**COC/2018/01**

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)**

# Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (EN(N)DS – e-cigarettes) – overview of available data on carcinogenicity.

## Background

1. The COT is currently reviewing the possible human health effects of electronic nicotine (and non-nicotine) delivery systems (EN(N)DS, 'e-cigarettes'). A paper (TOX/2018/16) was presented to the COT in which literature searches and full list of publications retrieved for genotoxicity and carcinogenicity of E(N)NDS were presented. After follow-up analysis of the abstracts obtained, it was agreed that the COC and COM should consider the available papers on carcinogenicity and genotoxicity respectively. The aim is for COC (and COM) to assess absolute risks from E(N)NDS and relative risk compared to conventional cigarettes, and if data are available to heated tobacco products.

2. E(N)NDS are battery-powered devices containing a liquid (E(N)NDS liquid or 'e-liquid'). The E(N)NDS liquid is heated on use to produce an aerosol that is inhaled by the user ('puffing', 'vaping'). E(N)NDS were first introduced commercially in China in 2004 and subsequently in the EU (2005) and USA (2007) as nicotine-delivery devices (Bansal and Kim 2016). The main constituent parts of an E(N)NDS device are a mouthpiece, cartridge (tank) containing E(N)NDS liquid, a heating element/atomizer, a microprocessor, a battery, and sometimes an LED light. Commercially available devices are sometimes categorised as first, second, or third generation. First-generation devices look like conventional cigarettes and thus are termed 'cigalikes'. Initial models comprised three principal parts; a lithium-ion battery, a cartridge and an atomizer. However, more recent models mostly consist of a battery connected to a 'cartomizer' (cartridge/atomizer combined), which may be replaceable, but is not refillable. Second-generation E(N)NDS are larger and have less resemblance to tobacco cigarettes. They often resemble pens or laser pointers (hence the name, 'vape pens'). They have a high-capacity rechargeable lithium-ion battery and a refillable atomizer (sometimes referred to as a 'clearomizer'). Third-generation models ('advanced personal vapers', 'mods') are also refillable, have very-high-capacity lithium-ion batteries and are highly customisable (different coil options, power settings, tank sizes). In addition, highly advanced 'fourth generation' E(N)NDS (innovative regulated mods) are now being described[1].

[1] see, http://ecigclopedia.com/the-4-generations-of-electronic-cigarettes/ (accessed 04/06/18)

3. A total of 178 references were retrieved from the initial searches and screened for relevance to COC and COM. Of these, 4 papers were identified as needing consideration by COC. Details of the search string are provided in Annex 1. In addition, a recent National Academies of Sciences, Engineering and Medicine (NAS) Report has been published which comprises a systematic review of current science to inform the understanding of public health risks and benefits of e-cigarettes. Chapter 10 of this report outlines the evidence on cancer and is attached at Annex 2. These papers are discussed, and a summary of the conclusions of the NAS report regarding carcinogenicity given, in the following sections.

**EN(N)DS literature relating to carcinogenesis**

4. Canistro et al. (2017) undertook an assessment of the potential harmful toxicological effects of e-cigarettes that may translate to enhanced risk of cancer in users. The authors used a rat lung model to assess the mutagenic and cancer-initiating potential of the aerosol of the E(N)NDS liquid 'Essential cloud, red fruit flavour'. *Only findings for the cancer-initiating events are discussed in detail here.* The liquid contains (per 100g of product): propylene glycol (PG), vegetable glycerine (VG), deionised water, flavours ("red fruits"), and nicotine (18 mg/mL). The liquid was delivered using a commercial e-cigarette (brand not stated) comprised of a 2.5 mL liquid tank in Pyrex glass and dual coil, using a voltage of 5.5V and wattage of around 15 W.

5. Male Sprague Dawley rats (8 weeks of age) were exposed by whole body inhalation to the E(N)NDS aerosol containing 18 mg nicotine (equivalent to 1 mL of liquid). The liquid was delivered in 11 cycles comprising 17 sec puff (6 sec on, 5 sec off, 6 sec on) and 20 min stop. Following each cycle animals were transferred to a clean chamber for delivery of the next cycle. Animals were treated to 11 cycles per day for 5 days per week for 4 weeks[2] after which animals were killed and lung microsomes made.

6. The major components of the volatile organic compound (VOC) profile emitted from heating the 'red fruit' liquid were PG, nicotine and VG. Minor components included 1,2-propanediamine, methyl propionate (flavour compound), indole, propanoic acid 1-methylpropyl ester, acetol, 1-methoxy-2-propyl acetate, 3-hexen-1-ol (flavour compound), diacetyl (flavour compound) and acrolein. These findings are in agreement with other published literature, however no formaldehyde was detected which the authors suggest is due to the type of VOC analysis undertaken by them. VOC composition was measured throughout the duration of exposure and within different chambers, and no statistically different differences were found.

7. Modulation of several carcinogen-metabolising enzymes involving cytochrome P450 (CYP450) was observed in the microsomal lung fractions of rats exposed to VOCs from e-cigarettes using several specific probes. A significant increase was

[2] Note that a small number of rats (n=5) received a single i.p. dose of mitomycin C (1 mg/kg bw) as a positive control for the micronucleus test.

observed in several CYP-linked monooxygenases when compared to the control group (non-exposed):

a. CYP1A1/2 which is linked with the activation of pre-carcinogens including polychlorinated biphenyls, aromatic amines, dioxins and PAHs ($p<0.01$):

b. CYP2B1/2 which is linked with the activation of olefins and halogenated hydrocarbons ($p<0.01$);

c. CYP2C11 which is linked to the activation of nitrosamines and mycotoxins ($p < 0.05$);

d. CYP3A which is linked to the activation of hexamethyl phosphoramide and nitrosamines ($p< 0.01$).

8. CYP induction is known to result in enhanced production of reactive oxygen species (ROS), which plays a key role in the cancer occurrence via a co-carcinogenesis mechanism. This was assessed by the authors using an electron paramagnetic resonance (EPR)-radical probe to evaluate the ROS content of the rat lungs. Exposure to e-cigarette aerosol was associated with a significant increase ($p <0.01$) in ROS/oxidative stress in the lungs of exposed rats compared with controls. Simultaneous measurements of the antioxidant enzymes catalase, DT-diaphorase and superoxide dismutase showed these to be significantly reduced ($p <0.01$) following exposure. Systemic antioxidant capacity (measured as ferric reducing antioxidant power (FRAP)) was also reduced in the lungs ($p <0.05$) of exposed rats.

9. From a mutagenic perspective, DNA damage (measured as increased tail length in the Comet assay) was observed in leucocytes, an increase in the percentage of immature micronucleated reticulocytes over normal reticulocyte indicative of chromosome fragmentation (possibly to the mitotic spindle or centromeres) and a positive Ames test in the urine. These aspects of this paper have been presented to the COM in more detail (MUT/2018/08).

10. The authors note that their findings relate to E(N)NDS vapour as a whole and not to individual components. In addition, the vaping conditions used were not reflective of human use but were used only as a preliminary investigation of pre-carcinogenic events.

11. The authors considered that if these findings were extrapolated to humans this would predispose an individual to an enhanced [lung] cancer risk. No quantitation of risk was provided by the authors to support this statement and, as such, these findings cannot be utilised for risk assessment purposes.

12. Fuller et al. (2018) carried out an assessment of the presence of known bladder carcinogenic amines and polycyclic aromatic hydrocarbon (PAH) metabolites in the urine of E(N)NDS users to better understand the risk profile associated with

their use. Urine samples were collected from non-smoking E(N)NDS users (n=13; average age 30.1 ± 7.7 years) and non-smoking, non- E(N)NDS using-controls (n=10; average age 39.4 ± 13.5 years); no information is given by the authors concerning the timing or duration of urine collection. All subjects were former smokers (average duration of 19.9 ± 11.9 years) but had not used conventional cigarettes (CC) for > 6 months prior to sampling. A variety of E(N)NDS devices were used by the exposed group and the frequency of use was >28 times a week for the majority (84.6% of individuals). Samples were analysed by LC-MS for the target compounds benz(a)anthracene, benzo(a)pyrene, 1-hydroxypyrene, o-toluidine and 2-naphthylamine.

13. The E(N)NDS users were found to have statistically significantly higher levels of the known carcinogens o-toluidine ($p = 0.0013$) and 2-napthylamine ($p = 0.014$) when compared to control subjects. PAHs were not detected, however, as the authors do not give details of the level of quantitation of the PAHs using their methodology, it is not possible to interpret these findings here.

14. As all subjects, including the controls, has been previous CC smokers, the authors used a Pearson correlation analysis to compare time since cessation of smoking and carcinogenic metabolite concentration. No correlation was found for either metabolite, with Pearson coefficients of 0.51 and 0.07 for 2-napththylamine and for o-toluidine respectively.

15. The authors conclude that the presence of known bladder carcinogens in the urine of users may suggest the E(N)NDS devices are not risk free from a bladder cancer perspective. However, there is no attempt to qualify the degree of risk in comparison to CC smokers.

16. The excess lifetime cancer risk (ELCR) associated specifically with the inhalation of particles within EN(N)DS aerosol in humans has been evaluated through generation of data on particle concentration and size range (to include sub-micron and super-micron particles) in combination with published information on particle mass, heavy metal content and tobacco-specific nitrosamines (Scungio et al., 2018). The authors measured particle-specific data for two scenarios under the same smoking pattern, i.e. puffs per EN(N)DS and puff duration:

a. exposure to mainstream aerosol (collected directly from the EN(N)DS mouthpiece); and

b. exposure to second hand aerosol (collected in a 40 $m^3$ naturally ventilated room with an air exchange rate of 0.2 $h^{-1}$, occupied by users of EN(N)DS vaping under the stated patterns).

17. Particle number and surface area concentration of generated aerosols were determined using a Condensation Particle Counter, with detection at levels to 4 nm diameter. Size distribution and total concentration were measured using a Mobility Particle Sizer spectrophotometer; for the direct exposure scenario, temperatures of

37$^{o}$C and 300$^{o}$C were selected to simulate the respiratory system conditions and to evaluate volatility respectively.

18. Using data from available literature, the authors determined that a number of IARC Group 1 carcinogenic compounds have been measured in mainstream and second-hand aerosols from EN(N)DS. These include the heavy metals, cadmium and nickel, arsenic and the nicotine specific nitrosamines nicotine-derived nitrosamine ketone (NNK) and *N*-nitrosonornicotine (NNN). The ELCR for both scenarios was estimated using a Monte Carlo method that was applied by varying the input data between the available measured values, i.e. concentration of hazardous compound, particle number and size distribution[3], surface area, $PM_{10}$, vaping patterns and e-cigarette consumption.

19. In mainstream EN(N)DS aerosol, the authors reported higher average particle numbers (2.34 ± 0.5 ×$10^{8}$ and 2.23 ± 0.8 and part. $cm^{-3}$ with and without nicotine, respectively at 37$^{o}$C) when compared with mainstream smoke of CC (data for comparison taken from published studies). At the higher temperature (300$^{o}$C) particle numbers were lower, both with and without nicotine (7.02 ± 0.8 and 6.23 ± 0.5 x $10^{7}$ part.$cm^{-3}$ respectively), than in mainstream EN(N)DS aerosols at 37$^{o}$C (no comparison given by the authors to mainstream smoke of CC).

20. In second-hand EN(N)DS aerosol, particle numbers were considerably lower than in mainstream EN(N)DS aerosol for all combinations of parameters, i.e. at 37$^{o}$C with and without nicotine (9.08 ± 0.2 and 6.30 ± 1.3 x $10^{3}$ part.$cm^{-3}$ respectively) and at 300$^{o}$C with and without nicotine (8.92 ± 0.2 and 5.97 ± 1.3 x $10^{3}$ part.$cm^{-3}$ respectively.

21. With regards to surface area, the authors reported that EN(N)DS aerosol contained particles of lower surface area (5.22 ± 1.5 and 6.99 ± 0.8 x $10^{11}$ $nm^{2}$ $cm^{-3}$, with and without nicotine respectively) at 37$^{o}$C when compared with mainstream smoke of CC (data for comparison taken from published studies). At the higher temperature (300$^{o}$C) the surface area of particles in the EN(N)DS aerosol were lower those at 37$^{o}$C, both with and without nicotine (3.35 ± 1.5 and 2.48 ± 0.8 x $10^{10}$ $nm^{2}$ $cm^{-3}$ respectively).

22. The surface area of particles from second-hand EN(N)DS aerosol, were considerably lower than in mainstream EN(N)DS aerosol for all combinations of parameters, i.e. at 37$^{o}$C, with and without nicotine (5.90 ± 1.4 and 5.16 ± 0.8 x $10^{7}$ $nm^{2}$ $cm^{-3}$ respectively) and 300$^{o}$C with and without nicotine (5.32 ± 1.4 and 3.51 ± 0.8 x $10^{7}$ $nm^{2}$ $cm^{-3}$ respectively).

23. To summarise, the authors showed that particle number and surface area were higher in aerosols from EN(N)DS with nicotine for both mainstream and

[3] A paper characterising the EN(N)DS aerosol droplet particle fraction has been reviewed by the COT (TOX/2017/49).

second-hand scenarios. For EN(N)DS aerosol with nicotine, a higher average particle number with lower surface area was found when compared to mainstream CC smoke.

24. Received particle doses per puff were calculated from the generated and published data for both mainstream EN(N)DS aerosol and CC smoke for males and females. The surface area received was higher in males than females but remained comparable across cigarette types (for males: $5.6 \times 10^{2} – 1.1 \times 10^{3}$ and $5.42 \times 10^{-1}$ $mm^2$ $puff^{-1}$ for CC and EN(N)DS, respectively; for females: $4.5 \times 10^{2} – 9.3 \times 10^{-2}$ and $4.93 \times 10^{-1}$ for CC and EN(N)DS, respectively). The received $PM_{10}$ content per puff was comparable in males and females and lower in EN(N)DS aerosol than in CC smoke (for males: $3.4 \times 10^{-2} – 6.3 \times 10^{-2}$ and $2.4 \times 10^{0}$ mg $puff^{-1}$ for CC and EN(N)DS, respectively; for females: $3.4 \times 10^{-2} – 5.6 \times 10^{-2}$ and $2.17x\ 10^{0}$ mg $puff^{-1}$ for CC and EN(N)DS, respectively).

25. ELCR values (particle specific) were calculated for males and females on the basis of actual smoking habits, i.e. number of CC and EN(N)DS per day, puff number and duration and years of smoking.

26. The ECLR values for mainstream aerosol from EN(N)DS with and without nicotine were calculated as $7.26 \times 10^{-6}$ and $7.3 \times 10^{-6}$ respectively for males, and $6.28 \times 10^{-6}$ and $6.11 \times 10^{-6}$ for females. These values correspond to a lung cancer incidence of 0.6 new cases per 100,000 population. This compares to a particle-specific ECLR in the Italian general population of $2 – 6 \times 10^{-1}$ related to CC use.

27. For second-hand CC and EN(N)DS aerosol, ECLR values with and without nicotine were $2.7 \times 10^{-8}$ and $1.29 \times 10^{-8}$ in males and $2.62 \times 10^{-8}$ and $1.24 \times 10^{-8}$ in females respectively. These values correspond to a lung cancer incidence of between 0.001 and 0.003 new cases per 100,000 population.

28. In summary, the authors reported that the particle-specific ELCR associated with mainstream aerosol exposure from EN(N)DS is two orders of magnitude higher than that of second-hand EN(N)DS aerosol exposure. ELCR are also higher for nicotine-containing aerosols, in comparison with non-nicotine containing aerosols, and for male users when compared with females. The authors conclude that the ELCR evaluated in the study for mainstream EN(N)DS aerosol is lower than the target limit of $1 \times 10^{-5}$ proposed by the WHO, and the target risk range of $10^{-6}$ to $10^{-4}$ from the US EPA, to be ‘safe and protective of public health’.

29. The contribution of each (perceived) hazardous component of EN(N)DS aerosol to the ELCR was also examined:

- Cadmium had the greatest contribution to the ELCR in EN(N)DS aerosol, with and without nicotine, and in CC smoke, contributing 42.2%, 63.9% and between 0% and 17%, respectively;

- NNK had the second largest contribution, explaining why the presence of nicotine *per se* increased the ELCR, with contributions of 27.9%, and between 69 and 88% for EN(N)DS aerosol and CC smoke, respectively.

- Arsenic, nickel and NNN were estimated to contribute 20.2%, 7.8%, and 1.7% in EN(N)DS aerosol with nicotine; 21.2%, 14.9%, and 0% for EN(N)DS aerosol without nicotine; and between 2 and 4%, 0%, and between 8 and 9% for CC smoke, respectively.

30. Taking the calculated ELCR into consideration, the authors conclude that the use of EN(N)DS as an alternative to CC significantly reduces the risk of developing lung cancer (for the Italian population) from $4 \times 10^{-1}$ to around $7 \times 10^{-6}$. In addition, exposure to second-hand aerosol from EN(N)DS is associated with a negligible increment in lung cancer cases. Higher risks are associated with nicotine containing aerosols due to the presence of NNK and NNN.

31. In recognising current issues with the assessment of the relative harm of aerosols from different vaporised nicotine products (VNPs), Stephen (2018) aimed to derive a procedure that assigns a single latent variable (potency) that reflects carcinogenic risk, to an emission data set. In the first step of their methodology, cancer potencies of various nicotine-delivering aerosols were modelled using published chemical analyses of emissions and their associated inhalation unit risks. Secondly, the calculated potencies were compared using a conversion procedure for expressing smoke and EN(N)DS vapours in common units. In the third step, lifetime cancer risks were calculated from the derived potencies using daily consumption estimates.

32. To enable the modelling, concentrations of several major carcinogens present in CC smoke and in VNP 'vapour' (from a prototype heat-not-burn device, and EN(N)DS devices including early-generation disposables, second-generation clearomisers and cartomisers and third-generation modules and tanks) were obtained from various published literature. Where available, data on EN(N)DS coil resistance and battery voltage were also collated. The resulting data set contained 93 analyses divided into three subsets, namely: the 'Goniewicz subset' used as a benchmark containing 12 EC samples, with analysis for 7 carcinogens (carbonyls, VOCs, nitrosamines and metals); the 'organics subset' was divided into two with the 'variable power (organic) subset' providing concentrations of some organic compounds (formaldehyde, acetaldehyde and, in some studies, VOCs) in conjunction with data on coil heating effects and constituted 32 analyses; the remaining 'organics only' subset provided data for the above organics only and comprised 48 analyses. Carcinogen emissions from an unheated medical nicotine inhaler device were considered to represent an 'accepted' level of exposure and uncontaminated air a reference baseline.

33. The compounds that were assessed comprised: acetaldehyde; formaldehyde; acrylonitrile; benzene; 1-3-butadiene; 2-amino-naphthalene; 4-amino biphenyl, benzo(a)pyrene; NNN; NNK; cadmium; lead; chromium; nickel and arsenic. These

are classified by IARC as either *human carcinogens* (Group I) or *possible human carcinogens* (Group 2B). The mean potency ratio of EN(N)DS relative to CC smoke was reported as $1.8 \times 10^{-3}$. The aerosols from all sources tested formed a spectrum of relative cancer potencies that spanned five orders of magnitude (around $10^{0} – 10^{-5}$); lowest relative potencies were assessed as ambient air and highest potencies as CC smoke. There was a large variation in potency calculated for EN(N)DS emissions which spanned most of this range. Although the majority of potencies for EN(N)DS were <1% of that for tobacco smoke (around $10^{-3}$ of the potency of tobacco smoke), these were two orders of magnitude higher than that of the medicinal nicotine inhaler (around $10^{-4}$ that of CC smoke).

34. A small number of the sub-sets assessed (organics-only and variable power subset) had noticeably higher potencies. These tended to be associated with high levels of carbonyls generated when excessive power is delivered to the atomiser coil.

35. The predominant carcinogens within the potency estimates were found to differ for the different devices. For CC, the authors state that 1,3-butadiene and acrylonitrile accounted for 75% of the cancer potency, whereas for EN(N)DS, formaldehyde and acetaldehyde accounted for >95% of organic compound contribution to cancer potency; cadmium was also found to influence potency but was not present in all devices tested.

36. The potential for cancer potencies to be positively influenced by the applied voltage to VNP devices was also highlighted by the authors. It was considered that carbonyl potency may be enhanced by an increased rate of heat energy transfer at the coil, although no consistent relationship was seen in the studies assessed.

37. Calculated mean lifetime cancer risks (for 15 cigarette equivalents per day for a lifetime[4]) were found to decline in the following sequence: CCs >> heat-not-burn >> e-cigarettes (normal power) ≥ nicotine inhaler; $2.4 \times 10^{-2}$, $5.7 \times 10^{-4}$, $9.5 \times 10^{-5}$ and $8.9 \times 10^{-6}$ respectively.

38. When compared with CC smoking, the authors state that the relative risks are lower for the other devices (0.024, 0.004 and 0.0004 for heat-not-burn, EN(N)DS and nicotine inhaler respectively). However, in comparison with the medical use device, the authors report a higher relative risk (11, 64 and 2700 for EN(N)DS, heat-not-burn CC respectively).

39. The authors concluded that optimal combinations of device settings, liquid formulation and vaping behaviour normally result in EN(N)DS emissions with much less carcinogenic potency than CC smoke. Nevertheless, they highlight the potential for increased risks when EN(N)Ds products are not used according to manufacturer's guidance.

[4] 15 traditional cigarettes per day or 15 heat-not-burn sticks or 30L e-cigarette liquid (normal power) or 30L nicotine liquid from a nicotine inhaler.

40. The authors note that the carcinogenic risks calculated in the study refer to chemical risk only and not to other factors such as small particle size. In addition, aggregate and/or synergistic risks were not taken into account using their methodology. A major limitation with the data used was the absence of measurements for metals[5] which were shown to have a large influence on the unit risk value, and this may have resulted in an underestimate of cancer potency values.

41. In conclusion, the study showed, using their methodology, that a considerable range of cancer risks can be derived from currently available emissions data for VNPs. Of particular note is the requirement for a better understanding of the influence of carbonyls and metals on cancer risk for these devices. This may subsequently lead to better control of exposure to these substances in aerosols through device and e-liquid formulation design and vaping behaviour.

42. As part of the recent NAS report, a systematic review of currently available evidence relating to a potential association between EN(N)DS use and carcinogenesis was carried out. The authors comment that due to the relatively recent introduction of these products and poor design of many of the studies currently available, there is a paucity of evidence on the long-term effects on cancer outcomes. As such, much of that reviewed is based on existing evidence regarding the carcinogenic potential of the major components of EN(N)DS products, for example, nicotine (NAS, 2018).

43. The authors considered that there are many biologically plausible pathways by which components of EN(N)Ds products could, theoretically, influence the development of cancer. It was considered that evidence showing the ability of EN(N)DS aerosols to form ROS and/or be converted to DNA binding reactive intermediates was of particular relevance to the outcome of chemical carcinogenesis. In addition, evidence showing the cytotoxic potential of EN(N)DS aerosols that may contribute to tissue repair and mitogenic response was also highlighted as an important pathway for chemically induced cancers.

44. The major findings of the review can be summarised as being:

- There are few epidemiology studies that allow meaningful interpretation about cancer or intermediate cancer endpoints and those that have been carried out are of poor quality. They do not provide an evidence base to allow even preliminary associations between the use of EN(N)DS products and the risk of cancer in humans to be interpreted.

- *In vivo* animal studies provide *limited evidence* of an increased risk of cancer following long-term use of EN(N)DS products, based on the intermediate cancer biomarker, 8-OHdG. This statement is cautioned by the authors as the utility of 8-OHdG as a predictive biomarker for carcinogenesis is limited.

[5] A paper concerning metal exposure from EN(N)DS aerosol has been reviewed by the COT (TOX/2018/15).

- No adequate long-term (2-year) animal studies of exposure to EN(N)DS aerosol were identified during the systematic review.

- There is *limited evidence* that the aerosol from EN(N)DS products is mutagenic or can cause DNA damage in humans, animal models and human cells *in vitro*.

- Substantial evidence is available that a number of chemicals present in the aerosols from EN(N)DS products cause DNA damage and are mutagenic (for example, formaldehyde and acrolein), supporting the biological plausibility of an increased risk of cancer through their use. However, the levels of exposure to these through EN(N)DS product use remains to be determined.

**Questions for the Committee**

45. Members are asked to consider this paper and in particular:

    i. Is the Committee able to comment on the absolute and relative risks of carcinogenicity of E(N)NDS compared to conventional cigarettes?

**NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat**
**June 2018**

## Abbreviations/Glossary

| | |
|---|---|
| Cartomiser: | Combination of cartridge and atomiser within e-cigarette device. |
| CC: | Conventional cigarettes |
| Clearomiser: | Transparent version of cartomiser e-cigarette device |
| CYP: | Cytochrome P450 |
| ELCR: | Excess lifetime cancer risk |
| EN(N)DS, 'e-cigarettes': | Electronic nicotine (and non-nicotine) delivery systems |
| EPR: | Electron paramagnetic resonance |
| FRAP: | Ferric reducing antioxidant power |
| NNK: | Nicotine-derived nitrosamine ketone |
| NNN: | *N*-nitrosonornicotine |
| PAH: | Polycyclic aromatic hydrocarbon |
| PG: | Propylene glycol |
| ROS: | Reactive oxygen species |
| VG: | Vegetable glycerine |
| VOC: | Volatile organic compound |
| VNP: | Vapourised nicotine product |

## References

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Stephens, W.E. (2018) Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tobacco control, 27, 10-17.

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)**

# Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (EN(N)DS – e-cigarettes) – overview of available data on carcinogenicity.

## *Search strategy*

Two searches were carried out in both SCOPUS and PubMed. Search terms in each database are as follows:

- Genotoxicity

  *Scopus*
  ( TITLE-ABS-KEY ( "e-cig*" OR "electronic cigarette*" OR "electronic nicotine delivery system*" ) AND TITLE-ABS-KEY ( genotox* OR mutagen* OR "genetic tox" ) ): 30 refs.

  *PubMed*
  ((("e-cig*" [Title/Abstract] OR "electronic cigarette*" [Title/Abstract] OR "electronic nicotine delivery system*"[Title/Abstract])) AND (genotox* [Title/Abstract] OR mutagen* [Title/Abstract] OR "genetic tox*"[Title/Abstract])) AND english[Language]: 12 refs.

- Carcinogenicity

  *Scopus*
  ( TITLE-ABS-KEY ( "e-cig*" OR "electronic cigarette*" OR "electronic nicotine delivery system*" ) AND TITLE-ABS-KEY ( carcin* ) ): 145 refs.

  *PubMed*
  ((((("e-cig*" [Title/Abstract] OR "electronic cigarette*" [Title/Abstract] OR "electronic nicotine delivery system*"[Title/Abstract])) AND (carcin* [Title/Abstract]))) AND english[Language]: 38 refs.

All papers were screened for relevance by assessing the title, keywords and abstract. Papers that reported data of interest regarding the genotoxicity or carcinogenicity of E(N)NDS were selected. Papers were then separated into those relevant for COM (presented here) and for COC (to be presented at the July COC meeting).

**NCET at WRc/IEH-C under contract supporting the PHE COC Secretariat**
**June 2018**

**CC/2018/01 Annex 2**

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Chapter 10 National Academies of Sciences, Engineering, and Medicine (2018) Public health consequences of e-cigarettes. Washington, DC: The National Academies Press. Available at: http://www.nas.edu/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx [accessed June 2018].

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**June 2018**