and metaplasia in the larynx
- developmental defects coupled with severe heart malformation
- neonatal exposure: diminished alveolar cell proliferation and a modest impairment in postnatal lung growth
- increased levels of activity by late prenatal and early postnatal exposure

3.5 Adverse events

(See Table 4 for overview of studies; for details see Annex 5.)

General findings. There are no studies with long-term follow-up. The longest follow-up period is two years. As most smokers have no or few and mild symptoms, for example

a mild cough for decades, potential serious adverse effects of e-cigarette use should not be expected in short-term studies.

Population-based survey. One large population-based survey with high representability has been performed in Chinese adolescents. The study included more than 45 000 students, aged approximately 12 to 18 years. E-cigarette use was significantly associated with respiratory symptoms in analyses adjusted for sex, age, perceived family affluence, second-hand smoke exposure, and school clustering effect *(146)*.

Surveys and interviews with e-cigarette users. Most adverse events have been from the mouth/throat and the respiratory system, but symptoms from many organ systems have been reported. On the other hand, many regular e-cigarette users reported a decrease in respiratory symptoms and improvements in general health. Regular users of e-cigarettes typically reported few negative symptoms, such as mouth and throat irritation, cough, vertigo, headache, gastrointestinal discomfort, epigastric burning or nausea, and many positive health effects, such as improved breathing, reduced cough and expectoration, improved health and physical fitness, improved quality of life, improved sleep, and improved smell and sense of taste *(147^, 148–150, 151^, 152, 153)*. Often, a majority or all of the regular users included in studies had quit smoking, and the positive side-effects are identical with health improvements after smoking cessation. On the other hand, vapers in a chat forum mostly reported negative symptoms, from many organ systems. In particular, symptoms for respiratory, mouth and throat, neurological, and sensory organ systems were reported, and users with negative symptoms often reported more than one symptom. Interactions were often seen between organ systems. Positive effects most frequently affected the respiratory system *(154)*. A summary of adverse events reported to the United States Food and Drug Administration *(155)* categorized eight out of almost 50 reports as serious adverse events: hospitalization for illnesses such as pneumonia, congestive heart failure, disorientation, seizure, hypotension, possible aspiration pneumonia, second-degree burns to the face, chest pain and rapid heartbeat, possible infant death secondary to choking on an e-cigarette cartridge, and loss of vision requiring surgery. In most cases (except burns, choking and loss of vision) there was no information on causality. Other adverse events reported were headache/migraine, chest pain, cough/sputum, nausea/vomiting, dizziness, feeling sick, confusion/stupor, sore throat, shortness of breath, abdominal pain, pleurisy, blurry vision, and sleepy/tired.

Prospective studies and randomized trials. One possible serious adverse event (myocardial infarction) was recorded in a study *(156)*. A randomized controlled trial on smoking cessation (13 weeks) found a higher number and proportion of adverse events occurred in the nicotine–e-cigarette group than in the nicotine–patches group; however, there was no evidence of an association with e-cigarettes, and the event rate was not significantly different *(157)*. A substudy of this trial found that mentally ill persons tolerated e-cigarette well *(158)*. Two other randomized trials reported that adverse events such as cough, dry mouth, shortness of breath and headache declined

over 12 months of follow-up *(159)*, whereas a short-term dual use group reported both positive and negative symptoms *(160)*. In some studies the time association between e-cigarettes and adverse events was registered by a health professional; participants primarily experienced mouth/throat and respiratory symptoms, headache, palpitations and nausea, but there were no serious adverse events *(159, 161–164)*. Causality seems probable. In three studies, symptoms waned spontaneously over weeks or months *(159, 162, 163)*. In one study, however, users experienced a slight increase in mouth/throat irritation and dry cough over time. This study had the longest follow-up period, amounting to two years *(164)*. One study included schizophrenic patients *(162)*. This study showed that positive and negative symptoms of schizophrenia did not increase after smoking reduction or cessation in patients using e-cigarettes. No safety concerns were raised during another prospective study, although the limitations in recording of adverse events prevented the authors from drawing any conclusions *(156)*.

Case reports. A case of contact dermatitis was most probably caused by use of a nickel-containing e-cigarette device *(165)*. Other case reports on different lung diseases *(166–168)*, reversible cerebral vasoconstriction syndrome *(169)*, atrial fibrillation *(170)*, lichen planus *(171)*, lingua villosa nigra *(172)*, colonic necrotizing enterocolitis in a newborn child (his mother was vaping an e-cigarette during pregnancy) *(173)*, relapse of colitis ulcerosa symptoms *(174)*, and remission in a colitis ulcerosa patient and beneficial effects on idiopathic chronic neutrophilia *(175)* have been reported, as they found time association or reversibility, but causality can only be hypothesized. One of the case reports is in a dual user *(169)*.

Box 6 summarizes the effects of reported adverse events.[8]

Box 6. Reported adverse events

Reported adverse events are summarized as follows:

- no long-term use effects reported
- large population-based survey: e-cigarette use significantly associated with respiratory symptoms
- a higher proportion of adverse events seen in e-cigarette group in a randomized trial, but difference not significant
- possible serious adverse events reported, but causality is not known
- most common adverse events: mild, such as mouth and throat irritation, cough, headache, nausea
- conflicting results on symptoms:
  - new users often report several negative symptoms from more organ systems
  - regular users often report improvement in cough and breath and general well-being – some of these attributed to smoking cessation
  - conflicting results on increase/decrease in reported adverse events over time
- many case reports from all organ systems – but causality is unknown

8 In general, studies with severe conflicts of interest have findings indicating little or no harm to health.

3.6 Passive exposure to vapour

(For details of studies see Annexes 2–4; relevant studies are marked with Θ)

Human experimental studies have shown that passive vaping resulted in short-term lung obstruction and increased cotinine *(119, 120)*, but passive vaping did not influence complete blood count indices in smokers and never smokers *(131)*. A "real-life" study found that non-smokers passively exposed to e-cigarette vapour absorb approximately as much nicotine as when exposed to smoke from conventional cigarettes *(176)*. Relatively high concentrations of propylene glycol and glycerol could be quantified in the air of chamber tests, indicating risk of passive vaping *(177)*. Two studies have investigated third-hand exposure to nicotine: an experiment showed significant increases in the amount of nicotine on all surfaces *(178)*, whereas a study in households showed significantly less nicotine on surfaces compared to smoking conventional cigarettes *(179)*. A study found that emission rates of organic compounds (including alkanes and organic acids), as well as total emission of inorganic elements and metals, were also significantly reduced in vaping compared to smoking. However, analysis of elemental emissions indicated the presence of toxic metals in ecigarette aerosol, with nickel and silver having higher indoor emission rates compared to conventional cigarettes *(180)*. Analyses of indoor air quality showed that there were high concentrations of ultrafine particles ($PM_{2.5}$), that the concentration of putative carcinogenic PAHs in indoor air increased by 20%, and that aluminium increased 2.4-fold after vaping sessions *(30)*. A real-life vaping study showed that e-cigarettes emit $PM_{2.5}$ although the concentration was notably lower than from smoking *(181)*. Benzene, toluene and 2,5-dimethylfuran were also found in the exhaled breath of e-cigarette users *(79)*.

One study investigated the interaction between radon (significant risk for lung cancer) and e-cigarette sidestream vapour and found that the increase in the attached potential alpha energy concentration was higher for the e-cigarette than for the traditional conventional cigarette. Therefore, the aerosol from e-cigarettes operates as a carrier of the radon progeny and, as a consequence, it decreases the plate-out of radon daughters *(182)*.

On the other hand, one study found that vaping does not produce detectable amounts of toxic and carcinogenic substances in the air of an enclosed space *(183^)*[9]. Formaldehyde was detected above the limit of quantification in indoor air in one study; however, these levels were overlapping the range of the background levels *(76*)*. A study investigating vapour and aerosol found that all of the types of e-cigarette samples generally contained little or none of most of the target VOCs, except for acetic acid *(80)*, and a real-life study showed trace quantities of metals and low levels of carbonyls in indoor air, below the WHO Indoor Air Quality Guidelines *(59*)*. Other studies performed by the tobacco industry concluded that exhaled e-cigarette aerosol did not increase bystander exposure for phenolics and carbonyls above the levels observed in exhaled breaths of air *(17*)*

9 Note: Study not sponsored by e-cigarette industry but first author has performed other studies sponsored by the industry.

and that exposure of bystanders to the chemicals in the exhaled e-cigarette aerosol was below current regulatory standards that are used for workplaces or general indoor air quality *(59*)*, and a mathematic modelling model concluded that the exposure of bystanders to nicotine in the exhaled aerosol is not at levels that would be expected to cause health concerns *(184*)*.

Box 7 summarizes the findings from studies on passive vaping (human experiments; indoor air, particles and emissions).[10]

Box 7. Findings from studies on passive vaping

Human experiments:

- short-term lung obstruction but no influence on complete blood count found in acute exposure studies
- non-smokers passively exposed to vapour absorb approximately as much nicotine as when exposed to smoke
- total phenols and carbonyls in exhaled aerosols not distinguishable from content in exhaled breaths blanks

Indoor air, particles and emissions:

- significant increases in the amount of nicotine on all surfaces
- high concentrations of ultrafine particles ($PM_{2.5}$), concentration of putative carcinogenic PAHs in indoor air increased by 20%, and aluminium increased 2.4-fold after vaping sessions
- benzene, toluene and 2,5-dimethylfuran found in exhaled breath
- vaping does not produce detectable amounts of toxic and carcinogenic substances in the air of an enclosed space
- formaldehyde above limit of detection but not higher than background levels
- phenols and carbonyls in exhaled aerosol as in exhaled breath blanks
- compared to smoking:
  - presence of toxic metals in aerosol, with nickel and silver having higher indoor emission rates compared to tobacco smoke
  - emission rates of organic compounds and inorganic elements and metals reduced compared to smoking
  - significantly less nicotine on surfaces compared to smoking
  - $PM_{2.5}$ notably lower than in smoke

3.7 The major ingredients: glycols, nicotine and flavours

Glycols. Of special concern is the fluid carrier or vehicle and major ingredient of e-cigarettes that create the visible fume: the glycols, propylene glycol and glycerine.

Even though these are recognized as safe for oral intake *(185)*, and concentrations found in ecigarettes typically have been below occupational safety standards *(186)*, it

10 In general, studies with severe conflicts of interest have findings indicating little or no harm to health.

must be noted that occupational safety standards are not intended to establish "safe" exposure concentrations for a general population but to diminish harm in exposed workers during working time *(187)*, and that eating and inhaling are not the same. The lungs have a very large surface and completely different values may apply when a vaper is exposed for several hundred daily direct inhalations in decades. An internal technical report commissioned by vapers and vendors of e-cigarettes concluded that estimated levels of exposure to propylene glycol and glycerine are close enough to threshold limit values to warrant concern, and that the threshold limit values are based on uncertainty rather than knowledge *(188, 189)*. Glycols are used as theatrical smokes and fogs and a study of more than 100 employees showed that chronic work-related wheezing and chest tightness were significantly associated with increased cumulative exposure to theatre fogs (mineral oil and glycols) over the previous two years. Acute cough and dry throat were associated with acute exposure to glycol-based fogs; increased acute upper airway symptoms were associated with increased fog aerosol overall. Lung function was significantly lower among those working closest to the theatre fog source *(190)*.

Propylene glycol is a solvent used in pharmaceutical products, in cosmetics, as a food additive, as theatrical fog and as industrial antifreeze. An old experimental study showed that continuous residence of monkeys and rats for a year or more in an atmosphere supersaturated with the vapour of propylene glycol was without deleterious effect on the lungs and functional activity of the body as a whole *(191)*; in fact the animals seemed to thrive somewhat better than the control groups, as judged by weight gain and increase in red blood cells and haemoglobin content. Another old experimental study exposed rabbits to 10% propylene glycol inhalations and found that there was a minimal alteration of the ultrastructure of the ciliated cells in the airways. The action of propylene glycol was manifested chiefly in the goblet cells, which rapidly discharged their mucus *(192)*. A recent industry-sponsored review found that none of the glycols reviewed presented evidence of carcinogenic, mutagenic or reproductive/developmental toxicity potential to humans, and that the propylene glycols present a very low risk to human health *(193*)*. Another newer study conducted by the tobacco industry exposed dogs and rats for 28 days and concluded that propylene glycol aerosol could be administered safely in humans *(194*)*. However, in the rats there was ocular and nasal irritation and laryngeal squamous metaplasia. In dogs the study found decreases in haemoglobin but no apparent tissue toxicity of the lung, liver and kidney *(194*)*.

Newer experimental studies with propylene glycol have shown an increased number of goblet cells in the respiratory tract and nasal haemorrhaging *(195)*, irritation to the upper respiratory tract and squamous metaplasia of the epiglottis following exposure at concentrations present in e-cigarettes *(196)*. Volunteers exposed to propylene glycol mist for one minute developed ocular and airway irritation and a few reacted with slight airway obstruction and increased self-rated severity of dyspnea *(197)*. Long-term exposure to propylene glycol has been found to exacerbate and/or induce multiple allergic symptoms in children *(198)*. A study with electronic shisha pens (e-cigarettes designed to mimic a water pipe) showed that already after one puff, the concentrations

of propylene glycol and glycerol are sufficiently high to potentially cause irritation of the airways *(199)*. When used in high doses or for prolonged periods, propylene glycol toxicity can occur. Reported adverse effects in paediatric patients include central nervous system toxicity, hyperosmolarity, haemolysis, cardiac arrhythmia, seizures, agitation and lactic acidosis *(200)*. One e-cigarette study found that the highest levels of carbonyls in e-cigarettes were observed in vapours generated from propylene glycol-based solutions, compared with a 50:50 solvent with glycerine *(10)*.

Glycerine is used in food as a humectant and as a solution carrier in flavours. Glycerine is considered generally safe for oral intake *(201)*, but the same considerations apply as for propylene glycol when inhaling it. **Ethylene glycol**, associated with pronounced toxicological risks *(202)*, has been found to replace glycerol/propylene glycol in several brands *(37)*. **Diethylene glycol**, associated with pronounced toxicological risks, has been detected in small quantities in very few studies *(22, 65*)*.

Nicotine. Almost all regular users report that they use e-cigarettes with nicotine *(203)*, with levels in ecigarette users *(204)* almost as much as in smokers *(205)*, and higher than in nicotine replacement therapy users *(206)*. It is well established that nicotine is highly addictive *(207, 208)*. More than 60% of smokers wish to quit because they do not like being dependent *(209)*, and switching to e-cigarettes does not break the nicotine addiction.

Nicotine is referred to by some health professionals as harmless, and a meta-analysis found no increased risk of serious adverse events, after 12 months or less *(210)*. To our knowledge, only one study has investigated the health effects of long-term pure nicotine or nicotine replacement therapy use, finding no increase in the risk of cancer after 12 years *(211)*. Others do not share this view. However, nicotine has significant biologic activity: in the central nervous system nicotine stimulates the release of important neurotransmitters and hormones *(212)*, and in the peripheral system it stimulates the release of catecholamines, with effects such as vasoconstriction, increase in heart rate and myocardial contractility *(213)*. In vitro evidence points to possible direct carcinogenic and genotoxic effects of nicotine *(214–221)*. Human and animal data support that nicotine exposure during periods of developmental vulnerability has multiple adverse health consequences, including impaired fetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents *(222)*. Animal studies (the applicability to human beings may be questioned) suggest that nicotine accelerates atherosclerosis *(213)*, reduces sperm quality *(223)*, promotes growth of cancer cells and the proliferation of endothelial cells, and reduces the responsiveness of several cancers to chemotherapy *(214, 224–227)*, and fetal and neonatal nicotine exposure leads to widespread adverse postnatal physical and mental health consequences *(228–230)*. Epidemiological evidence for such an effect of nicotine is still unavailable. While being on the "high priority" list for evaluation by the WHO International Agency for Research on Cancer, nicotine has so far not been classified by the agency.

Intentional *(231)* and non-intentional poisoning occurs. Poison centres are receiving many calls regarding e-fluid *(213, 232)*; mostly, exposures have resulted in minimal toxicity (e.g. vomiting, nausea, tachycardia) *(109)*, but a case of fatal nicotine poisoning in a child has been reported *(233)*.

The fatal dose of nicotine is unclear but has in adults been estimated at 30 to 60 mg, while for young children it is estimated at only 10 mg *(234)*.

Flavours. Flavour ingredients are an essential part of e-liquids. A recent study concluded that concentrations of some flavour chemicals in e-cigarette fluids are sufficiently high for inhalation exposure by vaping to be of toxicological concern, and almost half of the tested products on the United States market were more than 1% by weight flavour chemicals *(69)*. Many of the studies in this review have found flavours to be associated with potential harm *(5, 35*, 66, 69, 84, 89, 90, 96, 118, 235, 236^)*. As with propylene glycol it is important to note that "generally recognized as safe" applies only to *oral intake*. None of the primary safety assessment programmes for flavours, including the GRAS programme sponsored by the Flavour and Extract Manufacturers Association of the United States (FEMA), has evaluated flavour ingredients for use in products other than human food. A FEMA GRAS™ status for the use of flavour ingredients in food does not mean that these flavour ingredients are safe for use in e-cigarettes *(237)*. Diacetyl, a food sweetener, was approved as completely safe for oral intake but it turned out that workers exposed to inhalation of diacetyl during food manufacturing frequently had airway obstruction and this was caused by a rare lung disease, bronchiolitis obliterans, later popularly named as "popcorn lung" *(238)*. Diacetyl has in a recent study been found in 75% of the samples *(83)*.

The potentially tempting effect of candy-like tastes on youths should also be kept in mind. Finally, flavours are also known to affect the stability of products, and flavours may impact nicotine concentrations *(239)*.

4. General considerations

4.1 General considerations of quality of studies and other research challenges

The research field is new and very challenging. Serious methodological problems were identified:

1. The core problem is that any research only applies to the specific e-cigarette brand, model and batch tested, with no certainty that the findings will apply to other or future brands, models or batches. E-cigarettes are subject to very frequent modifications; there are currently approximately 500 brands and 8000 flavours, and with the third generation of e-cigarettes (the "mods"), and the fourth, consumers have even more choices to customize their own ejuices.

2. Studies sponsored or conducted by the tobacco industry have severe conflicts of interest. Studies sponsored or performed in collaboration with e-cigarette manufacturers also have a conflict of interest that might influence the results, the presentation of results or the conclusions. In general, most studies with severe conflicts of interest (as identified at the start of the reference list) found less or no potentially harmful effects from substances than studies without conflict of interest. Therefore, we must carefully consider whether these can be trusted.

3. Studies investigating fluid do not take into account that e-cigarettes can generate new compounds (e.g. formaldehyde, acetaldehyde and acrolein) that did not exist in the original solution – generally produced via oxidation of the glycols through heating, thereby underestimating the risks of vaping.

4. More than 80 compounds have been identified in e-cigarette aerosols and we lack knowledge of possible interactions between all these chemicals. A compound found in a harmless concentration might interact with other compounds of low concentration creating harmful effects.

5. There are no "standard vaping machines" or standards for testing of ingredients in ecigarettes, so studies are difficult to compare. E-cigarette use topography

is significantly different than smoking *(154)*. When vaping, vapers are sucking harder and have longer puffing duration, approximately double that of smoking, especially if the fluid content in the cartridge is low *(240)*. Therefore, the real uptake of harmful substances might be underestimated when testing on e-cigarette naive volunteers or standard smoking machines. Also, studies show that there are significant variations in puffing topography among users of various ecigarette models *(241)*, that production of harmful substances is influenced by battery voltage output *(10)*, vaporizer *(22)* and e-liquid levels left *(37)*, and that pH may influence the doses of nicotine delivered to users *(85)* – this complicates the research even more.

6. Human experiments were mostly based on very short-term exposure, for example vaping for a few minutes – not reflecting real-life exposure and thereby underestimating negative long-term effects.

7. Some animal studies might have overexposed the animals, thereby overestimating negative health effects. Also, it is important to remember that health effects in animal studies do not always apply to humans.

8. Some studies might have overheated fluid when generating vapour, thereby overestimating negative health effects.

9. Studies of adverse events are seriously biased by selection bias. Those based on new vapers probably overestimate harm, whereas those based on regular vapers probably underestimate harm.

Studies identifying negative health effects of vaping, or identifying high concentrations of harmful substances, have been targets of intense, sometimes even aggressive critique. In some cases it might be correct that there have been methodological problems causing overestimation of risk. However, it seems *very unlikely* that all of the many studies identifying increased risk of negative health effects by e-cigarette use should be poor science.

4.2 General health risk considerations

4.2.1 Impact of the diversity of products

While a smoker smoking a conventional cigarette of one brand has more or less the same risk as another smokers who smokes a conventional cigarette of another brand, a consumer vaping one e-cigarette might have a completely different risk than another consumer vaping another e-cigarette. First, there are approximately 500 different brands and 8000 different flavours *(242)*. Second, the risk seems to depend not only on the brand and batch of ecigarette or efluid, but also on the flavour, the heating of the e-cigarette, how dirty or worn the ecigarette is, the vaper, the vaporizer, and factors still unknown. As an example, a study found that two apparently identical vaporizers made by the same manufacturer and filled with the

same e-liquid yielded formaldehyde concentrations in vapour that differed by a factor of > 25 *(22)*. Therefore, *it is not meaningful to speak of risk of e-cigarettes as risk of one product*. Box 8 summarizes some higher risks that have been identified in studies.

Box 8. Higher risk as identified in studies

- Some brands
- Some flavours
- High voltage devices
- Second half of a vaping period
- Overheating
- "Dripping"
- "Dry puff" conditions
- The state of the heating element
- The vaporizer
- Vehicle/carrier: ethylene glycol, propylene glycol

4.2.2 Dual use

Replacing a very harmful product with a less harmful product is the logic idea behind the "harm reduction strategy".

However, as the large majority of e-cigarette users, almost 80% *(243–247)*, do not quit smoking when they switch to e-cigarettes, but instead continue with dual use, reductions in harm can hardly be expected.

Those who have not reduced their tobacco intake but supplement with e-cigarettes will have an increased risk of harm. But even those who substantially reduce their consumption will probably not have a (substantial) health benefit. Evidence from large cohorts shows that even a halving of daily intake of number of cigarettes or more does not reduce all-cause mortality, incidence of cardiovascular disease or smoking-related cancer/cancer mortality *(248–253)*, but reductions in lung cancer risk have been found in two studies *(252, 254)*.

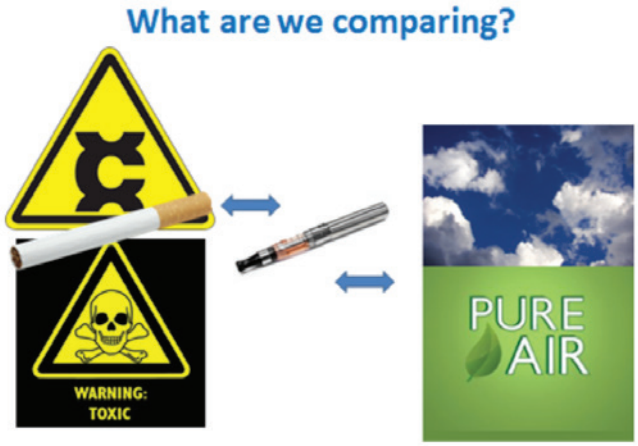
Substantial reductions in number of conventional cigarettes are not reported in dual users. One study reported that there was no change in conventional cigarette consumption after one year *(255)*, 86% did not cut back substantially in another study *(256)*, yet another study concluded that e-cigarette use is not linked with lower smoking quantity *(257)*, and a 12-month cohort study of more than 200 dual users found a reduction of only approximately five conventional cigarettes per day *(156)*. A study found that compared to single-product users, dual users puffed and smoked more, were more likely to smoke a conventional cigarette when they first woke up, and used products with higher nicotine levels compared to exclusive e-cigarette users. Taken together, these findings suggest that dual users are more addicted to nicotine *(245)*.

We have extremely little evidence on health effects of combined vaping and smoking. Some positive health effects have been described: a retrospective study describing pulmonary changes in eight dual users who had substantially reduced their tobacco consumption to a mean of less than four conventional cigarettes per day showed significant improvement in lung function after 12 months *(117)*. An observational study found that after four weeks of dual use (n=17) there was a reduction in conventional cigarette intake followed by a reduction in carbon monoxide, cotinine, creatinine and a main metabolite of acrolein (potentially carcinogenic) *(136)*, but dual users had 3 times higher levels of the metabolite of acrolein than quitters.

On the other hand, there are findings indicating harm. The largest study (n > 45 000) is a population-based survey performed in randomly selected schools in China, with a 95% participation rate, so it is representative for a general population of adolescents. Those with dual use reported slightly more respiratory symptoms than smokers who were not using ecigarettes. Analyses were adjusted for potential confounders, there were few cases and the difference was not significant *(146)*. A 12-month cohort study of more than 200 dual users found no significant improvement in health *(156)*. A case report describes a possible case of reversible cerebral vasoconstriction syndrome in a young healthy dual user who switched from 60 conventional cigarettes per day to use of 20 conventional cigarettes per day combined with e-cigarette use *(169)*. A prospective study found that those who switched to ecigarettes and completely quit smoking reported only health improvements, whereas the dual use group reported both positive and negative symptoms *(160)*. Long-term follow-up studies in non-selected populations are urgently needed. An eventual interaction ("cocktail effect") between smoking and vaping would be a worst-case scenario.

4.3 Other general risk considerations

Most studies have compared e-cigarettes with conventional cigarettes and it can be questioned whether this reference is the correct to use:



A conventional cigarette is the most harmful legal product that exists and everything will seem "harmless" compared with it. Also, by searching for harmful ingredients found in conventional cigarettes we may neglect or overlook other ingredients of potential harm (e.g. glycols, flavours, metals, rubber, silicone, ceramics and yet unknown ingredients), as the ecigarette is a radically different product. Are we comparing apples with pears?

Many of the harmful substances detected were identified at very low concentrations but we are dealing with intense and chronic exposure. Values below the threshold limit do not necessarily protect against the health effect of (for example) 300 daily inhalations *(24)* over decades – harm might accumulate over years and decades, as with conventional cigarettes. Further, the presence of, for example, 10 substances below the official threshold limit values may add up in a synergic way, and the safety of the combination of substances ("cocktail effect") has not been evaluated. Also, long-term inhalation of a warm aerosol may increase the risk of tuberculosis, as observed in smoking *(258)*.

5. Conclusions

1. Even though no firm conclusions can be drawn on the safety of e-cigarettes there is an increasing body of evidence indicating harm.

2. Due to the many methodological problems, the many studies with severe conflicts of interest, the inconsistencies and contradictions in results, the relatively few high-quality studies, the rapidly changing designs of the product and the lack of long-term follow-up, it seems very premature to perform calculations for *how* harmful vaping is compared with smoking, and much is still left to subjective interpretation.

3. It is not meaningful to speak of risk of vaping of e-cigarettes as risk of *one* product, as the risk seems to depend not only on the brand and batch, but also on, for example, the preferred flavour, the heating of the e-cigarette, the vaporizer, how dirty or worn the e-cigarette is, the method of vaping, and factors still unknown.

4. In a simple *product-to-product* comparison most e-cigarettes are probably less, and some products may even be much less, harmful than conventional cigarettes, but as the large majority of e-cigarette users continue to smoke, the health risks of dual use *must be taken into account in assessment of the harm of vaping.*

5. We have almost no evidence on the health effects of dual use of e-cigarettes and conventional cigarettes.

6. For ex-smokers and never smokers, use of e-cigarettes will increase the risk of harm on health.

7. Negative health effects should be expected from the pulmonary system but adverse effects from (for example) the cardiovascular system and a carcinogenic effect cannot be ruled out either.

8. E-cigarettes are highly addictive and there is insufficient evidence on the safety of long-term use of nicotine.

9. Comparing risk of vaping with the risk of (for example) drinking coffee is misleading.

10. Systematic high-quality research is urgently needed, especially on health effects of dual use.

Box 9 summarizes some of the findings causing concern.

Box 9. Some of the findings causing concern

Findings causing concern include the following:

- substantial levels of nanoscale particles
- detectable levels of many different toxic materials
- recent large sample toxicity assessment: none of the tested products were totally free of potentially toxic compounds and some liquids showed particularly high ranges of chemicals
- presence of diacetyl (causing "popcorn lung") found in most flavoured samples
- cytotoxicity, oxidative stress and inflammation found in most in vitro studies
- dysregulation of gene expression
- DNA strand breakage
- urinary toxicant and carcinogen metabolites found in vapers
- toxicants found in exhaled vapour
- airway obstruction in human experimental studies
- airway inflammation, asthma and chronic obstructive pulmonary disease development in animal studies
- impaired pulmonary antimicrobial defences in animal study
- interaction with radon

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Overview of studies investigating the effect of electronic cigarettes and health

Table 1. Studies investigating the content of fluid or vapor of electronic cigarettes and in-vitro experiments

where cells were exposed to fluid/vapor/vapor extract (n=105*).

For details in methodology and results please see appendix 2.

Name of first author Reference Year	Conflict of interest ▲=Yes ◆=Tobacco industry[1] ❖=EC industry[2]	Reference product	Fluid/ Vapor/ other	Conclusion
Allen JG [2] 2015	No	No	◦Vapor	◦Findings confirm the presence of diacetyl (causing bronchiolitis obliterans/"pop-corn lungs") and other high priority flavoring chemicals in flavored compounds in EC
Aug A [3] 2014	No	CC	◦Fluid	◦EC have immediate and profound adverse effects on the metabolomic state of primary human bronchial epithelial cells similar to those seen with CS condensate
Bahl V [4] 2012	No	No	◦Fluid	◦ Approx. one third of samples were highly cytotoxic to human embryonic stem cells and mouse neural stem cells
Behar RZ [8] 2014	No	No	◦Fluid	◦Cinnamon flavorings in refill fluids are linked to cytotoxicity
Bertholon JF [9] 2013	No	CC and water pipe	◦Vapor	◦Contrary to CC smoke, which has a half-life in air of 19 to 20 minutes, the half-life of EC is very short and risk of passive "smoking" exposure from EC is modest
Brot L [10] 2015	No	CC extract and PPG	◦Vapor extract	◦Results suggest that the intestinal epithelium inflammatory response is not altered by exposure to vapor from EC
Bush D [13] 2014	▲25	CC and no use	◦Nicotine on surface	◦Using EC indoors leads to significantly less third-hand exposure to nicotine compared to smoking
Cameron JM [14] 2013	No	No	◦Fluid	◦Large variability in nicotine concentrations was found

[1] Results of studies influenced by the tobacco industry are marked with an asterisk (*) in the paper.

[2] Studies funded by e cigarette manufacturers or performed in collaboration with the e cigarette industry are labelled with a chevron (^) in the paper.

Cervellati F [18] 2014	No	CC	◦Vapor	◦ Exposure to EC vapors is far less toxic than exposure to CC smoke
Chausse P [19] 2015	No	No	◦Heating of EC	◦It is possible for a 3.3 V EC to obtain the power of a 5 V EC, with risk of dissemination of formaldehyde
Cheah NP [20] 2012	No	No	◦Fluid	◦Contained nicotine even though they claimed to be nicotine free ◦Significant difference in the nicotine content across EC with same label, brand-to-brand and cartridge-to-cartridge variations ◦Polycyclic aromatic hydrocarbons and TSNAs compounds were not found
Chen L [22] 2015	No	CC smoke extract	◦Vapor extract	◦Preliminary evidence that e-vapor exposure may alter platelet functions associated with cardiovascular disease progression
Colard S [24] 2015	◆▲26	CC	◦Vapor	◦The exposure of bystanders to nicotine in the exhaled aerosol is not at levels that would be expected to cause health concerns
Costigan S [27] 2015	◆▲35	No	Risk assessment	◦Presents an approach to risk assessment of in-going flavoring ingredients in e-liquid and potential thermal breakdown and reaction products in the aerosol
Costigan S [26] 2014	◆▲36	No	Risk assessment	◦Presents a contact sensitization and risk assessment model
Cox C [28] 2015	No	No	◦ Vapor	◦The majority of EC produce very high levels of acetaldehyde and formaldehyde ◦High levels of these cancer-causing chemicals are produced even by some EC without nicotine
Czogala J [30] 2014	▲1	CC	◦Vapor	◦Using EC in indoor environments may involuntarily expose non-users to nicotine but not to toxic tobacco-specific combustion products
Davis B [31] 2015	No	No	◦Fluid	◦Nicotine concentration labeling on electronic cigarette refill products was often inaccurate but showed improvement recently in products from one company
El-Hellani A [38] 2015	No	No	◦Fluid and vapor	◦Nicotine partitioning varies considerably across commercial EC liquids and these differences can persist when the liquids are vaped.

Etter JF [41] 2013	▲2	No	◦Fluid	◦Half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia
Farsalinos KE [47] 2015	▲13	No	◦ Vapor	◦ Diacetyl and acetyl propionyl chemicals associated with respiratory disease when inhaled - were found in a large proportion of sweet-flavored EC liquids- many of them exposing users to higher than safety levels
Farsalinos KE [46] 2015	◆▲14	CC	◦Fluid	◦ Natural Extract of Tobacco liquids contained higher levels of phenols and nitrates, but lower levels of acetaldehyde compared to conventional EC liquids. ◦ All EC liquids contained far lower levels of the tobacco-derived toxins compared to CC
Farsalinos KE [52] 2015	▲15	No	◦ Vapor	◦ Levels of daily exposure from EC use are significantly lower compared to acceptable exposure from inhalational medications and by orders of magnitude lower than the regulatory limits for daily occupational exposure
Farsalinos KE [45] 2015	▲27	No	◦ Fluid and vapor	◦ Minimal levels of tobacco specific nitrosamines were found in the liquid samples
Farsalinos KE [49] 2013	❖▲ 29	CC smoke extract	◦ Vapor	◦ Study indicates that some EC samples have cytotoxic properties on cultured cardiomyoblasts - but sign less compared to CC. For EC extracts produced by high-voltage and energy, viability was reduced.
Feng Y [54] 2015	▲28	CC	◦ Vapor	◦The results indicate that EC-droplets, being more hygroscopic than CC smoke particles, tend to grow larger in maximum size in a typically highly humid environment
Fernández E [55] 2015	No	No	◦ Vapor	◦ ECs used under real-life conditions emit toxicants, including $PM_{2.5}$ although these are notably lower than those from CC
Fouco FC [59] 2013	No	CC	◦ Vapor	◦ Particle number distribution modes of the EC-generated vapor were similar to the CC ◦ ECs were found to be a major particle source, which can lead to significantly high deposition in vapers
Geiss O [60] 2014	No	No	◦ Vapor	◦ Relatively high concentrations of PPG and glycerol could be quantified in the air of the chamber tests

Goniewicz ML [65] 2013	▲5	CC	◦ Fluid and vapor	◦ There is very little risk of nicotine toxicity from major EC brands in the United Kingdom. ◦ Nicotine concentration in e-liquid is not well related to nicotine in vapor ◦ None of the tested products reached nicotine concentrations as high as CC
Goniewicz ML [66] 2013	▲3	Medicinal nicotine inhalator, CC	◦Vapor	◦Toxic compounds: metals, carbonyls and volatile organic compounds were found in almost all EC, but much lower levels than in CC smoke ◦Vapor of some EC contains traces of carcinogenic nitrosamines ◦Exposure to carcinogenic formaldehyde comparable with CC smoking
Goniewicz ML [67] 2013	▲4	No	◦Vapor	◦Vapor contains nicotine, but EC brands and models differ in their efficacy and consistency of nicotine vaporization
Goniewicz ML [64] 2015	▲17	No	◦Fluid	◦Most of the analysed samples had no significant discrepancies in labelled nicotine concentrations and contained low nicotine levels. Some products labelled as 'nicotine-free' had detectable levels of nicotine
Goniewicz ML [68] 2015	▲ 21	No	◦ Vapor	◦ Study indicates that there is a risk for third-hand exposure to nicotine from EC ◦Third-hand exposure levels differ depending on the surface and EC brand
Hadwiger ME [69] 2010	No	No	◦Fluid	◦Presence of unapproved active pharmaceutical ingredients ◦Nicotine-free products contained nicotine
Hahn H [70] 2014	No	No	◦Fluid	◦From all compounds tested, only nicotine reached exposures that fall into a high risk category
Han S [71] 2015	No	No	◦Fluid	◦ Compounds that may originate from tobacco, solvents or other sources, such as TSNAs, solanesol, VOCs, PAHs, phenolic compounds, and carbonyl compounds were all found with different levels and detection frequencies
Herrington JS [74] 2015	No	No	◦ Fluid and aerosol	◦Formaldehyde, acetaldehyde, acrolein, and siloxanes were found in the aerosol profiles; however, these compounds were never present in the solutions
Higham [75] AJ 2014	No	No	◦Vapor extract	◦In vitro study shows that EC exposure causes an inflammatory response from neutrophils and macrophages ◦The effects are similar to those caused by CC

Husari A[78] 2015	No	CC	◦Vapor	◦Both EC and CC smoke extracts reduced cell proliferation, however, CC smoke exhibited effects at lower concentrations
Hutzler C [79] 2014	No	No	◦ Fluid and vapor	◦ Many ECs labeled as 'nicotin free' contained nicotine ◦Release of aldehydes is strongly enhanced in the second half of the vaping period ◦ The occurrence of aldehydes seems to be associated with lower liquid levels within the cartridges
Ingebrethsen BJ [80] 2012	◆▲6	CC	◦Vapor	◦Particle diameters and particle number conc. as in CC smoke
Jensen RP [81] 2015	No	CC	◦Vapor	◦High levels of formaldehyde-releasing agents found by use of high-voltage battery -estimated formaldehyde hemiacetal to be 5 times as high in EC vapor as in CC smoke
Kavvalakis MP [82] 2015	No	No	◦Fluid	◦Nitrosamines and PAHs or diethylene glycol were not detected in any sample
Kienhus AS [83] 2015	No	No	◦ Fluid and vapor	◦Already after one puff of the shisha-pen, the concentrations of propylene glycol and glycerol are sufficiently high to potentially cause irritation of the airways
Kim H-J [84] 2013	No	No	◦Fluid	◦Almost all fluids contained carcinogenic compounds, tobacco specific nitrosamines ◦High maximum conc. of total tobacco specific nitrosamines ◦Great variability in content of the four measured tobacco specific nitrosamines
Kim S [85] 2015	No	No	◦Fluid	◦There is no standardization of EC liquid labelling; labels did not accurately reflect the content. One product labeled 'pure nicotine' raises concerns, since it may be poisonous to consumers
Kim YH [86] 2015	No	No	◦ Fluid, aerosol, vapor	◦All of the types of EC samples generally contained little or none of most of the target VOCs, except for acetic acid
Kirschner R [87] 2013	No	No	◦Fluid	◦Measured concentration of nicotine differed from declared by up to 50%
Kosmider L [88] 2014	▲7	Glycerin, PPG/ mixture of both	◦ Vapor	◦ ECs might expose their users to the same or even higher levels of carcinogenic formaldehyde than CC smoke ◦ Vapors from EC contain toxic and carcinogenic carbonyl compounds ◦ Both solvent and battery output voltage significantly affect levels of carbonyl compounds in EC vapors

Kubica P [89] 2014	No	No	◦Fluid	◦Sucrose was found in all samples of e-liquids; the presence of sucrose in EC may be a source of aldehydes and organic acid
Laugesen M[91] *(2 versions)* 2009	◆▲ 8	CC	◦Fluid and vapor	◦Very low score for toxic emissions (based on >50 toxicants) ◦Small particle size ◦Mercury detected *One version found acetaldehyde, the other states: not tested*
Laugesen M [93] 2008	❖▲9	CC	◦Fluid	◦Acetaldehyde, benzene, acrolein and tobacco specific nitrosamines detected at low levels ◦Metals, CO and other VOCs at lower limits than detection
Laugesen M [90] 2008	▲34	CC	◦Fluid and vapor	◦The composition of the cartridge liquid is not hazardous to health ◦After a revised formulation from 2007 to 2008: acetaldehyde, acrolein, benzene and cresols in EC decreased, or not measurable
Laugesen M [92] 2015	▲18	CC	◦Vapor	◦EC available in New Zealand in 2013 exposed users to higher nicotine levels than in older brand ◦Far lower levels of toxicant than in CC and older EC brand
Lauterbach JH [94] 2012	◆▲10	CC	◦Vapor	◦ Acetaldehyde, formaldehyde, TSNs and mercury detected ◦ Compared to CC level of toxins and carcinogens were reduced by >90%
Lauterbach JH [95] 2012	◆▲10	CC	◦Vapor	◦ Tobacco specific nitrosamines, tar, formaldehyde, acetaldehyde, acrolein, and other toxins found in vapor ◦ Most toxicants were reduced by over 98% compared with CC
Lerner CA [98] 2015	No	No	◦Liquid and vapor	◦ EC inhalation have an impact on cellular oxidative stress, redox imbalance, and lung inflammation, in vitro in lung cells and in vivo in lungs ◦The "dripping" method is potentially more hazardous
Lerner CA [97] 2015	No	CC	◦Vapor	◦There might be constituents with oxidizing properties associated with EC that are health hazards ◦Detection of a potentially cytotoxic metal as well as oxidants from EC
Lisko JG [100] 2015	No	No	◦Fluid	◦ A number of products contained tobacco alkaloids at concentrations that exceed U.S. pharmacopeia limits for impurities in nicotine used in pharmaceutical and food products. The alkalinity of nicotine seems to drive the pH of EC solutions

Long GA [101] 2014	◆▲23	CC	◦Indoor air	◦ Results indicate that exhaled e-cigarette aerosol does not increase bystander exposure for phenolics and carbonyls above the levels observed in exhaled breaths of air ◦ A few vapors had high acetaldehyde level in exhaled aerosol
Maloney JC [102] 2015	◆▲37	No	◦Indoor air	◦Indoor vaping of tested EC does not produce chemical constituents at quantifiable levels or background levels using standard industrial hygiene collection techniques and analytical methods
Manigrasso M [104] 2015	No	CC	◦Vapor	◦ Human lung model: EC: High dose - more than double the dose compared to CC- of 10^{10} particles are deposited in the lung ◦ In the tracheobronchial and alveolar regions, a single puff delivers total regional doses that represent 40% and 30% of the daily dose of a no-smoking Italian
Manigrasso M [103] 2015	No	No	◦Vapor	◦ Human lung model: EC are a source of extremely high particle doses ◦ 10^{10} particles were deposited in the respiratory tree after a single 2-s puff, approximately 30% of the daily doses of a non-smoking person
Marco E [106] 2015	No	CC	◦Vapor; exhaled breath	◦ Incorporation of higher burdens of VOCs in the smokers than in EC vapers ◦Benzene, toluene and 2,5-dimethylfuran found in exhaled breath
Martinez RE [109] 2015	No	No	◦Vapor	◦Aerosolized nicotyrine could facilitate nicotine absorption, inhibit the metabolism of nicotine, and reduce a user's urge to smoke
McAuley TR [110] 2012	▲11	CC	◦Vapor	◦Ethylbenzene, benzene, toluene, and m/p xylenes acetone, formaldehyde, and acetaldehyde detected ◦ Tobacco specific nitrosamines: typically found at lower levels than tobacco smoke ◦Conc. of pollutants were generally orders of magnitude lower than in CC smoke
Misra M [115] 2014	◆▲19	Medicinal nicotine product	◦Fluid and vapor	◦ EC liquids and vapor does not produce any meaningful toxic effects in four widely-applied in vitro test systems, in which the CC smoke preparations are markedly cytotoxic and genotoxic
Neilson L [118] 2015	◆▲22	CC	◦Vapor	◦Little cytotoxicity from EC aerosol and different aerosol formulations when compared directly with reference CC smoke, over the same exposure time

O'Connell G [120] 2015	◆▲ 24	No	◦Indoor air	◦Exposure of bystanders to the chemicals in the exhaled EC aerosol, at the levels measured within this study, are below current regulatory standards that are used for workplaces or general indoor air quality
Palpant NJ [122] 2015	No	CC	◦Vapor	◦Study indicate a negative effect of EC on heart development in vitro and in vivo ◦The impact of EC on heart development is the consequence of other components than nicotine
Papousek R [124] 2014	No	CC (cigar)	◦Vapor	◦Acrolein, a compound with toxic and potentially and mutagenic effects was found in all tested samples
Park S [125] 2014	No	CC	◦Vapor	◦Preliminary analyses indicate the observed EC-specific gene expression changes were concordantly changed following CC-conditioned media exposure
Pellegrino RM [126] 2012	No	CC	◦Fluid and vapor	◦Propylene glycol and vegetable glycerin are major ingredients – other ingredients = traces ◦ Particulate matter in vapor: fine + ultrafine particles; emissions are significantly lower than in CC smoke
Romagna G[132] 2013	❖▲12	CC	◦Vapor	◦Vapor from 1 out of 21 EC liquids examined had cytotoxic effects on cultured fibroblast ◦CC: significantly higher cytotoxicity
Romagna G [133] 2012	▲33	CC	◦Indoor air	◦Preliminary assessment: vaping does not produce detectable amounts of toxic and carcinogenic substances in the air of an enclosed space
Rubenstein DA[134] 2015	No	CC	◦Vapor	◦EC exposure resulted in inflammatory response, oxidative stress production and cytokine release –comparable to CC exposure ◦Inflammatory response may pass into the general systemic circulation
Ruprecht AA [135] 2014	No	CC	◦ Vapor	◦ EC produce less particulate matter than CC and therefore may be less hazardous in terms of secondhand exposure
Saffari [136]A 2014	No	CC	◦Particle phase of vapor	◦Study shows same concentration of zinc, nickel and silver, potentially toxic and redox active species, from EC and CC emission ◦ A remarkable decrease in secondhand exposure to all metals and organic compounds

Samways B [138] 2014	◆▲ 32	No	◦Vapor	◦Deposited aerosol mass varied greatly from repeat experiments with all products ◦Variability of aerosol cellular dose in vitro needs to be taken into consideration for future in vitro studies
Sancilio S [139] 2015	No	No	◦Fluid and vapor	◦ EC fluids induce an oxidative stress and early and late apoptosis, with a major extent in nicotine-treated samples, but present anyway in the samples treated with nicotine-free fluids
(Chandramani)-Shivalingappa P [144] 2015	No	Room-air controls	◦Vapor	◦EC vapor exposure induces proteostasis/ autophagy impairment leading to oxidative stress, apoptosis, and senescence that can be ameliorated by an autophagy inducer; potential role in chronic obstructive pulmonary disease–emphysema pathogenesis
Scheffler S [140] 2015	No	CC	◦Vapor	◦Toxicological effects of EC vapor and the pure carrier substances, whereas the nicotine concentration did not have an effect on the cell viability
Schober W [141] 2014	No	No vaping	◦ Vapor	◦ EC are not emission-free - could be of health concern for users and secondhand smokers ◦ Ultrafine particles can be deposited in the lung ◦ Release of inflammatory signaling molecule NO
Schripp T [142] 2013	No	CC	◦Vapor	◦Prominent components in the gas-phase: 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavorings, and traces of nicotine ◦Passive vaping must be expected ◦The aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles
Schweitzer KS [143] 2015	No	CC	◦Fluid and vapor	◦Results suggest that soluble components of EC, including nicotine, cause dose-dependent loss of lung endothelial barrier function, which is associated with oxidative stress and brisk inflammation ◦Anticipate dose-dependent inflammatory lung damage with imitation of endothelial repair in long-term EC use
Stepanov I [146] 2014	No	No	◦ Fluid	◦ ECs with the same nicotine content, but different pH, may deliver different doses of nicotine to users ◦ Most of the tested brands have basic pH - the long-term effect of chronic aero-digestive tract exposure is not known
Talih S [148] 2015	No	No	◦Vapor	◦Direct dripping of e-liquids may involve greater exposure to volatile aldehyde due to the potentially higher temperatures; may expose users to increased volatile aldehyde levels relative to conventional EC and even relative to CC, for a given nicotine yield

Talio MC [149] 2015	No		◦ Fluid	◦In all studied samples, lead contents in EC liquids were in the same order as in CC
Tayyarah R [150] 2015	◆▲20	CC	◦Vapor	◦The deliveries of harmful and potentially harmful constituents tested for EC products were similar to the study air blanks rather than to deliveries from CC smoke
Theophilus E [151] 2014	◆▲ 30	CC	◦Vapor	◦EC (Brand: VUSE) aerosol was not cytotoxic whereas CC smoke was cytotoxic
Tierney PA [153] 2015	No	No	◦Fluid	◦The concentrations of some flavor chemicals EC fluids are sufficiently high for inhalation exposure by vaping to be of toxicological concern ◦Almost half of the tested products on the US market were more than 1% by weight flavors chemicals
Trehy ML [154] 2011	No	CC	◦Fluid	◦Some products were found to contain high conc. of nicotine when labeled not to contain nicotine ◦The actual amount of nicotine delivered is likely to be highly variable ◦Transfer of rimonabant and aminotadalafil to the vapor phase is low ◦Impurity level is lower than for CC
Uchiyama S [156] 2013	No	No	◦Vapor	◦EC generate incidentally carbonyls ◦In some cases they are generated with extremely high concentrations
Uryupin AB [157] 2013	No	No	◦Fluid	◦The main components of mixtures were non-tobacco products
Vargas Trassiera C [164] 2015	No	CC	◦Vapor	◦The increase in the attached Potential Alpha Energy Concentration was higher for the EC than for traditional CC ◦The aerosol from EC operates as a carrier of the radon progeny and, as a consequence it decreases the “plate out” of the radon daughter
Varlet V [165] 2015	▲31	No	◦Fluid	◦None of the products under scrutiny were totally exempt of potentially toxic compounds ◦A minority of liquids, especially those with flavorings, showed particularly high ranges of chemicals

Visser W [166] 2015	No	CC	◦Fluid and vapor	◦The toxic substance-related health risks associated with the use of CC are far greater than those associated with EC, nevertheless, daily use of e-cigarettes is not without health risks ◦The concentration of formaldehyde can be up to 3 times higher in EC vapor than in tobacco smoke
Westenberger B [168] (FDA) 2009	No	Medicinal nicotine inhalator	◦Fluid	◦Diethylene glycol in one cartridge ◦Detectable levels of carcinogens and toxic chemicals
Willershausen I [169] 2014	No	Phosphate-buffered saline	◦Fluid	◦This in vitro study demonstrated that menthol additives of EC have a harmful effect on human periodontal ligament fibroblasts ◦The menthol-flavored liquid causeda highly significant reduction of cell migration
Williams M [170] 2013	No	CC	◦Fluid and vapor	◦ Harmful or potentially harmful elements detected ◦Aerosol: significant amounts of tin and other metals, silicate beads, and nanoparticles, mostly higher than or equal to corresponding conc's in CC smoke ◦Fluid with tin particles was cytotoxic
Wu Q [171] 2014	No	No	◦Fluid	◦Findings strongly suggest the deleterious health effects of EC in the airways of young people ◦Promotes proinflammatory cytokine IL-6 production and Human rhinovirus infection in primary human airway epithelial cells
Yu V [173] 2015	No	CC	◦Vapor	◦At biologically relevant doses, vaporized EC liquids induce increased DNA strand breaks and cell death, and decreased clonogenic survival in both normal epithelial and head and neck squamous cell carcinoma cell lines independently of nicotine content
Zervas E [174] 2014	No	Ambient air	◦Vapor	◦EC liquids generate nano-particles; 300-3000 more than ambient air
Zhang Y [175] 2013	No	CC	◦Vapor	◦CC produce more particles initially, but particle counts converge to a similar scale as the aerosols condense ◦EC and CC produce aerosols having generally similar particle sizes

*Four of these studies are also/partly mentioned in Table 3/Appendix 5 on animal experimental studies [98] [122] [143] [78]
Three studies [101, 106, 133] could as well have been described in Table 2/Appendix 4, human experimental studies

CC= conventional cigarette

EC =electronic cigarette

FDA = US Food and Drug Administration

PPG= propylene glycol

Conflicts of interest – Conflicts of interest of each study should be assessed individually.
▲1: MLG received research funding from manufacturer of medicinal products for smoking cessation. AS received research funds and travel expenses from
manufacturer of ECs
▲2 JFE: reimbursed by manufacturer of e-liquids for travels. EZ and SS: employed by manufacturer of medicinal products for smoking cessation
▲3 MLG: research funding from manufacturer of medicinal products for smoking cessation. NB: consultant for manufacturers of medicinal products for smoking cessation
▲4 MLG: research funding from manufacturer of medicinal products for smoking cessation
▲5: all received research funding and/or performed provided consultancy for manufacturer of medicinal products for smoking cessation
◆▲6: Study funded by tobacco company. Two of three authors affiliate to this tobacco company.
▲7: MLG received research funding from manufacturer of medicinal products for smoking cessation. AS received research funds and travel expenses from
manufacturer of ECs
◆▲8: Manufacturers of both EC and CC funded the study. ML is cited as one of 5 most influential persons in the EC industry, http://ecigarettereviewed.com/top-5-most-influential-people-in-the-electronic-cigarette-industry/
❖▲9: Research contract with manufacturer of EC. See also CI #8
◆▲10: No conflict stated, but JHL affiliates to Lauterbach & Associates - a consulting *firm* that specializes in providing contract scientific affairs and regulatory support to the *tobacco* industry Also see CI#8 for ML
▲11: Study sponsored by National Vapers Club and EC vendors. Subsequent to data-collection SB became part owner of EC company
❖▲12: Study funded by EC company
▲13: study funded by crowd funding in vaper community. A volunteer vaper is acknowledged for assistance with fund raising. Some of the studies by KF and VV were performed using funds provided to the institution by EC companies
◆▲14: A small number of KF's and VV's studies on electronic cigarettes were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. Enthalpy Analytical is a for-profit CRO and provides testing for the EC industry but did not receive any compensation for this study. MM was working at Enthalpy Analytical at the time of the study but is currently employed by a tobacco company
▲15: The authors declare no conflict of interest. A small minority of the studies by KF and VV were

performed using unrestricted funds provided to Onassis Cardiac Surgery Center by EC companies.
▲16: Some of the studies by K.F. and V.V. were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. EC manufacturer is thanked for free equipment
▲17: MLG reports a grant from a manufacturer of smoking cessation drugs, outside the submitted work; AS reports personal fees from eSmoking Institute, Poland, and nonfinancial support from a manufacturer of EC
▲18: Agencies which sold some of the tested EC contributed to expenses of testing
◆▲19: authors are employees of tobacco company which also manufactures EC
◆▲20: authors are employees of tobacco company which also manufactures EC
▲ 21: MLG received a research grant from a manufacturer of smoking cessation medications
◆▲22: authors are employees of tobacco company which also manufactures EC
◆▲23: authors are employees of tobacco company which also manufactures EC
◆▲24: authors are employees of tobacco company which also manufactures EC
▲25: MLG received a research grant from manufacturer of smoking cessation medication, outside scope of this work
◆▲ 26: All authors are employees of tobacco company. The work in this paper was supported by tobacco company
▲27: Some of the studies by KEF and VV were performed using funds provided to the institution by EC companies.
◆▲ 28: partly sponsored by Altria group which is parent company for tobacco company
❖▲ 29: Some of the studies by KEF and VV were performed using funds provided to the institution by EC companies. This study was funded in part by the Greek Association of E-cigarette Businesses (SEEHT) - the sponsor funded the expenses of the laboratory. The study was investigator-initiated and investigator-driven.
◆▲ 30: authors are employees of tobacco company which also manufactures EC
▲31: JFE was reimbursed by a manufacturer of e-liquids for traveling to London and to China, but he received no honoraria for these meetings aimed at mutual information. Some of the other studies performed by KF used unrestricted funds provided to research center by e-cigarette companies.
◆▲ 32: authors are employees of tobacco company which also manufactures EC
▲33: nothing is stated but previous study by RG was funded by EC company. Some of the studies by KEF were performed using funds provided to the institution by EC companies
▲34: None stated. Previous study was founded by manufacturers of both EC and CC. ML is cited as one of 5 most influential persons in the EC industry
◆▲ *35:* Study was joint funded by a manufacturer of *non-tobacco products* (a company set up in 2010 by tobacco company which also manufactures EC)and by tobacco company which also manufactures EC, and the authors are full time employees
◆▲ *36:* Study was joint funded by a manufacturer of *non-tobacco products* (a company set up in 2010 by tobacco company which also manufactures EC)
◆▲ 37: authors are employees of tobacco company which also manufactures EC

Table 2. Human experimental studies reporting health effects (n=32).

For details in methodology and results please see appendix 3.

Name of first author Reference Year	Conflict of interest ▲=Yes ◆=Tobacco industry ❖=EC industry	Reference product	Method Exposure	Numbers of participants	Conclusions
Ballbé M [5] 2014	No	CC or room air	◦Observational study with non-smokers ◦Exposure: real-use conditions with passive exposure to EC or CC for one week, or no exposure	◦54 non-smoker volunteers from homes with smokers, EC users, control homes	◦Non-smokers passively exposed to EC vapor absorb approx. as much nicotine as when exposed to smoke from CC
Battista L [7] 2013	No	CC	◦Experimental study ◦Exposure: 4 min of smoking/vaping	◦ 12 regular users of EC	◦ EC inhalation produces the same patho-physiological cardiovascular effects of CC smoking
Chorti M [23] 2012	No	CC	◦Volunteers in CC group smoked 2 CC ◦Volunteers in EC group puffed 1 EC	◦ 15 EC naive heavy-smokers	◦Passive but not active EC vaping resulted in short-term lung obstruction and increased cotinine
Colbyl H [25] 2015	No	0 mg nicotine EC	◦Experimental study ◦Volunteers inhaled vapor 18 mg or 0 mg nicotine on separate days (randomized)	◦13 subjects (not described)	◦Study suggests that nicotine, when acutely inhaled via EC does not impair the cerebral pressure-flow relationship
Czogala J [29] 2012	No	CC	◦A repeated measures design ◦Exposure: 5 min of smoking/vaping	◦42 EC naive daily smokers	◦Slight non-sign elevation in diastolic blood pressure, pulse and carboxyhemoglobin
Dawkins L [32] 2013	❖▲ 1	No	◦A repeated measures design ◦Exposure: 1) Ten puffs 2) 1 hour ad lib use	◦14 regular EC users	◦Low reporting of AE in regular users. Most frequent: light-headedness, throat irritation and dizziness
Dawkins L [33] 2013	❖▲2	0 mg nicotine EC	◦Within-subjects design ◦Exposure: 10 min. ad lib use	◦20 EC naive smokers	◦ EC can effectively deliver nicotine to impact on cognitive performance; improved time-based memory

Dawkins L [34] 2012	❖▲3	0 mg nicotine EC	◦Mixed experimental design ◦Exposure: 5 min. ad lib use	◦86 EC naive smokers	◦Improved nicotine withdrawal impaired concentration/memory
Dicpinigaitis PV [36] 2015	No	0 mg nicotine EC	Experimental study with ◦Exposure: 30 puffs 30 seconds apart	30 healthy nonsmokers	◦Single session of EC use, approximating nicotine exposure of one CC, induces significant inhibition of cough reflex sensitivity - probably due to nicotine
Eissenberg T [37] 2010	No	CC	◦Hemodynamic measurements ◦Exposure: Puffed ad libitum 10 times	◦16 EC naive smokers	◦No increase in heart rate
Etter JF [40] 2011	No	No	◦Saliva sampling in current vapers ◦Exposure: daily vaping	◦ 31 current users (30 daily users) of EC	◦Cotinine levels in experienced vapers were similar to levels previously observed in smokers and higher than in users of nicotine replacement therapy
Farsalinos K [44] 2014	▲8	CC	◦ Randomized cross-over design ◦Exposure: smokers: 2 CC ; vapers: use EC for 10 min.	◦51 smokers and 57 daily EC users who stopped smoking	◦Sign. decreased elasticity and elevated stiffness of ascending aorta after smoking, but not after EC-use
Farsalinos KE [53] 2015	▲6		◦Experimental study ◦ Experienced vapers took 4-s puffs at different power levels with single or double wick atomizers	◦ 7 experienced blinded vapers	◦EC produce high levels of aldehyde only in dry puff conditions, in which the liquid overheat. Hypothesis: vapers will avoid dry puff conditions
Farsalinos K [43] 2012	▲5	CC	◦Hemodynamic measurements + echocardiogram at baseline and after smoking/vaping ◦Exposure: 1 CC or 7 min. of vaping of EC	◦20 EC naive smokers and 20 EC users	◦Slight elevation in diastolic blood pressure but no effect on cardiac function in experienced EC users
Ferrari M [56] 2014	No	CC	◦Experimental study – cross over design? ◦Exposure: 5 min of vaping or smoking	◦10 smokers and 10 non-smokers	◦Sign. decrease in flow when 75% of forced vital capacity has been exhaled, indicating impact on lung function
Flouris AD [57] 2013	No	CC	◦Repeated-measures controlled study ◦Exposure: 30 min. of active/passive smoking or vaping	◦ 15 EC naive smokers and 15 never-smokers	◦ Short term passive vaping generated small non-sign decrease in lung function, approx. the half of smoking ◦Similar nicotinergic impact to CC

Flouris AD [58] 2012	No	CC	◦Three experimental sessions; active and passive exposure ◦Exposure: 2 CC within 30 min. or 'a number of puffs' within 30 min.	◦ 15 EC naive smokers and 15 never-smokers	◦Acute active and passive vaping did not influence complete blood count indices in smokers and never smokers
Gennimata S[61] 2012	No	?	◦Exposure: vaping for 10 minutes	◦8 never smokers and 24 EC naive smokers	◦Short-term exposure caused immediate airway obstruction
Hecht SS [73] 2014	No	CC	◦Urine sampling in current vapers who had not smoked CC for at least 2 months	◦28 current EC vapers	◦Urinary toxicant and carcinogen metabolites were significantly lower in EC users than in CC smokers ◦Some EC users had levels of total NNAL higher than when exposed to second hand smoking
Marini S [108] 2014	No	CC	◦Experimental study ◦Exposure: 4 puffs	◦ 25 smokers	◦Similar effect on human airways, and same particle dose received with smoking and vaping
McRobbie H [114] 2015	▲ 9	No	◦Experimental study ◦Exposure: free use of EC as smoking cessation aid, 4 weeks observation	◦40 adult smokers wanting to stop smoking	◦After 4 weeks: in dual users, EC use significantly reduced exposure to CO and acrolein because of a reduction in smoke intake
Palamidas A [121] 2014	No	No	◦Experimental study ◦Exposure: Gr. A: vaping in 10 min	◦70 volunteers (27 with asthma/ COPD). Smokers+ never smokers	◦Increased airway resistance and a concomitant decrease in specific airway conductance
Papaseit [123] 2014	No	CC	◦Rrandomized and crossover controlled trial ◦Exposure: 2 sessions; 10 puffs in 5 min./ 1 CC	◦6 EC naive regular CC smokers	◦EC use produces a moderate increase in vital parameters -increases in heart rate, diastolic and systolic arterial pressure
Polosa R [128] * 2014	▲10	No	◦ Retrospective review of changes in lung function and asthma control ◦Exposure: 6 and 12 months follow-up	◦ 18 smoking asthmatics who switched to regular EC use	◦Study indicates that regular use of EC to substitute smoking is associated with objective and subjective improvements in asthma outcomes
Popa C [131] 2015	No	CC	◦Experimental study ◦Exposure: 2 sessions of 10 min with vaping or smoking	◦5 current CC smokers and 5 current EC vapers	◦Increased oxidative stress after vaping but lower than after smoking

Tsikrika S [155] 2014	No	No	◦Experimental study ◦Exposure: vaping in 10 min	◦62 volunteers,non-smokers+ smokers:28 with COPD/asthma	◦Increased heart rate and symptoms like cough and sore throat
Vakali S [158] 2014	No	No	◦Experimental study ◦Exposure: vaping in 10 min	◦64 volunteers, non-smokers+ smokers	◦Increased heart rate, palpitations and a decrease in SpO2 ◦A decrease in fraction of exhaled nitric oxide
van Staden SR[159] 2013	❖▲4	No	◦A single group within-subject design ◦Exposure: switch to EC vaping in 2 weeks	◦ 15 smokers switched to EC, 2 drop-outs	◦Increase in oxygen saturation, no changes in blood pressure and pulse rate, cough worse/improved ◦ Phlegm increased in some but decreased in more
Vansickel A [161] 2010	No	CC	◦Repeated-measures controlled study ◦ Exposure: two, 10-puff EC bouts	◦32 EC naive heavy smokers	◦No changes in plasma nicotine and heart rate ◦No increase in CO
Vansickel A [162] 2012	No	CC	◦4 within-subject sessions ◦Exposure: six 10-puff bouts-separated by 30-mins	◦20 EC naive heavy smokers	◦Increase in heart rate
Vardavas CI [163] 2012	No	EC with cartridge removed	◦Exposure: ad lib use for 5 min	◦30 EC naive smokers of at least 5 pack years	◦Increased flow resistance ◦I Immediate adverse effects on the airways after short-term use; similar to some of the effects seen with smoking
Yan XS[172] 2015	◆▲7	CC	◦Experimental study ◦Two exposure scenarios from Day 1 to Day 11: half-hour controlled administration and one hour ad lib use	◦38 EC-naïve daily smokers included, withdrew: 14, included in analyses: 23	◦ Significantly increased blood pressure and heart rate after use of several EC products ◦ EC: less exposure of nicotine and thereby less cardiovascular effects compared to CC smoking

*This study could as well have been placed in appendix 3 showing adverse events [128]

EC= electronic cigarette
CC= conventional cigarette
total NNAL =4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and its glucuronides

Conflicts of interest - Conflicts of interest of each study should be assessed individually.
❖▲1: Study was funded and supported by manufacturer of EC. LD has received funding to speak at research conferences and benefits in kind from EC companies.
❖▲2: KD has a collaborative relationship with manufacturer of EC who provided free supplies of the EC for the study
❖▲3: KD has a collaborative relationship with manufacturer of EC who provided free supplies of the EC for the study
❖▲ 4: EC manufacturer sponsored the EC used in study
▲5: Some of the studies by KF and VV were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies.
▲6: Some of the studies by KF and VV were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. Other studies by GR have been sponsored by EC company.
◆▲7: employees in tobacco company which also manufactures EC
▲8: No stated, but some of the studies by KF were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. KF has a website "Ecigarette Research Advocate Group" which represents a strictly positive view on EC and provides several links to vapor clubs.
▲9: HR is Clinical Director at The Dragon Institute (research-based training, studies on the latest changes in the health industry etc.); reports receiving commercial research grant from manufacturer of smoking cessation medication; and has received speakers' bureau honoraria from manufacturers of smoking cessation medication. MLG reports receiving commercial research grant from manufacturer of smoking cessation medication. PJ has received speakers' bureau honoraria from and is a consultant/advisory board member for the manufacturers of stop-smoking medications. No potential conflicts of interest were disclosed by the other authors
▲10: RP has received grant support, has served as a speaker and has served as a consultant for anti-asthma drug manufacturers and has received payment for developing educational presentations and being a consultant for manufacturer of smoking cessation medication; he has also served as a consultant for EC distributor. JBM has received honoraria for speaking and financial support to attend meetings/advisory boards from anti-asthma drug manufacturers

Table 3. Animal experimental studies

reporting health effects (n=11*)

For details in methodology and results please see appendix 4.

Name of first author Reference Year	Conflict of interest ▲=Yes	Reference product	Animal type and number	Exposure	Conclusions
Geraghty P[62] 2014	No	Phosphate-buffered saline; Vehicle	◦A/J mice. 4 Cohorts of mice (n=8 per group)	◦Exposed for 1 hour/day, 5 days a week for 4 months by a small animal nebulizer	◦Study shows that longer-term exposure of EC causes asthma and emphysema
Husari A [78] 2015	No	Room air or CC smoke	◦Four-month maleC57BL/6J mice	◦Exposed for 6h/day for 3 days	◦Despite higher exposure conditions, EC exhibited less toxic effects on lungs of experimental animals than CC smoke
Lerner CA [98] 2015	No	No	◦Eight weeks old wild type C57BL/6J mice	◦ Mice were exposed to side-stream EC vapor for 5 h per day for 3 days (acute exposure) in inhalation chambers	◦ EC inhalation have an impact on cellular oxidative stress, redox imbalance, and lung inflammation, in vitro in lung cells and in vivo in lungs
Lim [99] 2014	No	CC	◦ 24 five-week-old female BALB/c mice	◦Diluted solution was intra-tracheally instilled to Ovalbumin -sensitized mice two times a week for 10 weeks	◦ Suggest that the inhalation of EC solutions can function as an important factor to exacerbate the allergy-induced asthma symptoms
McGrath-Morrow S [112] 2015	No	Room air	◦Timed pregnant C57BL/6J mice and their neonatal pups	◦ Neonatal mice were exposed to EC vapor or room air for 9 days of life or kept in room air	◦EC emissions ±nicotine during the neonatal period can adversely impact weight gain ◦Exposure to EC with nicotine caused diminished alveolar cell proliferation and a modest impairment in postnatal lung growth
Palpant NJ [122] 2015	No	CC extract	◦Wild-type zebrafish (Danio rerio)	◦Zebrafish embryos were exposed from the onset of differentiation (day 0) and added fresh at every media change	◦Study indicate a negative effect of EC on heart development in vitro and in vivo ◦Impact of EC on heart development seems to be the consequence of other components than nicotine

Ponzoni L [130] 2015	No	CC or room air	◦ 183 Male BALB/ c mice; one month old	◦Exposed three 30-min sessions/day for 7 weeks in inhalation chambers	◦EC vapor induces addiction-related neurochemical, physiological and behavioural alteration, independent of nicotine
Salturk Z [137] 2015	No	Room air	◦16 Female Wistar albino rats	Exposed to EC vapor for 1 hour/ day for 4 weeks in inhalation chambers	◦EC vapor exposed animals developed more frequently hyper-and metaplasia in the larynx than non-exposed animals; non-significant differences (small study)
Schweitzer KS [143] 2015	No	Saline	◦C57Bl/6 mice (4-mo-old females)	◦Exposure: nebulized and harvested immediately, or harvested after either 30 min or 24 h.	◦It is anticipated that long-term EC use will include dose-dependent sustained oxidative stress and inflammatory lung damage with limitation of endothelial repair
Smith D [145] 2015	No	PPG without nicotine + Room air	C57BL/6J mice (pregnant + male off-spring)	◦Exposed to 2.4% nicotine in PPG or 0% nicotine /PPG once a day from gestational day 15 until delivery. + 14 days from postnatal day 2 through 16	◦Male mice exhibited increased levels of activity when exposed to vapor containing nicotine during late prenatal and early postnatal life- indicating that nicotine exposure from EC may cause persistent behavioral changes
Sussan TE [147] 2015	No	Room air	◦Male C57BL/6 (age 8 weeks) mice	◦Exposure: via a whole-body exposure system for 1.5 h, twice per day for 2 weeks. ◦One hour after final exposure: infected intra-nasally with S. Pneumoniae bacteria or Influenza A virus	◦Exposure to EC vapor induced oxidative stress and moderate inflammatory response ◦Significant impairment in bacterial clearance in lungs ◦Enhanced susceptibility to influenza infection, based on increased percent weight loss, mortality, and viral titer

*Four of these studies are also/partly mentioned in Table 3/Appendix 5 on animal experimental studies [98] [122] [143] [78]

EC= electronic cigarette

CC= conventional cigarette

PPG= propylene glycol

Table 4. Studies reporting adverse events

(n=31)

For details in methodology and results please see appendix 5.

Name of first author **Reference** **Year**	**Conflict of interest** ▲=Yes	**Type of study** RCT=randomised controlled trial	**Number of participants** **Evt. duration of follow-up**	**Conclusion**
Adriens K [1] 2015	No	RCT	◦48 volunteers not willing to quit. 3 sessions over two months: vaped/smoked for 5 min	◦ EC users reported more benefits in prospective study ◦ Dual use group reported positive and negative symptoms
Bartram A [6] 2015	No	◦Case report	◦A 55-year-old healthy man; quit and switched to EC	◦ EC use was found to be associated with a florid lichenoid reaction
Bullen C [11] 2013	▲7	RCT	◦ 657 participants randomized to nicotine-EC (n=289), placebo EC (n=295) or nicotine patch (n=73) for 13 weeks	◦A higher number and proportion of adverse events occurred in the nicotine EC group than in the patches group; however, there was no evidence of an association with study product, and the event rate was not significantly different
Bullen C [12] 2010	▲1	◦Single blind randomised cross-over trial	◦40 adult dependent smokers of 10 or more CC per day.	◦Nausea and mouth and throat irritation were common ◦Less common: aching jaws, vertigo, feeling high, palpitations
Camus M[15] 2014	No	◦Case report	◦ A 49-year-old woman with colitis ulcerosa	◦ Patient presented with a "smoking-dependent form" of colitis ulcerosa, which recurred nearly immediately after replacing CC smoking by nicotine containing EC
Caponetto P [16] 2013	▲2	◦Prospective observational study	◦14 smokers with schizophrenia not intending to quit ◦12-months	◦Positive and negative symptoms of schizophrenia were not increased after smoking reduction/cessation in patients using EC ◦AE (cough, nausea, throat irritation, headache) declined over time

Caponetto P [17] 2013	▲2	◦RCT	◦300 smokers not intending to quit ◦12-months	◦ AE as cough, dry mouth, shortness of breath, and headache declined over time ◦Small reduction in CO compared with reduction in number CC
Chen IL [21] 2013	No	◦Adverse events reported to U.S. FDA	◦ Approximately half of all tobacco-related AE reports since late 1980ies concern EC	◦Many reports of AE and SAE ◦There is not necessarily a causal relationship between AEs reported and EC use, as some AEs could be related to pre-existing conditions or due to other causes not reported
Dawkins L [35] 2013	▲3	◦Online survey	◦1349 users of EC (218 current smokers + 1123 ex-smokers + 4 never smokers)	◦ Respondents (most had quit smoking) reported few negative symptoms and many positive health effects with EC ◦ Majority state: it feels healthier and use improved cough
Etter JF [39] 2010	▲4	◦A survey of users	◦ 81 respondents ever users of EC ◦ 72 daily users, 63% recently quit smoking CC	◦ Respondents reported more positive than negative effects with EC: many reported positive effects on the respiratory system, which were probably associated with stopping smoking
Farinha H [42] 2015	No	◦Case report	◦66-year old female patient, heavy smoker- had stopped smoking and initiated EC	◦A case of probable association between EC use and lingua villosa nigra is reported
Farsalinos KE [50] 2013	▲11	◦Interviews with vapors	◦111 experienced EC users who had switched from CC to EC use for at least 1 month	◦Side effects were mild and temporary ◦ The vast majority of participants reported better exercise capacity and improved olfactory and gustatory senses
Farsalinos KE [48] 2013	▲9	◦Case report	◦ 32 old male patient with idiopathic chronic neutrophilia. Then, quit smoking with EC	◦ Despite daily use of EC, the beneficial effects of smoking cessation on idiopathic chronic neutrophilia were maintained
Farsalinos [51] 2014	▲10	◦ Survey	◦ 19,414 EC regular users world wide ◦ Median use: 10 months	◦ Side effects were minor and health benefits were substantial, especially for those who completely substituted smoking with EC use
Gillen S [63] 2015	No	Case report	◦ A 1 day old boy born at full term◦ Mother: vaping EC in pregnancy and during labor	◦Antenatal exposure to EC vapor might be a possible etiology to total colonic necrotizing enterocolitits in a new born child

Heavner K [72] 2010	▲ 5	◦Online survey	◦303 users of EC	◦Respondents reported improvements in health, especially general health and cough by replacing CC with EC
Hua M [76] 2013	No	◦Online search	◦481 vapors	◦EC use: wide ranging positive and negative effects ◦Respiratory, mouth/throat, neurological, and sensory had the most symptoms associated with them ◦Users with negative symptoms often reported more than one symptom-interactions were often seen between systems
Hureaux J [77] 2014	No	◦Case report	◦ A 43 year old patient with smoking-related COPD and lung adenocarcinoma	◦ A patient who presented with subacute bronchial toxicity associated with deterioration of pulmonary function tests after starting use of EC
Lee S [96] 2013	No	◦Case report	◦ 35-year old man with history of pan-ulcerative colitis which began after smoking cessation + EC use	◦EC use was associated with steroid-free clinical remission in colitis ulcerosa patient
Manzoli L [105] 2015	No	◦Prospective cohort study	◦ Adults (30–75 years); 236 EC vapers, 491 CC smokers, and 232 dual smokers	◦No safety concerns raised during the study, although the limitations in adverse events recording prevent authors to draw any conclusions
Maridet C [107] 2015	No	◦Case report	◦52-year-old woman ◦1 negative symptom	◦A number of EC probably release nickel ◦Contact dermatitis caused by nickel due to the use of electronic cigarettes could become increasingly common
McCauley L [111] 2012	No	◦Case report	◦1 patient ◦1 negative symptom	◦EC use was suggested as possible cause of exogenous lipid pneumonia – supposed due to glycerin based oils
McQueen A [113] 2011	No ¤, 1	◦Interviews with vapors	◦13 vapors ◦Positive symptoms	◦Improved self-reported health and quality of life
Monroy AE [116] 2012	No	◦Case report	◦70 year old woman, smoking history: 40 pack-years. ◦Undergone hip-arthroplasty	◦Possible association between use of EC and atrial fibrillation

Munoz A [117] 2015	No	◦Survey in a smoking cessation clinic	◦64 ever-users of EC	◦ Health improvements by use of EC - in those who had quit -are reported
O'Brien B [119] 2015	▲8	◦Sub-study of [11] RCT	◦86 mentally ill volunteers ◦13% of participants in study [11]	◦Persons with mental illness seem to tolerate EC
Polosa R [127] 2011	▲6	◦Prospective study	◦40 smokers not intending to quit ◦6 month	◦Primarily mouth/throat and respiratory symptoms ◦No SAE
Polosa R [129] 2013	▲6	◦Prospective observational study	◦23 smokers not intending to quit (5 not using EC at follow-up) ◦24-month	◦Persistent mouth/throat and respiratory symptoms after one year of use ◦No SAE
Thota D[152] 2014	No	◦Case report	◦ A 20-year-old healthy man	◦ Possible case of acute eosinophilic pneumonitis
Vannier S [160] 2014	No	◦Case report	◦ A 39-year-old healthy man switched from 60 CC/day to dual use of 20 CC/day + EC	◦ Possible case of reversible cerebral vasoconstriction syndrome in new dual EC + CC user ◦A few previous cases have been described with nicotine patches alone or associated with CC smoking
Wang MP [167] 2015	No	◦Population-based survey	◦45,128 students; 95% of all invited ◦Respiratory symptoms	◦The first evidence of an association between e-cigarette use and respiratory symptoms in never- and ever-smoking adolescents, which is consistent with findings from other laboratory and adult studies on short-term adverse respiratory functions

EC=electronic cigarette
CC=conventional cigarette
AE= adverse events
SEA = serious adverse events

Conflicts of interest - Conflicts of interest of each study should be assessed individually.
▲1: This project was funded by EC manufacturer. The study sponsors supplied the ECs used in the trial and funded the trial. The trial design conduct, analysis and interpretation of results were conducted independently of the sponsors. HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. ML acted as contract manager with the sponsor, manufacturer of ECs. MG has provided consultancy to the manufacturers of smoking cessation medications
▲2: RP has received lecture fees and research funding from manufacturers of stop smoking medications. He has served as a consultant for manufacturers of smoking cessation medications and the distributor EC used.
▲3: LD has a collaborative relationship with manufacturer of EC and received funds to attend academic conferences. E-manufacturer reviewed and approved content of questionnaire and set up links from their websites.
▲4: JFE was previously consultant for manufacturer of smoking cessation medications
▲5: Study was funded and supported by manufacturer of EC and manufacturer is co-author. All other authors are employed at University of Alberta, which is financially supported by a large smokeless tobacco manufacturer. CVP advises on tobacco harm reduction and is compensated for this work.
▲6: RP has received lecture fees from manufacturer of EC and has been serving as a consultant for manufacturer of EC. Manufacturer of the EC supplied product, technical and consumer support
▲7: ML, via his company Health New Zealand, previously did research funded by an EC manufacturer. CB and HM have done research on ECs funded by Health New Zealand, independently of EC manufacturer. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications.
▲8: CB has undertaken research on e-cigarettes funded by Health NZ (funded by e-cig manufacturer), independently of e-cigarette manufacturer. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs
▲ 9 to 11: "No" stated, but some of the other studies performed by KF used unrestricted funds provided to research center by e-cigarette companies. KEF has a website "E-cigarette Research Advocate Group" which represents an unambiguously positive view on EC and provides several links to vapor clubs
¤, 1: AMQ acknowledges the support of the organizers and attendees at vapers' meeting where recruitment took place

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Annexes with search strategies and detailed description of studies

Annexes with search strategies and detailed description of studies

Annex 1. Systematic search in databases showing number of articles found (Identified/screened (title)/ screened (abstract)/eligible)

First search: all studies published before 2 September 2013.

	PubMed		**EMBASE**		**Cinahl**		+ Other source
Search word	#	Identified/screened (title)/ screened (abstract)/eligible	#	Identified/screened (title)/ screened (abstract)/eligible	#	Identified/screened (title)/ screened (abstract)/eligible	Found in searched articles/ included after reading of article
Electronic cigarette	1	342/93/36/36	5	98/96/30/7	13	11/11/4/0	
Electrically heated cigarette	2	34/22/22/22	9	31/31/22/0	14	4/3/3/0	
E-cigarette	4	71/55/21/3	10	67/59/20/0	15	17/17/4/0	
ENDS and cigarette	3	63/9/1/0	7	65/14/1/0	16	3/2/0/0	
Electronic nicotine delivery system	8	3/3/0/0	6	8/8/1/0	17	1/1/0/0	
Electronic nicotine delivery device	11	20/20/8/1	12	6/6/4/0	18	1/1/0/0	
E-liquid	19	1/1/0/0	20	8/1/0/0	21	1/1/0/0	
Total number: Identified/screened (title)/ screened (abstract)/eligible		534/203/88/**62**		283/215/78/**7**		38/36/11/0	8/7

Search number

1. **Update:**

PubMed: studies published between 2 September 2013 and August 5 2014.

EMBASE: studies published in 2013/2014

Cinahl: studies published between Sept 2013 and August 2014. Latest search 14 Aug 2014.

	PubMed		**EMBASE**		**Cinahl**	
Search word	#	Identified/screened (title)/ screened (abstract)/eligible	#	Identified/screened (title)/ screened (abstract)/eligible	#	Identified/screened (title)/ screened (abstract)/eligible
Electronic cigarette	1	683/165/26/16	8	296/209 /33/6	15	18/18/1/0
Electrically heated cigarette	2	0/0/0/0	9	0/0/0/0	16	0/0/0/0
E-cigarette	4	127/121/16/1	10	98/91/8/1	17	46/45/2/0
ENDS and cigarette	3	21/11/0/0	11	1/1/0/0	18	3/3/0/0
Electronic nicotine delivery system	5	13/13/3/1	12	19/13/0/0	19	1/1/0/0
Electronic nicotine delivery device	6	5/4/4/0	13	8/8/2/0	20	0/0/0/0
E-liquid	7	6/5/1/0	14	15/6/0/0	21	2/2/0/0
Total number: Identified/screened (title)/ screened (abstract)/eligible		855/319/51/**18**		437/328/43/**7**		70/69/3/0

Search number

In total INCLUDED in first published review [127], based on 2 searches: 68 + 8 identified elsewhere= 76

2. Update:

+Filter: Search field=title or title/abstract (starting with step: screened by title)
PubMed: studies published between 5 August 2014 and 7 July 2015.
EMBASE: studies published in 2014 to Current. Electronic cigarette: Selected: Map Term to Subject Heading (electronic cigarette = focus).
E-cigarette: Selected: Map Term to Subject Heading (all other search words = key word). Latest search: 1 October 2015.
Cinahl: studies published between Aug 2014 and October 2015. Latest search: 2 October 2015.
Finally, search #1 to #7 was repeated; in PubMed only: studies published between 7 July 2015 and 26 Nov 2015. Search field=title

	PubMed		**EMBASE**		**Cinahl**		+ Other source
Search word	#	Identified/screened (title)/ screened (abstract)/eligible	#	Found in searched articles/ included after reading of article	#	Identified/screened (title)/ screened (abstract)/eligible	Found in searched articles etc./ included after reading of article
Electronic cigarette	1	229/69/38/36 52/16/13/10	9		17	46/4/0/0	
Electrically heated cigarette (not searched, is non-combustible CC)	2	0/0/0/0	10		18	0/0/0/0	
E-cigarette	3	211/40/27/8 75/17/17/1	11	+ Other source	19	179/17/0/0	
ENDS and cigarette	4	14/1/1/0 0/0/0/0	12	Found in searched articles/ included after reading of article	20	0/0/0/0	
Electronic nicotine delivery system	5	9/2/1/0 1/1/0/0	13		21	5/1/0/0	
Electronic nicotine delivery device	6	7/1/1/1 0/0/0/0	14		22	0/0/0/0	
E-liquid	7	16/7/6/0 1/1/1/1	15	+ Other source	23	2/1/0/0	
E-juice (new)	8	3/1/0/0 0/0/0/0	16	Found in searched articles/ included after reading of article	24	0/0/0/0	
Total number: Screened (title)/ screened (abstract)/eligible/**included**		489/121/74/**45** 99/5/31**/12**				232/323/0/**0**	**11**

Search number

In total identified at 2. Update of search: 88 + 11 from elsewhere =99

In total INCLUDED: 76 from first search and first update + 99 from second update= 175

Annex 2. Studies investigating the content of fluid or vapor of electronic cigarettes and in-vitro experiments where cells were exposed to fluid/vapor/vapor extract (n=105*). Detailed version.

Name of first author. Reference Year	Conflict of interest ▲=Yes ◆ = Tobacco industry[1] ❖=EC industry[2]	Relevant for passive expo-sure to EC Θ=Yes	Type of product(s) Reference (ref) product	Fluid/vapor/ nicotine on surface Aim	Methods	Results	Method problems/ weaknesses	Conclusion
Allen JG [2] 2015	No		◦51 types of flavored EC sold by leading brands and flavors appealing to youth Ref: no	◦Vapor ◦Aim: to determine if the flavoring chemical diacetyl, and two other high-priority flavoring chemicals 2,3-pentanedione, and acetoin, are present in a ECs	◦Air stream was captured and analyzed for total mass of diacetyl, 2,3-pentanedione, and acetoin, according to OSHA Method 1012	◦At least one flavoring chemical was detected in 47 of 51 unique flavors tested ◦Diacetyl: detected above the laboratory limit of detection 39 of the 51 flavors tested, ranging from < limit of qualification to 239 µg/EC ◦2,3-pentanedione and acetoin: detected in 23 and 46 of the 51 flavors tested at concentrations up to 64 and 529 µg/EC, respectively	◦Possible that samples did not fully reflect the total chemical content if liquid remained in the EC at the time the sampler was turned off; underestimate of chemical content	◦Findings confirm the presence of diacetyl (causing bronchiolitis obliterans/"pop-corn lungs") and other high priority flavoring chemicals in flavored compounds in EC
Aug A [3] 2014	No		◦ "strong/high" AIRSmoke EC liquid Ref: CC smoke condensate	◦Fluid ◦Aim: to assess the impact of EC exposure on the metabolome of primary human bronchial epithelial cells (HBEC) and evaluate the effect of an antioxidant glutathione analogue UPF1 on the changes	◦Human bronchial epithelial cells , differentiated at air-liquid interface, were exposed to EC liquid or CC smoke condensate for 1h, followed by treatment with 0-10 µM UPF1 for 1-12 h. Cell lysates were analysed on an AB Q-Trap 3200 mass spectrometer	◦Exposure to EC: a rapid shift of the HBEC metabolic state, followed by a delayed approach to the initial state by 12 h. ◦The changes caused by EC occurred at similar direction with those produced by CC smoke condensate in 54.4%, 70.1%, 84.4%, 52.3% and 58.8% of signals at 1, 2, 5, 7 and 13 h, respectively ◦The effect of EC on the metabolites was stronger than that of CC smoke condensate in 38.0%, 56.5%, 79.2%, 63.3% and 49.1% of the signals at 1, 2, 5, 7 and 13 h, respectively ◦UPF1 diminished the metabolomics derangements in the EC-stimulated cells with its maximal effect being at 5 h	◦Tested one brand only ◦Use of fluid, not vapor	◦EC have immediate and profound adverse effects on the metabolomic state of primary human bronchial epithelial cells similar to those seen with CSC
Bahl V [4] 2012	No		◦35 different refill fluid samples from 4 major US brands	◦Refill fluids ◦Aim: test cytotoxicity of:	◦Human embryonic stem cells (hESC) ◦Mouse neural stem	◦Humectants: non-cytotoxic for all cells ◦15 samples were moderately	◦Vapors were performed at a maximum conc. of	◦ Approx. one third of samples were highly cytotoxic to hESC and

[1] Results of studies influenced by the tobacco industry are marked with an asterisk (*) in the paper.

[2] Studies funded by e cigarette manufacturers or performed in collaboration with the e cigarette industry are labelled with a chevron (^) in the paper.

			◦No ref product	◦Humectants: PPG, vegetable VG ◦Flavors: 29 different ◦Nicotine: 5 conc	cells (mNSC) ◦Human pulmonary fibroblasts (hPF) ◦MTT assay and NOAELs and IC_{50}s were determined from dose-response curves	cytotoxic to hESC and mNSC (generally, same response) ◦12 samples were highly cytotoxic to hESC and mNSC ◦Cinnamon Ceylon had strong cytotoxic effects on all three cell types ◦High levels of nicotine were not correlated to high levels of cytotoxicity ◦Within a flavor chemical composition and cytotoxicity were very variable	1%= 100 times less than a user would inhale-underestimation of effect on lung fibroblasts? ◦One-time exposure may underestimate cytotoxicity ◦Tested only one batch of liquid per brand/model ◦Fibroblasts, are normally not in direct contact with vapor	mNSC ◦ Cytotoxicity was not due to nicotine but to chemicals used in flavor fluids ◦Embryonic and neonatal stem cells were more sensitive to EC fluid than lung fibroblasts (= developmental defects during pregnancy?)
Behar RZ [8] 2014	No		◦10 (8) cinnamon-flavored refill fluids ◦ Different brands ◦Reference: no	◦Fluid ◦Aim: to determine if high cytotoxicity is a general feature of cinnamon-flavored EC refill fluids and to identify the toxicant(s) in Cinnamon Ceylon	◦Screened using the MTT assay gas chromatography– ◦Mass spectrometry and high-pressure liquid chroma-tography	◦ Nicotine concentration did not correlate with cytotoxicity ◦ Most cinnamon-flavored refill fluids were cytotoxic with IC50 concentrations below 1% for hESC and hPF ◦ Human embryonic stem cells were more sensitive than human adult pulmonary fibroblasts. ◦ Most products were highly volatile and produced vapors that impaired survival of cells in adjacent wells ◦ Cinnamaldehyde (CAD), 2-methoxycinnamaldehyde (2MOCA) were highly cytotoxic	◦ The IC50s established in the study may underestimate toxicity due to the continual loss of volatile test chemical from the culture medium during exposure of cells ◦Fibroblasts, are normally not in direct contact with vapor	◦Cinnamon flavorings in refill fluids are linked to cytotoxicity
Bertholon JF [9] 2013	No		◦ One brand: la Cigarettec ,model ZenAttitude, 16 mg nicotine ◦Reference: CC, Gauloise, and water pipe	◦Vapor ◦Aim: Measure aerosol particle sizes in three streams; inhaled by the user(S1), released by the device itself (S2)and, exhaled by the user (S3)	◦Electrostatic low-pressure impactor (ELPI), giving particle size distributions in real time and calculating median diameters, D50, and dispersion	◦26% of the total vapor would deposit, of which 14% would reach the alveoli -These data are close to those found with CC. ◦The half-life in air of the S3 stream was 11 seconds due to a rapid evaporation ◦The EC vapor, as measured here, is made of particles bigger than those of CC and water pipe aerosols	◦Tested one brand only	◦Contrary to CC smoke, which has a half-life in air of 19 to 20 minutes, the half-life of EC is very short and risk of passive ‘‘smoking’’ exposure from EC is modest
Brot L [10] 2015	No		◦Unknown EC brand, containing PPG ◦Ref: CC smoke extract; solvent: PPG	◦Vapor extract ◦Aim: to compare the impact of the EC with that of CC on inflammatory response in an epithelial intestinal cell culture model	◦The intestinal inflammatory response was evaluated using a human intestinal epithelial cell line model (HT29), transfected with bacterial LPS	◦Cells exposed to vapor showed inflammatory response comparable to control cells and significantly lower than those treated with CC smoke extracts. ◦Inflammatory response was greatly elevated in cells exposed to CC smoke, as measured by IL-8 release (pg/mg protein)	◦Unknown single brand	◦Results suggest that the intestinal epithelium inflammatory response is not altered by exposure to vapor from EC

					receptor, MD-2 ◦Release of interleukin (IL)-8, a marker of inflammation, was measured by ◦A smoking machine ◦MTT toxicity test	◦IL-8 release (pg/mg protein) : 79.6±10.1 (controls) vs 175.2±16.6 (CC) and 68.6±4 (EC) vs 77.7±10.7 (PPG) and for cells treated with 10 µg/ml LPS; 1507.8 ±228.6 (controls) vs 2684.7±632.1 (CC) and 1287,5±235 (EC) vs 1570,9±224,8 (PPG).		
Bush D [13] 2014	▲25	Θ	◦Unknown brands ◦Ref: CC(unknown brand) and no use of nicotine-containing products	◦Nicotine on surfaces in households ◦Aim: to examine the nicotine residue in EC users' homes	◦Households of 8 EC users (50-500 puffs daily), 6 CC smokers (5 -40 cigarettes per day), and 8 non-users of nicotine-containing products ◦Three surface wipe samples were taken from the floor, wall and window ◦Nicotine was extracted and analyzed using gas chromatography	◦Half of the EC users' homes had detectable levels of nicotine on surfaces whereas nicotine was found in all of the tobacco cigarette smokers' homes ◦The levels of nicotine in ECs users' homes were almost 200 times lower than the levels detected in CC smokers homes (average concentration 7.7 ± 17.2 vs. 1303 ± 2676 _g/m2; $p < 0.05$) ◦There was no significant difference in the amount of nicotine in homes of EC users and non-users ($p > 0.05$)	◦Pilot study - the traces of nicotine need to be confirmed with mass spectrometry analysis ◦Nicotine is a common environmental contaminant found on indoor surfaces even in non-smokers homes	◦Using EC indoors leads to significantly less third-hand exposure to nicotine compared to smoking tobacco cigarettes
Cameron JM [14] 2013	No		◦7 types of e-liquids ◦Obtained from local vendors in USA. Labeled brands: Vapour, Smart Smoke, BE112 ◦Prepackaged with marked conc. levels (n=2) + blank bottles with no conc. level (n=5, estimated) ◦No ref product	◦Fluids ◦Aim: measure nicotine concentration level	◦Triplicate 0.05 ml aliquots were taken from each sample of nicotine solution and then serially diluted with Milli-Q water ◦Samples were analysed by liquid chromatography-electrospray ionisationtandem mass spectrometry	◦All EC nicotine solutions assayed contained nicotine, as advertised ◦For all samples, the amount of nicotine present (mg/ml) was ≤than what was marked /expected	◦Only test of fluids ◦Nicotine level estimated in 5 samples	◦Large variability in nicotine concentrations was found
Cervellati F [18] 2014	No		◦Cloud-smoke (balsamic flavors with or without nicotine) Ref: CC smoke	◦Vapor ◦Aim: to compare the in vitro cytotoxicity of CC smoke and EC vapors on cells from lung and skin	◦Short term exposure of HaCaT cells (keratinocytes) and A549 cells (lung epithelial cells) to CC smoke and EC vapors with and without aroma or nicotine	◦The cytotoxic components of EC were restrained to the flavoring compound and, to a lesser extent, to nicotine although their effects were less harmful to that of CC smoke ◦Humectants alone exhibited no cytotoxicity but induced the release of cytokines and pro-inflammatory mediators	◦ One brand only	◦ Exposure to EC vapors is far less toxic than exposure to CC smoke
Chausse P [19] 2015	No		◦No ECs tested ◦No ref.	◦Heating of EC ◦Aim: to test the resistance value of the heating filament - as use of EC with high	◦Comparing the possible power of a 3.3 and 5V EC depending on the filament value	◦EC users can easily obtain filaments called "coil" with different ohmic values. ◦It is possible for a 3.3 V EC to obtain the same power as a 5 V EC.	◦Analytical model not testing of EC	◦It is possible for a 3.3 V EC to obtain the power of a 5 V EC, with risk of dissemination of formaldehyde

				heating power is reported to disseminate formaldehyde				
Cheah NP [20] 2012	No		◦20 variants of EC - cartridges ◦Products confiscated from the Immigration and Checkpoints authority, Singapore ◦No ref product	◦Cartridges ◦Aim: test content of: ◦Nicotine ◦Humectants: PPG, glycerol	◦Organic solvent extraction followed by detection by chromatography with flame ionisation detector. ◦Each compound was identified using the same instrument with mass spectrometer detection.	◦18 products: contained >100 mg of PPG per cartridge (max. 1320 mg) ◦2 products: contained a very high level of glycerol (max. 359 mg) ◦16 products: actual nicotine content did not correspond to the amount reported ◦4 products: contained nicotine even though they claimed to be nicotine free ◦Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamine compounds were not found	◦Tested only one batch of liquid per brand/model ◦Not vapor	◦Presence of a high amount of glycols (PPG and glycerol) in great quantities ◦Contained nicotine even though they claimed to be nicotine free ◦Significant difference in the nicotine content across EC with same label, brand-to-brand and cartridge-to-cartridge variations ◦Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamine compounds were not found
Chen L [22] 2015	No		◦EC of unknown brand, with nicotine of different conc Ref: CC smoke extract	◦Vapor extracts ◦Aim: to elucidate if the exposure to physiologically relevant levels of e-vapor can alter platelet functions	◦Exposed platelets to vapor extracts ◦Exposure time?	◦Platelet aggregation was enhanced ◦For the e-juice formulations with the highest concentration of nicotine, this enhancement mirrored the effects of mainstream and sidestream tobacco smoke extracts ◦Altered platelet aggregation was partially induced by an up-regulation of CD42b ◦Adhesion potential of platelets was also enhanced via an up-regulation of CD41a and CD62P, respectively ◦Platelets were more likely to participate in coagulation based reactions, suggesting an enhancement of the coagulation cascade	◦Unknown brand ◦Unknown duration of exposure	◦Study illustrates preliminary evidence that e-vapor exposure may alter platelet functions associated with cardiovascular disease progression
Colard S [24] 2015	◆▲26	Θ	◦No specific product tested	◦Vapor ◦Aim: to calculate whether the aerosol exhaled following the use of EC has implications for the quality of air breathed by bystanders	◦Mathematical models based on empirical emissions data and basic assumptions Simulation model of the cumulative effect of vaping over time	◦The maximum concentration of nicotine the bystander will be exposed to over the working day is approximately 1.8 µg/m3. (workplace exposure limit for nicotine: 500 µg/m3 over 8 h in the workplace) ◦The model showed good agreement with the published values of indoor air nicotine concentration	◦Calculations were based on published studies performed by persons with conflict of interest ◦Not real-life measurements	◦The exposure of bystanders to nicotine in the exhaled aerosol is not at levels that would be expected to cause health concerns
Costigan S [27] 2015	◆▲35		None	◦Aim: to suggest an approach to toxicological risk assessment of flavors	◦A flavor ingredient screening and risk assessment process flow	◦Suggested: a threshold concept that can be helpful when there is a lack of data on local and systemic toxicity is the toxicological threshold of concern (TTC) ◦Suggests use of toxicological threshold of concern (TTC). A TCC	◦No testing of fluid/vapor	◦Presents an approach to risk assessment of in-going flavoring ingredients in e-liquid and potential thermal breakdown and reaction products in the aerosol

						of 1800 lg/day is considered appropriate to apply to worst-case exposure estimates for Cramer class 1 contaminants and 90 lg/day for Cramer class 2 and 3 contaminants.		
Costigan S [26] 2014	◆▲36		None	◦Aim: To assess in an evaluation approach model if flavour ingredients have the potential to induce contact sensitisation (delayed "Type IV" hypersensitivity)	◦A flavor ingredient screening and risk assessment process flow	◦The approach developed here applies both to single ingredients and to constituents of naturals In example Geraniol 1% is not below 1000ppm but has no sensitization potential and the sensitizer level is supportable Isoeugenol 3% is not below 1000ppm and has sensitization potential and the sensitizer level is not supportable	◦Calculations only, no testing	◦Presents a contact sensitization and risk assessment model
Cox C [28] 2015	No		◦97 EC (15 disposable, 32 cartridge, 50 refillable) from 24 EC companies, including the leading US brands	◦Vapor ◦Aim: to test levels of one or both of two cancer-causing chemicals, acetaldehyde and formaldehyde in EC and compare with California's consumer protection law, Proposition 65	◦Tested in independent testing laboratory that is accredited by the American Association for Laboratory Accreditation and that has been testing both cigarettes and EC for many years ◦Standard smoking machines that simulate how consumers use the products	◦Formaldehyde exposures up to 473 times the Proposition 65 safety level and acetaldehyde exposures up to 254 times the safety level 21 of the 24 EC companies had at least one product that produced high levels acetaldehyde and/or formaldehyde, in violation of California's consumer protection law, Proposition 65 ◦Even nicotine-free EC produced high levels of both chemicals ◦One nicotine-free EC produced acetaldehyde exposures >13 times safety threshold and formaldehyde exposures > 74 times the safety threshold	◦No reference ◦Levels and methods not shown in detail	◦The majority of EC produce very high levels of acetaldehyde and formaldehyde ◦High levels of these cancer-causing chemicals are produced even by some EC without nicotine
Czogala J [30] 2014	▲1		◦ 3 models of EC (high, medium, low nicotine), popular brands in Poland: (a) Colinss Age with Camel High cartomizer, (b) Dekang 510 Pen with SGC Regular cartridge, and (c) Mild M201 Pen with Marlboro cartridge ◦Reference: own brand CC	◦Vapor ◦Aim: to evaluate the secondhand exposure to nicotine, PM2.5, CO, and VOCs	◦ Exposure chamber ◦ Study 1: A smoking machine and controlled exposure conditions ◦ Study 2: Compared secondhand exposure with e-cigarette vapor and tobacco smoke generated by 5 dual users	◦ Air concentrations of nicotine ranged from 0.82 to 6.23 µg/m3. ◦ The average concentration of nicotine resulting from CC was 10 times higher than from EC (31.60 ± 6.91 vs.3.32 ± 2.49 µg/m3, respectively; p = .008) ◦ The mean concentration of PM2.5 from CC was 7 times higher than from EC (819.3 ± 228.6 vs. 151.7 ± 86.8 µg/m3, respectively; p = .008). ◦Both studies: VOCs: only toluene was detected ◦ No changes in CO concentration after use of EC	◦Tested only 3 brands ◦ Measured a limited number of chemicals ◦ Assessed concentrations of several markers in the air but not serum concentrations in people exposed to secondhand vapor	◦Using EC in indoor environments may involuntarily expose nonusers to nicotine but not to toxic tobacco-specific combustion products
Davis B [31] 2015	No		◦ 71 EC refill fluids and 1 do-it-yourself product	◦Fluid ◦Aim: evaluate the accuracy of	◦High-performance liquid chromatography	◦35 of 54 nicotine-containing fluids had quantified nicotine concentrations that deviated by more than ± 10%	◦American products only	◦Nicotine concentration labeling on electronic cigarette refill products was

			◦ 5 different American manufacturers ◦Purchased on 4 different dates April 2011; summer 2011; February 2012; May 2012 ◦Detailed description of products and manufacturers Ref: no	nicotine concentration labeling on EC	◦Quantified data were compared to manufacturers labeled concentrations ◦Duplicate refill fluid products purchased at different times were evaluated by visual comparison of fluid coloration and quantified nicotine concentration	from the labels ◦Refill fluids labeled as 0 nicotine had no detectable nicotine ◦Of the 5 products that were unlabeled for nicotine concentration, 3 contained no detectable nicotine, whereas the remaining 2 contained nicotine in excess of 100 mg/ml and may have been intended for DIY use ◦16 of the 18 duplicate bottles of refill fluid varied greatly in their nicotine concentrations ◦1 of the 5 companies showed significant improvement in labeling accuracy		often inaccurate but showed improvement recently in products from one company
El-Hellani A [38] 2015	No		◦Prefilled EC cartridges of the Vapor for Life, V2, Green Smoke, Apollo, Bull Smoke, Halo, G6, Bluewater, and Blu brands in various nicotine concentrations were procured from US Internet vendors as were samples of EC liquid refill solutions: My Freedom Smoke Do It Yourself (100 mg/mL)	◦Fluid and vapor ◦Aim: to investigate not only total nicotine delivery from EC but also its partitioning: free-base and protonated forms	◦A solvent extraction method for determining total nicotine and its partitioning in EC liquids and aerosols by gas chromatography	◦Most of the nicotine was in the free-base form, with aerosols exhibiting higher free-base nicotine fraction than the parent liquids ◦Apparent pH was found to correlate with nicotine partitioning and can provide a useful indirect measure when chromatography is unavailable ◦Labeled liquid nicotine concentration was often inconsistent with measured nicotine	◦Bias: interaction between nicotine and filter materials	◦Nicotine partitioning varies considerably across commercial EC liquids and these differences can persist when the liquids are vaped. ◦Findings suggest that EC liquids of a given total nicotine concentration may result in different nicotine uptake efficiencies when vaped
Etter JF [41] 2013	▲2		◦20 refill fluids of 10 of the most popular brands of EC used in several countries (USA, UK, France, Switzerland) ◦No ref product	◦Refill fluids ◦Aim: test levels of: ◦Nicotine, ◦Nicotine degradation products ◦Specific impurities	◦E-liquids diluted with ammonia solution. Analyzed with a gradient method using Dionex UltiMate 3000 RS ultra-high performance liquid chromatography ◦Presence of ethylene glycol and diethylene glycol by gas chromatography	◦Within each brand: some differences between the duplicates ◦All samples: the area for the degradation products represented between 0 and 4.4% of the area for nicotine ◦ Most common nicotine-related impurities: cis-N-oxide, trans-N-oxide, myosmine, anatabine and anabasine ◦All solutions: contained a mixture of PPG and glycerol ◦ No ethylene glycol or diethylene glycol	◦Solutions were oily and viscous-exact volume can be difficult to pipette and disperse ◦Tested only one batch of liquid per brand/model ◦Not vapor	◦Half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia ◦The nicotine content in the samples generally corresponded to the labels on the bottles
Farsalinos KE [46] 2015	▲13		◦ 159 sweet-flavored samples from 36 manufacturers and retailers in 7 countries ◦ +3 liquids were prepared by dissolving	◦ Vapor ◦ Aim: to evaluate sweet-flavored EC liquids for the presence of DA and PA	◦ A modified version of the High Performance Liquid Chromatography (HPLC) carbonyl compound analysis	◦ DA and AP in 74.2% of the samples 7.3% of DA and 41.5% of AP-containing samples exposed consumers to levels higher than the safety limits ◦ Levels 100 and 10 times lower in EC	◦ Sweet flavors only ◦ No clinical evidence indicating that calculated cut-off level set by	◦ DA and PA - chemicals associated with respiratory disease when inhaled - were found in a large proportion of sweet-flavored EC liquids, with many of them

			a concentrated flavor sample of known DA and AP levels at 5%, 10%, and 20% concentration in a mixture of DA and PA	◦ Aim 2: measure the levels of these chemicals in aerosol	method ◦ An Agilent Model 1100, HPLC equipped with an Ultraviolet (UV) Detector ◦ A Cerulean SM 450 smoking machine used to collect 50 puffs from all samples	compared with smoking, for DA and PA ◦ The median daily exposure levels were 56 µg/day (IQR: 26–278 µg/day) for DA and 91 µg/day (IQR: 20–432 µg/day) for AP	National Institute on Occupational Safety and Hazards is applicable to EC use	exposing users to higher than safety levels
Farsalinos KE [45] 2015	◆▲14		◦ 21 samples (10 conventional EC liquids and 11 Natural Extract of Tobacco (NET) liquids) were obtained from the US and Greek market	◦ Fluids ◦Aim: to evaluate nicotine levels and the presence of tobacco-derived toxins in tobacco flavored conventional EC liquids and NET liquids	◦ Nicotine levels were measured and compared with labelled values ◦ The levels of tobacco-derived chemicals were compared with literature data on CC products	◦12 samples had nicotine levels within 10% of the labelled value ◦TSNAs were present in all samples at ng/mL levels. ◦Total TSNAs and nitrate were present at levels 200–300 times lower in NET liquids; Flavourart RY4 = 40 ng/ml ◦Nitrates were present almost exclusively in NET liquids. ◦Acetaldehyde was present predominantly in conventional liquids; liquid AtmosLab RY69=20 ng/ml ◦Formaldehyde was detected in almost all EC liquids at trace-levels. ◦Phenols were present in trace amounts, mostly in NET liquids. compared to CC	◦Not vapor ◦Inter-batch variability not tested ◦Compares levels in EC liquid with level of CC smoke ◦ Compares 1 ml EC liquid with 1 gram CC ◦ Formaldehyde and acetaldehyde are formed during the heating process of EC - underestimation of true exposure?	◦ Natural Extract of Tobacco liquids contained higher levels of phenols and nitrates, but lower levels of acetaldehyde compared to conventional EC liquids ◦ All EC liquids contained far lower (by 2–3 orders of magnitude) levels of the tobacco-derived toxins compared to CC
Farsalinos KE [52] 2015	▲15		◦Two studies were found in the literature, measuring metals emitted to the aerosol from 13 EC products	◦ Literature study ◦ Vapor ◦ Aim: to perform a risk assessment analysis, evaluating the exposure of EC users to metal emissions based on findings from the published literature	◦Exposure from 1200 puffs (+high exposure) was compared with the chronic Permissible Daily Exposure (PDE) from inhalational medications defined as safe by different regulatory agencies	◦The average daily exposure from 13 EC products was 2.6 to 387 times lower than the safety cut-off point of PDEs, 325 times lower than the safety limit of MRL and 665 to 77,514 times lower than the safety cut-off point of RELs. ◦Only one of the 13 products was found to result in exposure 10% higher than PDE for one metal (cadmium) at the extreme daily use of 1200 puffs ◦Significant differences in emissions between products were observed	◦ Literature study only ◦Products tested were used for the first time during the study sessions – but there might be a change in the stability and related metal emissions after some days of use ◦ Some safety limits are for occupational exposure	◦ The levels of daily exposure from EC use are significantly lower compared to acceptable exposure from inhalational medications and by orders of magnitude lower than the regulatory limits for daily occupational exposure
Farsalinos KE [44] 2015	▲27		◦EC liquids(18mg nicotine/ml) of tobacco flavor, Greek EC	◦ Fluid and vapor ◦ Aim: to compare the levels of	◦ Three 100-puff sets from each liquid were trapped in filter	◦ Only NAB was found at trace levels in two commercial liquids (1.2 and 2.3 ng/g), while the third	◦ Study was not designed to detect whether the	◦ Minimal levels of tobacco specific nitrosamines were found in the liquid samples

			companies EC device: Epsilon 1100, Nobacco, 2nd generation (eGo-style) lithium battery , 1100 mAh and a tank-type atomizer ◦Additional sample was prepared by adding known amounts of standard TSNAs solutions to one of the obtained liquids	TSNAs between liquids and generated aerosol	pads and were subsequently analyzed for the presence of TSNAs ◦ The expected levels of TSNAs (calculated based on the liquid consumption) were compared with the measured levels in the aerosol.	contained 1.5 ng/g NAB and 7.7 ng/g NNN. ◦ The 100-puff sets: 336–515 mg liquid consumption, with no TSNAs in the aerosol. ◦ Exposure of EC users to TSNAs can be accurately assessed based on the levels present in the liquid	source of aerosol TSNAs is the liquid alone or if additional amounts may be produced due to heating	
Farsalinos KE [48] 2013	❖▲ 29		◦ 20 EC liquid samples (17 tobacco flavors, 3 sweet or fruit flavors), 4 samples produced by using cured tobacco leaves 1.set: lithium battery (eGo), a 2.2-Ohms atomiser (510 T) and a tank-type cartridge 2.set: variable-voltage device (Lavatube), total energy 9.2 watts ◦ Ref: 1.“base” liquid sample (50% glycerol/50% propylene glycol, with no nicotine or flavorings) 2. CC Marlboro, 0.8 mg nicotine	◦ Vapor ◦ Aim: to evaluate the cytotoxic potential of the vapor of on cultured myocardial cells	◦ Cytotoxicity was tested according to the ISO 10993-5 standard ◦ CC smoke was produced according to ISO 3308 method ◦ The extracts, undiluted (100%) and in four dilutionswere applied to myocardial cells (H9c2); percent-viability was measured after 24 h incubation. According to ISO 10993-5, viability of <70% was considered cytotoxic	◦ Three EC extracts (produced by tobacco leaves) were cytotoxic at 100% and 50% extract conc. ◦ One (“Cinnamon-Cookies” flavour) was cytotoxic at 100% conc. ◦For EC extracts produced by high-voltage and energy, viability was reduced but no sample was cytotoxic according to ISO 10993-5 definition ◦ Cell survival was not associated with nicotine conc. of EC liquids ◦ CC smoke extract was cytotoxic at extract conc. >6.25% Inhibitory conc. 50 was >3 times lower in CC smoke extract compared to the worst-performing EC vapour extract.	◦ Are the EC extracts comparable to CC smoke extract?	◦ Study indicates that some EC samples have cytotoxic properties on cultured cardiomyoblasts ◦ Cytotoxicity was mainly observed in samples produced by using tobacco leaves ◦ All EC vapor extracts were significantly less cytotoxic compared to CC smoke extract For EC extracts produced by high-voltage and energy, viability was reduced
Feng Y [54] 2015	▲28		◦Hypothetical EC vapor and CC smoke	◦Vapor ◦Aim: to provide fundamental understanding of the dynamics and transport of aerosols from an EC in and idealized tubularG3–G6 respiratory tract model	◦A computational model has been developed that includes the effects of hygroscopic growth as well as evaporation from multicomponent aerosol droplets An experimentally validated computational fluid-particle dynamics (CF-PD) model is	◦Due to the combined multicomponent evaporation/ condensation effects, all EC-droplets will undergo size-changes Vaporization/condensation of a droplet will be influenced by its initial temperature for a negligible time duration after the droplet has been released from the inlet After the droplet temperature quickly approaches the ambient temperature, water vapor start to condensate at the droplet surface, leading to hygroscopic growth, i.e., droplet-size	◦Computer simulation model, not human experiment	◦The results indicate that EC-droplets, being more hygroscopic than CC smoke particles, tend to grow larger in maximum size in a typically highly humid environment

					presented	increase. Meanwhile, the other components (i.e., glycerol, PG, and nicotine) keep evaporating slowly due to the absence of their vapor species surrounding the droplet and their low volatilities. A correlation for the growth ratio of EC-droplets in TBUs is proposed		
Fernández E [55] 2015	No	Θ	◦ Unknown	◦Vapor ◦ Aim: to describe the emission of particulate matter ≤2.5 μm in diameter ($PM_{2.5}$) from CC and EC at home in real-use conditions	◦ Measured $PM_{2.5}$ in four different homes: one from a CC smoker, one from an EC user, and two from non-smokers	◦ The $PM_{2.5}$ median concentration was 9.88 μg/m3 in the EC user home and 9.53 and 9.36 μg/m3 in the smoke-free homes, with $PM_{2.5}$ peaks concurrent with the EC puffs ◦ PM2.5 peaks (over the 10 μg/m3 limit) concurrent with the EC puffs	◦ One vaper only	◦ ECs used under real-life conditions emit toxicants, including $PM_{2.5}$ although these are notably lower than those from CC
Fouco FC [59] 2013	No		◦ 2 rechargeable models A and B) and one disposable model (C) ◦ 4 liquid flavors, liquid nicotine contents (low, medium, high) ◦Reference: CC Marlboro, 0.8 mg nicotine	◦ Vapor ◦ Aim: to measure particle number concentrations and size distributions in order to identify the impact of the particles inhaled by EC vapor on human health and to put a new insight for assessing of respiratory dosimetry	◦ Instruments used: TSI model 3775 Condensation Particle Counter TSI model 3091 Fast Mobility Particle Sizer thermodilution system (two-step dilution) TSI model 3080 Electrostatic Classifier TSI model 4410 Flow meter	◦ The total particle number concentration peak (for 2-s puff), averaged across the different EC types and liquids, was measured equal to $4.39 \pm 0.42 \times 10^9$ part. cm^{-3}, then comparable to CC ◦ Greater particle number concentrations were measured for higher nicotine content liquids and longer puffs ◦ Particle number distribution modes of the EC-generated vapor were in the 120e165 nm range, then similar to the conventional cigarette one	◦ Few brands	◦ Particle number distribution modes of the EC-generated vapor were similar to the CC ◦ EC were found to be a major particle source, which can lead to significantly high deposition in vapers
Geiss O [60] 2014	No	Θ	◦Two 'second generation' refillable EC ◦TypeA and type B EC were equipped with a 280 mAh and a180 mAh battery, respectively ◦Two refill liquids: 'traditional'= approximately equal parts of PPG and glycerol as a base and 10% water. 'Velvet' consisted of only glycerol (80%) and water (20%) ◦Each with three	◦ Vapor ◦ Aim: to investigate and characterise the impact of vaping on indoor environments under controlled conditions	◦ Gas chromatographic system coupled to a flame ionisation detector ◦ Modified analytical smoking machine ◦30 m^3 emission chamber	◦ EC=source for PPG, glycerol, nicotine, carbonyls and aerosol particulates ◦ Estimated lung concentrations of 160 and 220 mg $m^{-3}$for PPG and glycerol were obtained, respectively ◦ Vaping refill liquids with nicotine concentrations of 9 mg mL^{-1}led to vapour condensate nicotine amounts comparable to those of low-nicotine CC (0.15–0.2 mg) ◦ In chamber studies: peak concentrations of 2200μg $m^{-3}$for PPG, 136 μg $m^{-3}$for glycerol and 0.6 μg $m^{-3}$for nicotine ◦Carbonyls: not detected above the detection limits in chamber studies ◦ Particles in the size range of 20 nm	◦Tested few brands ◦Did not test inhalation in passive vapers ◦ Design flaws such as leakages from the cartridge reservoirs	◦ Relatively high concentrations of PPG and glycerol could be quantified in the air of the chamber tests ◦ The extent to which people could be passively exposed to these depends on the ventilation rate, room size, indoor climate, room equipment and number of EC in use

			different amounts of nicotine			to 300 nm constantly increased during vaping activity and reached final peak concentrations of 7×10^6 particles L^{-1}		
Goniewicz ML [65] 2013	▲5		◦ 5 UK brands (6 products) with high internet popularity, high and extra high nicotine content ◦Ref product: CC	◦ Fluid and vapor ◦ Aim: determine the nicotine content in fluid and vapor and estimate the safety and consistency of nicotine delivery across batches	◦ Gas chromatography with the Thermionic Specific Detector	◦ The nicotine content of cartridges within the same batch varied by up to 12% relative standard deviation ◦ Mean difference between different batches of the same brand ranged from 1% to 20% for five brands and 31% for the sixth ◦ The puffing schedule vaporized 10–81% of the nicotine ◦ The nicotine delivery from 300 puffs ranged from approx. 2 mg to 15 mg and was not related significantly to the variation of nicotine content in e-liquid ($r = 0.06$, $P = 0.92$).	◦Tested few brands	◦ There is very little risk of nicotine toxicity from major EC brands in the United Kingdom. ◦ Variation in nicotine concentration in the vapor from a given brand is low. ◦ Nicotine concentration in e-liquid is not well related to nicotine in vapor ◦ None of the tested products reached nicotine concentrations as high as CC
Goniewicz ML [66] 2013	▲3		◦12 brands of EC ◦Most popular brands in Poland ◦Ref product: Medicinal nicotine inhalator Nicorette 10 mg and CC (not tested, used from other reference)	◦Vapor ◦Aim: test content of four groups of potentially toxic and carcinogenic compounds: ◦15 carbonyls ◦11 volatile organic compounds ◦2 nitrosamines ◦12 heavy metals	◦Vapours: using a modified smoking machine. ◦The selected toxic compounds were extracted from vapours into a solid or liquid phase ◦Analysed with chromatographic and spectroscopy methods	◦Detected in EC: 4 carbonyls (formaldehyde (2.0- 56.1 µg), acetaldehyde (1.1-13.6 µg), 0-methylbenzaldehyde (1.3-7.1 µg) and acrolein (0.7-41.9 µg) and 2 volatile organic compounds (toluene (0.2-6.3 µg), and p,m-xylene) identified in almost all EC. ◦In 9 vapors: Both nitrosamines, NNN (0.8 -4.3 ng), and NNK (1.1- 28.3 ng), identified ◦In all vapors: 3 metals, cadmium (0.01-0.22 µg), nickel (0.11-0.29 µg) and lead (0.03-0.57 µg) identified Nicorette inhalator: ◦Trace amounts of cadmium, nickel, lead, formaldehyde, acetaldehyde and o-methylbenzaldehyde were detected ◦No volatile organic compounds	◦Tested only one batch of liquid per brand/model ◦The puffing profile used may not reflect actual user puff topography-actual doses of toxicants inhaled by EC users might be higher ◦(Overheating?)	◦Toxic compounds: metals, carbonyls and volatile organic compounds were found in almost all EC ◦Vapor of some EC contains traces of carcinogenic nitrosamines ◦Exposure to carcinogenic formaldehyde comparable with CC smoking ◦Large variability in nicotine concentrations ◦Selected toxic compounds found in the smoke from a CC were 9–450-fold higher than levels in the vapour of an EC ◦The amounts of toxic metals in EC are comparable with amounts contained in nicotine inhaler
Goniewicz ML [67] 2013	▲4		◦16 EC ◦15 most popular brands in Poland, UK and USA ◦20 cartridges and 15 nicotine refill solutions ◦Paired each tested EC with cartridges of same brand and same batch and series ◦No ref product	◦Vapor ◦Aim: test efficacy and consistency of various EC in converting nicotine to vapor	◦Vapors: generated using an modified automatic smoking machine ◦Nicotine was absorbed in a set of washing bottles with methanol and analyzed with gas chromatography ◦Three samples of each refill solution	◦The total level of nicotine in vapor generated by 20 series of 15 puffs varied from 0.5 to 15.4 mg. ◦Most of the analyzed ECs effectively delivered nicotine during the first 150– 180 puffs. ◦On an average, 50% – 60% of nicotine from a cartridge was vaporized ◦High consistency between the results of one product tested in both studies	◦The puffing profile used may not reflect actual user puff topography-actual doses of toxicants inhaled by EC users might be higher ◦Small number of samples from each product	◦Vapor contains nicotine, but EC brands and models differ in their efficacy and consistency of nicotine vaporization ◦Up to 89% lower nicotine conc. than labeled ◦Up to 28% higher nicotine conc. than labeled

					model were tested			
Goniewicz ML [64] 2015	▲17		◦32, 29 and 30 e-liquids purchased between 2013 and 2014 from locations in the United States (US), South Korea, and Poland, respectively	◦Fluid ◦Aim: to test nicotine levels in samples of e-liquids from three countries	◦Nicotine concentrations were measured using gas chromatography with a nitrogen–phosphorous detector (GC-NPD, Agilent, USA). ◦Modified standard NIOSH 2551 method for determination of nicotine in air	◦Significant discrepancies (>20%) in the labelled nicotine concentrations in 19% of analysed e-liquids. ◦US: nicotine concentration varied from 0 to 36.6 mg/mL. Traces of nicotine were found in 3 products labelled as 'nicotine free'. ◦ South Korea: two-thirds of products did not contain detectable amounts of nicotine. Nicotine concentration in other products varied from 6.4 ± 0.7 to 150.3 ± 7.9 (labelled as 'pure nicotine') mg/mL. ◦Poland: nicotine concentration varied from 0 to 24.7 ± 0.1 mg/mL.	◦Tested only one batch of liquid	◦Most of the analysed samples had no significant discrepancies in labelled nicotine concentrations and contained low nicotine levels ◦Some products labelled as 'nicotine-free' had detectable levels of the substance ◦Quality of the products may differ across countries
Goniewicz ML [68] 2015	▲ 21	Θ	◦3 products, with different flavors based on their popularity: ◦eGo reusable tank system +Ecto Cooler liquid, 24 mg/ml nicotine, orange and tangerine flavor or Bubblegum eJuice, 32 mg/ml nicotine ◦801-T nicotine + Ecto Cooler liquid, 24 mg/ml nicotine, orange and tangerine flavor ◦Blu disposable, 20–24 mg nicotine, classic tobacco flavor ◦No reference	◦ Vapor ◦ Aim: to investigate whether nicotine from EC can be deposited on various surfaces	◦Released 100 puffs from each product directly into an exposure chamber ◦Surface wipe samples were taken from 5 indoor 100 cm^2 surfaces (window, walls, floor, wood, and metal) pre- and post-release of vapors ◦Nicotine was extracted from the wipes and was analyzed using gas chromatography	◦3 of the 4 experiments showed significant increases in the amount of nicotine on all five surfaces. ◦The floor and glass windows had the greatest increases in nicotine ◦The average amount of nicotine deposited on a floor during each experiment was 205 μg/m^2 and varied from limit of quantitation to 550 μg/m^2	◦ Small sample size ◦ Short term exposure ◦ Controlled laboratory settings, not real life ◦ Did not investigate the effect of exhaled vapors by the users but simulated exposure conditions	◦ Study indicates that there is a risk for third-hand exposure to nicotine from EC ◦Third-hand exposure levels differ depending on the surface and EC brand
Hadwiger ME [69] 2010	No		◦3 Cartridges + 2 refill liquids labeled as containing Cialis ◦3 Cartridges + 2 refill liquids labeled as containing Rimonabant ◦Labeled with nicotine content ◦No ref product	◦Cartridges and refill liquids ◦Aim: test the presence of unapproved active pharmaceutical ingredients	◦A high-pressure liquid chromate-graphy-diode array detection and multi-mode ionization tandem mass spectrometry method	◦Products advertised as containing E-Cialis did not contain tadalafil, rather they contained amino-tadalafil. ◦Products advertised as containing rimonabant, did contain rimonabant and a significant amount of an oxidative impurity of rimonabant ◦Products advertised as containing no nicotine, did contain nicotine	◦Tested only one batch of liquid ◦The used method was inadequate for resolution of certain nicotine impurities ◦Not vapor	◦Presence of unapproved active pharmaceutical ingredients added ◦Presence of undisclosed degradation of advertised ingredients ◦Nicotine-free products contained nicotine
Hahn H [70] 2014	No		◦54 samples ◦Liquids (n = 20) submitted for official medicines and tobacco control purposes ◦Samples suspected of	◦Fluid ◦Aim: to test the compounds contained	◦NMR spectroscopy ◦Risk assessment was based on probabilistic exposure estimation and comparison with toxicological	◦18 from 23 samples were confirmed as nicotine-free ◦In one EC liquid nicotine was not detected while being declared on the labelling. ◦Major compounds: glycerol, propylene glycol, and ethylene glycol	◦Fluid only ◦Used thresholds for oral exposure – not for inhalation	◦From all compounds tested, only nicotine reached exposures that fall into a high risk category ◦Solvents with more favourable toxicological profiles should be used

			containing illegal or unusual substances, tobacco and beverage flavour ◦All varieties of declared nicotine content ◦No ref product		thresholds using the margin of exposure (MOE) approach	◦Furthermore, 1,3-propanediol, thujone and ethyl vanillin were detected ◦The average exposure for daily users was estimated as 0.38 mg/kg bw/day for nicotine, 8.9 mg/kg bw/day for glycerol, 14.5 mg/kg bw/day for 1,2-propanediol, 2.1 mg/kg bw/day for ethylene glycol, and below 0.2 mg/kg bw/day for the other compounds. The MOE was below 0.1 for nicotine, but all other compounds did not reach MOE values below 100 except ethylene glycol and 1,2-propanediol		instead of ethylene glycol and 1,2-propanediol, which may fall into a risk category
Han S [71] 2015	No		◦55 refill solutions for 17 brands on the Chinese market	◦Fluid ◦Aim: to develop methods and to assess the levels of eight groups of compounds	◦Chromato-graphic and spectroscopic methods	◦The total mass% of propylene glycol and glycerol in most refill solutions ranged from 80%~97% ◦Triethylene glycol was detected in one sample and menthol was found in 16 samples including in samples that were not labeled as "mint". ◦The labeled concentrations of nicotine of the 25 samples were not consistent with, and were in most cases lower than the measured concentrations ◦The concentrations of nicotine in samples that were labeled at the same "strength" (eg, HIGH, MIDDLE, or LOW) differed significantly among brands ◦Selected groups of compounds including TSNAs, solanesol, VOCs, PAHs, phenolic compounds, and carbonyl compounds were all detectable, with varying levels and detection frequencies	◦ Only refills analysed, should also be vapor ◦Methods failed to separate positional isomeres	◦ Glycol and glycerol constitute the major ingredients of most refill solutions, and also indicated the necessity for clearly and accurately labeling nicotine content of e-liquids ◦ Compounds that may originate from tobacco, solvents or other sources, such as TSNAs, solanesol, VOCs, PAHs, phenolic compounds, and carbonyl compounds were all found with different levels and detection frequencies
Herrington JS [74] 2015	No		◦Four commercially available EC (first generation) were chosen from the "Best E-Cigarettes of 2014"	◦Fluid and aerosol ◦Aim: evaluating e-cigarette solutions and their resultant aerosol for potential differences	◦Multi-sorbent thermal desorption (TD) tube ◦Gas chromatography (GC) mass spectrometry (GC–MS) method	◦Detectable levels of >115 VOCs and semivolatile organic compounds (SVOCs) from a single 40 mL puff ◦Solution profiles produced upwards of 64 unidentified and identified (someonly tentatively) constituents and aerosol profiles produced upwards of 82 compounds. ◦Distinct analyte profiles between liquid and aerosol samples ◦Formaldehyde,acetaldehyde, acrolein, and siloxanes were found in the aerosol profiles; however, these	◦First generation EC only	◦Fluid profiles produced upwards of 64 unidentified and identified constituents, and aerosol profiles produced upwards of 82 compounds ◦Formaldehyde, acetaldehyde, acrolein, and siloxanes were found in the aerosol profiles; however, these compounds were never present in the solutions ◦The aerosolization process

						compounds were never present in the solutions		in the formation of compounds not found in solutions have potential implications for human health
Higham AJ [75] 2014	No		◦Unknown	◦Vapor extract ◦Aim: to investigate the effects of e-cigs on human innate immune cells in vitro	◦Blood neutrophils from six healthy non-smokers were exposed to EC vapor extract for 6 hr. ◦Alveolar macrophages isolated from resected lung tissue from three ex-CC smokers exposed to vapor extract for 24 hr. ◦ELISA ◦Zymography	◦EC exposure to cells: Increased MMP-9 and ◦CXCL8 release with the maximal effect observed at an optical density (OD) of 0.003 ◦Increase in MMP-9 gelatinase activity and increased p38 ◦MAPK activation ◦Neutrophil shape change, and dual CD11b and CD66b expression increased in response to vapor exctrat treatment compared to untreated cells ◦Increase in CXCL8 release from alveolar macrophages	◦ Unknown brand In vitro study only	◦In vitro study shows that EC exposure causes an inflammatory response from neutrophils and macrophages ◦The effects are similar to those caused by CC
Husari A [78] 2015	No		◦Pre-filled V4L CoolCart (strawberry flavor, 3.5 Ohm, 18 mg/mL labeled nicotine concentration) cartomizer cartridges, connected to an automatically actuated 4.2 V Vapor Titan Soft Touch battery Ref: CC smoke	◦Vapor ◦Aim: to investigate the effects of EC aerosol and CC smoke in an animal model and in human alveolar cell cultures (A549)	◦Human alveolar cell cultures were treated with various concentrations of EC and CC (3R4F) smoke aerosol extracts and the effects on cell proliferation were evaluated.	◦Concentrations of CC smoke TPM extract at of 2 mg/mL and higher were sufficient to attenuate cellular growth and to trigger cell death ◦EC TPM extract at a concentration higher than CC extract (64 mg/mL) was required to illicit similar findings	◦One brand	◦Both EC and CC smoke extracts reduced cell proliferation, however, CC smoke exhibited effects at lower concentrations
Hutzler C [79] 2014	No		◦ 28 liquids of seven manufacturers purchased in Germany ◦ 10 liquids were declared “free-of-nicotine” Reference: no	◦ Fluid and vapor ◦ Aim: to analyze content of e-fluids	◦ Gas chromatography method, in conjunction with a flame ionization detector (GC–FID) ◦ Standardized machine smoking protocol to mimic human smoking behavior, Borgwaldt RM20H smoking mahcine	◦ 7 out of 10 liquids declared as nicotin-free were identified containing nicotine in the range of 0.1–15 µg/ml. ◦ In 18 liquids, no declaration regarding nicotine was provided by the manufacturers – 16 contained nicotine. ◦ Ethylene glycol replaced glycerol and propylene glycol in 5 brands ◦ Coumarin and acetamide detected ◦ Significant amounts of formaldehyde, acetaldehyde and propionaldehyde wereonly found at 150 °C by headspace GC–MS analysis ◦ High amounts of aldehydes can be reached - comparable or even higher as in CC -in the last part of the	◦ Overheating?	◦ Many ECs labeled as ‘nicotin free’ contained nicotine ◦Release of aldehydes is strongly enhanced in the second half of the vaping period ◦ The occurrence of aldehydes seems to be associated with lower liquid levels within the cartridges, leading to an increased air flow - could promote overheating of the wire

						vaping period		
Ingebrethsen BJ [80] 2012	◆▲6		◦A rechargeable EC and a non-rechargeable EC ◦Ref: CC, Kentucky reference	◦Vapor ◦Aim: measure particle size and concentration in air	◦Particle size distribution of aerosols produced by EC was measured in an undiluted state by a spectral transmission procedure and after high dilution with an electrical mobility analyzer	◦Particle diameters of average mass in the 250–450 nm range and particle number conc. in the 109 particles/cm3 range, the same as in previous CC smoke studies	◦Tested only two fluids	◦Particle diameters and particle number conc. as in CC smoke
Jensen RP [81] 2015	No		◦Unknown commercial e-liquid vaporized with the use of a "tank system" EC featuring a variable voltage battery Ref: CC smoke	◦Vapor ◦Aim: to measure 'hidden' unstable formaldehyde, formaldehyde hemiacetal, concentrations in vapor	◦Aerosolized liquid was collected in an NMR spectroscopy tube	◦At low voltage (3.3 V): did not detect the formation of any formaldehyde-releasing agents (estimated limit of detection, approximately 0.1 µg per 10 puffs) ◦At high voltage (5.0 V): a mean (±SE) of 380±90 µg per sample (10 puffs) of formaldehyde was detected as formaldehyde-releasing agents ◦Extrapolating from the results at high voltage, an EC user vaping at a rate of 3 ml per day would inhale 14.4±3.3 mg of formaldehyde per day in formaldehyde-releasing agents	◦One unknown brand ◦Conservative estimate because all of the aerosolized liquid was not collected nor any gas-phase formaldehyde	◦High levels of formaldehyde-releasing agents found by use of high-voltage battery - estimated formaldehyde hemiacetal to be 5 times as high in EC vapor as in CC smoke
Kavvalakis MP [82] 2015	No		◦263 EC-liquid samples, produced by 13 companies obtained from the Greek market ◦No ref product	◦Fluid ◦Aim: measure multiple components in EC – develop a multicomponent analytical protocol for the analysis of the replacement liquids	◦Gas and liquid chromatography–mass spectrometry	◦Details on accuracy of measurement are described ◦The measured concentrations of nicotine correlated with the theoretical concentrations as reported by the manufacturers ◦An analog relation between the concentration of the glycerol and of propylene glycol was noticed. ◦141 volatile flavors detected ◦Nitrosamines and PAHs were not detected in any sample	◦Not vapor	◦Nitrosamines and PAHs or diethylene glycol were not detected in any sample ◦Complete analytical methods for rapid and simultaneous multicomponent identification
Kienhus AS [83] 2015	No		◦Disposable, nicotine-free shisha-pens (3 strawberry, 1 apple and 1 grape) bought in a local store ◦No ref product	◦ Fluid and vapor ◦Aim: to assess the potential harmful health effects caused by inhaling the vapor of a nicotine-free shisha-pen	◦Gas chromatography analysis on a Varian GC 3900/FID. ◦Risk assessment was performed using puff volumes of ECs and "normal" cigarettes and a 1-puff scenario(one-time exposure).	◦Main components: propylene glycol and glycerol (54%/46%). ◦One puff (50 to 70 mL) resulted in exposure of propylene glycol and glycerol of 430 to 603 mg/m3 and 348 to 495 mg/m3, respectively. ◦Exposure concentrations were higher than the points of departure for airway irritation based on a human study and a rat study	◦Few samples ◦Differences between studies and the actual exposure (e.g. differences in duration of exposure and differences between animals and human scan)	◦Already after one puff of the shisha-pen, the concentrations of propylene glycol and glycerol are sufficiently high to potentially cause irritation of the airways

					◦ Concentrations that reached the airways were calculated		were taken into account but this might not have been sufficient	
Kim H-J [84] 2013	No		◦105 refill liquid brands from 11 EC companies in South Korea ◦No ref product	◦Refill liquids ◦Aim: test for carcinogenic compounds and conc. of four TSNAs ◦NNN ◦NNK ◦NAB ◦ NAT	◦A liquid chromatography–tandem mass spectrometric method ◦Solid-phase extraction and liquid–liquid extraction were compared to each other to select the optimum cleanup method	◦The maximum conc. of total TSNAs were measured at 86.92µg/L ◦NNN: 0.34–60.08µg/L (64.8% detection frequency) ◦NNK: 0.22–9.84 µg/L (88.6% detection frequency) ◦NAB: 0.11–11.11 µg/L (54.3% detection frequency) ◦NAT: 0.09–62.19 µg/L (75.2% detection frequency) ◦High level of NNN compared to TSNA levels-NNN may be produced from nitrosation of nornicotine converted from nicotine?	◦Not vapor	◦Almost all fluids contained carcinogenic compounds, TSNAs ◦High maximum conc. of total TSNAs ◦Great variability in content of the four measured TSNAs
Kim S [85] 2015	No		◦32 liquid refill products (17 Korean domestic, 15 imported) and one pure nicotine product at 6 different EC retail stores in Seoul between May and June 2014 ◦No ref product	◦Fluid ◦Aim: to examine the level of heterogeneity of contents of the labels and discrepancy of the nicotine content between that indicated on the label and the actual values for EC liquid refill products in South Korea	◦Analysed at the Roswell Park Cancer Institute, Buffalo, NY, USA by a blinded analyst using gas chromatography with a thermionic specific detector	◦Refill products could be mixed with liquid nicotine from a separate bottle (=uncontrolled or inaccurate dose of nicotine) ◦3 out of 15 imported liquid refill products provided manufacturing dates ◦Expiration dates: on 8 products ◦The range of nicotine concentration: from 'not detected' to 17.5 mg/mL. ◦Labeling discrepancies of the concentrations ranged from −32.2% to 3.3% ◦Highest concentration (150.3 ± 7.9 mg/mL) found in a sample labeled as pure nicotine ◦70% of domestic products did not have a health warning statement	◦Only one of each product ◦A couple of products were purchased without a box - label information was summarized based on the information stated directly on the bottles	◦There is no standardization of EC liquid labelling ◦The labels did not accurately reflect the content ◦The measured nicotine concentration was significantly lower than the labeled nicotine concentrations ◦One product labeled 'pure nicotine' raises concerns, since it may be poisonous to consumers, especially to children
Kim YH [86] 2015	No	Θ	◦EC device (Korea) and an EC solution without nicotine (Korea)	◦Fluid, vapor, and aerosol ◦Aim: 1. To develop a technique for the quantitation of volatile organic compounds (VOC) in three different forms of EC: fluid, vapor, and aerosol 2. accurately assess mass transfer between different EC phases	◦Mass change tracking approach ◦TD-GC-MS system	◦The concentration of aerosol plus vapor decreased exponentially (559 to 129 g m−3) with increasing puff velocity (0.05 to 1 L min−1) ◦In the EC solution, acetic acid was considerably high (25.8 µg mL−1), along with trace quantities of some VOCs (methyl ethyl ketone, toluene, propionic acid, and i-butyric acid: 0.24 ± 0.15 µg mL−1 ◦In the aerosol samples, many VOCs (n-butyraldehyde, n-butyl acetate, benzene, xylene, styrene, n-valeric acid, and n-hexanoic acid) were newly produced (138 ± 250 µg m−3). In general, the	◦One brand only	◦All of the types of EC samples generally contained little or none of most of the target VOCs, except for acetic acid

						solution-to-aerosol (S/A) conversion was significant: e.g., 1,540% for i-butyric acid. ◦The emission rates of all targets computed based on their mass in aerosol/ consumed solution (ng mL−1) were from30.1 (p-xylene) to 398 (methyl ethyl ketone), while those of carboxyls were much higher from 166(acetic acid) to 5,850 (i-butyric acid).		
Kirschner R [87] 2013	No		◦ 6 samples of e-liquids with different flavors	◦Fluid ◦Aim: to test content of nicotine and compare with declared content	◦ Dissolved in menthanol ◦ Analyzed with liquid chromatograph mass spectrometer ◦ Isotope dilution method	◦ All bottles contained nicotine 14.8 to 87.2mg/ml ◦ Measured concentration of nicotine differed from declared by up to 50% ◦ No undeclared ingredients identified ◦Alkaline pH	◦ Small sample ◦ Fluid only	◦Measured concentration of nicotine differed from declared by up to 50%
Kosmider L [88] 2014	▲7		◦ Ten kinds of commercially available e-liquids- nicotine concentration 18 to 24 mg/ml ◦ Vapors were generated using three different battery voltages: 3.2, 4.0, and 4.8 V ◦ Reference: pure glycerin, pure propylene glycol, or a mixture of both solvents (50:50)	◦ Vapor ◦ Aim: to evaluate how various product characteristics, including nicotine solvent and battery output voltage, affect the levels of 12 carbonyls in EC vapor	◦ 1 ml of each e-liquid was collected and 10 clearomizers of the same type were refilled 24 hr before aerosol generation. ◦ Each clearomizer was used only for one e-liquid ◦Vapors from ECs were generated using the automatic smoking machine Palaczbot (2 series of 15 puffs with a 5-min interval)	◦ Formaldehyde and acetaldehyde were found in 8 of 13 samples. ◦ The highest levels of carbonyls were observed in vapors generated from PPG-based solutions. ◦ Increasing voltage from 3.2 to 4.8 V resulted in 4 to over 200 times increase in formaldehyde, acetaldehyde, and acetone levels. ◦ The levels of formaldehyde in vapors from high-voltage device were in the range of levels reported in tobacco smoke.	◦ Puffing topography may affect levels of carbonyls released from different ECs. ◦ There are some discrepancies between puffing regime used in this study and the results of clinical studies	◦ This finding suggests that in certain conditions ECs might expose their users to the same or even higher levels of carcinogenic formaldehyde than CC smoke ◦ High-voltage EC may expose users to high levels of carbonyl compounds ◦ Vapors from EC contain toxic and carcinogenic carbonyl compounds ◦ Both solvent and battery output voltage significantly affect levels of carbonyl compounds in EC vapors
Kubica P [89] 2014	No		◦37 samples from different producers of popular EC were purchased on the local market ◦The labels did not contain any information about carbohydrate content Ref: no	◦Fluid ◦Aim: to test high performance liquid chromatography in hydrophilic interaction liquid chromatography mode and tandem mass spectrometry for fast and simple determination of sucrose and other saccharides in	◦Q-Trap 4000 triplequadrupole mass spectrometer from Applied Biosystems with electrospray ionization in negative mode, using Analyst® 1.5.2. ◦The chromatographic separation was done using an Ascentis Express OH5 column	◦It was possible to determine the presence of sucrose and other saccharides such as fructose, glucose, maltose and lactose ◦Only sucrose was found in all samples of e-liquids ◦The detection limit of sucrose was 0.73 μg/g, and the sucrose content ranged from 0.76 to 72.93 μg/g (chocolate flavor)	◦The harmful effect of sucrose is hypothesized	◦Sucrose was found in all samples of e-liquids; the presence of sucrose in EC may be a source of aldehydes and organic acid ◦The source of sucrose in EC is unknown (flavor/taste additives or a contaminant from the production process?)

				e-liquids				
Laugesen M [91] *(abstract in 2 versions)* 2009	◆▲ 8		◦Ryan EC 16 mg nicotine ◦Ref: CC . 4 different: NZ Holiday regular and mild, Marlboro Red regular, Canadian regular brands	◦Liquid and vapor (mist) ◦Aim: test toxic emissions and nicotine dose and measure particle size ◦Selection of 59 toxicants for testing of mist was based on published priority lists , e.g. from WHO, of CC smoke toxicants	◦ Smoke tests by ISO smoking machine ◦Liquid and mist tested by different laboratories and methods (detailed) ◦Particle size distribution measured	◦A score for toxic emissions: CC=100-134, EC= 0 ◦Mercury detected in trace quantity, 0.17 ng per EC ◦Nicotine per puff: CC 48-103 (max puffing intensity), EC=9-10. ◦Not tested: acetaldehydes (shortage of reagent), hydrazine, chlorinated dioxans, oxides of nitrogen and urethane ◦Particle size: 0.04 microns. Smoke from CC: >0.15 microns (measured on a different instrument)	◦Tested only one brand/(batch?) ◦Only a score for toxic emissions presented, not individual toxins ◦Tobacco smoke measure on a different instrument ◦Tested by ISO smoking machine, not = human puffing behaviour ◦Very low operating temperature ◦In the version from April: Acetaldehyde both mentioned as present but also as not tested.	◦Very low score for toxic emissions (based on >50 toxicants) ◦Small particle size ◦Mercury detected ◦Nicotine dose and particle size too small to ensure deposition in the alveoli/bronchioles and rapid nicotine absorption as in cigarette smoking
Laugesen M [93] 2008	❖▲9		◦Ryan EC 16, 11, 6 and 0 mg nicotine ◦Ref: for CO measurement: CC	◦Fluid ◦Aim: test toxic emissions and nicotine dose, safety for bystanders (by CO in exhaled breath) and risk of microorganisms	◦Risk of microorganisms tested as aerobic plate count 35º in one unused and one repeatedly used cartridge	◦VOC: Acetaldehyde= 9.4 ppm Benzene= 1.5 ppm, Acrolein = 0.49 ppm. Other VOCs< LOQ ◦CO: in EC =1.5, compared to 9-14 in exhaled breath of CC smoker ◦Smoke toxicants as butadiene and acrylonitrile <0.3 ppm ◦Labeling of nicotine= actual content ◦No tendency for microorganisms to grow in the liquid ◦Metal (n=8) all <1 ppm, not a risk ◦ TSNAs= 8 ng/g, same as nicotine gum. CC smoke=500 ng/g ◦MAO inhibition= no sign. effect	◦Tested only one brand ◦No detailed description of test methods	◦Acetaldehyde, benzene, acrolein and TSNAs detected at low levels ◦Metals, CO and other VOCs at lower limits than detection
Laugesen M [90] 2008	▲34		◦Ruyan® EC with different nicotine content 0 to 16 mg ◦Ref: CC	◦Fluid and vapor ◦Aim: to test the safety of the Ruyan® EC	◦Use of different measurements methods ◦GC- Mass Spectrograph ◦SIFT- Mass Spectrograph ◦Head Space Solid-Phase Micro-Extraction ◦Selected Ion Flow Tube and Mass Spectrograph	◦TSNAs, found only in CC, were not found in the Ruyan® EC liquid except at trace quantity (Average TSNAs 3.9 ng/cartridge)- 1200 times less than in 20 CC ◦Absence of a MAO inhibitor effect: EC has no detectable addictive potential beyond that of nicotine ◦Compounds identified: propylene glycol, ethyl alcohol; nicotine, acetaldehyde, pyridine, acetone ◦Acetaldehyde and acrolein found in	◦Tested only one brand	◦The composition of the cartridge liquid is not hazardous to health ◦After a revised formulation from 2007 to 2008: acetaldehyde, acrolein, benzene and cresols in EC decreased, or not measurable

					◦CO measurement: 48 volunteer smokers: A non-smoker, not exposed to passive smoking: 20 inhalations of EC	head space measurements ◦After a revised formulation: acetaldehyde, acrolein, benzene and cresols decreased, or not measurable ◦PAH carcinogens found in CC smoke are not detectable in the EC liquid. PAHs that were detected are not rated as carcinogens by IARC. ◦No arsenic, antimony, cadmium, chromium, cobalt, copper, lead, manganese or nickel detected ◦No gamma-emitting nucleotides were found to be above the detection limit ◦No increase in CO		
Laugesen M [92] 2015	▲18		◦14 EC brands with tobacco flavour available in New Zealand (8 from China, 6 from UK and USA) purchased via internet ◦ Ref 1: Ryan Classic V8 (2008) Ref2: Marlboro KS	◦Vapor ◦Aim: to analyse EC brands available in New Zealand for nicotine content and toxicant yield ratings (toxic aldehydes and glycols)	◦Health Canada standards smoking machine (70 ml puff, 3 s puff duration, 10 s interval) ◦High-performance liquid chromatography with ultra-violet detection ◦Gas chromatography	◦Mean aldehydes in vapor were 73% lower than in ref-EC Ryan from 2008 ◦100 times less formaldehyde, 2800 times less acetaldehyde, 200 times less acrolein than CC ◦DEG and MEG below detection level ◦Mean nicotine level has increased since 2008 ◦Differences between labeled and actual nicotine level	◦Tested one batch ◦Tested by smoking machine, not = human puffing behaviour	◦EC available in New Zealand in 2013 exposed users to higher nicotine levels than in older brand ◦Far lower levels of toxicant than in CC and older EC brand
Lauterbach JH [94] 2012	◆▲10		◦Ryan classic V8 ◦Ref: Marlboro KS and very low tar 1.2 mg CC	◦Vapor (mainstream aerosol) ◦Aim: test toxic emissions and nicotine dose	◦ISO standards smoking machine (35 ml puff, 2 s puff duration, 60 puff interval)	◦Of 62 CC toxicants 37 were measurable in the very low tar CC and 11 in EC vapor (acetaldehyde 1.39 µg, formaldehyde 0.37 µg. Estimated relative toxicant emission scores: 0.4 for EC, 55 for very low tar CC and 137 for Marlboro KS CC ◦Mercury present at trace level ◦3 TSNs (NNN, NNK and NAT) present at trace level - much lower than CC ◦Low nicotine level 0.06 mg (compared with 1.02 in CC)	◦Tested only one brand ◦Tested by ISO smoking machine, not = human puffing behaviour	◦ Acetaldehyde, formaldehyde, TSNs and mercury detected ◦ Compared to CC level of toxins and carcinogens were reduced by >90%
Lauterbach JH [95] 2012	◆▲10		◦Not described ◦Ref: US-blend full flavor CC KS	◦Vapor (mainstream aerosol) ◦Aim: to suggest standard testing conditions and chemical and	◦ISO standards smoking machine (35 ml puff, 2 s puff duration, 60 puff interval) for EC and Health Canada Intensive Smoking Protocol (55 ml puff,	◦ Tar=11 mg/l, formaldehyde= 11µg /l, acetaldehyde= 21µg /l, acrolein= 3µg /l, NNN= 5 ng/l, NAT= 3 ng/l, NAB= 0,6 ng/l, NNK= 2 ng/l, traces of benzo(a)pyrene, benzene, total HCN, 1,3 butadiene, acrylonitrile, o-creosol, diethylen glycol ◦ TSNs (NNN, NNK, NAB and NAT)	◦ No description of brand/number of batches	◦ TSNAs, tar, formaldehyde, acetaldehyde, acrolein, and other toxins found in vapor ◦ Most toxicants were reduced by over 98% compared with CC

				toxicological properties of aerosol	2 sec puff duration, 30 s puff interval, 100% blocking of filter ventilation) for CC	present at trace level - much lower than CC ◦ This testing approach can detect toxicants in mainstream aerosol that would be missed by other analytical approaches		
Lerner CA [98] 2015	No		◦2 devices: refillable eGO Vision, Blu disposable ◦ E-liquids: Blu, Drip, Encore, ROC Juice, Upstate Vape, Vaper drops, Vapor dudes Different flavours; tobacco, cinnamon, menthol and fruits	◦Liquid and vapor ◦Aim: to investigate if exposure to EC vapor results in measurable oxidative and inflammatory responses	◦Cell-free ROS assay: vapor/smoke produced by smoking machine, levels of OX/ROS were determined using 2',7'di-chlorofluorescein diacetate fluorogenic probe ◦Human bronchial airway epithelial cells (H292) and human fetal lung fibroblasts (HFL1) were cultured and treated with e-liquids ◦Cell viability: 15 min exposure to Blu EC vapor in air-liquid interface chamber	◦Unvaporized EC were oxidative in a manner dependent on flavor additives ◦Flavors containing sweet or fruit flavors were stronger oxidizers than tobacco flavors ◦Exposure of human airway epithelial cells (H292) in an air-liquid interface to EC vapor resulted in increased secretion of inflammatory cytokines, such as IL-6 and IL-8 ◦Human lung fibroblasts exhibited stress and morphological change ◦Increased IL-8 in response to a cinnamon flavored e-liquid ◦Susceptible to loss of cell viability by e-liquid/aqueous CC smoke extract	◦The DCF fluorescence data should be interpreted as indicative of oxidant presence, but not an accurately direct measurement of specific ROS levels	◦ EC inhalation have an impact on cellular oxidative stress, redox imbalance, and lung inflammation, in vitro in lung cells and in vivo in lungs ◦Results indicate that the dripping method is likely to generate a larger amount of OX/ROS - "dripping" is potentially more hazardous
Lerner CA [97] 2015	No		◦Rechargeable Blu EC (7 batteries and 17 cartomizer) used over a 24 h Period ◦Ref: CC with filter	◦Vapor, EC components ◦Aim: to understand potential oxidative properties of EC	◦EC cartomizers were disassembled and metal casings separated ◦Residual fluid absorbed were submerged in 2'-7'-dichloro-dihydrofluorescein (DCFH) solution for 5 h ◦Semi-quantitative measurements of oxidative/reactive oxygen species (ROS) by 20,70 dichlorofluorescein diacetate fluorogenic probe ◦Cascade particle impactor	◦EC components exhibit oxidants/reactive oxygen species reactivity similar to used CC filters. ◦Oxidants/reactive oxygen species reactivity in EC aerosols was also similar to oxidant reactivity in CC smoke ◦Range of particle size distributions between 0.450 and 2.02 μm in aerosols from an EC ◦Copper: 6.1 times higher per puff than reported previously for CC smoke.	◦One brand only ◦The DCF fluorescence data should be interpreted as indicative of oxidant presence, but not an accurately direct measurement of specific ROS levels ◦Did not determine whether or not the copper particles specifically fell within nanoparticle size range (<100 nm)	◦Results suggest there might be constituents with oxidizing properties associated with EC that are health hazards which warrant further examination ◦The detection of a potentially cytotoxic metal as well as oxidants from EC and its components raises concern regarding the safety of EC use and the disposal of EC waste-products into the environment
Lisko JG [100] 2015	No		◦36 e-liquids brands from 4 manufacturers	◦Fluid ◦Aim: to evaluate the chemical	◦Quantitative analyses were performed	◦3/4 of the products contained lower measured nicotine levels than the stated label values (6%–42% by	◦The oxidation rate of nicotine is unknown, thus the	◦ A number of products contained tobacco alkaloids at concentrations

			◦Brands were chosen based upon consumer approval ratings from online review websites ◦No ref	composition including nicotine, tobacco alkaloids, pH, and flavors	using strict quality assurance/quality control validated methods previously established by the lab for the measurement of nicotine, alkaloids, pH, and flavors ◦Triplicate samples ◦Gas chromatography/ tandem mass spectrometry (GC-MS/MS)	concentration) ◦Free nicotine levels calculated from the measurement of pH correlated with total nicotine content ◦The pH for liquids ranged from 5.1–9.1 ◦Minor tobacco alkaloids (nornicotine, myosmine, anabasine, anatabine, and isonicoteine) were found in all samples containing nicotine, and their relative concentrations varied widely among manufacturers	source of impurities cannot be identified with certainty	that exceed U.S. pharmacopeia limits for impurities in nicotine used in pharmaceutical and food products ◦The direct correlation between the total nicotine concentration and pH suggests that the alkalinity of nicotine drives the pH of EC solutions
Long GA [101] 2014	◆▲23	Θ	◦eCigs Classic Tobacco Disposable ◦blu eCigs Magnificent Menthol Disposable ◦Ref: Marlboro Gold King Box filtered cigarette	◦Indoor air ◦Aim: to analyse quantities of phenolic and carbonyl compounds in the exhaled aerosols from human subjects using CC and EC without any dilution effects due to room volume or air exchange and determine mass balance and distribution of water, glycerin and nicotine in exhaled e-cigarette aerosols	◦ 20 current EC vapers and 10 smokers with a stable preference for one of the 3 specified products (≥6 months) ◦Each subject used their preferred product (= nine sessions; 3 replicates per subject in the 3 analyte classes) ◦Conducted in a 40 m^3 conference room ◦ 3 cigarettes /max. of 99 puffs per session ◦Vacuum-assisted filter pad capture system	◦Total phenolic content in exhaled EC aerosol: not distinguishable from exhaled breath blanks ◦Total phenolics in exhaled CC-smoke were significantly greater than in exhaled EC aerosol and exhaled breaths ◦ Total carbonyls in exhaled EC aerosols were not distinguishable from exhaled breaths or room air blanks ◦ Total carbonyls in exhaled CC smoke was significantly greater than in exhaled EC aerosols, exhaled breath and room air blanks ◦Large individual differences in phenols in exhaled aerosol. E.g. one EC vaper had high acetaldehyde levels	◦Only one brand of EC	◦ Results indicate that exhaled e-cigarette aerosol does not increase bystander exposure for phenolics and carbonyls above the levels observed in exhaled breaths of air ◦Individual variation. A few vapors had high acetaldehyde level in exhaled aerosol
Maloney JC [102] 2015	◆▲37	Θ	◦MarkTen® prototype EC with and without menthol	◦Indoor air ◦Aim: to determine indoor room air concentrations of major formulation constituents from MarkTen® prototype EC vapor	◦185 panelists in Study 1 and 145 panelists in Study 2 ◦137.2 m^3 room ◦Both studies: six 1-hour vaping sessions -over the course of a 12-hour day ◦6 puffs each of each of three ECs ◦Active air sampling for both studies ◦4 consecutive days ◦Direct sampling of	◦Only formaldehyde was detected above the LOQ of the analytical methods used, however these levels were overlapping the range of the background levels (6-8 µg/m^3 with background levels 5-7 µg/m^3) ◦EC does not produce airborne levels of chemical ingredients (e.g. menthol, nicotine, propylene glycol, glycerol or total suspended particulates) above the limit of quantitation of the standard industrial hygiene sampling and analytical methods used in this study	◦Studies do not represent *ad libitum* use ◦Standards not designed for inhalation	◦Indoor vaping of MarkTen® prototype EC does not produce chemical constituents at quantifiable levels or background levels using standard industrial hygiene collection techniques and analytical methods

					selected airborne constituents			
Manigrasso M [104] 2015	No		◦Unknown EC brand; rechargeable, commercial model comprising of a tank system and a 14 mg mL^{-1}nicotine ◦Ref: CC with 0.8 mg nicotine	◦Vapor ◦Aim: to estimate size segregated doses from EC aerosols as a function of the airway generation number in lung lobes	◦ Condensation Particle Counter and a Fast Mobility Particle Sizer spectrometer ◦ Mainstream aerosol measurements were performed for puffs of 2-s duration ◦ Particle deposition in the human respiratory system: Multiple-Path Particle Dosimetry model (MPPD v2.1, ARA 2009)	◦ 7.7 x 10^{10} particles (DTot) with a surface area of 3.6 x 10^3 mm2 (STot), and 3.3 x 10^{10} particles with a surface area of 4.2 x 10^3 mm2 were deposited in the respiratory system for the EC and CC, respectively ◦ Total regional doses, in head and lobar tracheobronchial and alveolar regions, ranged from 2.7 x 10^9 to 1.3 x 10^{10} particles and 1.1 x 10^9 to 5.3 x 10^{10} particles, for the electronic and conventional cigarettes, respectively ◦ Total regional doses in the right-upper lung lobe: about twice that found in left-upper lobe and 20% greater in right-lower lobe than the left-lower lobe	◦One brand only ◦Not tested on humans	◦ Human lung model: EC: High dose - more than double the dose compared to CC- of 10^{10} particles are deposited in the lung ◦ In the tracheobronchial and alveolar regions, a single puff delivers total regional doses that represent 40% and 30% of the daily dose of a no-smoking Italian ◦The lobar bronchi and right lung lobes represent sites where effects of the aerosol from EC may be more likely to occur
Manigrasso M [103] 2015	No		◦Unknown EC brand; rechargeable, commercial model comprising of a tank system and 8 different e-liquids in terms of nicotine content and flavor ◦No ref	◦Vapor ◦Aim: to give a contribution to fill the gap between source emission and related health effects providing dosimetry data useful to estimate both acute and long-term effects of the aerosols delivered by EC	◦ Condensation Particle Counter and a Fast Mobility Particle Sizer spectrometer ◦ Mainstream aerosol measurements were performed for puffs of 2-s duration ◦ Particle deposition in the human respiratory system: Multiple-Path Particle Dosimetry model (human lung model)	◦ Particle number concentrations varied between 3.26 x10^9 and 4.09 x 10^9 part cm^{-3} for e-liquids without nicotine and between 5.08 x10^9 and 5.29 x 10^9 part cm^{-3} for e-liquids with nicotine ◦ No flavor effects were detected on particle concentration data ◦ Particle size distributions: unimodal with modes between 107-165 nm and 165-255 nm, for number and volume metrics, respectively ◦ Averagely, 6.25 x10^{10} particles were deposited in respiratory tree after a single puff ◦ Highest deposition densities and mean layer thickness of EC liquid on the lung epithelium were estimated at lobar bronchi	◦Unknown EC ◦Not tested on humans	◦ Human lung model: EC are a source of extremely high particle doses in the human respiratory system ◦ 10^{10} particles were deposited in the respiratory tree after a single 2-s puff, approximately 30% of the daily doses of a non-smoking individual
Marco E [106] 2015	No	Θ	2 types EC: disposable (Type 1 e-cigarette) or rechargeable (Type 2 e-cigarette) Ref: CC, blend type American tobacco cigarettes with filters, low nicotine content (0.6 mg), low tar (8 mg)	◦Vapor and exhaled breath after vaping ◦Aim: to develop a method for a rapid analysis of volatile organic compounds (VOCs) in smoke from CC and vapor from EC and in exhaled breath of users of these smoking systems	◦Smoke/vapor or exhaled breath were collected in Bio-VOCs. VOCs were then desorbed in Tenax cartridges which were subsequently analyzed by thermal desorption coupled to gas chromatography–mass spectrometry.	◦Vapor of EC: mainly composed of PPG and glycerin, nicotine and related products such as miosmine and nicotyrine ◦Exhaled breath of vapers: chromatographic peaks of PPG and glycerin were absent, and there was decrease of the peaks corresponding to nicotine and related compounds, indicating that they remained in the respiratory system ◦Two main peaks in the chromatograms from exhaled breath	◦Contamination?All volunteers were asked to smoke CC and both types of EC ◦Only 2 types of EC	◦Comparison of the concentrations between smoke and equivalent exhaled breath illustrated the incorporation of higher burdens of VOCs in the smokers than in EC vapers

						were those corresponding to acetone and isoprene which likely represent endogenous sources. ◦In addition, benzene, toluene and 2,5-dimethylfuran were also found ◦Results from disposable EC were very similar to those from rechargeable EC ◦CC smoke and smokers breath contained numerous VOCs		
Martinez RE [109] 2015	No		◦Three e-liquids were tested: 1)an unflavored solution in PPG 2) an unflavored solution in PPG and VG 3) a flavored solution in PPG and VG	◦Vapor ◦Aim: to test for nicotyrine, a nicotine analog that could impede nicotine metabolism	◦Thermal Desorption Aerosol Gas Chromatograph ◦A heating duration experiment determined the nicotyrine to nicotine ratio (NNR) in particle phase as a function of the duration of e-cig activation ◦An aging experiment determined the NNR in e-liquids and vapor	◦Nicotine and nicotyrine were quantified in all 3 e-liquids and aerosols; NNR is higher in the aerosol when PPG only is used in the e-liquid ◦Duration of ECactivation was inversely related to NNR (NNR = 0.04 with 3-s activation, 0.26 with 0.5 s) ◦Aging influenced both e-liquid NNR and aerosol NNR ◦On average, the e-liquid NNR increased from 0.03 at 11 days after opening to 0.08 after 60 days ◦For similar heating durations, aerosol NNR increased from 0.05 at 11 days to 0.23 after 60 days ◦ Storage conditions had little effect on NNR	◦Few liquid, only one batch ◦VG only, unflavored solution not tested	◦E-cig aerosols have variable nicotyrine quantities ◦ Aerosol nicotyrine to nicotine ratio depends on vaping technique and time elapsed since the e-liquid was exposed to air ◦Aerosolized nicotyrine could facilitate nicotine absorption, inhibit the metabolism of nicotine, and reduce a user's urge to smoke
McAuley TR [110] 2012	▲11		◦12 new cartomisers were filled with e-liquid from 4 different bottles ◦4 popular e-liquid brands, tobacco flavored and the highest commonly used level of nicotine ◦Ref: CC (Marlboro Red)	◦Vapor ◦Aim: test for six different types of pollutants: ◦ 4TSNAs: ◦NNN ◦NNK ◦NAB ◦ NAT ◦PAHs ◦ Glycols: PPG, DEG ◦VOCs ◦ Carbonyls (formaldehyde, acrolein, acetaldehyde)	◦E-liquids were vaporized in two sets of experiments by generic 2-piece ECs ◦Modified smoking machine connected with polyethylene glove bags ◦Risk analyses were conducted based on dilution into a 40 m3 room and standard toxicological data	◦CC smoke particle number conc. was an order of magnitude higher than the highest conc. of any e-liquid (2963 ± 3122, liquid C vs. 21,352 ± 50,414) ◦Average VOC conc.s: below the limit of detection with exception of ethylbenzene, benzene, toluene, and m/p xylenes ◦For most carbonyls: low conc., with some exceptions, such as acetone, formaldehyde, and acetaldehyde ◦Most PAHs: below the limit of detection ◦TSNAs: typically found at lower levels than tobacco smoke ◦Nicotine levels were also significantly higher in CC smoke than in the e-liquid vapor	◦Cross-contamination with smoke ◦Particle count from vapor uncertain; could not be replicated in phase II due to instrumental problems ◦Total air emission conc.s for many pollutants were found to be very low, also in CC smoke ◦Excess Lifetime Cancer Risks values for main-stream CC smoke samples were low-did not include	◦Ethylbenzene, benzene, toluene, and m/p xylenes acetone, formaldehyde, and acetaldehyde detected ◦TSNAs: typically found at lower levels than tobacco smoke ◦Conc. of pollutants were generally orders of magnitude lower than in CC smoke

							side- stream smoke?	
Misra M [115] 2014	◆▲19		◦blu EC glycerol-based e-liquids, with and without nicotine and two market leader flavors (Classic Tobacco and Magnificent Menthol), Ref: 1. CC Kentucky Reference 3R4F, 1R5F and Marlboro Gold), 2.smokeless tobacco products (Marlboro Snus, Copenhagen Snuff) 3) NRT product (Nicorette Lozenge)	◦Fluid and vapor ◦Aim: to test toxicity of EC liquids; smokeless tobacco products; a NRT lozenge product; and of pad-collected particulate matter from freshly-generated CC smoke and EC vapor	◦Gas Chromatography-Flame Ionization ◦Detection Canadian Intense puffing conditions ◦ VITROCELL® VC10 smoking robot Wet Total Particulate ◦Matter and EC vapor were collected on Cambridge glass fiber filter pads ◦Cell cultures: Human lung epithelial carcinoma cells A549 and Chinese hamster ovary cells CHO-K1 ◦Ames reverse bacterial mutagenicity assays	◦ In all assays, exposures with EC liquids and collected aerosols, at the doses tested, showed no significant activity when compared to CC ◦Presence of nicotine and flavors, at the levels tested, did not induce any cytotoxic, genotoxic or inflammatory effects ◦No significant IL-8 release was observed for most of the products, with the exception of the blu MM-no nicotine, blu MM-High and blu CT-no nicotine treatments which resulted in higher IL-8 release only at extremely high doses of 6.9–13.8 mg/mL	◦One brand only ◦Did not use cell systems that are most sensitive to EC vapor	◦ EC liquids and vapor does not produce any meaningful toxic effects in four widely-applied *in vitro* test systems, in which the conventional cigarette smoke preparations are markedly cytotoxic and genotoxic
Neilson L [118] 2015	◆▲22		◦NJOY Bold 4.5% nicotine and NJOY Menthol 3.0% nicotine ◦Ref: 3R4F CC	◦Vapor ◦Aim: to develop physiologically relevant test methods to analyse potential irritant effects to the respiratory tract caused by EC aerosols	◦Method development and optimisation of an acute in vitro MTT cytotoxicity assay using human 3D reconstructed airway tissues and an aerosol exposure system ◦EpiAirway™ tissue exposed to aerosols generated by the VITROCELL smoking robot ◦Dosimetry tools (QCM) were used to measure deposited mass	◦CC smoke reduced cell viability in a time dependent manner to 12% at 6 h ◦EC vapor showed no such decrease in cell viability and displayed similar results to that of the untreated air controls	◦Two brands only ◦Tested by smoking machine, not = human puffing behaviour	◦Little cytotoxicity from EC aerosol and different aerosol formulations when compared directly with reference CC smoke, over the same exposure time
O'Connell G [120] 2015	◆▲ 24	Θ	◦ Disposable 'closed system EC: Puritane Ref: No	◦Indoor air ◦ Aim: to measure volatile organic compounds (including nicotine and low molecular weight carbonyls), polycyclic aromatic	◦ 5 male volunteers: 3 current vapers + 2 non-smokers/vapers ◦ Exposure: 165 min. ad libitum vaping session in a closed room (38.5 m3), real-life setting	Concentration in the indoor air during consumption of EC: ◦No increase in nicotine ◦Glycerol: <350 µg/m3 which is below the UK WEL of 10,000 µg/m3 ◦PPG: 203.6 µg/m3 which is below the UK WEL of	◦Only one brand	◦Exposure of bystanders to the chemicals in the exhaled EC aerosol, at the levels measured within this study, are below current regulatory standards that are used for workplaces or general indoor air quality

				hydrocarbons, tobacco-specific nitrosamines and trace metal levels in the air before, during and after EC use in a typical small office meeting room		474,000 µg/m3 ◦Total volatile organic compounds (TVOCs): 379.8 µg/m3; UK Building Regulations: 8 h average: 300 µg/m3 ◦No measurable increase in any of 16 PAHs during the vaping period (all <1.25 µg/m3) ◦Metals: <1.0 µg/m3 for antimony, arsenic, barium, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickel, selenium and zinc; <2.0 µg/m3 for aluminium, beryllium, silver and thallium, and <10 µg/m3 for phosphorus; all below UK WEL ◦No increase in *N*'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*'-nitrosoanatabine (NAT) and *N*'-nitrosoanabasine (NAB)		
Palpant NJ [122] 2015	No		◦Vapor from EC cartridge (South Beach Smoke, Tobacco Classic, Full Flavored, 16 mg nicotine/ cartridge) ◦Ref: smoke from University of Kentucky, 3R4F Research grade CC	◦Vapor ◦Aim: to determine the impact of EC and CC on heart development in vitro and in vivo.	◦Human embryonic stem cells ◦Undifferentiated RUES2 female line	◦Both EC and CC exposure resulted in decreased expression of cardiac transcription factors in cardiac progenitor cells, suggesting a persistent delay in differentiation ◦In definitive human cardiomyocytes, both EC and CC treated samples showed reduced expression of sarcomeric genes such as MLC2v and MYL6 ◦Cells differentiated in purified nicotine were not significantly different on the basis of all endpoints compared to control samples	◦ One brand only	◦Study indicate a negative effect of EC on heart development in vitro and in vivo ◦The finding that nicotine treatment alone recapitulated untreated controls indicates that the impact of EC on heart development is the consequence of other components
Papousek R [124] 2014	No		◦1.disposable EC with a Marlboro flavor ◦2. refillable EC with flavored refill liquids (cherry or Turkish) Ref: cigar	◦Vapor ◦Aim: to describe a fast and simple procedure for simultaneous determination of both acrylamide and acrolein under standard conditions	◦Gas chromatography–mass spectrometry (GC–MS) method ◦The derivatization of acrylamide and acrolein was carried out by a bromination method with elemental bromine	◦Acrolein was found in all tested samples ◦Acrylamide was detected only in smoke from cigar –side-stream smoke contained a significant amount [2.40 and 1.52 µg (cig. eq.)−1].	◦Few brands ◦Tested by smoking machine, not = human puffing behaviour	◦Acrolein, a compound with toxic and potentially and mutagenic effects was found in all tested samples
Park S [125] 2014	No		◦EC of unknown type Ref: CC smoke	◦Vapor ◦ Aim: to assess the impact of EC exposure on the carcinogenic potential of	◦Epithelial cells were exposed to both a low and high concentration of nicotine in the EC vapor- or CC smoke-	◦Enhanced colony growth in the H3mut-P53/KRAS cells following a 10-day treatment with the high nicotine EC- and CC-conditioned media compared to the untreated and low nicotine treatment groups	◦ One brand only?	◦Preliminary analyses indicate the observed EC-specific gene expression changes were concordantly changed following CC-conditioned media exposure.

				immortalized human bronchial epithelial cells on a background of silenced p53 and activated KRAS (H3mut-P53/KRAS) (these mutations are often observed in the airway of current and former smokers at risk for lung cancer)	conditioned media	◦The high nicotine EC-conditioned media induced a gene expression pattern similar to CC- conditioned media and whole CC smoke exposure in the H3mut-P53/KRAS cells ◦Gene expression studies show 263 differentially expressed genes following in vitro exposure to EC-conditioned media for 96hrs		
Pellegrino RM [126] 2012	No		◦2 types of Italian brand ◦One with and one without nicotine Ref: CC (nicotine 0.8mg/tar 10 mg)	◦E-liquid and vapor ◦Aim: test for toxicity during a "smoking" simulation ◦Quali-quantitative determination of the aromatic mixture and the vapor content	◦E-liquid: ◦Gas-chromatograhy/ mass-spectometry ◦Vapor: modified smoking machine, vapor collected ◦Indoor emission of PM: laser operated aerosol mass analyser	◦PPG and VG together: >90% of the total ingredients. Other ingredients detected in trace levels. ◦Vapor: 11 and 10 substances found in +nicotine/-nicotine EC: major compound is PPG and VG ◦PM in vapor: fine + ultrafine particles: density ratio compared with CC 6-21 lower Total PM: 15 times lower from EC than CC	◦Tested only 2 brands ◦Tested only one batch of liquid per brand	◦PPG and VG are major ingredients – other ingredients = traces ◦PM in vapor: fine + ultrafine particles ◦PM emissions are significantly lower than in CC smoke
Romagna G [133] 2013	❖▲12		◦21 commercially available e-liquids with different flavouring ◦Manufactured by same manufacturer, Italy ◦Ref: CC (1mg of nicotine, 10 mg of tar and 10 mg of carbon monoxide)	◦Vapor ◦Aim: test for in vitro cytotoxicity of vapor extract and to compare it with the cytotoxicity of CC smoke extract	◦Vapor: e-liquid evaporated and extracted in culture medium. ◦CC extract from one cig. was produced ◦The extracts, undiluted and in five dilutions were applied to cultured murine fibroblasts (3T3) ◦Viability was measured	◦Only ''Coffee'' exhibited a cytotoxic effect; this was observed at the highest extract conc. only ◦All e-liquids: the range of fibroblast viability was 88.5–117.8% at 3.125%, 86.4–115.3% at 6.25%, 85.8–111.7% at 12.5%, 78.1–106.2% at 25%, 79.0–103.7% at 50% and 51.0–102.2% at 100% extract ◦Conc. of CC extract: significant cytotoxicity at extract conc. >12.5%	◦Tested only one brand ◦Tested only one batch of liquid per brand ◦Too low CC exposure? ◦Fibroblasts, are normally not in direct contact with vapor	◦Vapor from 1 out of 21 EC liquids examined had cytotoxic effects on cultured fibroblast ◦CC: significantly higher cytotoxicity
Romagna G [134] 2012	▲33	Θ	◦E- liquid (FlavourArt), nicotine concentration 11 mg/ml Ref: CC, 0.6mg nicotine	◦Room air ◦Aim: to identify and quantify the chemicals released on a closed environment from the use of EC	◦60m3 closed-room ◦Two sessions: 5 smokers and 5 users of EC. Both sessions lasted 5 h. total organic carbon (TOC), toluene, xylene, carbon monoxide (CO), nitrogen oxides (NOx), nicotine, acrolein, poly-	◦During the sessions: EC session, 1.6 ml of liquid was consumed, 17.6mg of nicotine; CC: 19 cigarettes were smoked, 11.4mg of nicotine ◦EC: TOC =0.73 mg/m3 and glycerin=72 µg/m3. No toluene, xylene, CO, NOx, nicotine, acrolein or PAHs were detected on room air during the e-CIG session ◦CC: TOC=6.66mg/m3, toluene=1.7 µg/m3,	◦Two brands only ◦Preliminary assessments ◦Several harmful substances from smoke were not detected in air either	◦Preliminary assessment: vaping does not produce detectable amounts of toxic and carcinogenic substances in the air of an enclosed space

					aromatic hydrocarbons (PAHs) glycerin and propylene glycol levels on the Room air	xylene=0.2 µg/m3, CO=11 mg/m3, nicotine=34 µg/m3, acrolein=20 µg/ml and PAH=9.4 µg/m3.		
Rubenstein DA [135] 2015	No		◦NJoy, OneJoy Traditional Flavor, 1.2% and 1.8% Nicotine ◦eGo, OKC Vapes, Desert Sands Flavor with 0 mg, 12 mgor 18 mg nicotine ◦Pure nicotine 50 nM ◦ Ref: Marlboro 100s (16 mg tar and 1.2 mg nicotine	◦Vapor ◦Aim: to identify the response of Kupffer cells to both CC and EC extracts and to elucidate whether or not this response can be transmitted to other locations within the cardiovascular tree	◦Immortalized Kupffer cells (from Sprague–Dawley Rats) ◦Incubated with CC smoke extracts, EC vapor extracts or pure nicotine	◦Robust inflammatory response, oxidative stress production and cytokine release after Kupffer cells were exposed to CC or EC extracts ◦Both gC1qR and cC1qR have an enhanced expression after exposure to CC, EC and pure nicotine ◦All CC and EC product extracts significantly increased the Kupffer cell production of hydrogen peroxide by peroxidase and xanthine oxidase ◦Marginal decrease in cell viability coupled with a significant decrease in cell density - this was not a function of the extract formulation(e.g. CC vs. EC products or the formulation of the product)	◦Two brands only ◦Use of an immortalized cell line ◦Extraction method only provides limited representation of lung extraction ◦Absence of other cell types	◦EC exposure resulted in inflammatory response, oxidative stress production and cytokine release – comparable to CC exposure ◦An inflammatory response is initiated that may pass into the general systemic circulation
Ruprecht AA [136] 2014	No		◦ Elips Serie C, Tank System (Ovale Europe Srl), refilled with and without 16 mg nicotine Reference: CC, popular brand	◦ Vapor ◦ Aim: to investigate the emission of PM and UFP generated by EC and CC under real-life conditions	◦ 50 m3 office ◦ One volunteer smoker ◦ PM mass as PM1, PM2.5, PM7, PM10, total suspended particles (TSP) measured by use of pre-calibrated Aerocet, Model 531 ◦ UFP by condensation particle counter, Model 3007 concentrations ◦ Measure of urban background pollution	◦ EC generated consistently less PM of all measured sizes than CC ◦ This difference was particularly evident for the nicotine-refilled device, which showed only marginal PM production in its sidestream smoke, while the EC without nicotine showed low but present production of all PM	◦Tested one brand only ◦Tested particle emission only ◦Underestimation due to EC-naïve volunteers	◦ EC produce less PM than CC and therefore may be less hazardous in terms of secondhand exposure
Saffari [137]A 2014	No	Θ	◦Elips Serie C, Tank System) with and without nicotine Ref: a widely used brand of normal CC (i.e. tobacco-containing)	◦Particle phase of EC emission ◦Aim: to quantify the degree of secondhand exposure to particulate organic compounds and metals in a real-life setting	◦Room: volume of 48 m^3 ◦Samples of total suspended particles were collected indoors on Quartz filters, using a high-volume PM sampler operating at a low rate of 240 liters per minute (lpm) ◦The conc. of black	◦No sign difference between EC and CC samples for zinc (Zn), nickel (Ni) and silver (Ag) ◦Despite the 10-fold decrease in the total exposure to particulate elements in EC compared to normal cigarettes, specific metals (e.g. Ni and Ag) still displayed a higher emission rate from EC ◦Similar levels of total PM concentrations outdoor during EC use and CC smoking -presence of	◦Only particle phase examine and vapor-phase EC emissions might be useful to uncover ◦Is vaping time=smoking time in real life?	◦Study shows same concentration of zinc, nickel and silver, potentially toxic and redox active species, from EC and CC emission ◦The consumption of EC otherwise resulted in a remarkable decrease in secondhand exposure to all metals and organic compounds

					carbon (BC)measured by Aethalometer ◦EC were vaped at a rate of one puff per minute, lasting for 7min., followed by 3 min. of pause and continuing again for another 7 minutes	nicotine in the e-liquid had a very small effect (less than 0.1%) on the EC's total PM emissions ◦Organic species had lower emission rates during EC consumption compared to CC ◦ Polycyclic aromatic hydrocarbons (PAHs) from EC: non-detectable emission, while substantial emission of these species was observed from CC		
Samways B [139] 2014	◆▲ 32		◦4 commercially available disposable, non-refillable and non-rechargeable 2 with menthol 4.5 or 3% nicotine Ref: no	◦Vapor ◦Aim: to assess the suitability of QCMs as an *in vitro* dosimetry tool for EC aerosols, using the Vitrocell® VC 10 Smoking Robot. Product durability before battery depletion, and how this relates to *in vitro* dose was also investigated	◦Four QCMs (Vitrocell® Systems,) were installed into the 6/4 CF Stainless module The VC 10 Smoking Robot (Vitrocell® Systems) smoked 4 EC ◦QCMs read real-time aerosol particle deposition at a resolution of 10 ng/cm2/second ◦Ten repeats per product	◦Aerosol mass deposition ranged from 40.71 –88.95µg/cm², 24.20 – 71.77µg/cm², 73.84 – 111.23µg/cm² and 32.12 – 128.98µg/cm² for Product A , Product A Menthol, Product B and Product B Menthol ◦Menthol products produced less mass in comparison to their higher nicotine concentration, non-mentholated equivalents, despite lasting similar durations before exhaustion ◦Deposited aerosol mass varied greatly from repeat experiments with all products	◦Unknown brand	◦Deposited aerosol mass varied greatly from repeat experiments with all products ◦Variability of aerosol cellular dose *in vitro* needs to be taken into consideration for future *in vitro* studies
Sancilio S [140] 2015	No		◦Two cartridge solutions (nicotine content 0 and 24 mg/ml, respectively) from Halo Company containing propylene glycol, glycerin, and natural artificial flavorings Ref: no	◦Vapor and fluid ◦Aim: to investigate the effects of the liquids of EC on human gingival fibroblasts and to compare the effects of nicotine-containing fluid to the fluid itself	◦Cells were treated with different concentrations for different times (0–72 h) ◦Cytotoxicity: MTT assay ◦Apoptosis occurrence and Bax expression: flow cytometry ◦Reactive oxygen species (ROS) production:fluorescence optical microscopy	◦Metabolic activity was reduced in a time-and dose-dependent manner ◦Both nicotine-containing and nicotine-free fluids induced an increased ROS production after 24 h, along with an increased Bax expression, ◦Apoptosis occurrence after 48 h of exposure ◦Extreme toxicity for concentrations higher than 1 mg/mL just after 24 h ◦The cytotoxicity exerted on human gingival fibroblasts by EC fluids is not entirely ascribable to nicotine	◦One brand only	◦Findings indicated that EC fluids induce an oxidative stress and early and late apoptosis, with a major extent in nicotine-treated samples, but present anyway in the samples treated with nicotine-free fluids
(Chandramani)-Shivalingappa P [145] 2015	No		◦Unknown EC 2.5 mg or 7.5 mg ◦Ref: room-air controls	◦Vapor ◦Aim: to quantitate the impact of ECupon proteostasis and to evaluate if short-term effects of EC exposure	◦Beas2b cells exposed for 1, 3 and 6 h ◦Immunoblotting ◦Fluorescence microscopy and immunoprecipitation	◦Vapor induced protein-aggregation can activate oxidative stress, apoptosis (caspase-3/7) and senescence ($p<0.01$) as compared to controls ◦Sign increase in accumulation of total polyubiquitinated-proteins with time-dependent decrease in proteasomal-activities of vapor-	◦Unknown brand ◦Exposure not sufficiently described ◦One brand only?	◦EC vapor exposure induces proteostasis/ autophagy impairment leading to oxidative stress, apoptosis, and senescence that can be ameliorated by an autophagy inducer ◦EC vapor-induced

				modulate mechanisms known to be involved in CC induced COPD emphysema		exposure as compared to control ◦Even minimal exposure (1 hr) induces valosin containing protein ($p<0.001$), sequestosome-1/p62 (aberrant-autophagy marker; $p<0.05$) and aggresomeformation ◦Inhibition of protein synthesis by 6 hr cyclohexamide (50 µg/ml) treatment sign ($p<0.01$) alleviates vapor-induced (1 hr) aggresome-bodies		autophagy impairment and aggresome formation suggest their potential role in chronic obstructive pulmonary disease–emphysema pathogenesis
Scheffler S [141] 2015	No		◦Reevo Mini-S 1) E-liquid with or without nicotine 2) carrier substances PPG and glycerol ◦Ref: mainstream smoke from K3R4F research CC	◦Vapor ◦Aim: to test toxicological effects of EC vapor and pure carrier substances	◦Primary human bronchial epithelial cells (NHBE) of two different donors ◦Smoking robot ◦CULTEX® RFS compact module ◦24 h post-exposure: cell viability and oxidative stress levels	◦Toxicological effects of EC vapor and the pure carrier substances, whereas the nicotine concentration did not have an effect on the cell viability ◦The viability of cells exposed to mainstream CC smoke was 4.5–8 times lower and the oxidative stress levels 4.5–5 times higher than those of EC vapor exposed cells, depending on the donor ◦The pure carrier substances PPG and glycerol exhibited toxicological effects	◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Short term exposure ◦The number of puffs taken was not identical for CC and EC/carrier substance- adjusted by multiplying the results	◦Toxicological effects of EC vapor and the pure carrier substances, whereas the nicotine concentration did not have an effect on the cell viability
Schober W [142] 2014**	No	Θ	◦ Red Kiwi, without and with 18 mg nicotine ◦ Reference: no vaping	◦ Indoor air ◦ Aim: to measure inner and outer exposure assessment of EC emissions in terms of PM, particle number concentrations, VOC, PAH, carbonyls, and metals under real-life conditions	◦ Room size: 18 m^2 and its volume: 45 m^3 ◦ In 6 vaping sessions 9 volunteers (occasional smokers) consumed EC with and without nicotine in a thoroughly ventilated room for two hours. ◦ Monitored effects on FeNO release and urinary metabolite profile of the subjects	◦ Substantial amounts of 1,2-propanediol, glycerine and nicotine were found in the gas-phase, as well as high concentrations of PM2.5 (mean 197 µg/m3) ◦ PAH in indoor air increased by 20% to 147 ng/m3 ◦ Aluminum showed a 2.4-fold increase ◦ Particle number concentrations ranged from 48,620 to 88,386 particles/cm3(median), with peaks at diameters 24–36 nm ◦ FeNO increased in 7 of 9 individuals ◦Urine: 3-HPMA, the mercapturic acid metabolite of the pyrolysis product acrolein, was elevated after nicotinic vaping ◦ The nicotine content of the liquids varied and was 1.2-fold higher than stated	◦Tested one brand only ◦Underestimation due to EC-naïve volunteers?	◦ EC are not emission-free and their pollutants could be of health concern for users and secondhand smokers ◦ In particular, ultrafine particles formed from supersaturated 1,2-propanediol vapor can be deposited in the lung ◦ Aerosolized nicotine from EC seems capable of increasing the release of the inflammatory signaling molecule NO upon inhalation ◦ Whether effects also occur in passive smokers, is uncertain.
Schripp T [143] 2013**	No		◦3 types of e-liquids ◦2 apple-and one tobacco flavored ◦With nicotine or	◦Vapor ◦Determination of the release of VOC and (ultra)fine	◦Near-to-real-use conditions; a volunteering smoker/vaper in an	◦1,2-propanediol: detected in the chamber atmosphere - below the limit of determination ◦High amount of 1,2-propanediol	◦Evaporation under the sampling conditions?	◦High amount of 1,2-propanediol in the exhaled air ◦Emissions of aerosols and

			nicotine-free ◦Three different types of EC were filled with e-liquid from the same stock ◦Ref: CC	particles (FP/UFP)	emission test chamber ◦ Inhaled mixture analysed in small chambers ◦Thermal desorption and gas chromatography coupled with mass spectrometry	in the exhaled air ◦The release of formaldehyde was below the limit of detection ◦The VOC emission strength seems to differ with different types of ECs ◦With one type of EC almost three times more propylene glycol was released per puff ◦Aerosol release: ultrafine particle mode increased ◦Particle size distribution of the CC provides a single mode with a maximum at 100 nm and a higher total number conc.		VOC s ◦Prominent components in the gas-phase: 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavorings, and traces of nicotine ◦Passive vaping must be expected from the consumption of ECs ◦The aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles
Schweitzer KS [144] 2015	No		Nicotine solutions Vanilla, Kentucky Prime, and nicotine-free Kentucky Prime EC used to generate vapor: iClear 16 Ref: filtered research-grade CC (2R4F) or nicotine-free CC (1R5F)	◦Fluid and vapor Aim: to investigate the contribution of nicotine in CS or EC to lung endothelial injury	Cell cultures: Primary rat lung endothelial cells (RLEC) and human bronchial epithelial cells (Beas-2B) Primary mouse lung endothelial cells (MLEC) Primary human microvascular cells-lung derived (HMVEC-LBl) ◦+Animal experiments ◦Exposed to nicotine, EC solution, or condensed EC vapor (1–20 mM nicotine) or to nicotine free CC smoke extract or EC solutions ◦NMR, mass spectrometry and gas chromatography ◦Electric cell-substrate impedance sensing	◦Nicotine-independent effects of EC solutions as endothelial barrier dysfunction were noted, which may be attributable to acrolein, detected along with PPG, glycerol, and nicotine in both EC solutions and vapor ◦Detected acrolein not only in condensed vapor, but also in all EC solutions tested; heating was not a necessary ◦Although nicotine at sufficient concentrations to cause endothelial barrier loss did not trigger cell necrosis, it markedly inhibited cell proliferation.	◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Short term exposure	◦Results suggest that soluble components of EC, including nicotine, cause dose-dependent loss of lung endothelial barrier function, which is associated with oxidative stress and brisk inflammation ◦Nicotine-independent deleterious effects of EC solutions were noted; identified acrolein as putative mediator for nicotine-independent toxicity ◦Anticipate dose-dependent sustained oxidative stress and inflammatory lung damage with imitation of endothelial repair in long-term EC use
Stepanov I [147] 2015	No		◦ Green Smoke, NJOY, V2, Blu ◦ No nicotine, low, medium and high nicotine ◦ Regular tobacco taste and menthol	◦ Fluid ◦ Aim: to study the pH in EC	◦ To measure pH, the contents of each cartridge were removed, extracted with 10 mL ultrapure water, and the pH of the	◦ pH of EC cartridge content ranges widely, from 4.78 to 9.60, depending on the brand and nicotine level ◦ While pH of nicotine-free cartridges is generally neutral or even slightly acidic, over 50% of nicotine-	◦ Tested fluid only	◦ ECs with the same nicotine content, but different pH, may deliver different doses of nicotine to users ◦ Most of the tested brands have basic pH - the long-term effect of chronic aero-

			Reference: no		aqueous extracts was measured with a pH-meter according to a standard protocol	containing cartridges have a pH greater than 9 ◦ pH generally increases with increasing nicotine content ◦ pH of menthol-flavored varieties is generally higher than that of traditionally flavored ones		digestive tract exposure is not known
Talih S [149] 2015	No		◦ Direct drip atomizer + eGo-T battery (Joyetech), PPG-based liquid (Liquid Express, WaterMelon Chill, 0 or 18 mg/mL nicotine concentration) Ref: no	◦Aerosol ◦Aim: to investigate whether "dripping" e-liquids directly onto a heater coil can produce significant levels of non-nicotine toxicant emissions	◦Aerosols were machine-generated from an NHALER 510 Atomizer = direct drip atomizer ◦High-performance liquid chromatography-mass spectrometry ◦Heater coil temperatures were measured using an infrared camera	◦Depending on the condition, volatile aldehyde emissions, including formaldehyde, greatly exceeded values previously reported for conventional EC and CC, both per puff and per unit of nicotine yield ◦Increasing the inter-drip interval resulted in greater volatile aldehyde emissions, and lower total particulate matter and nicotine yields ◦Maximum heater coil temperature ranged from 130°C to more than 350°C	◦One brand ◦One puffing topograhy regimen ◦Some portion of the measured volatile aldehyde yields may have been present at the outset ◦There may be significant quantities of volatile aldehyde (particle phase) that was trapped on the sampling filter pad	◦Direct dripping of e-liquids apart from its clear implications for drug abuse liability, may also involve greater exposure to volatile aldehyde due to the potentially higher temperatures attained in the atomizer ◦May expose users to increased volatile aldehyde levels relative to conventional EC and even relative to CC, for a given nicotine yield
Talio MC [150] 2015	No		◦Refill liquids: Tobacco USA Mix(18mg nicotine), Cappuccino (12mg nicotine), Ice Mint(0mg nicotine), Tobacco Winston(11mg nicotine) Ref: CC	◦Fluid ◦Aim: to develop A new environmental friendly methodology based on fluorescent signal enhancement of rhodamineB dye for lead traces quantification in EC and measure lead in EC	◦Fluorescent signal enhancement of rhodamineB dye, using a preconcentration step based on the coacervation phenomenon	◦In all studied samples, lead contents in EC liquids were in the same order as in CC ◦The proposed methodology showed to be an alternative environmental friendly, simple, economical, rapid, and precise for determination of lead traces	◦Not vapor	◦Lead contents in EC liquids were in the same order as in CC
Tayyarah R [151] 2015	◆▲20		◦ Three blu eCigs products and two SKYCIG products (most popular) Ref: CC (Marlboro Gold Box, and Lambert & Butler Original and Menthol products) and ambient air	◦Vapor ◦Aim: to test for harmful and potentially harmful constituent in EC vapor	◦ISO 17025 accredited analytical methods were used ◦Health Canada Test Method T-115 Tested for: delivery of major ingredients and for select constituents (carbon monoxide (CO), carbonyls, phenolics, volatile organic compounds (volatiles), metals, tobacco-specific	Aerosol nicotine for EC samples was 85% lower than nicotine yield for the CC ◦Mainstream CC smoke delivered approximately 1500 times more harmful and potentially harmful constituents tested when compared to EC aerosol or to puffing room air were estimated as <5% of threshold limit value.	◦Two brands ◦One puffing topography regimen ◦Puff procedure = real life?	◦The deliveries of harmful and potentially harmful constituents tested for EC products were similar to the study air blanks rather than to deliveries from CC smoke

					nitrosamines (TSNAs), polyaromatic amines (PAAs), and polyaromatic hydrocarbons (PAHs)).			
Theophilus E [152] 2014	◆▲ 30		◦EC VUSE ◦Ref: different commercial EC and CC	◦Vapor (Mainstream aerosol) VUSE aerosol was generated using the VitroCell® VC10® aerosol exposure system and cells were exposed at the air–liquid interface ◦Aim: to test for harmful and potentially harmful constituent in EC vapor	◦Aerosol was collected using a machine puffing regimen (55 ml puff volume/30 s inter-puff interval/3 s puff duration) and either bell shaped or square wave puffing profiles. Chemistry test: subset of compounds listed on FDA's Harmful and Potentially Harmful Constituents list for CC. In vitro toxicology test program	◦Individual constituent yields, chromatographic profiling, and in vitro data for commercial VUSE products tested under the conditions of these studies indicated that: (1) VUSE aerosol was chemically significantly less complex than mainstream smoke from CC and (2) consistent with the simpler aerosol chemistry, VUSE aerosol was not cytotoxic (i.e., IC50 could not be derived) whereas CC smoke was cytotoxic (IC50 was derived).	◦Only abstract available – not possible to see details, values or brands of other EC	◦EC (Brand: VUSE) aerosol was not cytotoxic whereas CC smoke was cytotoxic
Tierney PA [154] 2015	No		◦30 flavored fluids ◦BLU and NJOY, disposable-cartridge, in five flavours: tobacco, menthol, vanilla, cherry and coffee and refill bottles in five other confectionary flavors (chocolate/cocoa, grape, apple, cotton candy and bubble gum) Ref: no	◦Fluids ◦Aim: to determine concentration levels and class of flavors in EC	◦Gas chromatography (Agilent DB-5MS UI)/mass spectrometry	◦Flavored products do not typically list the levels of specific flavor chemicals present, and most do not identify the major flavor chemicals present ◦In many liquids, total flavor chemicals were found to be in the ∼1–4% range (10–40 mg/mL); labeled levels of nicotine were in the range of 0.6–2.4% (6 to 24 mg/mL) ◦A significant number of the flavor chemicals were aldehydes, a compound class recognized as 'primary irritants' of mucosal tissue of the respiratory tract ◦Many of the products contained the same flavor chemicals: vanillin and/or ethyl vanillin was found in 17 of the liquids as one of the top three flavor chemicals	◦Not vapor ◦Few brands/flavors	◦The concentrations of some flavor chemicals EC fluids are sufficiently high for inhalation exposure by vaping to be of toxicological concern ◦Almost half of the tested products on the US market were more than 1% by weight flavors chemicals
Trehy ML [155] 2011	No		◦ A random sampling of 4 of US suppliers of cartridges, refills, and EC devices	◦Cartridges, refill e-liquid, and vapor ◦Aim: determine	◦Sample extracts of the products were analyzed using a validated gradient HPLC	◦One manufacturer: some cartridges labeled as containing nicotine, did not contain nicotine and some cartridges labeled as not containing nicotine, did contain nicotine	◦Puff procedure = real life?	◦Some products were found to contain high conc. of nicotine when labeled not to contain nicotine ◦The actual amount of

			◦Ref: CC	nicotine and the nicotine related impurities	method ◦Vapor was analyzed following a ‘‘puff’’ procedure developed to simulate the use of a EC ◦A 100mL puff was drawn through the device at 1 min intervals.	◦Cartridge contents vary sign. from one cartridge to another ◦The impurity level as a % of the area for nicotine appears to be lower in the trapping solution from the EC than in the trapping solution from a CC ◦The Cialis E-Cartridges and E-Liquids were mislabeled –contained amino-tadalafil not tadalafil		nicotine delivered is likely to be highly variable ◦Transfer of rimonabant and aminotadalafil to the vapor phase is low ◦Impurity level is lower than for CC
Uchiyama S [157] 2013	No		◦363 EC ◦13 Japanese brands	◦Vapor ◦Aim: to measure carbonyl compounds in EC	◦Carbonyl compounds in EC vapor mist were measured using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, followed by high-performance liquid chromatographyLM1 /PLUS ◦Smoking machine ◦HPLC analysis	◦9 of the 13 brands generated various carbonyl compounds ◦In some cases they are generated with extremely high concentrations e.g. (mg/m3) Formaldehyde 61±64; Acetaldehyde 48±51; Acrolein 34±12; Propanal 27±14 Gloxal 29±12; methylglyoxal 22±10 ◦The carbonyl concentrations of the ECs did not show typical distributions, and the mean values were largely different from the median values	◦No reference	◦EC generate incidentally carbonyls. ◦In some cases they are generated with extremely high concentrations
Uryupin AB [158] 2013 (Russian original paper from 2012)	No		◦7 samples/types with presumed country of origin: USA or China ◦3-4 samples of each type ◦Ref: none	◦E-fluids ◦Aim: study the composition of fluids	◦One and two-dimensional homo- and heteronuclear 1H and 13C NMR spectroscopy + electrospray ionization mass spectrometry	◦Samples differed sharply in water content ◦1,2-propyleneglycol and glycerin identified ◦NMR spectroscopy enabled components in fluids for ECs at conc. of at least 0.1% to be determined reliably	◦Tested few fluids ◦No reference	◦The main components of mixtures were non-tobacco products
Vargas Trassiera C [165] 2015	No	Θ	◦Rechargeable EC filled with a tobacco flavor liquid, nicotine level of 9 mg mL^{-1} ◦Ref: CC with nicotine 0.8 mg per cigarette	◦Vapor (side-stream vapor) ◦Aim: characterization of the interaction between radon (significant risk for lung cancer) progeny with aerosol both from EC and from CC	◦Walk-in radon chamber inner volume of 150 m^3 ◦4 tests were carried out in the radon chamber. Three of them were made generating aerosol from e-cigarette at different radon concentration ◦Radon gas obtained by natural emanation from the underneath soil	◦Increase of the Potential Alpha-Energy Concentration (PAEC) due to the radon decay products attached to aerosol for higher particle number concentrations. This varied from 7.47 ± 0.34 MeV L_1 to 12.6 ± 0.26 MeV L_1 (69%) for the EC ◦CC and at the same radon concentration: the increase was from14.1 ± 0.43 MeV L_1 to 18.6 ± 0.19 MeV L_1 (31%). ◦The equilibrium factor increases, varying from 23.4% ± 1.11% to 29.5% ± 0.26% and from 30.9% ± 1.0% to 38.1 ± 0.88 for the EC and CC, respectively.	◦Tested one brand	◦The increase in the attached Potential Alpha Energy Concentration was higher for the EC than for traditional CC ◦Therefore, the aerosol from EC operates as a carrier of the radon progeny and, as a consequence it decreases the “plate out” of the radon daughter

					◦Particle number concentration and particle size distribution: Potential Alpha Energy (PAEC) Concentration ◦Radon activity concentration: Alpha Guard Professional Radon Monitor	◦These growths still continue for long time after the combustion, by increasing the exposure risk ◦The radon progeny, in presence of aerosol, tends to attach to airborne particles. Therefore, the particles emitted by cigarettes (CC and EC) operate like carrier of the radon or thoron progeny		
Varlet V [166] 2015	▲31		◦42 models from 14 popular brands purchased on the Internet in 2013 Ref: no	◦Fluids ◦Aim: to test refill liquids for the presence of micro-organisms, diethylene glycol, ethylene glycol, hydrocarbons, ethanol, aldehydes, tobacco-specific nitrosamines, and solvents	◦Microbiological tests as described in the European Pharmacopoeia Section 2.6.13 ◦Gas chromatography-mass spectrometry (GC-MS) ◦Chemical ionisation GC-MS (selected ion monitoring) ◦Headspace GC-MS Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) ◦Liquid chromatography coupled with ultra-violet detection and MS (LC-UV/MS)	◦All liquids: with norms for the absence of yeast, mold, aerobic microbes, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* ◦Diethylene glycol, ethylene glycol and ethanol were detected, but remained within limits authorized for food and pharmaceutical products. ◦Terpenic compounds and aldehydes were found in the products, in particular formaldehyde and acrolein ◦Formaldehyde concentrations ranged from 0.1 to 9.0 µg/g and acetaldehyde concentrations from 0.05 to 10.2 µg/g ◦No sample contained nitrosamines at levels above the limit of detection (1 µg/g). ◦Residual solvents such as 1,3-butadiene, cyclohexane and acetone, were found in some products	◦Limit of detection was high for TSNAs ◦The measured Chronic Oral Toxicity Associated with Intended Use is based on content of liquids not vapor ◦Some popular brands were not included	◦None of the products under scrutiny were totally exempt of potentially toxic compounds ◦A minority of liquids, especially those with flavorings, showed particularly high ranges of chemicals, causing concerns about their potential toxicity in case of chronic oral exposure
Visser W [167] 2015	No		◦183 e-liquids available on the Dutch market chosen on the basis of their popularity, their flavors and their nicotine content	◦Fluid and vapor ◦Aim: to investigate the composition of different kinds of e-liquids available in the Dutch market and that of the resulting vapor	◦Presence of VOCs and TSNAs was investigated in a sample group of 60 liquids ◦Headspace GC-MS ◦For each category of substance 15 different e-liquids were vaporised using a vaping robot and a commercially available vaporizer ◦An 'exposure scenario' was developed	◦All the tested e-liquids contained the propylene glycol (range 0-1.14 g/ml) and/or glycerol (range 0-1.16 g/ml). ◦Small quantities of diethylene glycol (poisonous) detected in 2 liquids ◦Nicotine content varied from 0 to 37.4 mg/ml; in 15 e-liquids the measured nicotine concentration differed from the supplier's stated value by more than 25% ◦Formaldehyde: present in 63 liquids, with the highest recorded concentration being 24 µg/ml ◦Acetaldehyde: found in 12 liquids, the highest being 300 µg/ml ◦Acrolein: detected in 4 liquids, at a		◦The toxic substance-related health risks associated with the use of CC are far greater than those associated with EC ◦Nevertheless, daily use of e-cigarettes is not without health risks ◦Concentrations of most relevant substances in vapor from e-liquids are lower or much lower than that in smoke ◦The concentration of formaldehyde can be up to 3

						max. concentration of 1.6 µg/ml. ◦The flavorant diacetyl: present in 34 liquids, with the highest concentration 5591 µg/ml ◦Almost all samples contained other aldehydes and ketones, sometimes in high concentrations, probably due to use as flavorants ◦2 of the liquids were found to have a measurable concentration of VOCs: 9.5 µg/ml of benzene and 0.58 µg/ml toluene. ◦In 15 liquids, a measurable quantity of one or more TSNAs was present, the highest concentration detected being 80 ng/ml ◦Various metals were found in extremely varied concentrations ◦ Concentrations of cadmium, lead, nickel and arsenic are considerably lower than in smoke ◦Chromium concentrations are comparable to smoke ◦Further 150 substances were detected, many of them flavorants ◦Many substances will pass into in the vapor unchanged, while others will decompose under the influence of heat during vaping		times higher in EC vapor than in tobacco smoke ◦On the other hand, the concentrations of carcinogenic TSNAs were up to 400 times lower in vapor than in smoke ◦Vapor concentrations of TSNAs are sufficiently high in some cases to give an elevated risk of tumor development ◦The vapor concentrations of aldehydes can be sufficient to induce effects on the respiratory tract ◦Exposure to the polyols can damage the respiratory tract and influence the leukocyte pattern
(FDA) Westen-berger BJ [169] 2009	No		◦Two samples of EC and components from leading US brands, 18 cartridges, various flavours, +/- nicotine ◦Ref: Nicotrol inhaler 10 mg for smoking cessation	◦Cartridges ◦Aim: test the content of nicotine and presence of tobacco constituents	◦A sparging apparatus and headspace GC analysis were used to stimulate actual use of products. Repeated testing. Diethylene glycol presence was confirmed with proton NMR. Nicotine quantification by methanol extraction and a acetnitrile/phosphoric acid in water extraction	◦Detected: ◦Diethylene glycol in one cartridge at 1% ◦Certain tobacco-specific nitroamines in half of the sample ◦Tobacco specific impurities (anabasine, myosmine, beta-nicotrine) in the majority ◦Large variability in nicotine concentrations was found within cartridges with same label ◦Low nicotine in No-nicotine cartridges, in all, except one ◦One High-nicotine cartridge delivered twice as much nicotine as by an inhalation product for smoking cessation	◦Not vapor	◦Diethylene glycol in one cartridge ◦Detectable levels of carcinogens and toxic chemicals
Willers-hausen I [170] 2014	No		◦E-liquids all contained in addition to various flavors the components	◦Fluid ◦Aim: to assess the influence of the different	◦Human Periodontal Ligament Fibroblasts were incubated up to 96 h with the	◦The proliferation rates of the cells incubated with nicotine or the various flavored liquids of the e-cigarettes were reduced in comparison to the	◦Small study ◦Not vapor	◦This in vitro study demonstrated that menthol additives of EC have a harmful effect on human

			nicotine (20–22 mg/ml) and propylene glycol ◦Selected flavors: hazelnut, lime and menthol ◦Ref: Phosphate-buffered saline (PBS)	liquids on the viability and proliferation of human periodontal ligament fibroblasts	different liquids, and cell viability was measured by using the PrestoBlue® reagent, the ATP detection and the migration assay ◦Fluorescence staining	controls ◦After an incubation of 96 h with the menthol-flavored liquid the fibroblasts were statistically sign reduced ($p < 0.001$) ◦Similar results were found for the detection of ATP in fibroblasts; the incubation with menthol-flavored liquids ($p < 0.001$) led to a statistically sign reduction. ◦The cell visualization tests confirmed these findings		periodontal ligament fibroblasts ◦The menthol-flavored liquid caused a highly significant reduction of cell migration
Williams M [171] 2013	No		◦22 cartomizers from a leading manufacturer ◦Purchased from one manufacturer on four different occasions over a two year period ◦Ref: CC (Marlboro brand)	◦Cartomizers (fluid + aerosol) ◦Aim: test for structural and elemental contents, cytotoxicity, and aerosol emissions	◦Light and electron microscopy, cytotoxicity testing, x-ray microanalysis, particle counting, and inductively coupled plasma optical emission spectrometry	◦Apparent electrophoretic movement of the cartomizer fluid towards the battery, deposition of tin particles on the inner and outer fibers, and burning of the inner fibers ◦Fluid with and without particles inhibited human pulmonary fibroblasts (hPF) survival at a dose of 1% ◦Fluid with tin particles inhibited both attachment and proliferation of hPF dose dependently ◦One puff of cartomizer aerosol contained numerous particles (mainly tin, silver, nickel and aluminum) ◦Nano particles in vapor (<100 nm): tin, chromium, and nickel ◦ Silicon, calcium, aluminum, and magnesium- the most abundant elements in vapor ◦Lead and chromium conc.s in aerosols: within the range of CCs, while nickel was about 2–100 times higher than in CC ◦Room air contained relatively few particles; small end of the size range	◦Tested one brand only	◦A total of 22 elements were identified in EC aerosol, and three of these elements (lead, nickel, and chromium) appear on the FDA's ''Harmful and potentially harmful chemicals'' list ◦Aerosol: significant amounts of tin and other metals, silicate beads, and nanoparticles ◦Conc's of most elements in aerosol were higher than or equal to corresponding conc's in CC smoke ◦Cytotoxicity: cartomizer fluid containing tin particles inhibited attachment and survival of hPF ◦ Metals in aerosol: from poor solder joints, wires, other metal components ◦Silicate particles: from the fiberglass wicks ◦Evidence of use/presale testing prior to packaging
Wu Q [172] 2014	No		◦InnoVapor tobacco-flavored e-liquid without nicotine or with 18 mg/ml of nicotine Ref:no	◦Fluid ◦Aim: to determine if EC use alters human young subject airway epithelial functions such as inflammatory response and innate immune defense against respiratory viral (i.e., human	◦Experimental study ◦Lung cells (normal hTBE cells from the tracheas and bronchi) from organ donors (8–10 years old) whose lungs were not suitable for transplantation cells were treated with medium, tobacco-	◦E-fluid did not decrease primary human airway epithelial cell viability ◦Nicotine-free e-liquid promoted IL-6 production and Human rhinovirus infection -addition of nicotine into e-liquid further amplified the effects ◦E-liquid inhibited the expression of SPLUNC1 (an important antimicrobial protein in airways against various bacterial infections) in primary human airway epithelial cells	◦Tested one brand only	◦Findings strongly suggest the deleterious health effects of EC in the airways of young people ◦EC promotes proinflammatory cytokine IL-6 production and Human rhinovirus infection in primary human airway epithelial cells ◦EC inhibits the expression of SPLUNC1, a host

				rhinovirus) infection	flavored e-liquid at various concentrations ◦Cells were infected with Human rhinovirus-16			defense molecule against Human rhinovirus infection in mice
Yu V [174] 2015	No		◦V2 and VaporFi, two of the most popular EC on the market flavor ‘‘Classic Tobacco” 70% PG/30%VG liquid formula 1.2% nicotine or 0% nicotine ◦Ref: CC Marlboro Red filter extract	◦Vapor extract ◦Aim: to evaluate the cytotoxicity and genotoxicity of short- and long-term EC vapor exposure on a panel of normal epithelial and head and neck squamous cell carcinoma (HNSCC) cell lines	◦Experiments were performed both in normal and cancer cells ◦Cells were treated with vapor extract for periods ranging from 48 h to 8 weeks ◦Cytotoxicity : Annexin V flow cytometric analysis, trypan blue exclusion, and clonogenic assay ◦Genotoxicity: neutral comet assay and c-H2AX immunostaining	◦Both brands produced a significant induction of DNA double-strand breaks in human epithelial cell line as compared to the untreated control, with foci number increased by up to 1.5-fold in nicotine-free EC-treated cells and up to 3-fold in nicotine-containing EC-treated cells extract led to the highest number of DNA double-strand breaks in human epithelial cell line and head and neck squamous cell carcinoma cell lines, but were not significantly higher than V2 nic 1% ◦Significantly reduced cell viability and clonogenic survival, along with increased rates of apoptosis and necrosis, regardless of EC vapor nicotine content	◦Tested one brand only ◦Cells exposed to EC vapor extracts for up to 8 weeks but for CC smoke extract for only 24 h. Comparable?	◦At biologically relevant doses, vaporized EC liquids induce increased DNA strand breaks and cell death, and decreased clonogenic survival in both normal epithelial and head and neck squamous cell carcinoma cell lines independently of nicotine content
Zervas E [175] 2014	No		◦7 different EC fluids,± nicotine 1.2%, ± flavor 2% or 5% Ref: Ambient air	◦Vapor ◦Aim: to study direct particle emission of EC liquids	◦Scanning Mobility Particle Sizer in order to determine the number and size of particles inhaled by e-cigs users	◦EC emit 10^6 -10^7 particles with a size distribution peaked at 10-20nm & 100-500nm and a median diameter of 200-400nm	◦Unknown brand	◦EC liquids generate nano-particles; 300-3000 more than ambient air
Zhang Y [176] 2013	No		◦Bloog MaxX Fusion EC ◦Cartridges were filled with solutions of 16 mg/ ml nicotine in PPG or VG ◦Reference: a filtered University of Kentucky reference CC	◦Vapor ◦Aim: test for basic physical characteristics of aerosols produced by a smoking machine ◦Apply a lung deposition model to predict distribution of the aerosolin the respiratory tract	◦Aerosol generated by a smoking machine ◦Scanning mobility particle sizer counted particles ◦A single puff experiment counted particles immediately and after aging ◦A steady-state experiment counted particles emitted from a collection chamber, untreated and after desiccation or organic vapor removal	◦Stable peak diameters- particles reach steady state with gas phase content ◦Particle counts decline rapidly for both peaks over time, suggesting that particles frequently adhered to equipment surfaces ◦CC generated more particles initially, but were otherwise similar ◦The variety of sizes suggests heterogeneous condensation from vapors and coagulation in this concentrated environment ◦ 9% -17% of the total volume of EC aerosol is predicted to deposit in regions characterized by venous absorption and 9%- 18% in the alveoli, where arterial absorption is expected ◦Total predicted deposition	◦Tested only two types of liquid ◦Tested only one batch of liquid per brand ◦Particles were adsorbed to the experimental apparatus or were diluted after generation? ◦Underestimation of absorption is expected	◦CC produce more particles initially, but particle counts converge to a similar scale as the aerosols condense ◦EC and CC produce aerosols having generally similar particle sizes in the range of 100–600 nm ◦Lung deposition model predicts: one eighth of particles will deposit in the alveoli where arterial absorption of nicotine could occur; one eighth deposit elsewhere, mostly the oropharynx, where venous absorption of nicotine could occur; and three quarters are exhaled

						20%-27%, with the remainder exhaled - CC deposition is slightly higher at 25%–35%		

*Four of these studies are also/partly mentioned in Table 3/Annex 5 on animal experimental studies [98] [122] [144] [78]

Three studies [101, 106, 134] could as well have been described in Table 2/Annex 4, human experimental studies

AP= acetyl propionyl
EC =electronic cigarette
CC= conventional cigarette
CO = carbonmonoxyde
Conc.=concentration
DA= diacetyl
DEG= diethylene glycol
HPHC = harmful and potentially harmful constituents
hESC= human embryonic stem cells
mNSC= mouse neural stem cells
hPF= human pulmonary fibroblasts
LOQ= limit of quantification
LOD= lower limit of detection
MEG=monoethylene glycol
MOE= Margin of exposure approach; toxicological threshold. MOE < 10 is judged to pose "high risk", while MOE < 100 are judged as "risk"
NNN= N'–nitrosonornicotine
NNK= 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone)
NAB= N'-nitrosoanabasine
NAT= N'-nitrosoanatabine
NET= natural extract of tobacco, extracts of cured tobacco leaves produced by a process of solvent extraction and steeping
NO = nitric oxide
NRT= nicotine replacement therapy
OX/ROS= oxidants or reactive oxygen species
PA= acetyl propionyl
PAH= polyaromatic hydrocarbon
PM = particular matter
PPG= propylene glycol
ROSA= reactive oxygen species
TSNAs= tobacco specific nitrosamines
UFP= ultra fine particles
UPF1= 4-methoxy-L-tyrosinyl-γ-L-glutamyl-L-cysteinyl-glycine)
VG = vegetable glycerin

VOCs= volatile organic compounds

Conflicts of interest - Conflicts of interest of each study should be assessed individually.

▲1: MLG received research funding from manufacturer of medicinal products for smoking cessation. AS received research funds and travel expenses from manufacturer of ECs

▲2 JFE: reimbursed by manufacturer of e-liquids for travels. EZ and SS: employed by manufacturer of medicinal products for smoking cessation

▲3 MLG: research funding from manufacturer of medicinal products for smoking cessation. NB: consultant for manufacturers of medicinal products for smoking cessation

▲4 MLG: research funding from manufacturer of medicinal products for smoking cessation

▲5: all received research funding and/or performed provided consultancy for manufacturer of medicinal products for smoking cessation

◆▲6: Study funded by tobacco company. Two of three authors affiliate to this tobacco company.

▲7: MLG received research funding from manufacturer of medicinal products for smoking cessation. AS received research funds and travel expenses from manufacturer of ECs

◆▲8: Manufacturers of both EC and CC funded the study. ML is cited as one of 5 most influential persons in the EC industry, http://ecigarettereviewed.com/top-5-most-influential-people-in-the-electronic-cigarette-industry/

❖▲9: Research contract with manufacturer of EC. See also CI #8

◆▲10: No conflict stated, but JHL affiliates to Lauterbach & Associates - a consulting *firm* that specializes in providing contract scientific affairs and regulatory support to the *tobacco* industry Also see CI#8 for ML

▲11: Study sponsored by National Vapers Club and EC vendors. Subsequent to data-collection SB became part owner of EC company

❖▲12: Study funded by EC company

▲13: study funded by crowd funding in vaper community. A volunteer vaper is acknowledged for assistance with fund raising. Some of the studies by KF and VV were performed using funds provided to the institution by EC companies

◆▲14: A small number of KF's and VV's studies on electronic cigarettes were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. Enthalpy Analytical is a for-profit CRO and provides testing for the EC industry but did not receive any compensation for this study. MM was working at Enthalpy Analytical at the time of the study but is currently employed by a tobacco company

▲15: The authors declare no conflict of interest. A small minority of the studies by KF and VV were performed using unrestricted funds provided to Onassis Cardiac Surgery Center by EC companies.

▲16: Some of the studies by K.F. and V.V. were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. EC manufacturer is thanked for free equipment

▲17: MLG reports a grant from a manufacturer of smoking cessation drugs, outside the submitted work; AS reports personal fees from eSmoking Institute, Poland, and nonfinancial support from a manufacturer of EC

▲18: Agencies which sold some of the tested EC contributed to expenses of testing

◆▲19: authors are employees of tobacco company which also manufactures EC

◆▲20: authors are employees of tobacco company which also manufactures EC

▲ 21: MLG received a research grant from a manufacturer of smoking cessation medications

◆▲22: authors are employees of tobacco company which also manufactures EC

◆▲23: authors are employees of tobacco company which also manufactures EC

◆▲24: authors are employees of tobacco company which also manufactures EC

▲25: MLG received a research grant from manufacturer of smoking cessation medication, outside scope of this work

◆▲ 26: All authors are employees of tobacco company. The work in this paper was supported by tobacco company
▲27: Some of the studies by KEF and VV were performed using funds provided to the institution by EC companies.
◆▲ 28: partly sponsored by Altria group which is parent company for tobacco company
❖▲ 29: Some of the studies by KEF and VV were performed using funds provided to the institution by EC companies. This study was funded in part by the Greek Association of E-cigarette Businesses (SEEHT) - the sponsor funded the expenses of the laboratory. The study was investigator-initiated and investigator-driven.
◆▲ 30: authors are employees of tobacco company which also manufactures EC
▲31: JFE was reimbursed by a manufacturer of e-liquids for traveling to London and to China, but he received no honoraria for these meetings aimed at mutual information. Some of the other studies performed by KF used unrestricted funds provided to research center by e-cigarette companies.
◆▲ 32: authors are employees of tobacco company which also manufactures EC
▲33: nothing is stated but previous study by RG was funded by EC company. Some of the studies by KEF were performed using funds provided to the institution by EC companies
▲34: None stated. Previous study was founded by manufacturers of both EC and CC. ML is cited as one of 5 most influential persons in the EC industry
◆▲ *35:* Study was joint funded by a manufacturer of *non-tobacco products* (a company set up in 2010 by tobacco company which also manufactures EC)and by tobacco company which also manufactures EC, and the authors are full time employees
◆▲ *36:* Study was joint funded by a manufacturer of *non-tobacco products* (a company set up in 2010 by tobacco company which also manufactures EC)
◆▲ 37: authors are employees of tobacco company which also manufactures EC

Annex 3. Human experimental studies reporting health effects (n=32)

Name of first author Reference Year	Conflict of interest ▲= Yes ◆ = Tobacco industry[3] ❖ =EC industry[4]	Passive expo-sure to EC Θ=Yes	Type of product(s) Reference product	Method Exposure	◦Numbers of participants ◦ Aim of study / Outcome measure	Results	Weakness	Conclusions
Ballbé M [5] 2014	No	Θ	◦PPG-based liquids: Totally Wicked, Puff, and Free Life Ref: no	◦Observational study with non-smokers ◦Exposure: real-use conditions with passive exposure to EC or CC for one week ◦Control group: no exposure	54 non-smoker volunteers from different homes: 25 living at home with conventional smokers, 5 living with nicotine EC users, and 24 from control homes (not using EC or CC) Aim: to characterize passive exposure to nicotine from e-cigarettes' vapor and conventional cigarettes' smoke at home among non-smokers under real-use conditions	◦The airborne markers: statistically higher in CC-homes than in EC-homes (5.7 times higher). ◦Concentrations of urine and saliva cotinine in non-smokers exposed to CC smoke or EC vapor were statistically similar (only 2 and1.4 times higher respectively). ◦Control homes: no exposure	◦ Very small sample of EC homes ◦Potential exposure to smoke/vapor in other places than at home possible (but exposure was also registered by detailed questionnaire)	◦Non-smokers passively exposed to EC vapor absorb approx. as much nicotine as when exposed to smoke from CC
Battista L [7] 2013	No		◦EC of unknown type Ref: CC	◦Experimental study ◦Exposure: vaping of own EC at the usual concentration of nicotine (4 to 9 mg/ml) in 4 min.	◦ 12 regular users of EC Aim: to investigate the acute hemodynamic effects of nicotine	◦CO increased and systemic vascular resistances decreased after 2 and 4 minutes ◦ Diastolic BP and mean arterial pressure increased at 4 minutes. Oxygen saturation did not change	◦Selected regular users? ◦Low-moderate nicotine content in EC	◦ EC inhalation produces the same pathophysiological cardiovascular effects of CC smoking

[3] Results of studies influenced by the tobacco industry are marked with an asterisk (*) in the paper.

[4] Studies funded by e cigarette manufacturers or performed in collaboration with the e cigarette industry are labelled with a chevron (^) in the paper.

Chorti M [23] 2012	No	Θ	◦Unknown (probably same as in Flouris AD 2012) Ref: ◦Unlit CC ◦Lit own brand CC	◦Experimental study ◦Exposure: Volunteers in CC group smoked 2 CC ◦Volunteers in EC group puffed 1 EC	◦ 15 heavy-smokers ◦Aim: assess acute impact of active and passive EC and CC smoking on the pulmonary function tests ◦FEV1, FEV1/FVC, FEF25-75, FeNO, CO	◦Active EC vaping: no sign change in lung function but sign increase in cotinine ◦Exposure to EC vapor (passive vaping): FEV1/FVC ratio was reduced and cotinine increased ◦CC smoking sign decreased lung function, FeNO and increased CO and cotinine	◦Only one brand of EC ◦EC naïve participants ◦Stronger pulmonary reaction with passive than active vaping indicates insufficient inhalation ◦Small study	◦Passive but not active EC vaping resulted in short-term lung obstruction and increased cotinine
Colbyl H [25] 2015	No		◦Unknown label, 18 mg nicotine ◦Ref: same EC, 0 mg nicotine	◦Experimental study ◦Volunteers inhaled vapor 18 mg or 0 mg nicotine on separate days (randomized) ◦Non-invasive measurements ◦Oscillatory lower body negative pressure (OLBNP) between 0 and -60mmHg was applied for 20 cycles at 0.05 Hz and 0.1 Hz	◦13 subjects ◦Aim: to explore if acute inhalation of EC vapor would impair cerebral blood flow in response to variations in arterial pressure.	Heart rate, mean middle cerebral velocity, Mean arterial pressure and cerebral oxygen saturation were similar at baseline in the two groups. Mean arterial pressure and cerebral oxygen saturation very low frequency power and low frequency power were higher under the placebo condition (p= 0.03-0.06) Cross-spectral analysis in the low and very low frequency revealed that gain between mean arterial pressure - mean middle cerebral velocity was similar (p= 0.128)	◦Small study ◦Unknown brand ◦Unknown intensity and duration of exposure ◦No information on volunteers: smokers, vapers, non-smokers?	◦Study suggests that nicotine, when acutely inhaled via EC does not impair the cerebral pressure-flow relationship
Czogala J [29] 2012	No		◦MILD model M201, 14 mg nicotine ◦Ref: CC, L&M Blue Label, 0.7 mg nicotine, 8 mg tar	◦Experimental study ◦Two sessions. 1. session: smoking of CC, 2. session 7 days after the 1.: vaping of EC ◦Sessions preceded by 12 hours abstinence of smoking and coffee ◦Exposure: 5 min of smoking/vaping	◦42 healthy adult daily smokers ◦Aim: evaluate the hemodynamic effect ◦Blood pressure, COHb, heart rate	◦EC: slight elevation in diastolic blood pressure (2%), pulse and COHb – non-sign. changes ◦CC: sign elevation in systolic and diastolic blood pressure, COHb and pulse	◦Only one brand of EC ◦EC naïve participants	◦Slight non-sign elevation in diastolic blood pressure, pulse and COHb
Dawkins L [32] 2013	❖▲ 1		◦SKYCIG 18-mg/ml nicotine	◦Experimental study ◦A repeated measures design ◦Experimental sessions after 12 hours of abstinence ◦Exposure: 1) Ten puffs 2) 1 hour ad lib use	◦14 regular EC users - using at least one 18-mg nicotine cartridge per day). ◦Smokers or ex-smokers ◦Aim: to explore the effect of EC on blood nicotine, tobacco withdrawal symptoms, AE and urge to smoke	◦Plasma nicotine concentration: mean maximum of 13.91 ng/ml by the end of the ad lib puffing period. ◦Very low level of the total mean AE score: 13 (max. =200). ◦Light-headedness showed the highest mean, followed by throat irritation, dizziness, salvation, mouth irritation. 21 different negative symptoms reported.	◦Only one brand of EC ◦Selected regular users who probably tolerate EC and have positive experiences ◦AE were pre-defined symptoms, no spontaneous reporting	◦Low reporting of AE in regular users. Most frequent: light-headedness, throat irritation and dizziness

							◦Small study	
Dawkins L [33] 2013	❖▲2		◦Tornado EC was supplied by Totally Wicked liquid 18 mg nicotine ◦Ref: 0 mg nicotine, same EC brand	◦Experimental study ◦Within-subjects design ◦Experimental sessions after 8-10 hours of abstinence, completed two experimental sessions under nicotine (18 mg) and placebo (0 mg) EC conditions ◦Exposure: 10 min. ad lib use	◦20 smokers ◦ Aim: measure prospective memory: Desire to smoke, The Cambridge Prospective Memory Test, Mood and Physical Symptoms Scale	◦Improved time-based but not event-based prospective memory ◦Reduced desire to smoke and tobacco withdrawal symptoms	◦Only one brand of EC ◦EC naïve participants ◦Small study	◦Findings suggest that the EC can effectively deliver nicotine to impact on cognitive performance
Dawkins L [34] 2012	❖▲3		◦The 'White Super' EC ◦Randomly allocated to: • 18 mg nicotine EC • 0 mg nicotine EC • just hold the EC	◦Experimental study ◦Mixed experimental design ◦Abstinence of 1-2 hours. ◦Exposure: 5 min. ad lib use	◦86 EC naive smokers ◦Aim: memory tests ◦Letter Cancellation and Brown–Peterson Working Memory Tasks, performed by 60	◦The nicotine containing EC improved working memory performance compared with placebo at the longer interference intervals. ◦There was no effect of nicotine on Letter Cancellation performance.	◦Only one brand of EC ◦Paper gives the impression that EC improve memory. In reality, nicotine withdrawals impair concentration and nicotine in the EC reverse the poor concentration	◦Improved nicotine withdrawal impaired concentration /memory
Dicpinigaitis PV [36] 2015	No		◦Disposable EC Blu, Classic Tobacco flavor, 20-24 mg nicotine Ref: non-nicotine-containing EC	◦Experimental study ◦Capsaicin cough challenge at baseline, 15 minutes, and 24 hours after EC exposure (30 puffs 30 seconds apart) ◦A subgroup of subjects subsequently underwent an identical protocol with a non-nicotine-containing EC	◦30 healthy nonsmokers ◦Subgroup: 8 ◦Aim: to evaluate the effect of a single exposure to EC vapor on cough reflex sensitivity cough reflex sensitivity (Subjects were not aware that the EC being evaluated in the second phase of the study did not contain nicotine)	◦Cough reflex sensitivity was significantly inhibited (C5 increased) 15 minutes after electronic cigarette use (-0.29, 95% CI (-0.43)-(-0.15), (p<0.0001); 24 hours later C5 returned to baseline (0.24, 95% CI 0.10-0.38, p=0.0002 vs. post-15-minute value) ◦A subgroup of 8 subjects demonstrating the largest degree of cough reflex inhibition had no suppression after exposure to a non-nicotine-containing electronic cigarette (p=0.0078 for comparison of HC5 after nicotine vs. non-nicotine device) ◦More coughing was induced by the nicotine-containing vs. non-nicotine-containing device (p=0.0156)	◦One brand only ◦Short term exposure ◦Some degree of unintentional unblinding may have occurred in non-nicotine testing phase	◦Single session of EC use, approximating nicotine exposure of one CC, induces significant inhibition of cough reflex sensitivity ◦Exploratory analysis suggests that nicotine is responsible for this observation
Eissenberg T [37] 2010	No		◦ 'NPRO' ,16 mg nicotine cartridge, or 'Hydro', 16 mg nicotine cartridge. ◦Menthol or regular flavor	◦Experimental study ◦Hemodynamic measurements >12 hours abstinence from smoking vein catheter insertion	◦16 smokers ◦ Aim: evaluate the hemodynamic effect; heart rate	◦ EC: No increase in heart rate ◦CC: increased heart rate	◦Only one type of EC ◦Only one brand of EC ◦EC naïve participants	◦No increase in heart rate

			◦Ref: own brand CC	and continuous heart rate recording ◦Exposure: Puffed ad libitum 10 times (30-s interpuff interval)			(EC delivered little to no nicotine and suppressed craving less effectively than CC) ◦Small study	
Etter JF [40] 2011	No		◦The most used brands were Joye and Janty and the most used models were Ego and 510 ◦Mean conc. of nicotine in liquids: 18 g/ml ◦Ref: no	◦Saliva sampling in current vapers ◦196 vapers asked to participate, 16% returned saliva sample ◦Exposure: daily vaping	◦ 31 current users (30 daily users) of EC (median use 94 days) ◦ Aim: measure saliva cotinine levels in users of EC	◦Participants puffed a median of 200 times/day (25th and 75th percentiles: 100 and 400 puffs/day, range 50–1,000 puffs/day, mean ±SD 250±205 puffs/day) ◦Median cotinine level was 322 ng/ml (25th and 75th percentiles: 138 and 546 ng/ml, range 13–852 ng/ml, mean±SD 338±227 ng/ml ◦Correlation between cotinine and puffs/day was r=0.39	◦A minority of vapers responded – selection-bias? ◦Small study	◦Cotinine levels in experienced vapers were similar to levels previously observed in smokers and higher than levels previously found in users of nicotine replacement therapy
Farsalinos K [51] 2012	▲8		◦Nobacco with ‘‘tobacco taste’’, nicotine 11 mg/ml ◦Ref: CC (1mg nicotine, 10 mg tar, 10 mg CO)	◦Experimental study ◦Hemodynamic measurements + echocardiogram at baseline and after smoking/vaping ◦Exposure: 1 CC or 7 min. of vaping of EC	◦36 smokers and 40 EC users ◦ Aim: examine the immediate effects of electronic cigarette use on left ventricular (LV) function	◦ In EC group no differences were observed after device use. ◦ No difference between EC and CC regarding peak slight elevation in diastolic blood pressure, early and late velocities and E wave deceleration time CC: Isovolumetric relaxation time and corrected-to-heart rate were prolonged, diastolic velocities and diastolic strain rate were decreased, and both Doppler flow and tissue Doppler were elevated after smoking.	◦Only one brand of EC ◦Small study ◦Short term exposure	◦Slight elevation in diastolic blood pressure but no effect on cardiac function in experienced EC users
Farsalinos K [43] 2014	▲6		◦EC with nicotine-containing liquid (18mg/ml) ◦Ref: CC (0.7mg nicotine)	◦ Randomized cross-over design ◦Smokers were asked to smoke 2 CC and use an EC for 10 minutes ◦Two-dimensional guided M-mode evaluation of diameters of the ascending aorta measured at baseline (8 hours abstinence from smoking, alcohol and caffeine), 20 min. after smoking and 20 min. after EC use	◦108 healthy participants; 51 smokers, and 57 daily EC users who had stopped smoking since 10.5 ± 8.7 months. Aim: to evaluate the acute effects of electronic cigarette (EC) use on the elastic properties of the ascending aorta and compare them with the effects of tobacco cigarette smoking	◦EC use in smokers: No difference from baseline was observed (strain: 10.32 ± 4.44%, P = 0.694; distensibility: 3.26 ± 1.49, P = 0.873; aortic stiffness index: 5.86 ± 2.76, P = 0.655) ◦EC users: no difference was observed between baseline and post-use measurements (aortic strain: 10.85 ± 3.99% vs. 11.05 ± 3.77%; distensibility: 3.39 ± 1.39 vs. 3.29 ± 1.16; aortic stiffness observed after using the EC (aortic index: 5.37 ± 2.58 vs. 5.24 ± 1.84, P = NS for all). ◦Smoking: sign elevation in aortic strain and distensibility and sign elevation in aortic stiffness index	◦Short term exposure ◦EC-naïve smokers will inhale insufficiently ◦Unknown label ◦ Is 10 min of vaping giving the same level/impact as 10 min of smoking?	◦Significantly decreased elasticity and elevated stiffness of ascending aorta was observed after smoking, but no adverse effects were observed after using the EC
Farsalinos KE [53] 2015	▲5		◦ Two customizable atomizers (Kayfun Lite plus; SMtec GmbH) Ref:no	◦Experimental study ◦Two customizable atomizers were prepared so that one (A1) had a double wick= high liquid	◦ 7 experienced vapers blinded to set up of each atomizer ◦Aim: to evaluate aldehyde emissions at different	◦ All vapers identified dry puff conditions at 9Wand 10W with A2. ◦ A1 did not lead to dry puffs at any power level. ◦ Minimal amounts of aldehydes per 10	◦Single atomizer and a liquid with specific composition only	◦EC produce high levels of aldehyde only in dry puff conditions, in which the liquid overheats, causing a

				supply and lower chance of overheating at high power levels, while the other (A2) was a conventional setup (single wick). ◦ Experienced vapers took 4-s puffs at 6.5 watts (W), 7.5W, 9Wand 10W power levels with both atomizers and were asked to report whether dry puffs were generated	power levels associated with normal and dry puff conditions ◦ Atomizers were attached to a smoking machine and aerosol was trapped	puffs were found at all power levels with A1 (up to 11.3 μg for formaldehyde, 4.5 μg for acetaldehyde and 1.0μg for acrolein) and at 6.5Wand 7.5Wwith A2 (up to 3.7 μg for formaldehyde, 0.8μg for acetaldehyde and 1.3 μg for acrolein). ◦ The levels were increased by 30 to 250 times in dry puff conditions (up to 344.6μg for formaldehyde, 206.3 μg for acetaldehyde and 210.4 μg for acrolein, P<0.001) ◦ Acetone was detected only in dry puff conditions (up to 22.5 μg).	◦ Few vapers	strong unpleasant taste ◦ It is hypothesized that vapers will avoid dry puff conditions
Ferrari M [56] 2014	No		◦NaturSmoke with flavor, low dose nicotine or no nicotine? ◦Ref: smoking of CC	◦Experimental study – cross over design? ◦Exposure: 5 min of vaping or smoking	◦10 smokers and 10 non-smokers ◦Aim: to assess the impact of the short term exposure on lung function, fraction of exhaled CO and nitric oxide	◦Use of EC: sign decrease in FEF75% (61.6 ±18.7 vs. 55.4 ±17.7, p=0.04) in smokers ◦Use of EC without nicotine: no immediate adverse physiologic effects after short-term use in the non-smokers and a small effect on FEF75% in the smokers group. ◦Smoking: sign increase in fraction of exhaled CO, sign decrease in FEV1 and FEF75%, while no significant changes were observed in fractional *exhaled* Nitric Oxide	◦Short term exposure ◦The design of study is unclear ◦Flavour of EC unknown ◦Only one brand of EC ◦Small study ◦EC naïve participants	◦Short-term usage of flavored EC resulted in sign decrease in flow when 75% of forced vital capacity has been exhaled, indicating impact on lung function
Flouris AD [57] 2013	No	Θ	◦Giant, Nobacco with ‘‘tobacco taste’’, nicotine 11 mg/ml ◦Ref: own brand CC	◦Experimental study ◦Repeated-measures controlled study ◦Smokers’ sessions: control, active CC smoking, and active EC vaping ◦Never smokers’ sessions: control, passive CC smoking, and passive EC vaping (60 m^3 controlled chamber,1 hour) ◦Exposure: 30 min. of smoking or vaping	◦ 15 smokers and 15 never-smokers ◦ Smokers reporting previous use of EC were excluded ◦ Aim: evaluate the acute effect of active and passive EC and CC smoking on lung function and s-cotinin, exhaled CO and nitric oxide	◦ EC and CC generated similar (p<0.001) effects on serum cotinine levels after active (60.6±34.3 versus 61.3±36.6 ng/ml) and passive (2.4±0.9 versus 2.6±0.6 ng/ml) smoking ◦ Neither a brief session of active EC smoking (indicative: 3% reduction in FEV1/FVC) nor a 1 h passive EC vaping (indicative: 2.3% reduction in FEV1/FVC) significantly affected the lung function (p>0.001) ◦ Active (indicative: 7.2% reduction in FEV1/FVC; p<0.001) but not passive (indicative: 3.4% reduction in FEV1/FVC; P=0.005) CC smoking undermined lung function ◦ No effect of active EC smoking on FeNO	◦Only one brand of EC ◦Small study ◦EC naïve participants	◦ Short-term usage of EC and short term passive vaping generate small non-sign decrease in lung function, approx. the half of smoking ◦Similar nicotin-ergic impact to CC ◦Present results do not suggest that the acute effects of EC on lung function are completely different than those of CC ◦ No effect on FeNO
Flouris AD [58] 2012	No	Θ	◦Nobacco with ‘‘tobacco taste’’, nicotine 11 mg/ml ◦Ref: own brand CC	◦Experimental study ◦Volunteers participated in three experimental sessions - separated by ≥7 days of wash-out ◦Smokers’ sessions: control, active CC smoking, and active EC vaping	◦ 15 smokers and 15 never-smokers ◦ Smokers reporting previous use of EC were excluded ◦ Aim: evaluate the acute effect of active and passive EC and CC smoking on CBC	◦CBC indices remained unchanged during the control session and the active and passive EC vaping sessions (P > 0.05). ◦Active and passive CC smoking increased white blood cell, lymphocyte, and granulocyte counts for at least one hour in smokers and never smokers (P < 0.05).	◦Only one brand of EC ◦EC naïve participants ◦Small study	◦Acute active and passive vaping did not influence complete blood count indices in smokers and never smokers, respectively

				◦Never smokers' sessions: control, passive CC smoking, and passive EC vaping (60 m^3 controlled chamber,) ◦Exposure: 2 CC within 30 min. or 'a number of puffs' within 30 min.				
Gennimata S. A. [61] 2012 (abstract)	No		◦Unknown	◦Experimental study ◦Exposure: vaping for 10 minutes	◦32 consecutive subjects, 8 never smokers and 24 smokers (11 with normal spirometry, and 13 patients with COPD and asthma) ◦Aim: investigate the acute effects of an EC on respiratory functions in healthy subjects and in smokers with and without chronic airway obstruction ◦Spirometry, static lung volumes, airway resistance, airway conductance and a single breath nitrogen test - measured before and after use	◦Immediately after vaping: significant increase in airway resistance and in the slope of phase III, and a decrease in airway conductance ◦statistically significant increase in airway resistance %pred (from 223±80 to 246±86, p=0.008) ◦statistically significant decrease in airway conductance %pred (from 46±20 to 41±17, p=0.005) ◦statistically significant increase in single breath nitrogen test, ΔN2/L %pred (from 146±100 to 164±121, p=0.002)	◦Only one brand of EC ◦EC naïve participants ◦Small study	◦Short-term exposure caused immediate airway obstruction
Hecht SS [73] 2014	No		21 different from US market ◦Ref: values found in 3 studies on CC smokers	◦Urine sampling in current vapers ◦Current vapers who had not smoked CC for at least 2 months provided urine samples which were analyzed by validated methods for a suite of toxicant and carcinogen metabolites. Levels were compared to those found in CC smokers from three previous studies.	◦28 current EC vapers ◦Aim: to assess the potential toxic effects of EC by quantifying the urinary toxicant and carcinogen metabolites in people using EC and comparing their levels to those found in CC smokers.	◦Levels of 1-HOP, total NNAL, 3-HPMA, 2-HPMA, HMPMA, and SPMA were significantly lower in the urine of EC users compared to CC smokers ◦ 4 EC users had higher than expected levels of total NNAL, albeit lower than typically seen in smokers ◦Levels of nicotine and cotinine were significantly lower in EC users compared to CC smokers in one study but not in another	◦Sample size of EC users was relatively small ◦Sampled at only one time point ◦High NNAL due to smoking?	◦Urinary toxicant and carcinogen metabolites were significantly lower in EC users than in CC smokers ◦Some EC users had higher than expected levels of total NNAL; lower than seen in smokers but higher than seen when exposed to second hand smoking
Marini S [108] 2014	No		◦A tobacco flavor e-liquid (low + high nicotine) ◦Ref: CC 0.8 mg nicotine	◦Experimental study ◦Exposure: asked to smoke a CC and to vape an EC (with and without nicotine), and an EC without liquid (control session). Three puff profiles made up of four consecutive puffs with a 30-s inter puff interval were performed for each test	◦ 25 smokers Aim: to compare the short-term respiratory effects due to the inhalation of EC and CC-generated mainstream aerosols through the measurement of the exhaled nitric oxide (eNO)	◦ The mean eNO variations measured after each smoking/vaping session were equal to 3.2 ppb, 2.7 ppb and 2.8 ppb for EC without nicotine, with nicotine, and for CC, respectively. ◦ Total particle number concentrations in the mainstream resulted equal to $3.5\pm0.4 \times 10^9$, $5.1\pm0.1 \times 10^9$, and $3.1\pm0.6 \times 10^9$ part. cm^{-3} for EC without nicotine, with nicotine, and for CC, respectively. ◦ Alveolar doses for a resting subject were estimated equal to 3.8×10^{10}, 5.2×10^{10} and	◦Only one brand of EC ◦EC naïve participants ◦One EC/CC smoked/ vaped only ◦Small study	◦Similar effect on human airways, and same particle dose received with smoking and vaping

						2.3 × 10^{10} particles for EC without nicotine, with nicotine, and for CC, respectively.		
McRobbie H [114] 2015	▲ 9		◦Green Smoke EC (labeled 2.4% nicotine), a first-generation "cig-a-like" device Ref: no	◦Experimental study ◦Exposure: at target quit date participants were provided with their EC and received instructions on its use Instructed to use EC ad-lib ◦Received standard withdrawal-oriented behavioral support x 2	◦40 adult smokers wanting to stop smoking, recruited through advertisements in free newspapers ◦Excluded: women who were pregnant or breast-feeding, smokers with any current serious illness, and those who had used EC for more than 1week in the past	After 4 weeks of EC: ◦Use: 33 participants were using EC, 16 (48%) were abstinent (CO-validated) from smoking during the previous week (EC only users), and 17 (52%) were "dual users." ◦Sign reduction in CO in EC-only users (–12 ppm)) and dual users (–12 ppm), Cotinine levels: declined, but to a lesser extent ◦Mean 3-HPMA (primary metabolite of acrolein) levels: decreased 1,28 ng/mg creatinine in EC-only users and by 1,47 ng/mg creatinine in dual users	◦ Tested one brand only ◦Longer follow-up needed to investigate if dual users can maintain significant reduction in smoking	◦In dual users, EC use significantly reduced exposure to CO and acrolein because of a reduction in smoke intake
Palamidas A [121] 2014	No		◦EC of unknown type	◦Experimental study ◦Exposure: Gr. A: vaping in 10 min, EC with 11mg nicotine Gr. B: same, but 0mg nicotine	Gr.A: 60 subjects 9 never smokers and 51 smokers (24 without airway disease, 11 with asthma, 16 with COPD) Gr. B: 10 never smokers	◦Group A: a significant increase in airway resistance in smokers and in never smokers (0.284±0.13-0.308±0.14; p= 0.033, 0.246±0.07-0.292±0.05; p=0.006) with significant decrease in specific airway conductance (1.197±0.50-1.060±0.42; p= 0.009, 1.313±0.22-1.109±0.18; p= 0.043). ◦Increased slope in phase III was shown only in asthmatic patients (p=0.008). ◦Group B: increase in airway resistance (0.247±0.03-0.333±0.08; p=0.005) and a decrease in specific airway conductance (1.213±0.29-0.944±0.18; p=0.009)	◦ Tested one brand only ◦EC naïve participants ◦Short term exposure	◦The present study supports our preliminary results showing increased airway resistance and a concomitant decrease in specific airway conductance. ◦ These changes might be due to the vaporizing liquid but not to the inhaled nicotine per se.
Papaseit [123] 2014	No		◦Nhoss 16 mg/mL nicotine second-generation EC Ref: CC Marlboro.	◦Rrandomized and crossover controlled trial ◦Exposure: nicotine 0.8 mg/cig was administered in two successive doses separated by an interval of 1 h: baseline, 10 puffs in 5 minutes (equivalent to smoking one CC), 55-min of rest period, 10 puffs and a 55-min of rest period	◦6 healthy male regular CC smokers who were abstinent from nicotine use for 12 h	◦Nicotine produced increases in heart rate, diastolic and systolic arterial pressure immediately after administration, being more intense after CC than EC use ◦Temperature and pupil diameter was not consistently changed	◦ Tested one brand only ◦EC naïve participants ◦Short term exposure	◦EC use produces a moderate increase in vital parameters
Polosa R [129] * 2014	▲10		◦EC of unknown type	◦ Retrospective review of changes in lung function and asthma control ◦Exposure: self-selected switch from smoking to	◦ 18 smoking asthmatics who switched to regular EC use (10 EC only, 8 dual use, all dual users smoked ≤5 conventional cigarettes/day)	◦ Significant improvements in spirometry data, asthma control and airway hyper-responsiveness ◦Dual users smoked 3.9 CC pr. day only. They also had sign. improvement in lung	◦Selected regular users who probably tolerate EC and have positive	◦Study indicates that regular use of EC to substitute smoking is associated with objective and subjective

				regular EC use – with follow-up after 6 and 12 months follow-up	Aim: to investigate the effect of switching to EC on spirometry data, airway hyper-responsiveness, asthma exacerbations and subjective asthma control	function after 12 months ◦ Reduction in exacerbation rates was reported, but was not significant ◦ No severe AE	experiences ◦Small retrospective study	improvements in asthma outcomes
Popa C [132] 2015	No		◦Unknown brand 0.5mg nicotine /drop and 10 mg/20drops Ref: CC	◦Experimental study ◦Exposure: 2 sessions of 10 min with vaping or smoking,	◦10 volunteers, 5 current CC smokers and 5 current EC vapers ◦ CO_2 laser-photoacoustic spectrometri ◦Aim: to examine the ethylene changes at different time intervals in the exhaled breath composition of EC vapers and CC smokers, before and after vaping/smoking	◦Ethylene level (marker of oxidative stress) in exhaled breath was sign. increased by vaping (approx. 50 ppb) ◦Ethylene level was found in smaller concentrations in EC vapers than CC smokers (approx. 3-4 times lower)	◦Unknown brand ◦Small study	◦Vaping of EC increased levels of oxidative stress, but these were 3-4 times lower than after a smoking session
Tsikrika S [156] 2014	No		◦EC of unknown type	◦Experimental study ◦Exposure: Gr. A: vaping EC with 11mg nicotine in 10 min	◦62 volunteers 10 non-smokers/52 smokers: 16 with COPD 12 with asthma, 24 no airway disease ◦Aim: to assess the acute effect of smoking an e-cigarette on vital signs, clinical symptoms and exhaled markers	◦Cough and sore throat in both non-smokers and smokers ◦Sore throat and cough were reported by 90% of asthmatics and 63% of COPD ◦A significant increase in heart rate ($p<0.05$) with palpitations was also noted with a decrease in SpO2 ,mainly smokers ($p<0.05$) ◦Significant increase in exhaled CO in the group of non-smokers ($p<0.05$)	◦ Tested one brand only ◦EC naïve participants ◦Short term exposure	◦ Single use of an EC increased heart rate and gave symptoms like cough and sore throat
Vakali S [159] 2014	No		◦EC of unknown type	◦Experimental study ◦Exposure: Gr. A: vaping in 10 min, EC with 11mg nicotine Gr. B: same, but 0mg nicotine	◦64 volunteers Gr. A: 12 never-smokers and 29 smokers Gr.B: 14 never-smokers and 9 smokers ◦Aim: to assess the effect of a single EC use on clinical symptoms, vital signs and airway inflammatory markers	◦All subjects reported symptoms immediately after smoking. ◦Sore throat, cough and palpitations were reported more often in Gr. A compared with Gr. B. ◦Dizziness: more frequently reported in non-smokers Gr.B. ◦An increase in HR and decrease in SpO2 in Gr. A ◦A decrease in FeNO was detected in smokers and non-smokers of Group B, with an increase in airways temperature ($p=0.051$) in smokers of Group A.	◦ Tested one brand only ◦EC naïve participants ◦Short term exposure	◦Increased heart rate, palpitations and a decrease in SpO2 , are related to the use of a nicotine containing EC but airways symptoms (sore throat, cough) and inflammatory markers are independent of nicotine use
van Staden SR [160] 2013	❖▲4		◦ eGo	◦A single group within-subject design ◦Exposure: switch from smoking to EC vaping in 2 weeks	◦ 15 smokers switched to EC, 2 drop-outs ◦Aim: determine the effects of EC on arterial and venous COHb levels and evaluate participants' perception on their health	◦ COHb levels (%) were significantly reduced after EC use for 2 weeks ◦ A decrease in cotinine levels ($p=0.001$) and an increase in oxygen saturation, 1.3% ($p=0.002$) ◦ No significant changes in the blood pressure and pulse rate ◦ Cough increased in 23% and decreased in 23%	◦ One brand only ◦EC naïve participants	◦ Improvement of symptoms -EC may be a healthier alternative to smoking tobacco cigarettes

						◦ Phlegm increased in 31% and decreased in 54% ◦ Taste, smell, appetite improved in majority		
Vansickel AR [162] 2010	No		ECs: ◦'NPRO' 18 mg nicotine cartridge ◦'Hydro' 16mg nicotine cartridge Ref: ◦Own brand CC ◦ Sham= unlit CC	◦Experimental study ◦Repeated-measures controlled study ◦Refrained from smoking in 12 hours ◦4 Latin-square ordered conditions ◦ Exposure: two, 10-puff EC bouts	◦32 healthy smokers of at least 15 cig ◦Aim: describe clinical laboratory methods that could be used to characterize EC users' nicotine and CO exposure, cardiovascular response	◦EC or sham conditions, pre- and post administration: ◦No significant changes in plasma nicotine ◦No significant changes in heart rate ◦No significant changes in CO level ◦No reporting of "lightheaded" and "dizzy" within the first five minutes following the first administration	◦Only one brand of EC ◦Short experiment duration ◦Experiment failed to deliver nicotine to blood ◦EC naïve participants ◦Very few puffs of EC ◦1 puff of EC is not = 1 puff of CC ◦Only one type of EC ◦Small study	◦No changes in plasma nicotine and heart rate ◦No increase in CO
Vansickel AR [163] 2012	No		◦ "Vapor King" + "WOW Cowboy" or "WOW Cowboy Menthol" tobacco flavored cartomizers (18mg/ml nicotine) ◦Ref.: own brand CC	◦Experimental study ◦4 within-subject sessions ◦Exposure: six 10-puff bouts - separated by 30-mins	◦20 healthy smokers of at least 15 cig ◦Aim: abuse liability assessment of EC in current CC smokers ◦Plasma nicotine, cardiovascular response, and subjective effects	After 5 minutes: ◦Mean plasma nicotine increased from a pre-administration level of 2.2 (SD=0.78) ng/ml to 7.4 (SD=5.1) ng/ml (4 bouts of 10 puffs needed) ◦Heart rate increased from a pre-administration average of 67.5 (SD: 6.2) bpm to 75 (SD: 8.3) bpm ◦No adverse events	◦Short experiment duration ◦EC naïve participants ◦Few puffs of EC ◦1 puff of EC is not = 1 puff of CC ◦Only 2 types of cartomizers, one brand of EC ◦Small study	◦Increase in heart rate
Vardavas CI [164] 2012	No		◦NOBACCO EC + NOBACCO MLB-MED filter cartridge 11 mg nicotine Ref: control group inhaled with cartridge removed	◦Experimental study ◦Exposure: ad lib use for 5 min	◦30 healthy smokers of at least 5 pack years (10 volunteers were in both control and experimental group) ◦Aim: assess acute impact on the pulmonary function tests and F ENO, impedance, respiratory resistance	◦Statistically significant decrease in F ENO and an increase in impedance by 0.04 kPa/(L/s) (P = .003), respiratory resistance at 5 Hz by 0.04 kPa/(L/s) (P = .003), at 10 Hz by 0.034 kPa/(L/s) (P = .008), at 20 Hz by 0.043 kPa/(L/s) (P= .007), and overall peripheral airway resistance (beta , 0.042 kPa/[L/s]; P = .024), after using an EC	◦Only one brand of EC ◦EC naïve participants ◦Lack of proper control group ◦Overlap of control and experiment group ◦5 min vaping only ◦Small study	◦Immediate adverse effects on the airways after short-term use that are similar to some of the effects seen with tobacco smoking ◦Usage was associated with increased flow resistance even though spirometry-assessed lung function was deemed normal

Yan XS [173] 2015	◆▲7		◦blu EC ◦2 commercial products that contain 16 mg/mL nicotine, 3 non-commercial products that contain 24 g/mL nicotine ◦Flavors: Classic Tobacco or Menthol ◦Glycerin and/or PPG based ◦Ref: CC; Marlboro_ Gold King Size 0.8 mg nicotine	◦Experimental study ◦Two exposure scenarios from Day 1 to Day 11: half-hour controlled administration and one hour ad lib use	◦38 healthy EC-naïve daily smokers included from start, 14 withdrew, 23 included in analyses ◦Aim: to characterize EC users' exposure to nicotine, and to investigate the acute effects of EC on the hemodynamic measurements (blood pressure and heart rate) in comparison with the effects of regular smoking	◦ Significantly increased blood pressure and heart rate after use of several EC products ◦Especially diastolic blood pressure was increased by EC use - comparable to increase in CC smoking ◦Use of EC had no impact on the exhaled CO levels ◦Nicotine plasma concentrations after 1.5 h: significantly lower in the users of EC than of CC ◦The combination of glycerin and propylene glycol as the vehicle facilitated delivery of more nicotine than glycerin alone	◦Only one brand of EC ◦1 person missing (38-14=24) – what happened? ◦EC-naïve daily smokers= low nicotine exposure in EC users and under-estimation of real effect in current vapers ◦Drop-outs not described ◦Small short-term study	◦ Significantly increased blood pressure and heart rate after use of several EC products ◦The studied EC delivered less exposure of nicotine and thereby less cardiovascular effects compared to CC smoking

*This study could as well have been placed in annex 3 showing adverse events [129]

EC = electronic cigarette
CC= conventional cigarette
SAE= serious adverse event
AE= adverse events
COHb =Carboxyhemoglobin
CO= Carbon monoxide
COHb= carboxyhemoglobin
CBC= complete blood count
HPHC = harmful and potentially harmful constituents
HMPMA= 3-hydroxy-1-methylpropylmercapturic acid
F ENO = Fraction of exhaled nitric oxide
FEV1
FEV1/FVC
FEF25-75
ECG= electrocardiography
HDL=High-density lipoprotein
HMPMA= 3-Hydroxy-1-methylpropylmercapturic acid
hs-CRP High-sensitivity
IL-6=interleukin-6
MHBMA= monohydroxybutenyl mercapturic acid
MPO=myeloperoxidase
NEq =Nicotine equivalents
o-TOL =o-Toluidine
ox-LDL=low-density lipoprotein
PPG= propylene glycol

RBC = Red blood cell count
S-PMA =S-phenyl mercapturic acid
total 1-OHP =1-hydroxypyrene
total NNAL =4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and its glucuronides
vWF=von Willibrand factor
WBC =White blood cell count
1-HOP= hydroxypyrene
2-NA=2-Naphthylamine
2-HPMA= 2-hydroxypropylmercapturic acid
3-HPMA= 3-hydroxypropyl mercapturic acid
3-HPMA= 3-hydroxypropylmercapturic acid
4-ABP =4-Aminobiphenyl 8-epi-PGF2a= Urinary 8-epi-prostaglandin
11-DTXB2= F2a and 11-dehydro-thromboxane B2

Conflicts of interest - Conflicts of interest of each study should be assessed individually.

❖▲1: Study was funded and supported by manufacturer of EC. LD has received funding to speak at research conferences and benefits in kind from EC companies.
❖▲2: KD has a collaborative relationship with manufacturer of EC who provided free supplies of the EC for the study
❖▲3: KD has a collaborative relationship with manufacturer of EC who provided free supplies of the EC for the study
❖▲ 4: EC manufacturer sponsored the EC used in study
▲5: Some of the studies by KF and VV were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies.
▲6: Some of the studies by KF and VV were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. Other studies by GR have been sponsored by EC company.
◆▲7: employees in tobacco company which also manufactures EC
▲8: No stated, but some of the studies by KF were performed using unrestricted funds provided to the Onassis Cardiac Surgery Center by EC companies. KF has a website "Ecigarette Research Advocate Group" which represents a strictly positive view on EC and provides several links to vapor clubs.
▲9: HR is Clinical Director at The Dragon Institute (research-based training, studies on the latest changes in the health industry etc.); reports receiving commercial research grant from manufacturer of smoking cessation medication; and has received speakers' bureau honoraria from manufacturers of smoking cessation medication. MLG reports receiving commercial research grant from manufacturer of smoking cessation medication. PJ has received speakers' bureau honoraria from and is a consultant/advisory board member for the manufacturers of stop-smoking medications. No potential conflicts of interest were disclosed by the other authors
▲10: RP has received grant support, has served as a speaker and has served as a consultant for anti-asthma drug manufacturers and has received payment for developing educational presentations and being a consultant for manufacturer of smoking cessation medication; he has also served as a consultant for EC distributor. JBM has received honoraria for speaking and financial support to attend meetings/advisory boards from anti-asthma drug manufacturers

Annex 4. Animal experimental studies reporting health effects (n=11*).

Name of first author Reference Year	Conflict of interest ▲=Yes	Relevance for passive exposure to EC (Yes= Θ)	Type of product(s) Type/number of animal	Method Exposure Reference groups	Aim of study/ Outcome measure	Results	Weakness	Conclusions
Geraghty P [62] 2014	No		◦A/J mice ◦Cohorts of mice (n=8 per group) 1. EC liquid (American eLiquid Store) 18 mg/ml nicotine in 50%PPG/50% VG 2. EC liquid, 36 mg/ml nicotine in 50% PPG/50% VG	◦Exposure by a small animal nebulizer. ◦Exposed for 1 hour/day, 5 days a week for 4 months ◦Reference: 1. Nebulized phosphate-buffered saline (PBS), 2. Vehicle (50% PPG/50% VG),	◦Aim: to assess the safety and lung effects of e-cigarettes	◦Exposure to EC vapor with nicotine increased lung cytokine and protease expression, mucin staining in the airways, caspase 3/7 activity in the tissue and TUNEL staining in the lung parenchyma. ◦Exposure to EC vapor induced emphysema and airway hyper-reactivity while the vehicle had no effect	◦Few animals in each group ◦One brand ◦Relatively short daily exposure	◦Animal study shows that longer-term exposure of EC causes asthma and emphysema
Husari A [78] 2015	No		◦Four-month maleC57BL/6J mice ◦Pre-filled V4L	◦Smoke generator, mixing/conditioning chamber and “nose-only” rodent exposure	◦Aim: to investigate the effects of EC aerosol and CC smoke in an animal	◦Wet-to-dry ratio was higher in CC when compared to EC but sign higher in EC than in control group	◦The aerosol constituents and size	◦Despite higher exposure conditions, EC exhibited less

			CoolCart (strawberry flavor, 3.5 Ohm, 18 mg/mL labeled nicotine concentration) cartomizer cartridges, connected to an automatically actuated 4.2 V Vapor Titan Soft Touch battery	chambers 6h/day for 3 days ◦Reference: 1. Control (air) 2. CC smoke (3R4F) ◦Total particulate matter exposure for the EC was set at higher levels compared to CC smoke.	model and in human alveolar cell cultures (A549) ◦Lung injury was determined by: (1) measurement of wet-to-dry ratio; (2) albumin concentration in the bronchoalveolar lavage fluid; (3) transcriptional expression of inflammatory mediators IL-1β, IL-6, TNF-α; (4) oxidative stress; (5) assessment of cell death; and (6) lung histopathology.	◦Albumin leak in bronchoalveolar lavage fluid was evident in CC but not in EC. ◦EC exposure was associated with a significant increase in IL-1β In contrast, CC exposure resulted in significant increases in IL-1β, IL-6, TNF-α expression, and oxidative stress	distribution by the nose-only exposure apparatus are maybe not equivalent for the EC and CC smoke conditions ◦One brand tested ◦Short term exposure	toxic effects on lungs of experimental animals than CC smoke
Lerner CA [98] 2015	No		◦Blu EC (Classic tobacco flavor; 16 mg nicotine) ◦Eight weeks old wild type C57BL/6J mice	◦ Mice were exposed to side-stream EC vapor for 5 h per day for 3 days (acute exposure) in inhalation chambers ◦ No reference group	◦Aim: to investigate if exposure to EC vapor results in measurable oxidative and inflammatory responses in the lung	◦ Exposure to EC vapor caused lung inflammation and pro-inflammatory response ◦ MCP-1, a potent macrophage chemotactic cytokine was significantly increased ◦ Levels of IL-6, IL-1α and IL-13 were significantly increased ◦ Increased pro-inflammatory cytokines and diminished lung glutathione levels which are critical in maintaining cellular redox balance	◦ Short term exposure ◦ One brand ◦ Few animals	◦ EC inhalation have an impact on cellular oxidative stress, redox imbalance, and lung inflammation, in vitro in lung cells and in vivo in lungs
Lim HB [99] 2014	No		◦Z-company, 16 mg/ml nicotine ◦ 24 Five-week-old female BALB/c mice	◦ 1.Normal group (n = 8) given drinking water 2. Ovalbumin (OVA)-sensitized group(n = 8) 3. OVA sensitized EC treated group (n = 8) ◦Exposure: cartridge solution of EC was diluted 50 times and 100 µl of the diluted solution was intratracheally instilled two times a week for 10 weeks	◦ Aim: to investigate the effects of an EC solution on allergen related asthmatic airway inflammation (AI) and airway hyper-responsiveness (AHR), when it is delivered by intra-tracheal route in mice	◦ No remarkable changes in the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase enzymes in serum ◦ Increased infiltration of inflammatory cells including eosinophils, into airways from blood, aggravated the asthmatic AI and AHR, and stimulated the production of cytokines such as interleukin (IL)-4, IL-5 and IL-13, and OVA-specific IgE production.	◦ Fluid not vapor ◦ Few animals ◦Single brand ◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Intra-tracheally installed EC solution instead of inhalation of vapor	◦ EC inhalation can function as an important factor to exacerbate the allergy-induced asthma symptoms
McGrath-Morrow S [112] 2015	No	Θ	◦Joyetech 510-T EC with 510-T tank cartridges, atomizer and auto switch battery; Liquid: 0% and 1.8% nicotine solution with no flavoring	◦ Neonatal mice were exposed to EC vapor or room air ◦The size of the chamber was 13.5 cm x 9 cm x 8.7cm. 1) I group: 1.8% nicotine PPG or 0% nicotine PPG once a day for days 1 and 2 of life then twice a day from days 3 to 9 of life. 2) Control: kept in	◦ Aim: to determine if neonatal exposure to EC emissions would lead to impaired postnatal lung growth and systemic nicotine absorption ◦Outcome: weight gain, postnatal alveolar growth and systemic	◦Mice exposed to 1.8% nicotine/PPG had a 13.3% decrease in total body weight compared to room air controls ◦Decreased mean weight in the 0% nicotine/PPG mice compared to room air controls suggest that nicotine alone did not entirely account for the lower weights ◦Plasma cotinine levels were found to be elevated in neonatal mice exposed to	◦Short term study ◦Single brand ◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Impaired lactation in the mother	◦EC emissions (with or without nicotine) during the neonatal period can adversely impact weight gain ◦Exposure to EC with nicotine cause detectable levels of

			◦Timed pregnant C57BL/6J mice and their neonatal pups	room air	nicotine metabolites	1.8% nicotine/PPG E-cigarettes (mean 62.34± 3.3 ng/ml) ◦Nicotine exposed mice were found to have modestly impaired lung growth by mean linear intercept compared to room air control mice (p<.054 trial 1; p<.006 trial 2).	and/or disruption of nursing may might be a contributing factors	systemic cotinine, diminished alveolar cell proliferation and a modest impairment in postnatal lung growth
Palpant NJ [122] 2015	No		◦Wild-type zebrafish (Danio rerio) ◦Vapor from EC cartridge (South Beach Smoke, Tobacco Classic, Full Flavored, 16 mg nicotine/ cartridge)	◦Zebrafish embryos were exposed to either control, EC extract or CC extract ◦A vacuum was used to draw smoke or vapor into the media through a gas diffuser ◦Extracts were added from the onset of differentiation (day 0) and added fresh at every media change ◦At approximately 72 hours post exposure, incidence and severity of heart malformation was scored ◦Ref: smoke from University of Kentucky, 3R4F Research grade CC	◦Aim: to determine the impact of EC and CC on heart development in vitro and in vivo.	◦Exposure to both types of cigarettes resulted in broad, dose-dependent developmental defects coupled with severe heart malformation, pericardial edema and reduced heart function ◦CC are more toxic than EC at comparable nicotine concentrations	◦Single brand ◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Short term exposure	◦Study indicate a negative effect of EC on heart development in vitro and in vivo ◦The finding that nicotine treatment alone recapitulated untreated controls indicates that the impact of EC on heart development is the consequence of other components
Ponzoni L [131] 2015	No	Θ	◦ 183 Male BALB/ c mice; one month old ◦Unknown brand EC vapour containing 5.6 mg of nicotine/ session (for a total of 16.8 mg/day) Ref: CC containing 0.8 mg of nicotine/ cig (for a total of 16.8 mg/day), 10 mg of tar and 10 mg of carbon monoxide	◦3 groups of mice ◦Inhalation chambers (22cm wide x40 cm long x20 cm high) connected to Rodent Ventilator ◦Exposed three 30-min sessions/day for seven weeks 1) CC smoke of 21 cigarettes 2) EC vapour containing, both= 16.8 mg of nicotine 3) room air	◦Aim: to compare the effects of CC smoke and EC vapor containing the same amount of nicotine on mice	◦Second-hand exposure to EC vapor or CC smoke led to similar brain cotinine and nicotine levels, urine cotinine levels up-regulation of α4β2 nicotinic acetylcholine receptors in different brain areas ◦EC and CC had different effects on body weight, food intake, and the signs of mecamyl-amine-precipitated and spontaneous withdrawal episodic memory and emotional responses ◦No sign. reduction in food intake and body weight in the EC group but sign reduction in CC group ◦ EC withdrawal increases highly repetitive/perseverative responses more than CC	◦Single brand ◦Experimental dose of EC, not necessarily reflecting real-life exposure	◦EC vapor induces addiction-related neurochemical, physiological and behavioural alterations ◦The fact that inhaled CC smoke and EC vapor have partially different dependence-related effects indicates that compounds other than nicotine contribute to tobacco dependence
Salturk Z [138] 2015	No	Θ	◦16 Female Wistar albino rats ◦Ego Tfilled with a solution of 0.9% nicotine Ref :room air	◦Two groups ◦Exposure: The study group was exposed to EC vapor for 1 hour/day for 4 weeks in inhalation chambers (30 x 40 x 50 cm) ◦Control/ref: no chemical or physical stimulus	◦Aim to examine the vocal folds of rats exposed to EC vapor (histopathologically by hematoxylin and eosin staining and immune-histochemically by Ki67 staining)	◦Squamous metaplasia was detected in 4/8 rats in the study group but in only 1/8 rat in the control group; not significant (P = 0.106) ◦2/8 larynges in the study group developed hyperplasia, compared with 0/8 in the control group; not significant (P = 0.131) ◦The extent of inflammation did not differ between the two groups	◦Few animals ◦Single brand ◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Insufficient power	◦EC vapor exposed animals developed more frequently hyper-and metaplasia in the larynx than non-exposed animals; non-significant differences
Schweitzer	No		◦C57Bl/6 mice (4-	◦Exposed to nicotine, EC	◦Aim: to investigate acute	◦Nicotine and EC extracts	◦Experimental	◦Based on results it

KS [144] 2015			mo-old females) ◦Nicotine solutions Vanilla, Kentucky Prime, and nicotine-free Kentucky Prime EC used to generate vapor: iClear 16 ◦Ref: filtered research-grade CC (2R4F) or nicotine-free CC (1R5F)	solution, or condensed EC vapor (1–20 mM nicotine) or to nicotine free CC smoke extract or EC solutions	lung and systemic effects of nebulized nicotine and EC extracts, mimicking the inhalation of EC vapors by humans	caused rapid oxidative and nitroxidative stress observed in the bronchoalveolar lavage fluid and plasma as well as a trend toward greater neutrophil lung inflammation at 24 h following inhalation as measured by the relatively less sensitive method of bronchoalveolar lavage fluid cytospins, ratherthan intravital microscopy	dose of EC, not necessarily reflecting real-life exposure ◦Short term exposure	is anticipated that long-term EC use will include dose-dependent sustained oxidative stress and inflammatory lung damage with limitation of endothelial repair
Smith D [146] 2015	No	Θ	◦Timed-pregnant C57BL/6J mice ◦13 male mice underwent (off-spring) ◦Joyetech 510-T EC with 510-T tank cartridges, atomizer and battery ◦The nicotine solutions were obtained from Johnson Creek in 0% and 2.4% nicotine solutions with no flavoring. ◦Ref: 1.Untreated mice 2. no nicotine	◦Exposed to 2.4% nicotine in PPG or 0% nicotine /PPG once a day from gestational day 15 until delivery. ◦After delivery, offspring and mothers were exposed to EC vapors for an additional 14 days from postnatal day 2 through 16 ◦13 male mice underwent behavioral testing at 14 weeks of age to assess sensorimotor, affective, and cognitive functional domains	◦Aim: to determine if exposure to EC nicotine vapors during late prenatal and early postnatal life altered behavior in adult mice	◦Adult male mice exposed to 2.4% nicotine/PPG vapors had significantly more head dips in the zero maze test and higher levels of rearing activity in the open field test compared to 0% nicotine/PPG exposed mice and untreated controls. ◦In the water maze test after reversal training, the 2.4% nicotine/PPG mice spent more than 25% of time in the new location whereas the other groups did not ◦The mean serum cotinine levels in the 2.4% nicotine/PPG exposed mice was 23.7±4.2 ng/ml ◦A modest but significant difference in weights between the 2.4% nicotine/PPG and 0% nicotine/PPG mice	◦One brand of EC ◦Low dose nicotine contamination in the 0% E-cigarette solution used ◦Test order interactions might exist	◦Mice exhibited increased levels of activity when exposed to vapor containing nicotine during late prenatal and early postnatal life- indicating that nicotine exposure from EC may cause persistent behavioral changes
Sussan TE [148] 2015	No	Θ	◦Male C57BL/6 (age 8 wks) mice ◦NJOY menthol bold (1.8% nicotine) rechargeable A subset: NJOY traditional bold Ref: room air	◦Exposure: via a whole-body exposure system for 1.5 h, twice per day for 2 weeks ◦Control: filtered air ◦One hour after final exposure mice were infected intranasally with S. Pneumoniae bacteria or Influenza A virus.	◦Aim: to determine whether EC exposure impacts pulmonary responses in mice	◦EC exposed mice: ◦Significantly elevated levels of oxidative stress ◦A 58% increase in macrophage infiltration ($p<0.05$) ◦Significant reduction in IL-6 concentration ◦Significant increases in pulmonary bacterial burden ◦Impaired anti-bacterial defenses, including defective bacterial phagocytosis, leading to enhanced bacterial propagation ◦Reduced anti-viral defenses and increased virus-induced morbidity and mortality ◦Increased neutrophilic inflammation at day 8 after virus infection, compared to	◦Few animals ◦Single brand ◦Experimental dose of EC, not necessarily reflecting real-life exposure ◦Short term exposure	◦Exposure to EC vapor induced oxidative stress and moderate inflammatory response ◦Significant impairment in bacterial clearance in lungs ◦Enhanced susceptibility to influenza infection, based on increased percent weight loss, mortality, and viral titer

						air exposure, but decreased Th1 and Th17 cytokine levels		

*Four of these studies are also/partly mentioned in Table 3/Annex 5 on animal experimental studies [98] [122] [144] [78]

EC= electronic cigarettes

CC= conventional cigarettes

PPG= propylene glycol

VG = vegetable glycerin

IL-6= *Interleukin 6*

Th= T-helper cells

Annex 5. Studies reporting adverse events (n=31)

Name of first author Reference Year	**Con-flict of interest** ▲ = Yes	**Type of product(s)**	**Type of study**	**Participants** **Symptoms reported**	**Symptoms**	**Weakness/strength** Association between EC and symptoms?	**Conclusion**
Adriens K [1] 2015	No	◦ "Joyetech eGo-C" and the "Kanger T2-CC"; 30 mL bottles of tobacco-flavored e-liquid (Dekang "Turkish Blend"), containing 18 mg/mL of nicotine	◦Prospective study; randomized controlled smoking reduction trial with three arms three lab 3 sessions (over two months): vaped/smoked for five minutes	◦48 volunteers not willing to quit ◦EC group reported only positive symptoms /improvements, dual use group reported positive and negative	◦The control group reported more complaints about CC than the EC groups about using EC ◦Not possible to discriminate EC related symptoms as a symptom table reports EC and CC users' complaints together	◦Only two brands ◦It is not possible to discriminate symptoms of EC users from CC users ◦ Prospective study ◦ Time association	◦ EC users reported more benefits in prospective study
Bartram A [6] 2015	No	◦Unknown but high content of PPG	◦Case report	◦A 55-year-old healthy man; drank 40 units of alcohol/week and smoked 30CC/day, and but quit and switched to EC	8-week history of ulceration on the right buccal mucosa associated with white patches throughout the mouth and lower lip after he started to use EC ◦Examination: a typical appearance of lichen planus with white reticular patterned striae on the oral mucosa and the lower lip ◦Biopsy: hyperkeratosis with lichenoid inflammation ◦Responded to conventional management after partial removal of the causative agent (switched to low PPG EC)	◦ One patient ◦ Time association	◦ EC use was found to be associated with a florid lichenoid reaction
Bullen C [11] 2013	▲7	◦Elusion + 16mg or 0 mg nicotine	◦Prospective study; randomized controlled smoking cessation trial	◦Total 657 participants were randomized to nicotine-EC (n=289), no-nicotine/placebo EC (n=295) or nicotine patch (n=73) for 13 weeks	◦AE= 107 participants in the nicotine EC group (137 events); 96 participants in the patches group (119 events); 26 participants in the EC placebo group (36 events) ◦The difference between the AE rates in the nicotine EC group and patches	◦Only one brand ◦ Time association ◦No selection bias	◦A higher number and proportion of adverse events occurred in the nicotine EC group than in the patches group; however, there was no evidence of an association

					group were not significant (incidence rate ratio 1.05, 95% CI 0.82–1.34, p=0.7). ◦SAE events: death (n=1, in nicotine EC group), life threatening illness (n=1, in nicotine EC group), admission to hospital (12% of all events in nicotine EC group, 8% in patches group, and 11% in placebo EC group), persistent or significant disability or incapacity, congenital abnormality, medically important (6% of all events in nicotine EC group, 4% in patches group, and 3% placebo EC group) ◦No serious AE in any groups were related to product use		with study product, and the event rate was not significantly different
Bullen C [12] 2010	▲ 1	◦RuyanV8, 16 mg nicotine or 0 mg capsules ◦Ref: Nicorette nicotine inhalator or usual CC	◦Single blind randomised repeated measures cross-over trial	◦40 adult dependent smokers of 10 or more CC per day. ◦Positive and negative symptoms	◦Most frequently reported AE: mouth and throat irritation; statistically significantly more frequent than with inhalator ($p<0.001$). ◦Nausea, aching jaws, vertigo, feeling high, palpitations: most commonly reported after 16 mg EC use; non-sign difference ◦No SEA	◦Only one brand of EC ◦EC naïve participants- do not inhale sufficiently long and deep (1/3 of EC users had no increase in blood nicotine) ◦Small study	◦Nausea and mouth and throat irritation were common ◦Less common: aching jaws, vertigo, feeling high, palpitations
Camus M [15] 2014	No	◦EC of unknown type	◦Case report	◦ A 49-year-old woman with colitis ulcerosa ◦ Negative symptom?	◦ Patient restarted smoking 9 months after colitis ulcerosa diagnosis while symptoms were still present, stopped any medication and went into clinical remission within a few days ◦ After 9 years stopped smoking and switched to EC – after one week: relapse of symptoms of colitis ulcerosa	◦ One patient ◦ Time association	◦ Patient presented with a "smoking-dependent form" of colitis ulcerosa, which recurred nearly immediately after replacing CC smoking by nicotine containing EC
Caponetto P [16] 2013	▲ 2	◦Categoria 7.2mg nicotine for 52 weeks	◦Prospective 12-months observational study	◦14 smokers with schizophrenia smoking ≥20 CC pr day and not intending to quit ◦Product use, number of cigarettes, CO and positive and negative symptoms of schizophrenia,	◦Most frequent AE: Nausea, throat irritation, headache (all 14%) and dry cough 29%. AE diminished substantially by week-24 ◦No SAE ◦Positive and negative symptoms of schizophrenia not increased after smoking reduction/cessation in	◦Only one brand of EC ◦Comparison with other smoking cessation products not possible ◦ No information on whether reduction in symptoms only	◦Positive and negative symptoms of schizophrenia were not increased after smoking reduction/cessation in patients using EC ◦AE (cough, nausea, throat irritation, headache)

				AE	patients using EC ◦Substantial reduction in CO in those who reduced smoking min 50% or quit	occurred in those who quit smoking and vaping ◦ Time association registered by health professional	declined over time
Caponetto P [17] 2013	▲ 2	3 Study groups: ◦Categoria 7.2mg nicotine for 12 weeks ◦Categoria 7.2 mg nicotine for 6 weeks and 5.4 mg for 6 weeks ◦Ref: Categoria without nicotine	◦Prospective 12-month randomized controlled trial with 3 study groups	◦300 smokers not intending to quit ◦CO, abstinence, smoking reduction, AE	◦Sign. reduction in frequency of cough, dry mouth, shortness of breath, and headache was observed in all three study groups ($p<0.001$) ◦Shortness of breath substantially decreased after 2 weeks (20% to 4%) ◦Common side effects of cessation reported: insomnia, irritability, anxiety, and depression ◦No SAE ◦No sign changes in mean body weight, resting heart rate, blood pressure ◦> 50% CC reduction in all three groups but high CO levels, 18-19 ppm at week 52	◦Only one brand of EC ◦Comparison with other smoking cessation products not possible ◦High drop-out rate – could be caused by AE ◦ No information on whether reduction in symptoms also occurred in those who continued using the EC (27%) or reflect those who quit smoking and vaping ◦ Time association registered by health professional	◦ AE as cough, dry mouth, shortness of breath, and headache declined over time ◦Small reduction in CO compared with reduction in number CC
Chen IL [21] 2013	No	◦Unknown	◦Summary of adverse events reported to U.S. Food and Drug Admini-stration	◦ Approximately half of all tobacco-related AE reports since late 1980ies concern EC ◦Negative symptoms	◦ Of the 47 reports on ECs, 8 reported SAE ◦ SAE reported: hospitalization for illnesses such as pneumonia, congestive heart failure, disorientation, seizure, hypotension, possible aspiration pneumonia, second-degree burns to the face (product exploded in consumer's mouth), chest pain and rapid heartbeat, possible infant death secondary to choking on EC cartridge, and loss of vision requiring surgery. ◦ AE reported: headache/migraine, chest pain, cough/sputum, nausea/vomiting, dizziness, feeling sick, confusion/stupor, sore throat,	◦ No information on how many/which AE were estimated to be causally associated with EC	◦Many reports of AE and SAE ◦There is not necessarily a causal relationship between AEs reported and EC use, as some AEs could be related to pre-existing conditions or due to other causes not reported

					shortness of breath, abdominal pain, pleurisy, blurry vision, and sleepy/tired.		
Dawkins L [35] 2013	⍰ 3	◦TECC and Totally Wicked E-Liquid	◦Online survey ◦Users of the two most popular brands in UK ◦EC users' nature, use of EC, effects of EC	◦1349 users of EC (218 current smokers + 1123 ex-smokers + 4 never smokers) ◦Primarily asked about positive effects	◦74% reported they had not smoked for weeks/months since using the EC ◦The most common was throat irritation, followed by mouth irritation. <16% reported experiencing any degree of effect, <3% reported a high level of AE Very much so: ◦81% stated that EC feels healthier ◦70% stated that EC use improved cough ◦1% stated that EC irritates their airways more than smoking	◦Only two brands of EC ◦Selected vapers; those who tolerate EC , have a regular use and experience positive changes they want to share ◦Those who had persistent AE had probably stopped using the ECs	◦ Respondents (most had quit smoking) reported few negative symptoms (mouth and throat irritation) and many positive health effects with EC ◦ Majority state: it feels healthier and use improved cough
Etter JF [39] 2010	⍰4	◦Sixteen different brands, most frequent: Janty , Joye , Sedansa	◦A survey of users	◦ 81 respondents ever users of EC who indicated the most used brand ◦ 72 daily users, 63% recently quit smoking CC ◦Positive and negative symptoms	◦ EC positive symptoms, 134: improved breathing and reduced cough and expectoration, fewer sore throats, improved health and physical fitness, improved sleep, smell and sense of taste ◦ EC negative symptoms, 61: dry mouth and throat, vertigo, headache or nausea, weight gain	◦Self-reports ◦Selected vapers, probably more motivated to quit smoking, slightly less dependent on tobacco, and more highly educated	◦ Respondents reported more positive than negative effects with EC: many reported positive effects on the respiratory system, which were probably associated with stopping smoking
Farinha H [42] 2015	No	◦EC of unknown type	◦Case report	◦66-year old female patient, heavy smoker and coffee drinker, with hypertension and history of depression. ◦She had stopped tobacco smoking and initiated EC a few weeks before ◦1 negative symptom	◦Presented with an asymptomatic black discoloration of the tongue she noted that day, no other sign associated ◦The diagnosis of lingua villosa nigra was established ◦She stopped using the EC and started smoking again and the lesions started disappearing spontaneously in less than one week ◦The lesions worsened when she began using EC again	◦Time association ◦Symptoms reversed when patient stopped using EC and worsened when she started again	◦A case of probable association between EC use and lingua villosa nigra is reported
Farsalinos KE [49] 2013	▲ 11	◦Second or third generation EC	◦Interviews with vapors (32 visitors to a hospital + 81 members of consumers' internet	◦111 experienced EC users who had completely substituted smoking with EC use for at least 1 month ◦Positive and negative symptoms	◦42% had quit during the first month of using ECs ◦Reported AE: throat irritation (27%) cough (14%), gastrointestinal discomfort/epigastric burning (7%), palpitations (5%), headache, sleepiness, sleeplessness, atypical chest pain, gum and nose bleeding	◦Selected vapers; those who tolerate EC , have a regular use and experience positive changes they want to share ◦Those who had persistent AE had quit	◦Side effects were mild and temporary ◦ The vast majority of participants reported better exercise capacity and improved olfactory and gustatory senses

			forum; 2 excluded)		(<5%)- resolved completely in almost all ◦No SAE ◦Improved exercise capacity (77%), improved sensory and gustatory senses (82%), less morning cough (59%) and better sleep (22%)	use	
Farsalinos KE [47] 2013	▲ 9	One unknown brand	◦Case report	◦ 32 old male smoking patient with idiopathic chronic neutrophilia ◦ Then, quit smoking with EC ◦A positive effect	◦After 6 months of smoking cessation, laboratory examination showed normalized leukocyte count and C-reactive protein levels, confirmed immediately by a second laboratory and by repeated tests after 1 and 2 months	◦One case ◦ Time association between smoking cessation and relieved chronic idiopathic neutrophilia	◦ Despite daily use of EC, the beneficial effects of smoking cessation on idiopathic chronic neutrophilia were maintained
Farsalinos [50] 2014	▲ 10	◦EC of unknown type	◦ Survey	◦ 19,414 EC regular users world wide ◦ Median use: 10 months ◦Positive and negative symptoms	◦ 60% reported AE ◦ Most common AE: sore/dry mouth and throat; side effects were mild and in most cases were subsequently resolved ◦ Participants experienced significant benefits in physical status and improvements in pre-existing disease conditions ◦ Being former smoker was independently associated with positive effects in health and improvements in disease conditions	◦Selected vapers; those who tolerate EC , have a regular use and experience positive changes they want to share ◦Those who had persistent AE had quit use	◦ Side effects were minor and health benefits were substantial, especially for those who completely substituted smoking with EC use
Gillen S [63] 2015	No	◦EC of unknown type	Case report	◦ A 1 day old boy born at full term ◦ Negative symptoms from two organ systems ◦ Mother had been consistently vaping EC throughout the pregnancy from 30-50 times per day. During the time of active labor, she vaped EC approx. 50-70 times	◦ Admitted for abdominal distention and respiratory distress. ◦ Physical exam: a distended abdomen with upper abdominal tenderness ◦ Abdominal X-rays: extensive pneumatosis intestinalis without free-air ◦ Intraoperative findings: the ascending, transverse, and descending colon had patchy areas of superficial necrosis ◦ A suction rectal biopsy: ruled out Hirschsprung's disease as a possible etiology of profound and isolated colonic necrotizing enterocolitis	◦ Time association	◦Antenatal exposure to EC vapor might be a possible etiology to total colonic necrotizing enterocolitits in a new born child
Heavner K	⍰ 5	◦Products sold by	◦Online	◦303 users of EC	◦ Most had replaced CC by EC	◦Selected vapers;	◦Respondents reported

[72] 2010		one EC manufacturer	survey	◦Positive symptoms	◦ Better health (94%), cough (98%), exercise ability (88%), sense of smell (82%), sense of taste (77%)	those who tolerate EC , have a regular use and experience positive changes they want to share ◦Those who had persistent AE had quit use	improvements in health, especially general health and cough by replacing CC with EC
Hua M [76] 2013	No	◦Many different	◦Online search	◦481 vapors ◦492 (405 different symptoms) ◦78 positive, 326 negative, 1 neutral	◦Health effects were broadly distributed: 10 organ systems (eg, respiratory, neurological) and two anatomical regions (chest and mouth/throat) ◦Respiratory, mouth/throat, neurological, and sensory had the most symptoms ◦Mouth and throat had most negative symptoms ◦A significant number of health effects appeared in the digestive, muscular/ skeletal, and integumentary systems ◦34% of the individuals had negative effects in more than one system- such as the circulatory and neurological systems. ◦Few individuals had positive effects in more than one system	◦Self-reported ◦Causality can't be assessed in most cases ◦47: stated that symptoms occurred 1 week or less after use began. ◦19: symptoms occurred more than 1 week after use began ◦Some symptoms occurred during EC use, such as "metal taste in mouth" ◦Others occurred just after use, such as "choking after use" ◦Selection bias: probably new vapors that experience negative AE they want to discuss	◦EC use can have wide ranging positive and negative effects ◦Respiratory, mouth/throat, neurological, and sensory had the most symptoms associated with them ◦Users with negative symptoms often reported more than one symptom-interactions were often seen between systems ◦Positive effects usually occurred singly and most frequently affected the respiratory system
Hureaux J [77] 2014	No	◦ 'La dynamique' and two 'e-liquids' Kentucky (19 mg/mL of nicotine) and Eastern (19 mg/mL of nicotine)	◦Case report	◦ A 43 year old patient with history of stage II smoking-related COPD + primary lung adenocarcinoma with an isolated brain metastasis treated by radiotherapy, lobectomy and chemotherapy -under surveillance for 7 months ◦Negative pulmonary symptoms	◦ After 48 h use of EC: onset of cough with whitish secretions and subsequently developed progressive breathlessness on minimal exertion ◦ Severe dyspnoea with mixed ventilatory disorder are primarily suggestive of bronchiolitis ◦ After having stopped for 48 h: marked improvement of cough, sputum and breathlessness. ◦ After 7 days, all symptoms had completely resolved with no treatment	◦ One patient ◦ Time association ◦Time association registered by health professional ◦ Reversibility of symptoms after cessation of EC	◦ A patient who presented with subacute bronchial toxicity associated with deterioration of pulmonary function tests after starting use of EC ◦ It is impossible to formally conclude on the causal role of the EC in the onset of the clinical features despite the observed temporal correlation

					◦ Pulmonary function parameters returned to usual values		
Lee S [96] 2013	No	◦EC of unknown type	◦Case report	◦ 35-year old man with 1½ year history of pan-ulcerative colitis which began 4 weeks after smoking cessation ◦ Refractory to treatment ◦ Initiated EC use, mean 105 puffs/day	◦ 4 weeks after start of EC use: Mayo score decreased from 8 to 2 Fecal calprotectin decreased from 424 to 25 µg/g No gastrointestinal symptoms ◦At week 12: infliximab through concentration were >34	◦ One patient ◦ Time association	◦EC use was associated with steroid-free clinical remission in colitis ulcerosa patient
Manzoli L [105] 2015	No	◦EC of unknown type	◦Prospective cohort study subjects recruited through direct contact with general practitioners and EC shops, via internet and social networks	◦ Adults (30–75 years); 236 EC vapers, 491 CC smokers, and 232 dual smokers (overall response rate 70.8%) ◦ All EC vapers were ex-smokers Positive and negative symptoms	◦At 12 month follow-up: although significant, a minimal increase from baseline in self-rated health score was observed among vapers only (+0.3±1.5; p = 0.013) ◦SAE: 2 among the EC vapers (both switched to tobacco smoking during follow-up); 6 among CC smokers (3 quit all smoking); 4 among dual smokers (all switched smoking but one) ◦Possibly related adverse event: acute myocardial infarction	◦Self-selection; only those who were current vapers (tolerated EC) were included ◦ Data were collected on internet/phone interview after 12 months	◦No safety concerns raised during the study, although the limitations in adverse events recording prevent authors to draw any conclusions
Maridet C [107] 2015	No	◦EC of unknown type	◦Case report ◦Experiment: performed Dimethylglyoxime (DMG) nickel spot test on 11 different EC models found in 4 EC shops	◦52-year-old woman ◦1 negative symptom	◦Itchy erythematous dermatitis on the right hand that had started 8months previously ◦History of contact allergy(nickel) ◦The front part of the EC-device was corroded, probably by the sweat of the hands of the patient, which may have increased nickel release ◦Patient was advised to use a nickel-free device -2 months later, the dermatitis had cleared ◦Of 11 EC models tested, three were positive for nickel	◦One case ◦Possible time association ◦After stopping use of EC-device with nickel the symptoms improved	◦A number of EC probably release nickel ◦Contact dermatitis caused by nickel due to the use of electronic cigarettes could become increasingly common
McCauley L [111] 2012	No	◦EC of unknown type	◦Case report	◦1 patient ◦1 negative symptom	◦7-month history of dyspnoea, productive cough and subjective fevers ◦Diagnosed with exogenous lipid pneumonia (chronic inflammatory reaction to the deposition of lipid	◦One case ◦Possible time association, 7 month use of EC. After stopping use of EC the symptoms	◦EC use was suggested as possible cause of exogenous lipid pneumonia – supposed due to glycerin based oils

					substances as a result of aspiration or inhalation of oil-based products) ◦Presence of lipid-laden macrophages in bronchoalveolar lavage	improved (some claim that symptoms were not time associated, but we find no information on this) ◦Glycols belong to alcohol-family not lipids	
McQueen A [113] 2011	No ¤, 1	◦EC's of unknown type	◦Interviews with vapors	◦13 vapors ◦Positive symptoms	◦Improved sense of taste and smell, ability to be physically active, and less coughing and breathlessness ◦Improved quality of life	◦Few persons ◦Selected vapers; those who tolerate EC, have a regular use and experience positive changes they want to share ◦Time association not investigated	◦Improved self-reported health and quality of life
Monroy AE [116] 2012	No	◦One unknown brand	◦Case report	◦70 year old woman, smoking history: 40 pack-years. ◦Undergone total hip arthroplasty; infected hematoma ◦1 negative symptom	◦3 asymptomatic episodes of atrial fibrillation with rapid ventricular response ◦Normal cardiac enzyme levels ◦No episodes of atrial fibrillation after she stopped using EC	◦One case ◦Self-reported ◦Pt. recalled that use of EC had preceded each episode ◦ Time association	◦Possible association between use of EC and atrial fibrillation
Munoz A [117] 2015	No	◦Unknown brands	◦Survey in a smoking cessation clinic	◦64 ever-users of EC	◦Benefits from smoking cessation: less coughing, improved breathing and better physical fitness reported by 60%	◦Selections bias possible ◦Health improvements by use of EC cannot be distinguished from health improvements of quitting smoking	◦ Health improvements by use of EC -in those who had quit -are reported
O'Brien B [119] 2015	8	◦Elusion + 16mg or 0 mg nicotine	◦Prospective study; randomized controlled smoking cessation trial	◦Mentally ill volunteers ◦86 (13%) of the total 657 participants in study [11] reported using ≥1 medication associated with mental illness	◦In persons with mental illness: adverse event counts relative to the number of participants were similar (these were not subject to statistical testing due to small numbers) ◦No serious study-related adverse events were noted in any group	◦Only one brand ◦ Time association ◦No selection bias ◦Small numbers ◦Sub-study of study[11] - not powered to detect differences	◦Persons with mental illness seem to tolerate EC
Polosa R [128] 2011	6	◦One Italian brand ('Categoria')	◦Prospective 6 month pilot study	◦40 smokers not intending to quit ◦Negative symptoms	◦The most frequently reported adverse events: mouth irritation (21%), throat irritation (32%), and dry cough (32%)	◦Symptoms commonly reported at the beginning of the study waned spontaneously	◦Primarily mouth/throat and respiratory symptoms ◦No SAE

					◦Side effects commonly recorded during smoking cessation trials with drugs for nicotine dependence were absent (i.e. depression, anxiety, insomnia, irritability, hunger, constipation) ◦No SAE	after 6 months ◦ Time association registered by health professional	
Polosa R [130] 2013	?6	◦Different brands	◦A 24-month prospective observational study	◦23 smokers not intending to quit (5 not using EC at one year follow-up) ◦Negative symptoms	◦Mouth irritation, throat irritation, and dry cough were most common and reported in 9–13% at 24 months ◦Headache 4% ◦No SAE ◦Slight increase in mouth irritation and dry cough over time	◦ Mouth irritation, throat irritation, and dry cough persisted over one year and are probably causally associated ◦ Time association registered by health professional	◦Persistent mouth/throat and respiratory symptoms after one year of use ◦No SAE
Thota D [153] 2014	No	◦EC of unknown type	◦Case report	◦ A 20-year-old healthy man with no history of exposure to any pulmonary irritants (other than EC) ◦Negative pulmonary symptoms	◦ 3 days of persistent cough, shortness of breath, and facial flushing ◦ Symptom cluster began 1 h after smoking an EC ◦ Tachycardia, tachypnea, mild leukocytosis, 2.0% eosinophils ◦ X-ray: ‘‘subtle diffuse patchy reticulo-nodular opacities’’ ◦ A chest CT scan: bilateral diffuse infiltrates ◦ Bronchoscopy: many white blood cells with eosinophilia in the lavage ◦ No infectious etiologies ◦ Treated with 60 mg of prednisone - discharged from the hospital with improvement in his symptoms	◦ One patient ◦ Time association ◦ Reversibility of symptoms after cessation of EC?	◦ Possible case of acute eosinophilic pneumonitis ◦ If seeing a patient in the with pulmonary symptoms after use of EC, acute eosinophilic pneumonitis should be considered in the differentia
Vannier S [161] 2014	No	◦EC of unknown type	◦Case report	◦ A 39-year-old healthy man switched from 60 CC/day to dual use of 20 CC/day + EC (due to wish to quit)	◦ Daily severe thunderclap headaches, after 7 days: two seizures ◦ Magnetic resonance imaging (MRI) of the brain: a posterior reversible encephalopathy syndrome(PRES) ◦ Multiple cerebral artery irregularities with alternations of segmental multifocal constrictions	◦ One patient ◦ Time association ◦ Reversibility of symptoms after cessation of EC	◦ Possible case of reversible cerebral vasoconstriction syndrome in dual user ◦A few previous cases have been described with nicotine patches alone or associated with CC smoking

					and dilatations ◦ Treatment: oral calcium-channel antagonist and EC cessation ◦ Continued to smoke 10–15 CC/ day ◦ Headache disappearance on the third day and no seizure recurrence ◦ Follow-up after 1 month: MRI: spontaneously resolving stenosis, and there was an improvement of the corpus callosum PRES. ◦ Physical and neurological examination results were normal; no headaches		
Wang MP [168] 2015	No	◦EC of unknown type	◦Population-based survey in schools ◦High participation rate, 95% of all invited	◦75 randomly selected schools in Hong Kong ◦45,128 students ◦Approx. 12 to 18 years old ◦Paper published negative symptoms from respiratory system	◦There was a higher prevalence of respiratory symptoms in EC users regardless of smoking status ◦Overall, EC-use was significantly associated with respiratory symptoms (OR, 1.28; 95% CI, 1.06-1.56) in analyses adjusted for sex, age, perceived family affluence, secondhand smoke exposure, and school clustering effect ◦The corresponding ORs (95% CIs) were 2.06 (1.24-3.42) in never-smokers, 1.39 (1.14-1.70) in ever-smokers, and1.40 (1.02-1.91) in ex-smokers ◦Positive but non-significant associations were observed in experimenters (OR, 1.09; 95% CI, 0.66-1.80) and current smokers (OR, 1.15; 95% CI, 0.81-1.62) ◦Current smoking was defined as smoking at least once in the last 30 days ◦Current EC use was use of EC in the past 30 days	◦Unknown EC consumption (brand, intensity, duration)	◦The first evidence of an association between e-cigarette use and respiratory symptoms in never- and ever-smoking adolescents, which is consistent with findings from other laboratory and adult studies on short-term adverse respiratory functions

EC=electronic cigarette
CC=conventional cigarette
AE= adverse events
SEA = serious adverse events

Conflicts of Interest - Conflicts of interest of each study should be assessed individually.

▲1: This project was funded by EC manufacturer. The study sponsors supplied the ECs used in the trial and funded the trial. The trial design conduct, analysis and interpretation of results were conducted independently of the sponsors. HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. ML acted as contract manager with the sponsor, manufacturer of ECs. MG has provided consultancy to the manufacturers of smoking cessation medications

▲2: RP has received lecture fees and research funding from manufacturers of stop smoking medications. He has served as a consultant for manufacturers of smoking cessation medications and the distributor EC used.

▲3: LD has a collaborative relationship with manufacturer of EC and received funds to attend academic conferences. E-manufacturer reviewed and approved content of questionnaire and set up links from their websites.

▲4: JFE was previously consultant for manufacturer of smoking cessation medications

▲5: Study was funded and supported by manufacturer of EC and manufacturer is co-author. All other authors are employed at University of Alberta, which is financially supported by a large smokeless tobacco manufacturer. CVP advises on tobacco harm reduction and is compensated for this work.

▲6: RP has received lecture fees from manufacturer of EC and has been serving as a consultant for manufacturer of EC. Manufacturer of the EC supplied product, technical and consumer support

▲7: ML, via his company Health New Zealand, previously did research funded by an EC manufacturer. CB and HM have done research on ECs funded by Health New Zealand, independently of EC manufacturer. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications.

▲8: CB has undertaken research on e-cigarettes funded by Health NZ (funded by e-cig manufacturer), independently of e-cigarette manufacturer. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs

▲ 9 to 11: “No” stated, but some of the other studies performed by KF used unrestricted funds provided to research center by e-cigarette companies. KEF has a website “E-cigarette Research Advocate Group” which represents an unambiguously positive view on EC and provides several links to vapor clubs

¤, 1: AMQ acknowledges the support of the organizers and attendees at vapers’ meeting where recruitment took place

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