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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Literature update to mid-2019.

Background

1. The COT has been reviewing potential toxicity of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS). Discussion papers on this topic that have been considered by the Committee from November 2017 onwards have addressed aspects including studies of constituents of E(N)NDS liquids and aerosols, the nature of the particulate matter produced on E(N)NDS use, potential exposures of users and bystanders, and toxicological data on some of the principal individual constituents and on E(N)NDS aerosol mixtures. This current paper presents the findings from an updated literature search on these aspects.

Search strategy

3. A search of the PubMed and Scopus databases for publications relating to E(N)NDS was performed for the period 06/04/2018 to 05/06/2019, as described in Annex A. In total, 891 citations were retrieved. These citations were screened on title/abstract for relevance to aspects of E(N)NDS exposure or toxicity that have been addressed during the COT review process, which, for the purposes of this update, was divided into 4 categories: constituents and user exposure, bystander exposure, human health effects, and experimental studies in animals. A total of 722 references were excluded, including: reports addressing social aspects, perceptions, marketing, demographic studies of E(N)NDS use, and studies of the utility of E(N)NDS as an aid to the cessation of CC smoking[1] (n = 498); reviews, commentaries and opinions (n = 131); *in vitro* studies (n = 33); reports for which the topic of the publication could not be clearly determined from the title and/or abstract, or no abstract was available (n = 27); modelling studies and studies reporting methodological developments (n = 21); case reports of injuries from E(N)NDS devices (n = 11).

4. The 169 citations that were retained from this first round of screening included 66 publications relating to E(N)NDS constituents and user exposure, 17 publications on bystander exposure, 66 on human health effects, and 20 reporting experimental studies in animals. On a second screening, a further 36 of these citations were excluded, either because they had already been included in previous COT

[1] Except where is was clear that reports addressed adverse effects

discussion papers[2] (n = 5 on constituents and user exposure, 7 on bystander exposure, 3 on human health effects and 3 on experimental studies in animals) or because they were not considered to be directly relevant when the text was examined in more detail (n = 3 on constituents and user exposure, 1 on bystander exposure, 12 on human health effects and 2 on experimental studies in animals).

5. Thus, a total of 133 new publications are included in the following update. The summaries given are based on the abstracts.

Constituents and user exposure

6. Fifty-eight citations were identified that addressed the presence of individual constituents or contaminants in E(N)NDS liquids or aerosols, the nature of aerosol particulate matter, thermal degradation products, studies of puff topography, and biomonitoring data.

Constituents and contaminants

Nicotine

7. Czoli et al. (2018) reported an analysis of E(N)NDS products sold at 80 retail outlets in Canada, where the sale of nicotine-containing E(N)NDS products is prohibited. Approximately equal proportions (40–45%) of products were labelled as containing or not containing nicotine, with around 15% being unlabelled. In many cases, labelled nicotine content was not consistent with levels measured in the product. In a study reported by Dai et al. (2018), measured nicotine concentrations in 8 retail E(N)NDS liquids (sold as containing nicotine) were found to be in the range of 5.7 to 14.7 mg/g, varying by up to 9.0% from label concentrations. Investigations of nicotine transfer showed that nicotine levels in aerosol were on average 12.7% lower than in corresponding E(N)NDS liquids. The 'mean nicotine vaping emission factor' was reported as 39.6 µg/puff over the 8 samples tested. A report by Farsalinos et al. (2018a) noted that machine puffing of CC, heat-not-burn (HNB) product, or various ENDS products using Health Canada Intense puffing regime led, in general, to nicotine delivery rates: CC > HNB > ENDS. Talih et al. (2019) investigated operating characteristics of several 'JUUL' E(N)NDS products, including evaluation of nicotine delivery and partitioning in aerosol. Liquid nicotine concentration was reported as 69 mg/mL, with a propylene glycol (PG):glycerol ratio of 30:70. In 15 puffs, 2.05 mg nicotine were emitted to aerosol, the majority of which was in the protonated form.

8. Some studies assessed factors affecting rate of nicotine delivery to aerosol. A study by Kosmider et al. (2018c), using a 2nd generation ENDS product, indicated that PG:glycerol ratio affected nicotine delivery at lower, but not higher, power ratings. Peace et al. (2018) used a glass trap system to determine nicotine delivery to ENDS aerosol from a tank system at different applied voltages. Nicotine yield in

[2] The publication dates of some citations have been updated in public databases

the trap increased with increasing applied voltage, with doses delivered to aerosol from a 12 mg/mL nicotine formulation in 50:50 PG:glycerol reported as 88 ± 12, 91 ± 15, and 125 ± 22 µg at 3.9, 4.3, and 4.7 V, respectively. Bitzer et al. (2019) found that nicotine delivery to aerosol was increased with puff volume and puff duration for 2 commercial products tested, but this was not the case when a 'standardized research e-cigarette' (SREC) was tested.

Metals and solid particulates

9. Kamilari et al. (2018) reported the development of a fluorescence spectroscopic methodology for the detection and quantitative analysis of cadmium, lead, nickel, copper, arsenic, and chromium, and used the method to analyse the presence of these metals in commercially available E(N)NDS liquids. However, details of findings were not described in the publication abstract.

10. Over a 5-year period, Williams, Bozhilov and Talbot (2019) analysed atomizers from E(N)NDS products by stereoscopic microscopy and by scanning electron microscopy coupled with energy dispersive X-ray spectroscopy (SEM/EDS). Chromium, nickel, copper, silver, tin, silicon, aluminium, and zinc were identified in most products. Iron and lead were found in some but not all products, while manganese, cobalt, molybdenum, titanium, and tungsten were only found in a few of the products. The metals used in various components were often similar in cartomizer and tank models. Filaments were usually chromium and nickel (nichrome), although in some newer products, the filament also contained iron, copper, and manganese. The thick wire in earlier products was usually copper coated with silver, while in some newer products, it was predominantly nickel. In all products, the wick was silica, and sheaths, when present, were fibreglass (silicon, oxygen, calcium, aluminium, magnesium). Wire-to-wire joints were either brazed or clamped with brass (copper and zinc), and air-tube/thick wire joints, when present, were usually soldered with tin. Tank-style products generally lacked a thick wire and sheaths. Authors concluded that, in general, atomizer components in E(N)NDS were similar over time and between brands.

11. The presence of 6 metals was evaluated in E(N)NDS liquids under 3 conditions: in newly obtained liquids, after storage in a clearomizer with no puffing, and from the clearomizer after puffing. Zinc and lead were detected in all types of samples, while cadmium was below the method limit of detection (LOD) in all cases. Iron, nickel, and chromium were generally below the LOD in new liquids, but detectable in clearomizer-stored samples. Zinc, lead, and nickel levels increased significantly with E(N)NDS use. Maximum 'after:before use' ratio values for each metal were reported as 463 (zinc), 315 (nickel), 131 (iron), 47.9 (chromium), and 36.0 (lead) (Na et al. 2019).

12. Zhao et al. (2019) reported that power setting and device type (open or closed system) affect metal release from device to aerosol. Open-system devices ('mods') generated aerosol with higher metal concentrations than closed-system devices (a 'cigalike' and a 'pod'). The release of metal concentrations from open-system

devices firstly increased with device power, which then levelled off for most of the 14 metals evaluated.

13. One study investigated the potential emission of glass particles to E(N)NDS aerosol. Samples at puff number 0-10, 101-110, and 201-210 from a cartomizer containing PG:glycerol liquid were collected on polycarbonate filter and analysed by SEM/EDS. The presence of glass fragments was noted in some of the samples above puff number 100 (Shin et al. 2018).

14. Farsalinos and Rodu (2018) performed a risk assessment of metal exposure from E(N)NDS, based on data in the published literature. Metals evaluated were cadmium, chromium, copper, nickel, lead, antimony, tin, manganese, aluminium, iron, and zinc. Findings were calculated as the daily e-liquid consumption required to exceed published daily exposure limits (where available) for each individual metal. Based on published data for median and 75th percentile metal concentrations measured in aerosols, the following e-liquid intakes would exceed safety limits: for nickel 73 g/day e-liquid containing the median nickel concentration or 17 g/day at 75th percentile nickel concentrations, for chromium 358 g/day e-liquid containing the median chromium concentration or 68 g/day at 75th percentile chromium concentrations, for lead 338 g/day e-liquid containing the median lead concentration or 135 g/day at 75th percentile lead concentrations. For other metals, intakes would need to be much higher. Authors concluded that for almost all metals, unrealistically high levels of liquid need to be consumed in order for total daily exposure to exceed established limits.

Flavourings, sweeteners, and other food additives

15. Four publications reported results of analyses of commercially available E(N)NDS liquids for content of flavouring chemicals (Aszyk et al. 2018, Behar et al. 2018, Hua et al. 2019, Omaiye et al. 2019). Overall, more than 150 different flavouring chemicals were identified, at concentrations ranging from ‘negligible’ to > 10 mg/mL (1% by weight). In addition, one study noted the presence of sugars (glucose, fructose, and sucrose) (Fagan et al. 2018) and another study detected synthetic food dyes (tartrazine, Brilliant Blue FCF, and Allura Red AC) (Korzun et al. 2019).

16. Studies also evaluated the fate of flavourings and the sweetener, sucralose, in E(N)NDS liquids upon puffing. Findings reported included the transfer of pyrazines (El-Hage et al. 2018) and of carbonyl compounds (Farsalinos and Voudris 2018, Qu, Kim and Szulejko 2018) from flavourings in e-liquid to aerosol, the formation of degradation products from sucralose (Duell et al. 2019), and modelling of the amount of aroma compounds (benzaldehyde, estragole, and different terpenoids) that may reach the lung (Noel et al. 2019).

Studies that evaluated multiple constituent types

17. Czoli et al. (2019) examined constituents of 166 E(N)NDS products purchased in Canada (primarily Ontario) during January-February 2015, including disposable products (33%), refillable products (14%), and E(N)NDS liquids (53%). Overall, products contained an average of 6.2 (standard deviation (SD) = 3.6) flavouring chemicals. E(N)NDS products with sweet flavours (with names such as desserts or alcoholic drinks) had a significantly greater number of flavouring chemicals compared with tobacco- and menthol-flavour product names. Twenty-one percent of products contained flavouring chemicals that the authors cited as potential risk of inhalation toxicity (benzyl alcohol, benzaldehyde, vanillin). An additional 8 toxicants (for example, acrolein or diacetyl) were detected in a total of 14 E(N)NDS products. Measurable levels of tobacco-specific nitrosamines (TSNAs) were detected in 70% of tested products. Authors concluded that E(N)NDS products purchased in Ontario, Canada, contained several constituents that may present excess risk, including some flavouring chemicals and carcinogenic nitrosamines, and that these findings reveal policy gaps that may be addressed by developing regulatory product standards and labelling practices for E(N)NDS.

18. A study reported by Girvalaki et al. (2018) analysed the composition of 122 common E(N)NDS liquids purchased in 9 European Union (EU) Member States (MS) prior to adoption of the Tobacco Product Directive (TPD)[3]. Qualitative analysis identified 171 different compounds. Authors reported the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Danger and Warning codes for the most commonly detected. Forty-one (85.4%) compounds had been assigned Warning GHS codes, 11 Danger GHS codes and 9 both codes. Of the total number of the detected compounds, numbers attributed to flavours were as follows: fruit (293), tobacco (204), non-alcoholic drinks (64), desserts and sweets (50), menthol–mint (42), alcohol (39). Menthol was the most frequently detected compound. Discrepancies in measured versus reported nicotine concentrations were noted.

19. Wagner et al. (2018) evaluated the potential presence of combustion-related harmful and potentially harmful compounds (HPHCs) (three aromatic amines, five volatile organic compounds, and the polycyclic aromatic hydrocarbon, benzo[*a*]pyrene) in commercial and reference E(N)NDS liquids and ‘cigalike’ products and/or transfer efficiency to aerosol. HPHCs were not detected at measurable levels in liquids or aerosols. In subsequent tests in which combustion-related HPHCs were added to E(N)NDS liquids, transfer efficiencies to aerosol ranged from 49% to 99%.

[3] The TPD became applicable to EU Member States in May 2016.

Other compounds

20. Angerer et al. (2019) noted the detection of synthetic cannabinoid (SC) compounds in 10 of 21 E(N)NDS liquids tested[4] and reported studies of the metabolism and potency of these SC compounds in humans. Authors concluded that the extreme potency of SCs added to E(N)NDS liquids poses a serious threat to public health.

21. Lee, Allen and Christiani (2019) investigated the presence of endotoxins and glucan in E(N)NDS products, with a focus on examining differences according to the type and flavour of products. E(N)NDS cartridges (n=37) and liquid products (n=38) with the highest nicotine content from the 10 top-selling brands in the US were selected and classified into 4 flavour groups: tobacco, menthol, fruit, and other. Endotoxin and glucan concentrations were above the LOD in 17 (23%), and 61 (81%) of 75 products tested respectively. After adjusting for brand and flavour, the mean glucan concentration was 3.2 times higher in cartridges compared with E(N)NDS liquid samples. After adjusting for brand and type of product, glucan concentrations in tobacco- and menthol-flavoured E(N)NDS were 10.4 and 3.5 times higher than concentrations found in fruit-flavoured products.

Products formed on aerosolization

22. Several new reports described the potential for emission of carbonyl compounds in E(N)NDS aerosols, and factors that may influence this. Studies were carried out using machine puffing (Farsalinos et al. 2018b, Kosmider et al. 2018b, Lee, Szulejko and Kim 2018a, Salamanca et al. 2018, Saliba et al. 2018, Beauval et al. 2019, Qu et al. 2019), direct sample introduction (DSI) gas chromatography-tandem mass spectrometry (Bisceglia et al. 2018), or measured aldehydes in exhaled breath of users (Samburova et al. 2018). One study measured the heating coil temperature of a 2nd generation 'top coil' clearomizer E(N)NDS device under different conditions of coil wetness, applied power, and E(N)NDS liquid PG:glycerol composition. Authors concluded that the large temperature variations that can occur may explain the large variations in formaldehyde formation reported in the literature for these devices (Chen et al. 2018). The study by Talih et al. (2019) (see paragraph 7) found that nicotine-normalised formaldehyde and total aldehyde emissions from the 'JUUL' brand of E(N)NDS were similar to those from other closed-system E(N)NDS devices, and lower than emissions from CC.

23. Studies also investigated emissions of other degradation products, including carbon monoxide and small hydrocarbon gases (El-Hellani et al. 2019) or reactive oxygen species (Haddad et al. 2019) from sub-ohm devices, and hydroxyl radicals (Son et al. 2019). Bitzer et al. (2019) found that emission levels of free radicals and carbonyls into E(N)NDS aerosols were affected by puff duration and puff volume.

[4] 21 e-liquids bought via internet between May 2014 and June 2015 from retailers who also sell herbal blends

24. One study noted that hydrolysis of the flavouring additive, triacetin, acted as a catalyst for the degradation of PG and glycerol to increase the formation of formaldehyde hemiacetals, acrolein, and acetaldehyde (Vreeke, Peyton and Strongin 2018b).

25. Vreeke et al. (2018a) noted that dihydroxyacetone (DHA) can be formed in E(N)NDS aerosols via free radical oxidation of glycerol. DHA is used as the active ingredient in spray tanning products, and is restricted by the U.S. Food and Drug Administration (FDA) for external use only, due to concerns about potential genotoxicity. Authors tested 3 E(N)NDS devices to evaluate production of DHA, noting that DHA concentrations in aerosols were proportional to the power setting used and individual coil design.

Aerosol particulate matter and gas/liquid partitioning

26. Three studies noted that E(N)NDS device power output (Floyd et al. 2018, Pourchez et al. 2018) and/or E(N)NDS liquid PG/glycerol ratio (Pourchez et al. 2018, Zervas et al. 2018) affect the particle characteristics (size distribution and/or particle number) in the aerosol produced.

27. Aszyk et al. (2019) reported the development of a method to evaluate partitioning of E(N)NDS liquid components between the gas and the liquid phase of the aerosol, noting that, on puffing, most compounds are deposited in the liquid phase of the aerosol, with only trace levels of some substances observed in the non-condensed gas phase. Pankow et al. (2018) estimated compound-dependent gas/particle partitioning equilibrium constants ($K_{p,i}$) for 32 compounds in simulated E(N)NDS liquids in 50:50 PG:glycerol, including nicotine and some flavouring compounds. Benzene, toluene, and limonene were predicted to partition mostly to the gas phase, while cinnamyl alcohol, maltol, and free-base nicotine would be mostly in the particle phase.

Puff topography

28. Four publications reported studies in which portable topography monitors were used to analyse puff topography of E(N)NDS use. Two studies compared patterns during use of E(N)NDS by either regular CC smokers or E(N)NDS users (Lee et al. 2018d, Vansickel et al. 2018), while 2 other studies compared patterns between different E(N)NDS users (Kosmider et al. 2018a, Lee et al. 2018c). Details reported included factors such as amount of E(N)NDS liquid used, puff volume, puff duration, and flow rate. Substantial variability in puffing patterns between users was noted.

Biomonitoring

29. Five publications were identified that reported biomonitoring in E(N)NDS users compared with users of other tobacco products, users of marijuana, dual users of E(N)NDS with another product, or non-users.

30. A study of 20 E(N)NDS users in Turkey found that urinary cotinine levels correlated with the amount of E(N)NDS fluid consumed (Aslan et al. 2019). Boykan et al. (2019) also reported that urinary cotinine levels correlated well with self-reported E(N)NDS use (14.3% of participants) in a study of 517 adolescents in the U.S., although the authors also noted that subjects were unaware of their nicotine exposure. Analysis showed higher cotinine levels in daily E(N)NDS users compared with non-daily users (315.4 [interquartile range (IQR) 1375.9] vs. 1.69 [28.2] ng/mL), and significantly higher median cotinine levels in 'pod' users (259.03 [1267.69] ng/mL) compared with non-pod users (1.61 [16.3] ng/mL). A study reported by Carroll et al. (2019) noted that nicotine metabolite ratio (NMR) did not appear to be linked with total nicotine equivalents (TNE) or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) exposure in a study of E(N)NDS users, CC smokers, and dual users of American Indian descent. Authors considered these findings to indicate that higher CC smoking and E(N)NDS use prevalence in this community may not be related to nicotine metabolism, but rather that environmental and social factors may be involved.

31. A study by Fuller et al. (2018) measured levels of five known bladder carcinogens in urine samples from 13 E(N)NDS users (of whom 9 were long-term non-CC smokers) and 10 non-users. Levels of two of the carcinogens evaluated were significantly higher in the E(N)NDS users: o-toluidine (mean 2.3-fold higher, p=0.0013), 2-naphthylamine (mean 1.3-fold higher, p=0.014). Authors considered that further work is required to clarify the safety profile of E(N)NDS with respect to potential contribution to bladder cancer.

32. A study of data from the US National Health and Nutrition Examination Survey for 2013–2016, including 1139 participants who were users of tobacco products (cigars, CC, dual cigar/CC, E(N)NDS, dual E(N)NDS/CC) showed no differences in blood cadmium, lead, or mercury levels between E(N)NDS users compared with other groups (Jain 2019).

Bystander exposure

33. The 9 citations identified included studies of E(N)NDS constituents in exhaled breath, ambient air and deposited on surfaces, the physical nature of exhaled particulate matter, biomonitoring studies, and evaluation of adverse health effects in individuals exposed to second-hand E(N)NDS emissions.

Particle type and distribution

34. Martuzevicius et al. (2018) compared particle size and distribution of second-hand E(N)NDS aerosol and CC smoke emissions in the vicinity of bystanders. Various differences were reported, including more rapid decrease in particle number concentration (PNC) from E(N)NDS compared with CC product. Khalaf, Mostafa and Zhukovsky (2019) reported that particle size distributions of E(N)NDS aerosols generated into indoor air and/or a chamber were bimodal, mostly in the range up to 1.0 µm. A study that measured $PM_{2.5}$ and ultrafine particles (UFP) in the vicinity of an

E(N)NDS user in an office room found that levels increased > 100-fold at 0.5 m and 1.0 m from the user during use (Volesky et al. 2018).

Exhaled breath, ambient air, and surface monitoring

35. Exhaled breath of E(N)NDS users was monitored during vaping for levels of nicotine, PG, glycerol, formaldehyde, acetaldehyde, acrolein, TSNAs, and some metals. Increased[5] levels of nicotine, PG, TSNAs, and copper were noted. Authors used these data to calculate exposure to bystanders in two hypothetical scenarios: a non-ventilated car in which 2 users were using E(N)NDS, and a well-ventilated office containing 1 E(N)NDS user. Authors concluded that their results indicated that bystanders may experience irritation of the respiratory tract as a result of exposure to PG and glycerol, and that systemic effects of nicotine should be expected if nicotine-containing e-liquid is used, including palpitations and an increase of systolic blood pressure. Specifically referring to the car scenario, increased risk of tumours could not be excluded (due to emission of TSNAs) (Visser et al. 2019).

36. van Drooge et al. (2019) monitored ambient air in a non-ventilated room in which E(N)NDS use occurred for 12 hours and in exhaled breath of non-users present in the room during this time-period, compared with a 12 h period during which no E(N)NDS use took place. The study reported on particulate and gas phase analyses. Further details of study findings were difficult to ascertain clearly from the report abstract.

37. One report addressed the persistence of nicotine deposited on glass or fibre surfaces (third-hand exposure). Deposition on terrycloths was more long-lasting than on glass, with levels returning to background equivalent after 16 or 4 days, respectively. Authors commented on the potential for risk in terms of exposure to TSNAs produced from long duration of deposited nicotine (Marcham et al. 2019).

Biomonitoring

38. A study in which volunteers, who were not users of nicotine products, attended a vaping event for 6 h and underwent biomonitoring for various chemicals and metabolites indicated a significant increase in biomarkers of nicotine and acrolein, but not TSNAs (Johnson et al. 2019). A study reported by Quintana et al. (2019) used silicone wristbands to monitor nicotine exposure in young children exposed to second-hand CC smoke or E(N)NDS emissions, and noted a correlation between wristband nicotine levels and urinary cotinine levels. Authors considered that wristbands may be a useful tool for monitoring in epidemiological studies.

Health effects

39. Bayly et al. (2019) reported an analysis from the 2016 Florida Youth Tobacco Survey, including data from 11,830 young people (aged 11–17 y) with a self-reported

[5] The report abstract does not state what the comparator was.

diagnosis of asthma. Second-hand exposure to E(N)NDS aerosol was associated with increased odds of an asthma attack in the previous 12 months (adjusted odds ratio (OR) = 1.27, 95% confidence interval (CI) 1.11–1.47).

Human health data

40. The 51 citations identified included case reports, clinical studies, and epidemiological studies.

Case reports and case series

41. Eight publications described individual case reports (n = 6) or data sets of cases reported to national poison centres (n = 2).

42. Of the 6 individual clinical case reports, 5 described adverse effects that appeared to be associated with E(N)NDS use, including spontaneous pneumomediastinum (Marasco et al. 2018), hypersensitivity pneumonitis and acute respiratory distress syndrome (Sommerfeld et al. 2018), lipoid pneumonia and respiratory failure (Viswam et al. 2018), acute eosinophilic pneumonia (Arter et al. 2019), and a case of spontaneous coronary artery dissection in a post-partum E(N)NDS user (Ahmed et al. 2018). Conversely, one report described an apparent beneficial effect of E(N)NDS use, with resolution of a chronic nasal *Staphylococcus aureus* infection in a non-CC-smoker after starting to use a glycerol-based E(N)NDS product (Miler and Hajek 2018).

43. Govindarajan et al. (2018) gathered data on exposures to liquid nicotine (including ENDS devices and liquids) among children < 6 years old from the United States National Poison Data System for January 2012 through April 2017. A total of 8269 liquid nicotine exposures were reported, of which 92.5% were via ingestion, and 1.4% required admission to hospital. Authors noted that such exposures to liquid nicotine had decreased since January 2015, which they considered may, in part, be attributable to legislation requiring child-resistant packaging and greater public awareness of risks associated with electronic cigarette products, although it was noted that liquid nicotine continues to pose a serious risk for young children.

44. Hughes and Hendrickson (2019) conducted a prospective study to collect data during calls to a poison centre over a 42-month period from 2014–2017, with data recorded on route of exposure, E(N)NDS product type (71 brands) and flavour, nicotine concentration, and type and duration of symptoms experienced. Data were collected during 265 calls relating to E(N)NDS, of which 193 related to children and 72 to adults. The majority of exposures involved e-liquid refill containers or fluid. Fifty-six percent (n = 108/193) of pediatric exposures involved ingestion of refill liquid. Although children who ingested e-liquid received only a small amount, initial symptoms were evident in 32% (n = 35/108) of cases. Children who did not ingest or inhale the products were less likely to develop toxicity. Two children who were asymptomatic on initial call became symptomatic on follow-up. In most patients, symptoms resolved within 4 hours. Seventy-one specific products/brands were

identified with nicotine concentrations ranging from 0 mg/mL to 60 mg/mL, and one product contained 3000 mg in a single bottle. A variety of flavours were identified, including several with names that may be attractive to toddlers or adolescents.

Clinical studies

45. Clinical studies (n = 18) evaluated endpoints including effects on the respiratory system, vascular function and oxidative stress, neurobehavioral aspects relating to desire for and/or satisfaction from product use, nicotine delivery and kinetics, and potential adverse clinical symptoms associated with product use.

Respiratory effects

46. Some, but not all, studies of respiratory system endpoints reported adverse effects associated with E(N)NDS use.

47. A double-blind crossover study in which healthy volunteers inhaled E(N)NDS aerosols on 2 separate occasions (product without nicotine and product containing 19 mg/mL nicotine; no flavourings) indicated an association between nicotine exposure and effects of acute airway obstruction (sudden increase in flow resistance measured by impulse oscillometry) (Antoniewicz et al. 2019).

48. A study reported by Brozek, Jankowski and Zejda (2019) indicated reduced exhaled nitric oxide (FeNO), decreased airflow indices (PEF, MEF75), and increased temperature of exhaled air after 5 min use of ENDS containing 12 mg/mL nicotine and ‘multi-fruit’ flavours by both regular CC smokers and regular dual E(N)NDS/CC users. Authors considered that these changes were similar to those that have been observed on exposure to CC smoke.

49. Chaumont et al. (2019) found that acute exposure to 50:50 PG:glycerol (no flavourings) from a 4th generation E(N)NDS product operated at high power setting (60 W), both without and with 3 mg/mL nicotine, induced airway epithelial injury and decreased transcutaneous oxygen tension in studies in which CC smokers underwent test sessions variously using E(N)NDS with nicotine, E(N)NDS without nicotine, and E(N)NDS-sham.

50. A randomised, controlled trial in which CC smokers were given E(N)NDS or non-electronic cigarette substitute (cig-sub) showed greater achievement of CC smoking reduction at follow-up (1–3 months) in the E(N)NDS group, while no significant differences in lung function were noted between the groups (Veldheer et al. 2019).

51. Lee et al. (2018b) observed a greater improvement in pulmonary function in patients randomised to ENDS compared with nicotine replacement therapy (NRT) patches, both given to aid perioperative CC smoking cessation. However, the 10 patients in the ENDS arm had higher baseline smoking disease burden, including worse obstructive spirometry values.

Cardiovascular effects

52. Studies added weight to the concept that exposure to nicotine in ENDS can affect parameters of vascular function and oxidative stress.

53. Chaumont et al. (2018) assessed the effects of E(N)NDS components, PG, glycerol, and nicotine, on microcirculatory function, arterial stiffness, haemodynamic parameters and oxidative stress in a randomised, single-blind, 3-period crossover study in 25 CC smokers. Use of ENNDS without nicotine or sham-E(N)NDS use did not affect the parameters evaluated, but ENDS containing 3 mg/mL nicotine impaired vasodilation and increased indices of arterial stiffness, systolic and diastolic blood pressure, heart rate, and plasma myeloperoxidase. Authors concluded that alterations of micro- and macro-vascular function and oxidative stress associated with E(N)NDS use were attributable to the presence of nicotine.

54. Franzen et al. (2018) also found that use of nicotine-containing products (CC or ENDS) led to increased systolic blood pressure and heart rate, in a randomised cross-over study in 15 CC smokers. These effects were not observed when an ENNDS (non-nicotine) product was used.

55. Pywell et al. (2018) reported that 5 min exposure to ENDS containing 24 mg/mL nicotine led to reduced superficial (-77%) and deep (-29%) flow in hand microcirculation in healthy young adult CC smokers, while tests with non-nicotine product led to increased superficial flow (+70%) and no effect on deep flow. Tests in non-smoking participants indicated no effect of either nicotine-containing or non-nicotine-containing E(N)NDS product on superficial or deep microcirculation. Authors recommended that CC smokers undergoing hand surgery should be advised to avoid using high-dose nicotine-containing ENDS.

56. A double-blind crossover study including 17 healthy volunteers (occasional users of tobacco products[6]) examined acute effects of E(N)NDS, with and without nicotine, on vascular and pulmonary function. Exposure to aerosol containing nicotine caused a significant increase in heart rate and arterial stiffness, while aerosols with and without nicotine caused an increase in blood pressure. Pulmonary effects in this study are described in paragraph 47 (Antoniewicz et al. 2019).

57. Nocella et al. (2018) reported that smoking a CC or using ENDS containing an equivalent amount of nicotine was associated with altered parameters of platelet function, including increased platelet aggregation, in healthy CC smokers and non-smokers tested with each product at 1-week interval in a single-blind crossover study.

58. Mastrangeli et al. (2018) found that blood indices of oxidative stress and endothelial dysfunction were affected to a greater extent on use of ENDS (9 puffs of a nicotine-containing product) in non-CC smokers compared with regular CC

[6] Max 10 CC per month

smokers. Chatterjee et al. (2019) also found that serum indices of oxidative stress and endothelial dysfunction increased significantly, although transiently, in tests in which healthy 'smoking naïve' subjects inhaled ENNDS aerosol that did not contain nicotine.

Neurobehavioral effects

59. Four publications described clinical studies that addressed effects of E(N)NDS use on neurobehavioral aspects, such as factors affecting product preference, craving reduction, dependence and motivation for product use.

60. Two studies used functional magnetic resonance imaging (fMRI) to determine effects of E(N)NDS use on resting state functional brain connectivity (rsFC), taken to indicate states of smoking behaviour (e.g. withdrawal symptoms, reinforcing effects). Hobkirk et al. (2018) noted that nicotine in ENDS produced similar effects to other forms of nicotine. Kroemer et al. (2018) found using fMRI that the presence of sweet taste associated with an E(N)NDS flavour-product was more highly linked with product preference (stimulation on visual and olfactory cues) than pairing of the flavour with nicotine presence, and additionally, that sweet taste could effect a liking response for otherwise non-liked nicotine-paired flavours. A study reported by DeVito et al. (2019) evaluated the effect of flavours to modulate self-administration of nicotine from E(N)NDS products, finding that menthol but not fruit flavours ameliorated aversion to the presence of nicotine, while fruit flavours were more highly preferred and used when non-nicotine-containing products were tested.

61. One study investigated behavioural effects related to PG and/or glycerol in E(N)NDS liquids. E(N)NDS users were nicotine abstinent for 1 h, then completed five sessions of 2 sampling puffs from liquid formulations containing PG:glycerol at ratios of 100:0, 75:25, 50:50, 25:75, and 0:100 in random order separated by 20 min. Liquids containing glycerol produced greater visibility of the exhalant ('cloud'), while mixtures of PG and glycerol produced greater airway sensory effects than PG or glycerol alone. When given the choice of either use of the E(N)NDS test product or receipt of a monetary reward, E(N)NDS were rarely chosen over even the smallest monetary option ($0.05), suggesting minimal reinforcing efficacy of the test products (Harvanko et al. 2019).

Nicotine delivery/kinetics

62. Thirty experienced E(N)NDS users underwent 12 h of nicotine abstinence then completed four conditions consisting of two 10-puff sessions using an ENDS product containing 18 mg/mL nicotine, with differing PG:glycerol ratios in the liquid base (2:98, 20:80, 55:45, 100:0). Nicotine delivery, subjective effects, heart rate, and puff topography were assessed. PG-based liquid was associated with higher nicotine exposure (area under the curve), although participants using the 100% PG liquid took shorter and smaller puffs and described this test product as less pleasant and satisfying than the others. There was no difference between products in terms of suppression of craving symptoms or increase in heart rate. Authors considered that

the findings indicated that factors other than nicotine delivery influence user satisfaction with ENDS products (Spindle et al. 2018).

63. O'Connell et al. (2019) conducted a randomised, open-label clinical study in 15 CC smokers to compare pharmacokinetic profiles of nicotine delivery, subjective effects, and tolerability of ENDS devices containing various nicotine concentrations and CCs. Nicotine delivery from ENDS was described as rapid and comparable to, but not exceeding, that from CCs. Pharmacokinetic properties varied depending on ENDS device. ENDS products were considered as 'little' to 'moderately' effective in satisfying craving to smoke, and products were well tolerated with no adverse effects reported.

Clinical symptoms

64. Hajek et al. (2019) reported a clinical trial in which 886 adults attending U.K. National Health Service stop-smoking services were randomly assigned to either nicotine replacement therapy (NRT) products of their choice or ENDS (initially containing 18 mg/mL nicotine, subsequently users own choice). The primary outcome was abstinence from CC smoking for 1 year (which was low in both groups), but secondary outcomes included respiratory symptoms and participant-reported treatment usage. Of 79 participants who were abstinent from CC at 1 year in the ENDS arm, 63 (80%) were still using the ENDS product, while in the NRT group 44 participants were abstinent from CC at 1 year, with only 4 (9%) still using an NRT product. Overall, throat or mouth irritation was reported more frequently in the ENDS group (65.3%) compared with NRT (51.2%) group, while nausea was more frequent in the NRT group (37.9% NRT, 31.3% ENDS). Cough and phlegm production declined from baseline to 52 weeks more in the ENDS than NRT group, while there were no significant between-group differences in the incidence of wheezing or shortness of breath.

Epidemiological studies

65. A total of 25 publications were identified that reported epidemiological studies of potential health effects associated with exposure to E(N)NDS products, including oral/periodontal health (n = 10), effects on the respiratory (n = 4) and cardiovascular (n = 3) systems, neurobehavioral outcomes (n = 3), and general health and safety outcomes associated with E(N)NDS use (n = 5). The key aspects of these studies are summarised in Table 1, below.

Table 1. Epidemiological studies of potential health effects associated with exposure to E(N)NDS products.

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Oral health					
Dental problems during previous 12 months (self-reported)	Current use of CC and/or E(N)NDS	Adolescents aged 12–17 y in PATH study; n=13,650; USA	Prevalence odds ratio (POR) = 1.50, 95% CI 1.18–1.90 for CC; POR = 1.11, 95% CI 0.79–1.55 for E(N)NDS; POR = 1.72, 95% CI 1.24–2.38 for dual use	Dual use of E(N)NDS and CC is associated with poor oral health outcomes among adolescents. Longitudinal studies are needed to confirm these findings.	Akinkugbe (2018)
Clinical and molecular indices of peri-implant health	CC smoking, waterpipe smoking, E(N)NDS use	CC smokers (CS), waterpipe smokers (WS), E(N)NDS users (E(N)NDS), non-smokers (NS) n=40 total; (Saudi Arabia, Brazil, Pakistan)	Peri-implant plaque index (PI), probing depth (PD), radiographic bone loss (RBL), TNFα, and levels of IL-6 and IL1β significantly higher in all groups compared with NS; Bleeding on probing (BOP) was significantly different between all groups compared with NS; PD and RBL were significantly higher in CC and WS compared with E(N)NDS	CC and waterpipe smoking are associated with poor peri-implant health	AlQahtani et al. (2018)
Clinical and molecular indices of peri-implant health	CC smoking, E(N)NDS use	CC smokers (CS, n=32), E(N)NDS users (E(N)NDS, n=31), non-smokers (NS, n=32); (Saudi Arabia)	BOP significantly higher in NS compared with CS and E(N)NDS; PI, PD, and concentration of MMP-9 and IL1β significantly higher in CS and E(N)NDS compared with NS; IL1β was significantly correlated with marginal bone loss (MBL) in E(N)NDS group	Increased levels of proinflammatory cytokines in CC smokers and E(N)NDS users may suggest peri-implant inflammatory response	ArRejaie et al. (2019)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Oral mucosal lesions (OML)	Previous CC smoking, current E(N)NDS use	Prospective, case-control study of dental outpatients; former smokers (n=45), E(N)NDS users (n=45); (Italy)	OMLs detected in 34.5% of former smokers and 65.4% of E(N)NDS users; Three types of OMLs (nicotine stomatitis, hairy tongue, and angular cheilitis) were significantly more prevalent in E(N)NDS users than former smokers	There was no significant difference in overall prevalence of OMLs between the 2 groups, while 3 types of OML were more prevalent in E(N)NDS users than former smokers	Bardellini et al. (2018)
Clinical periodontal status and gingival crevicular fluid (GCF) cytokine profile	CC smoking, E(N)NDS use	CC smokers (CS, n=46), E(N)NDS users (E(N)NDS, n=44), never smokers (NS, n=45); (Saudi Arabia, Pakistan, USA)	PI, PD, clinical attachment loss (CAL) significantly higher in CS than NS; BOP significantly higher in NS than CS or E(N)NDS; IL1β, IL-6, IFN-g, TNFα, MMP-8 significantly higher in CS compared with E(N)NDS or NS	Periodontal status is poorer and GCF levels of proinflammatory cytokines are higher in CC smokers compared with E(N)NDS users and never smokers; The probability of increases in these parameters in E(N)NDS users compared with never smokers cannot be ruled out	BinShabaib et al. (2019)
Oral health, as indicated by number of permanent teeth removed due to non-traumatic causes	Use of E(N)NDS, either daily or within the last 30 days	Cross-sectional study of 2016 'Behavioral Risk Factor Surveillance System' study; n=456,343 total; USA	n=4957 used E(N)NDS daily, of whom approximately 52% had had 1 or more permanent teeth removed due to tooth decay or gum disease; OR=1.78 (95% CI 1.39–2.30) for association of daily E(N)NDS use with poor oral health in multivariate analysis (adjusted for factors associated with poor oral health, survey clustering, strata and weight)	Daily, but not intermittent, use of E(N)NDS in a population of US adults was independently associated with poor oral health. Care must be exercised when seeking 'healthier' cigarette alternatives	Huilgol et al. (2018)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Presence of oral *Candida* species	CC smoking, waterpipe smoking, E(N)NDS use	Male CC smokers (CS, n=34), waterpipe smokers (WS, n=33), E(N)NDS users (E(N)NDS, n=30), never smokers (NS, n=32); (Saudi Arabia, United Arab Emirates, USA)	*Candida* carriage rates: 100% (CS), 100% (WS), 83.3% (E(N)NDS), 50% (NS); *C. albicans* (the most common species) was significantly more prevalent in CS, WS, and E(N)NDS compared with NS; there were no significant differences between CS, WS, and E(N)NDS	*C. albicans* carriage was significantly higher among CC and waterpipe smokers and E(N)NDS users than never smokers, while no significant differences were noted among the groups for carriage of other *Candida* species	Mokeem et al. (2019)
Clinical, radiographic, and molecular parameters of periodontal inflammation	CC smoking, waterpipe smoking, E(N)NDS use	Male CC smokers (CS, n=39), waterpipe smokers (WS, n=40), E(N)NDS users (E(N)NDS, n=37), never smokers (NS, n=38); (Saudi Arabia, USA, Germany)	IL1β and IL-6 were significantly higher in CS and WS compared with E(N)NDS and NS; PD, CAL, MBL, and whole salivary IL1β and IL-6 were not significantly different between E(N)NDS users and NS	Clinical and radiographic parameters of periodontal inflammation were poorer in CC and waterpipe smokers than E(N)NDS users and never smokers. Whole salivary IL-1ß and IL-6 levels were higher in CC and waterpipe smokers than E(N)NDS users and never smokers	Mokeem et al. (2018)
Oral and gut microbiota profiles (rRNA sequencing in buccal, saliva, and faecal samples)	CC smoking, E(N)NDS use	CC smokers (n=10), E(N)NDS users (n=10), non-smoking controls (n=10); (USA, UK)	Bacterial profiles were significantly different in all sample types from CC smokers compared with controls; Bacterial profiles were significantly different in buccal and faecal samples from CC smokers compared with E(N)NDS users; No significant differences were found between E(N)NDS users and controls.	CC smoking is associated with significant differences in the oral and gut microbiome in humans. Validation in larger cohorts and greater understanding of the short and long-term impact of E(N)NDS use on microbiota composition and function is warranted.	Stewart et al. (2018)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Gene expression in oral epithelium (RNA sequencing analysis)	CC smoking, E(N)NDS use	CC smokers, E(N)NDS users (no further details); (USA)	Significant number of aberrantly expressed transcripts in both E(N)NDS users and CC smokers relative to non-smokers. Deregulated transcripts in smokers were predominately from protein-coding genes in CC smokers, but showed more aberrantly expressed transcripts in regulatory non-coding RNAs in E(N)NDS users. In molecular pathway and functional network analyses, 'cancer' was the top disease associated with the deregulated genes in both E(N)NDS users and CC smokers.	Deregulation of critically important genes and associated molecular pathways in the oral epithelium of E(N)NDS users was observed, which both resembles and shows differences with that of CC smokers. These findings have significant implications for public health and tobacco regulatory science	Tommasi et al. (2019)
Respiratory					
E(N)NDS use, CC smoking habits, respiratory symptoms (postal questionnaire)	CC smoking (current and former), E(N)NDS use, dual use combinations	Cross-sectional study of randomly selected participants from the 'Obstructive Lung Disease in Northern Sweden'(OLIN) study and 'West Sweden Asthma Study' (WSAS); n=30,272 participants aged 20–75 y; Sweden	CC smokers (n=3694 current, n=7305 former), E(N)NDS users (n=529); dual current CC smoker/E(N)NDS user (n=350), dual former CC smoker/E(N)NDS user (n=79), non-CC-smoker/E(N)NDS user (n=96); All respiratory symptoms were most common among dual users and former smokers and non-smokers who used E(N)NDS	Use of E(N)NDS was most common among CC smokers; Dual users had the highest prevalence of respiratory symptoms; On a population level, this study indicates that the present use of E(N)NDS does not adequately serve as a smoking cessation tool	Hedman et al. (2018)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Wheezing and related respiratory symptoms	CC smoking, E(N)NDS use, dual use	Population Assessment of Tobacco and Health (PATH) study, wave 2 (October 2014 – October 2015); n=28,171 (USA)	E(N)NDS users only (n=641), CC smokers only (n=8525), dual users (n=1106), non-users (n=17,899); Coughing and wheezing: adjusted odds ratio (AOR)=1.67 (95% CI 1.23–2.15) for current E(N)NDS users compared with non-users; AOR=0.68 (95% CI 0.53–0.87) for current E(N)NDS users compared with current CC smokers; AOR=1.06 (95% CI 0.91–1.24) for dual users compared with current smokers.	E(N)NDS use was associated with increased risk of wheezing and related respiratory symptoms. Current E(N)NDS users had lower risk in wheezing and related respiratory symptoms than current smokers or dual users but higher than non-users. Both dual use and smoking significantly increased the risk of wheezing and related respiratory symptoms.	Li et al. (2019)
Lung function and fraction exhaled nitric oxide (FeNO)	E(N)NDS use in non-CC smokers	Young, healthy male adults who were not current or former tobacco users; Daily E(N)NDS users (n=30), not E(N)NDS users (n=30); (Saudi Arabia)	Forced expiratory volume in the first second (FEV 1), forced expiratory ratio (FEV 1/FVC), forced expiratory flow (FEF) 25%, FEF 50%, FEF 75%, FEF 25%-75%, and FEF 75%-85% were significantly decreased in E(N)NDS users compared with non-users; FeNO was lower in E(N)NDS users than non-users but the difference was not statistically significant	The use of e-cigarettes significantly impaired various lung function parameters and the pattern of impairment exhibited a peripheral obstructive airway involvement. These findings have a general message for the global health community on the potential harm of E(N)NDS on lung function	Meo et al. (2019)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Diagnosis of respiratory disorder (random-dial telephone survey)	E(N)NDS use	Behavioral Risk Factor Surveillance Survey (BRFSS); n=8087, mean age 55 y; Hawaii USA	In the whole sample, E(N)NDS use was associated with chronic pulmonary disorder (AOR=2.58, CI 1.36–4.89, P<0.01); In non-smokers, E(N)NDS use was associated with asthma (AOR=1.33, CI 1.00–1.77, p<0.05).	A significant independent association of E(N)NDS use with chronic respiratory disorder was observed; several aspects of the data indicated that this was not because E(N)NDS were being used for smoking cessation by persons with existing respiratory disorder	Wills et al. (2019)
Cardiovascular disease (CVD)					
Myocardial infarction (MI)	CC smoking, E(N)NDS use (never, former, some days, daily)	National Health Interview Surveys 2014 (n=36,697) and 2016 (n=33,028); (USA)	For MI: OR=1.79 (95% CI 1.20–2.66, p=0.004) for daily E(N)NDS use; OR = 2.72 (95% CI 2.29–3.24, p<0.001) for daily CC use; p=0.608 for former E(N)NDS use; p=0.392 for some-day E(N)NDS use; OR=1.70, p<0.001 for former CC smoking; OR=2.36, p<0.001 for some-day CC smoking	Daily E(N)NDS use, adjusted for smoking CC as well as other risk factors, is associated with increased risk of MI	Alzahrani et al. (2018)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Cardiovascular disease (self-reported coronary heart disease, MI, or stroke)	E(N)NDS use (daily or occasional) in current and never CC smokers	Behavioral Risk Factor Surveillance Survey (BRFSS), 2016 and 2017 pooled data; n=449,092; USA	Current E(N)NDS users (n=15,863), dual E(N)NDS users/CC smokers (n=12,908), participants with CVD (n=44,852); For CVD: no association with E(N)NDS use in never-CC smokers; OR=1.36 (95% CI 1.18–1.56) for dual CC smoker/E(N)NDS users compared with CC smokers who didn't use E(N)NDS; subgroup analysis showed a consistent results of premature CVD in women <65 y and men <55 y	The results suggest a significantly higher odds ratio of CVD among dual users of E(N)NDS and CC compared with smoking CC alone. These data, although preliminary, support the critical need to conduct longitudinal studies exploring CVD risk associated with E(N)NDS use, particularly among dual users	Osei et al. (2019)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Cardiopulmonary symptoms (19 symptoms/ conditions)	CC smoking, E(N)NDS use, dual use	Health eHeart Study; n=39,747 English-speaking adults; mostly USA	E(N)NDS-only (n=573), CC-only (n=1693), dual use (n=514) (dual users consumed more CC per day and had lower overall health scores); History of arrhythmia was significantly different between CC-only users (14.2%) and dual users (17.8%) (p=0.02); E(N)NDS-only use was associated with generally lower health scores, higher breathing difficulty scores and higher rate of 'yes' response to having chest pain, palpitations, coronary heart disease, arrhythmia, chronic obstructive pulmonary disease (COPD), and asthma	These data suggest the added use of E(N)NDS alone may have contributed to cardiopulmonary health risks, particularly respiratory health risk	Wang et al. (2018)
Neurological					
Symptoms of E(N)NDS dependence	Exclusive E(N)NDS use, dual E(N)NDS/ CC use	Cross-sectional study within the Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS) Wave 4; n = 2891 /N = 461,069; Texas, USA	Symptoms of dependence were experienced by exclusive E(N)NDS users and dual E(N)NDS/CC users, with prevalence of symptoms higher for dual users; users reporting dependence were less likely to want to or attempt to quit within the previous 12 months	Adolescent E(N)NDS users are experiencing symptoms of dependence specific to E(N)NDS. In addition, symptoms of dependence may be barriers to E(N)NDS cessation. Future research is needed to determine if characteristics of E(N)NDS use (e.g. frequency and intensity) are associated with dependence	Case et al. (2018)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Depressive symptoms and suicidality (adolescents)	E (N)NDS use, dual use of E(N)NDS and marijuana	Adolescents in the Youth Risk Behavior Survey, 2015 and 2017 – participants with complete data for age, sex, race/ethnicity, and exposure to E(N)NDS and marijuana (89.5% of survey respondents); n=26,821; (USA)	E(N)NDS-only use (9.1%), marijuana-only use (9.7%), dual E(N)NDS/ marijuana use (10.2%); Multivariate logistic regression for association of single or dual use with suicidal ideation and depressive symptoms, Suicidal ideation: E(N)NDS-only (AOR=1.23, 95% CI 1.03–1.47), marijuana-only (AOR=1.25, 95% CI 1.04–1.50), dual use (AOR=1.28, 95% CI 1.06–1.54) Depressive symptoms: E(N)NDS only (AOR=1.37, 95% CI 1.19–1.57); marijuana-only (AOR=1.49, 95% CI 1.27–1.75), dual use (AOR=1.62, 95% CI 1.39–1.88)	Youths with single and dual E(N)NDS and marijuana use had increased odds of reporting depressive symptoms and suicidality compared with youth who denied use. There is a need for effective prevention and intervention strategies to help mitigate adverse mental health outcomes in this population.	Chadi et al. (2019)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Internalizing symptoms and vulnerabilities (adults)	E(N)NDS users, dual E(N)NDS and CC users (with and without a history of combustible tobacco use)	Not described in report abstract; (USA)	E(N)NDs-only users without combustible use histories reported significantly greater stress and anxiety symptoms than E(N)NDs-only users with combustible use histories; E(N)NDs-only users without combustible use histories reported greater anxiety and difficulty regulating their emotions than dual-users; Dual- and E(N)NDS-only users with prior combustible use histories did not differ in internalizing pathology or vulnerability presentations.	This suggests that pathology and vulnerability presentation among nicotine users are influenced by both current and past nicotine use history	Versella et al. (2019)
General					
Patterns of E(N)NDS use, health outcomes (self-reported)	Use of E(N)NDS (overall product), ENDS (containing nicotine), or CC	National survey data from 2013–2014; n=not stated in publication abstract; USA	'Relative risk ratio' (RRR)=0.66 for 'good mental health' in E(N)NDS users compared with non-users; RRR=1.87 for 'poor mental health' for use of ENDS (containing nicotine). Further associations were also described, but it was difficult to make an assessment of the information as presented in the abstract of the report.	Health practitioners should evaluate the benefits and harms of using E(N)NDS and the effects on human health.	Chang et al. (2019)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Long-term E(N)NDS-use effectiveness (4-y tobacco abstinence, number of CC per day) and safety (potentially smoking-related diseases)	CC smoking, E(N)NDS use, dual use	Observational study – comparison of tobacco smokers and E(N)NDS users at 4-year follow-up; adults 30–75 y: E(N)NDS users (ex-tobacco smokers) (n=228), tobacco smokers (n=471), dual users; (Italy)	Abstinence from tobacco: E(N)NDS users (63.3%), dual users (33.8%), tobacco smokers (26.8%); Abstinence from all products: dual users (20.2%), tobacco smokers (19.4%); Around 40% of participants switched product at least once	After four years, a scarce, non-significant harm reduction was observed among E(N)NDS or dual users. Given the long-lasting health effects of tobacco smoking, the benefits of E(N)NDS use may start being detectable at the next follow-up (six years). The complete switch to E(N)NDS may help tobacco quitters remain abstinent, but E(N)NDS use in addition to tobacco did not increase the likelihood of smoking cessation or reduction.	Flacco et al. (2019)
Adverse symptoms, including cough, dry or irritated mouth or throat, dizziness or light-headedness, headache or migraine, shortness of breath, change in or loss of taste, others (most commonly nausea, tight chest, congestion)	E(N)NDS use, CC smoking	Cross-sectional telephone survey, August 2016 – May 2017; n=4964 adults aged 18 y and over; USA	E(N)NDS ever use (n=1624), of which current CC smokers (40.3%), former CC smokers (30.7%), never smokers (29.0%); At least 1 symptom reported by 58.2% of E(N)NDS ever-users, average rate = 1.6 symptoms; Among past-30-day E(N)NDS users, current and never CC smokers were more likely than former smokers to report any symptoms (AOR=5.25, CI 2.05–13.46 and AOR=2.58, CI 0.85–7.81, respectively).	A majority of E(N)NDS users reported at least one symptom, most commonly cough or dry or irritated mouth or throat. Former CC smokers who used E(N)NDS in the past 30 days were less likely than current or never smokers to report adverse symptoms of E(N)NDS use. Future research should examine frequency of symptoms among different user groups to understand how E(N)NDS may influence public health.	King et al. (2019)

Endpoint(s) reported	Exposure assessed	Study / cohort[1]	Results	Author conclusions	Reference
Effectiveness (CC cessation) and safety (self-reported adverse events and withdrawal symptoms) over a 6-month period of use	E(N)NDS use, dual E(N)NDS and CC use	June – November, 2015; n=218 sole E(N)NDS users and dual E(N)NDS/ CC users; Malaysia	Quitting rates: quit both CC and E(N)NDS (3.3%), quit CC (20.5%); quitting rates were higher in E(N)NDS-only users than dual users; No severe health issues were reported over the entire study period.	Quitting rates were higher in sole E(N)NDS users than in dual users. No serious health effects were reported over 6 months in either group. E(N)NDS may serve as a smoking cessation aid in Malaysia, but appropriate regulations are necessary to encourage sole E(N)NDS use to ensure product quality. Large randomised clinical trials (RCTs) with a longer follow-up are required to better measure the effectiveness and safety of E(N)NDS use alone and in combination with CCs.	Mohamed et al. (2018)
Body weight changes (by review of medical records over time)	Regular E(N)NDS use or CC smoking	E(N)NDS users (n=86, of whom approximately 50% also used CC), CC smokers (n=93), 'quitters' (n=44) followed over 12 months; (Italy)	Gain in weight from baseline to 12 months: quitters (4.8%), E(N)NDS users (1.5%), dual users (no weight gain)	By reducing weight gain and tobacco consumption, E(N)NDS-based interventions may promote an overall improvement in quality of life.	Russo et al. (2018)

[1] **Location**: not in brackets – refers to study population; in brackets – refers to author address(es) in cases where publication abstracts did not mention the study location.

Abbreviations used in the table: AOR – adjusted odds ratio, BOP – bleeding on probing, CAL – clinical attachment loss, CS – cigarette smoker, CVD – cardiovascular disease, COPD – chronic obstructive pulmonary disease, FEF – forced expiratory flow, FEV 1 – forced expiratory volume in 1 second, FVC – forced vital capacity, GCF – gingival crevicular fluid, MBL – marginal bone loss, MI – myocardial infarction, NS – non-smoker, OLIN – Disease in Northern Sweden (study), OML – oral mucosal lesion, PATH – Population Assessment of Tobacco and Health (study), PD – probing depth, PI – plaque index, POR – prevalence odds ratio, RBL – radiographic bone loss, TATAMS – Texas Adolescent Tobacco and Marketing Surveillance System, WS – waterpipe smoker, WSAS – West Sweden Asthma Study

Animal data

66. The 15 publications reporting studies using animal models addressed adverse effects on the respiratory, neurological and cardiovascular systems, reproductive and developmental toxicity, and effects on the liver and on wound healing.

Respiratory effects

67. A study reported by Khan et al. (2019) found that whole-body exposure of mice to ENDS aerosol (PG + nicotine) for 2 h/day over 3 days was associated with altered expression of some circadian clock genes and proteins in lung tissue, compared with exposure to ambient air or ENNDS without nicotine (PG). Alterations were also noted with exposures to waterpipe tobacco smoke, but these were different to those seen with exposure to PG + nicotine.

68. Khosravi, Lin and Lee (2018) investigated effects of acute exposure to E(N)NDS aerosol in anaesthetized guinea pigs. After exposure to 1 puff of aerosol containing nicotine, a transient bronchoconstriction response was observed, which was considered to have been elicited by cholinergic reflex mechanism. The effect was blocked by pre-treatment with nicotine acetylcholine receptor (nAChR) antagonist and did not occur on exposure to aerosol without nicotine, leading the authors to conclude that it was mediated by nicotine.

69. Glynos et al. (2018) compared effects of exposure to E(N)NDS aerosols (PG + glycerol; PG + glycerol + nicotine; PG + glycerol + nicotine + flavour) and CC smoke on respiratory system mechanics, oxidative stress, and inflammatory response in mice. Exposure to E(N)NDS aerosols for 3 days or 4 weeks increased bronchoalveolar lavage fluid (BALF) cellularity, Muc5ac production, and BALF and lung oxidative stress markers to a comparable or greater degree than CC smoke. The effects were particularly notable after exposure to the aerosol containing PG + glycerol + nicotine + flavour, and this was the only treatment that was associated with increased BALF protein. Tissue elasticity, static compliance, and airway resistance were altered after 3-day exposure to aerosol containing PG + glycerol, while after 4 weeks these parameters were only affected by CC smoke. Airway hyper-responsiveness in response to methacholine was increased similarly in the CC smoke and PG + glycerol + nicotine + flavour groups. Authors concluded that exposure to E(N)NDS aerosol can trigger inflammatory responses and adversely affect respiratory system mechanics, and that the inclusion of flavouring can exacerbate the adverse effects (Glynos et al. 2018).

Cardiovascular effects

70. A study reported by Qasim et al. (2018) indicated that whole body exposure of mice to E(N)NDS aerosol (no further information available) was associated with enhanced platelet function and shortened thrombosis occlusion and bleeding times, leading the authors to conclude that E(N)NDS exposure may lead to increased risk of thrombogenic events. In another study, whole body exposure to ENDS aerosol

(50:50 PG:glycerol + 24 mg/mL nicotine) showed that exposure of mice, 3 h/day for 14 days, did not alter cardiac contractile function, but was associated with increased angiogenesis in heart tissue (Shi et al. 2019).

Neurological effects

71. One study reported effects of inhalation exposure to ENDS (PG + nicotine) on spontaneous locomotion and thermoregulation in male rats. The effects were blocked by pre-treatment with a nicotinic antagonist (Javadi-Paydar et al. 2019).

72. Cardenia et al. (2018) reported that exposure to E(N)NDS formulations for 4–8 weeks altered brain lipid profile in rats. The route of exposure was probably by inhalation, although this is not clear from the publication abstract. Constituents of E(N)NDS liquids tested were not described in the abstract.

73. Harris and colleagues reported 2 studies in rats that evaluated effects of parenteral administration of E(N)NDS liquids on intracranial self-stimulation (ICSS) (taken as a measure of anhedonia-like behaviour). PG (25% or 60%) was found to attenuate nicotine reinforcement-enhancing effects on ICSS at high nicotine dose, but not at moderate or low doses. Low concentrations of PG (1% or 3%) had a moderate effect on attenuating reinforcement-enhancing effects of high-dose nicotine (Harris et al. 2018a). A follow-on study suggested that non-nicotine components of E(N)NDS liquids did not contribute to nicotine-associated reinforcement-enhancing behaviour, but confirmed that these components may attenuate such effects, which the authors considered to suggest may play a role in moderating abuse liability and/or toxicity of E(N)NDS (Harris et al. 2018b).

Reproductive/developmental effects

74. Two studies reported effects of E(N)NDS exposure on testicular function, considered to be mediated through an inflammatory mechanism. In a study reported by Rahali et al. (2018), injection of E(N)NDS liquid (with or without nicotine) into rat testis led to reduced sperm vitality, increased abnormal sperm morphology, and alteration of redox status. A study reported by Vivarelli et al. (2019) indicated that exposure of rats to ENNDS aerosol (no nicotine) produced at low voltage was associated with reduced testis weight, increased levels of lactate dehydrogenase (tissue damage), and alterations in enzymes involved in steroidogenesis. Authors considered that these findings indicated that use of E(N)NDS, even on ‘weak’ settings, may lead to altered gonad function in male E(N)NDS users.

75. Orzabal et al. (2019) reported that chronic exposure to E(N)NDS aerosol during development causes vascular dysfunction and offspring growth deficits. In this study, rat dams were exposed either during the prenatal period only or during the prenatal and early postnatal periods to E(N)NDS aerosols, either with or without nicotine. Exposure to nicotine-containing aerosols was associated with decreased fetal weight at postnatal day (PND) 4–10 and decreased crown-rump length on PND 10, and with reduced maternal uterine and fetal umbilical blood flow.

Biomonitoring

76. Conklin et al. (2018) reported that levels of urinary metabolites of formaldehyde, acetaldehyde, acrolein, and crotonaldehyde in mice exposed to E(N)NDS aerosol were dependent on E(N)NDS liquid PG:glycerol ratio and the presence of flavourings. Metabolites of formate, acetate, and acrolein were increased in urine after E(N)NDS aerosol or CC smoke exposure, but the crotonaldehyde metabolite was increased only after CC smoke exposure. Exposure to menthol-flavour E(N)NDS aerosol increased the levels of urinary 3-HPMA (acrolein metabolite) and summed nicotine exposure (nicotine + cotinine + trans-3'-hydroxycotinine) relative to exposure to a tobacco flavour.

Other

77. In a study to examine adverse effects of ENDS on liver, apolipoprotein E-null (ApoE-/-) mice on a western diet (WD) were exposed to saline (control) or ENDS with 2.4% nicotine aerosol for 12 weeks. The nicotine-delivery was considered to be equivalent to human CC use. Compared with controls, mice exposed to ENDS had a marked increase in hepatic lipid accumulation, associated with increased oxidative stress, hepatic triglyceride levels, and hepatocyte apoptosis, independent of adenosine monophosphate-activated protein kinase signalling. Hepatic RNA sequencing analysis indicated 433 genes that were differentially expressed in ENDS-exposed compared with saline-exposed mice. Functional analysis indicated that genes associated with lipid metabolism, cholesterol biosynthesis, and circadian rhythm were the most significantly altered in the liver in response to ENDS. Authors concluded that these results demonstrated profound adverse effects of ENDS on the liver (Hasan et al. 2019).

78. A study by Troiano, Jaleel and Spiegel (2019) indicated that exposure to ENDS aerosol or smoking CC are equally detrimental to wound healing. Rats were randomised to 1 of 3 groups: negative control, experimental (exposed to ENDS aerosol), or positive control (exposed to CC smoke). Rats in the ENDS and positive control groups were exposed to ENDS aerosol or CC smoke in a smoking chamber for 30 min, twice per day, for 30 consecutive days. Serum cotinine levels were maintained between 150 ng/mL and 200 ng/mL. After 30 days, random pattern dorsal skin flaps were raised and the percentage flap necrosis per group was measured. The highest rate of flap necrosis was present in the positive control group (mean (SD), 68.7% (8.6%)), followed by the ENDS group (65.9% (11.8%)). The rate in the negative control group was 50.8% (9.4%), which was significantly lower than ENDS or positive control. No statistically significant difference in flap necrosis was noted between the rats in the ENDS and positive control groups.

Summary

79. Literature relating to potential health effects of E(N)NDS exposure was updated from 06/04/2018 to 05/06/2019 through searches of the Scopus and PubMed databases. A total of 891 publications were identified from the searches, of

which 133 were considered to be of relevance and had not been included in previous COT discussion papers on E(N)NDS. The findings reported in these 133 publications were summarised using the information contained in the abstracts.

Constituents and user exposure

80. New publications add further information to the database on constituents present in E(N)NDS liquids and aerosols, the transfer of constituents from liquid to aerosol during puffing, and the potential for formation of degradation products during this process. Additional data on biomonitoring in human E(N)NDS users were also published. These aspects have been covered in previous COT discussion papers, TOX/2017/49, TOX/2018/15, TOX/2018/16, TOX/2018/20, and TOX/2019/39.

Bystander exposure

81. New studies add to the existing database on potential exposure of bystanders to E(N)NDS constituents exhaled by users, which was addressed in the previous COT discussion paper, TOX/2019/11. The report of Visser et al. (2019), which described exposure scenario calculations based on exhaled-breath measurements, concluded that levels of exhaled PG and glycerol would be sufficient to lead to respiratory tract irritation in bystanders, while nicotine levels could be sufficient to cause systemic effects including palpitations and increased systolic blood pressure. An epidemiological study that analysed data from the 2016 Florida Youth Tobacco Survey found an association between second-hand exposure to E(N)NDS aerosol and increased odds of asthma attack during the previous 12 months in young people aged 11–17 y (Bayly et al. 2019).

Human health effects

82. There were further clinical case reports of adverse effects potentially associated with exposure to E(N)NDS aerosols, adding to the database of case reports described in the previous COT discussion papers, TOX/2018/24 and TOX/2019/01. The new reports mostly relate to effects on the respiratory system. There were also further reports of poisonings due to exposure to E(N)NDS liquids, many of which relate to accidental ingestion of nicotine-containing liquids by young children. This adds to the existing database of cases, which was overviewed in COT discussion paper, TOX/2019/38.

83. Several new clinical studies were reported. These studies assessed effects of exposures to E(N)NDS aerosols on endpoints including effects on the respiratory system, vascular function and oxidative stress, neurobehavioral aspects relating to desire for and/or satisfaction from product use, nicotine delivery and kinetics, and potential adverse clinical symptoms associated with product use.

- Brozek et al. (2019) reported that acute exposure to aerosol containing nicotine and flavourings led to decreased FeNO and indices of airflow. A study reported by Antoniewicz et al. (2019) showed that exposure to

ENDS aerosol containing 12 mg/mL nicotine (no flavourings) led to effects of airway obstruction, while these effects were not observed in the absence of nicotine. Conversely, another study, in which a 4th generation product was used at high power setting, showed effects of airway epithelial injury associated with exposure to E(N)NDS aerosols both without or with 3 mg/mL nicotine (no flavourings) (Chaumont et al. 2019). Two longer-term clinical studies showed either no effect or favourable effect of use of E(N)NDS on lung function in subjects randomised to use these products as an aid to CC smoking reduction or cessation (Lee et al. 2018b, Veldheer et al. 2019). Clinical studies that evaluated effects of E(N)NDS aerosols on the respiratory system published prior to this update were reviewed in TOX/2018/24.

- Clinical studies focussing on cardiovascular endpoints generally added weight to the concept that nicotine exposure from ENDS can adversely affect parameters of vascular function and oxidative stress. Some studies that compared exposures with and without nicotine showed that effects were limited to nicotine-containing products. Antoniewicz et al. (2019) reported that exposure to aerosol containing nicotine, but not aerosol without nicotine, caused a significant increase in heart rate and arterial stiffness, but blood pressure was increased by exposure to aerosols both with or without nicotine. A study reported by Chatterjee et al. (2019) observed adverse effects of oxidative stress and endothelial dysfunction in 'smoking naïve' subjects exposed to ENNDS aerosols without nicotine (Chatterjee et al. 2019). Clinical studies that evaluated effects of E(N)NDS aerosols on the cardiovascular system published prior to this update were reviewed in TOX/2018/24.

84. A substantial body of new literature was available reporting outcomes of epidemiological studies of potential health effects associated with exposure to E(N)NDS products. The largest part of the literature set reported effects on oral/periodontal health, and overall these reports suggested that E(N)NDS use is associated with adverse effects on oral health, but to a lesser extent than CC smoking. A study reported by Li et al. (2019) showed that E(N)NDS use was associated with wheezing and respiratory symptoms to a greater extent than no use of tobacco products, but to a lesser extent than CC smoking or dual product use. Additionally, 2 studies observed an association of E(N)NDS use with respiratory disorders in non-CC smokers (Meo et al. 2019, Wills et al. 2019). A small number of studies indicated possible contribution of E(N)NDS use to cardiovascular disease (Alzahrani et al. 2018, Wang et al. 2018, Osei et al. 2019). Some data indicated a negative effects of E(N)NDS on neurobehavioral endpoints such as anxiety and depression (Chadi et al. 2019, Versella et al. 2019). Epidemiological studies of E(N)NDS exposures published prior to this update were reviewed in TOX/2018/24.

Experimental studies in animals

85. Studies in animal models showed various effects of E(N)NDS exposures on the respiratory, cardiovascular, neurological, and reproductive/developmental systems. Different aerosol mixture formulations were tested, both with or without nicotine. In some cases, adverse effects were reported associated with the presence of nicotine in the test product but not when the same product was tested without nicotine (Khosravi et al. 2018, Khan et al. 2019 – respiratory effects; Orzbala et al. 2019 – effects on reproduction/development). Two studies reported adverse effects of ENNDS products (not containing nicotine), on respiratory inflammation (Glynos et al. 2018) and testicular function (Vivarelli et al. 2019). However, a number of the studies reported had only tested aerosol mixtures containing nicotine, and in some cases, it was not possible to determine details of the formulations tested from publication abstracts. Previous COT discussion papers that have summarised data from experimental studies of E(N)NDS aerosol exposures in animal models include TOX/2018/24 and TOX/2018/46. Studies relating to individual E(N)NDS constituents were reported in TOX/2018/19 and TOX/2018/23 (glycerol and propylene glycol), and TOX/2018/45, TOX/2019/01 and TOX/2019/38 (nicotine).

Questions for the Committee

i. Are any of the publications highlighted likely to provide important new information of relevance to the Committee's evaluation of the potential health effects of E(N)NDS?

ii. Given that the summaries in this update are based on information provided in publication abstracts, do Members wish to be presented with more detail from the full text of any of the citations included?

iii. Should any of these new data be included in the COT statement on E(N)NDS?

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
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Abbreviations

BALF	Bronchoalveolar lavage fluid
CC	Conventional cigarette
CI	Confidence interval
DHA	Dihydroxyacetone
E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ENDS	Electronic nicotine delivery system
ENNDS	Electronic non-nicotine delivery system
EU	European Union
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
fMRI	Functional magnetic resonance imaging
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HNB	Heat not burn
HPHC	Harmful and potentially harmful compounds
ICSS	Intracranial self-stimulation
IQR	Interquartile range
LOD	Limit of detection
MS	Member State
nAChR	Nicotinic acetylcholine receptor
NMR	Nicotine metabolite ratio
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NRT	Nicotine replacement therapy
OR	Odds ratio
PG	Propylene glycol
PNC	Particle number concentration
PND	Post-natal day
rsFC	Resting state functional brain connectivity
SC	Synthetic cannabinoid
SEM/EDS	Scanning electron microscopy coupled with energy dispersive X-ray spectroscopy
SD	Standard deviation
SREC	Standardized research e-cigarette
TNE	Total nicotine equivalents
TPD	Tobacco product directive
TSNA	Tobacco-specific nitrosamine
UFP	Ultrafine particles
WD	Western diet

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Literature update to mid-2019.

Details of Literature search carried out by NCET at WRc/IEH-C

Searches performed on 05/06/2019

SCOPUS 2019

TITLE ("e-cig*" OR "electronic cigarette*" OR "electronic nicotine delivery system*") AND PUBYEAR > 2017 AND (LIMIT-TO (PUBYEAR , 2019)) AND (EXCLUDE (LANGUAGE , "French") OR EXCLUDE (LANGUAGE , "German") OR EXCLUDE (LANGUAGE , "Spanish")) AND (EXCLUDE (DOCTYPE , "re")): 320 refs

SCOPUS 06/04/2018 to 31/12/2018

TITLE ("e-cig*" OR "electronic cigarette*" OR "electronic nicotine delivery system*") AND PUBYEAR > 2017 AND (PUBDATETXT (april 2018) OR PUBDATETXT (may 2018) OR PUBDATETXT (june 2018) OR PUBDATETXT (july 2018) OR PUBDATETXT (august 2018) OR PUBDATETXT (september 2018) OR PUBDATETXT (october 2018) OR PUBDATETXT (november 2018) OR PUBDATETXT (december 2018)) AND (LIMIT-TO (PUBYEAR , 2018)) AND (EXCLUDE (LANGUAGE , "German") OR EXCLUDE (LANGUAGE , "Chinese") OR EXCLUDE (LANGUAGE , "French") OR EXCLUDE (LANGUAGE , "Italian") OR EXCLUDE (LANGUAGE , "Japanese") OR EXCLUDE (LANGUAGE , "Polish") OR EXCLUDE (LANGUAGE , "Swedish TITLE")) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "bk")): 398 refs

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((((((e-cig* [Title] OR "electronic cigarette*" [Title] OR "electronic nicotine delivery system*"[Title])) AND ("2018/04/06"[PDat] : "2019/12/31"[PDat]))) AND english[Language])) AND (((((("comparative study"[Publication Type]) OR "clinical study"[Publication Type]) OR "comparative study"[Publication Type]) OR "evaluation studies"[Publication Type]) OR "journal article"[Publication Type]) OR "technical report"[Publication Type]) AND ("2018/04/06"[PDat] : "2019/12/31"[PDat]: 607 refs.

Total combined = 891 refs.