TOX/2020/37

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

‘E-cigarette, or vaping, product use – associated lung injury’ (EVALI): an overview

Background

1. During 2018 and 2019, the COT reviewed the potential toxicological risks from electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS). A draft statement reflecting the Committee’s discussions and conclusions on this topic is being finalised.

2. From mid-2019 onwards an outbreak of vaping-related respiratory illness was observed in the US. This was recognised as a new disease entity, designated ‘e-cigarette, or vaping, product use – associated lung injury’ (EVALI). The COT review of E(N)NDS did not address EVALI as it occurred outside the time-frame of that review process. This current paper provides the Committee with a summary of the EVALI outbreak, for awareness, within the context of the ongoing watching brief on potential E(N)NDS-relating toxicity.

3. This overview describes the timeline and demographics of the EVALI outbreak, clinical characteristics and case definition, investigations into potential aetiology and mechanisms of lung injury, and outstanding knowledge gaps.

4. Information presented in this paper is taken from sources including the US Centers for Disease Control and Prevention (CDC) and US Food & Drug Administration (FDA) websites, and scientific publications focussing on this topic. A full systematic search of the scientific literature was not undertaken.

Introduction

5. An outbreak of severe respiratory illness was signalled to the CDC in the summer of 2019. The first cluster was reported by Wisconsin Children’s Hospital on 1st August (Layden et al. 2020). Standard procedures for outbreak investigation by CDC excluded an infective aetiology and determined that the outbreak was likely to be of chemical origin. Cases often comprised young adults or adolescents (see paragraph 7) who reported recent use of E(N)NDS products (CDC 2020).

6. Subsequently, multiple clusters were reported across the US (CDC 2020). Hospital admissions and emergency department visits for EVALI increased sharply during August and peaked in early/mid-September 2019, followed by a steady

decline (Krishnasamy et al. 2020). Latest data listed on the CDC website indicate that, as of 18th February 2020, a total of 2807 hospitalised EVALI cases had been reported to CDC from 50 states plus the District of Columbia and two US territories (Puerto Rico and the US Virgin Islands). Of these cases, death had occurred in 68 of the patients. The median age of deceased patients was 49.5 years (range, 15-75 years) (CDC 2020).

7. As at 14th April 2020, the CDC website provided a detailed breakdown of data for hospitalised cases listed to 14th January 2020, as follows:

- 66% were male, median age 24 years (range, 13-85 years); 15% < 18 years; 37% 18-24 years; 24% 25-34 years; 24% ≥ 35 years (no comparison given to the profile of E(N)NDS users as a whole).

- 2022 hospitalised cases provided data on substance use during the previous 30 days: 82% had used tetrahydrocannabinol (THC)-containing products[1], with 33% reporting exclusive use of THC-containing products; 57% had used nicotine-containing products, with 14% reporting exclusive use of nicotine-containing products

- 50% of cases who reported using THC-containing products provided data on source: 16% acquired products only from commercial sources (recreational and/or medical dispensaries, vape or smoke shops, stores, pop-up shops); 78% acquired products only from informal sources (family/friends, dealers, online, other sources); 6% acquired products from both commercial and informal sources

- 54% of cases who reported using nicotine-containing products provided data on product source: 69% acquired products only from commercial sources; 17% acquired products only from informal sources; 15% acquired products from both commercial and informal sources (CDC 2020).

8. Very few cases of EVALI have been noted in countries other than the US. According to the Health Canada website, as of 11th March 2020, 19 cases had been reported to the Public Health Agency of Canada, with symptom onset between May 2019 and February 2020. Fifteen of these cases required admission to hospital. Products used were reported as nicotine only (n=11); THC only (n=4); flavoured e-liquid only (n=1); and nicotine, THC, and other substances (n=3). Nine patients bought products in Canada, two online, and for the others the source was unknown (Health-Canada 2020).

9. Three published reports of EVALI cases in Europe were identified. One of these reports related to an individual who was resident in the US and developed EVALI while on vacation in Barcelona, Spain, in September 2019 (Casanova et al.

[1] The sale of THC-containing products is legally permitted in some but not all of the US states in which cases were reported

2019). A case in Belgium related to an 18-year-old male tobacco smoker and cannabis user who died four weeks after admission to hospital with a diagnosis of EVALI[2]. The patient had used an E(N)NDS product containing nicotine and cannabidiol (CBD) during the three weeks prior to admission, with an e-liquid of unknown country-of-origin purchased over the counter in a shop in Belgium (Marliere et al. 2020). In Toulouse, France, a 28-year-old female heavy conventional cigarette (CC) smoker admitted to hospital[3] with a diagnosis of EVALI had used a nicotine-containing E(N)NDS[4] product for two days, one month prior to admission. The patient had not used CBD or THC, and had not travelled outside France (Villeneuve et al. 2020).

10. Discussion paper TOX/2018/24, which was considered by the COT at the July 2018 meeting, summarised publications reporting a handful of cases of vaping-associated lung disease between 2012 and 2018 worldwide, with various clinical characteristics and patient backgrounds. Individual case details are summarised in Table 1 of TOX/2018/24.

Clinical characteristics and case definition

11. Common signs and symptoms exhibited by EVALI patients are related to respiratory system (breathing difficulty, shortness of breath and/or chest pain), gastrointestinal system (nausea, vomiting, abdominal pain), and constitutional (fever, fatigue, weight-loss). Onset of symptoms can occur within hours up to weeks after product exposure. EVALI has been recognised by the CDC as a new clinical syndrome and a case definition established as follows: history of E(N)NDS use within 90 days prior to symptoms of respiratory failure + pulmonary opacities on chest radiograph or ground-glass opacities on chest computerised tomography (CT) scan + negative for infection + exclusion of other possible causes of respiratory failure (CDC 2019, Siegel et al. 2019). Imaging patterns indicate a pattern of acute lung injury on the spectrum of organising pneumonia and diffuse alveolar damage, with other less common forms including acute eosinophilic pneumonia and diffuse alveolar haemorrhage. Imaging characteristics suggest that inflammation plays a large role in EVALI. Other radiographic presentations include pleural effusions, pneumomediastinum and pneumothoraces (*summarised in* (Winnicka and Shenoy 2020). Up to one-third of patients may require intubation and mechanical ventilation (Layden et al. 2020). Treatment for EVALI includes systemic glucocorticoids, supportive care, and advice to cease use of E(N)NDS products (Crotty Alexander et al. 2020, Winnicka and Shenoy 2020).

[2] The report does not state when this case occurred, but information obtained from an internet search suggested that an 18-year-old patient in Belgium died of vaping-related disease in early November 2019.
[3] The report does not give an indication of when this case occurred.
[4] 10 mL e-liquid with 12 mg/mL nicotine salt. Analysis of e-liquid sample by GC-MS indicated presence of glycerol, nicotine, propane-1,2-diol (PG), ethyl maltol, and ethyl lactate – consistent with information subsequently obtained from the manufacturer.

Analytical evaluation of the E(N)NDS products used

12. Data collected on product-brands used by EVALI cases indicated a large number of different product names. Many cases had used products marketed under a label used generally to sell THC-containing products, many of which are counterfeit[5] (Navon et al. 2019).

13. The US Food & Drug Administration (FDA) collected around 1300 product samples (E(N)NDS devices and products containing e-liquids, packaging and other documentation), 1090 of which were associated with EVALI cases (FDA 2020). As at 12th February 2020, FDA had conduced forensic analysis of 843 EVALI case-associated product samples. The FDA website notes that samples were analysed for the presence of a broad range of chemicals including nicotine, THC and other cannabinoids, cutting agents/diluents and other additives, pesticides, opioids, poisons, heavy metals and toxins. Nicotine-containing products were tested for the presence of propylene glycol (PG), glycerol and flavourings. In many cases, analyses were prioritised for high-suspect chemicals due to limited sample volume available for testing, in addition to which samples were often of a very thick, oily consistency.

14. No specific chemical was found to be commonly present in all samples. A total of 511 samples were determined to contain THC. Fifty percent of these also contained vitamin E acetate (VEA) as a diluent (concentration ranging from 23%-88%) and 29% contained other diluents, for example medium chain triglycerides (MCTs)[6]. Some products contained both VEA and MCT oil. Analysis of nicotine-containing products indicated findings consistent with the expected product components (FDA 2020).

15. Some work has also been carried out to link product-sample analyses with patient case numbers. As at 12th February 2020, 93 EVALI case-associated samples had been analysed. Of these, 73% contained THC, 81% included VEA as diluent, 32% contained aliphatic esters (for example, triglycerides), and 9% contained polyethylene glycol (PEG) as diluent (FDA 2020).

Bioanalytical evaluations of specimens from EVALI patients

16. The CDC carried out analytical studies of bronchoalveolar lavage (BAL) fluids obtained from 51 patients from across the US who had been diagnosed with EVALI (n=25 confirmed diagnosis; n=26 probable diagnosis) (Blount et al. 2020). The results were compared with a control group of BAL samples that had been obtained from 99 healthy young adults who were participants in an ongoing study of tobacco

[5] Empty, ready-to-fill product boxes and cartridges can be purchased online

[6] VEA is a synthetic form of vitamin E added to various products including supplements, cosmetics, and dietary products. MCTs are found in food oils, such as coconut or palm kernal oils. These products are in some cases marketed as diluents for THC use with E(N)NDS devices (see https://www.fda.gov/news-events/public-health-focus/lung-injuries-associated-use-vaping-products (accessed 20/04/2020).

product use (52 non-users of tobacco products; 18 exclusive E(N)NDS users; 29 exclusive CC smokers). BAL fluids were analysed using isotope dilution mass spectrometry for priority toxicants including VEA, plant oils, MCT oil, coconut oil, petroleum distillates, and diluent terpenes.

17. VEA was identified in BAL samples of 48/51 EVALI cases and 0/99 controls. Coconut oil was identified in 1/48 (VEA-positive) EVALI and 0/63 control samples analysed. Limonene[7] was identified in 1/39 (VEA-negative) and 0/97 control samples. All of the case and control samples tested were negative for MCT oil, plant oil, squalene, α-pinene, β-pinene, 3-carene, and petroleum distillates.

18. THC was identified in BAL fluid from 40/47 (85%) EVALI cases tested and 5.1% of controls[8]. Nicotine was identified in 30/47 (64%) EVALI samples tested and in 52% of controls.

19. Overall, the authors concluded that the data showed a strong link between the incidence of EVALI and the presence of VEA. Nevertheless, analysis of BAL fluid from three EVALI cases was negative for the presence of VEA. Regarding this point, the authors noted that EVALI is a diagnosis of exclusion, and case status could not be confirmed for these three samples. Two of the cases were interviewed by public health officials and reported not vaping THC during the previous 90 days. The patient for whom BAL fluid tested positive for limonene reported daily use of flavoured nicotine products. The authors also noted that BAL fluids had been collected in hospitals during case presentation/treatment and thus some samples may have been inadequate for use, as collection and storage procedures were not standardised (Blount et al. 2020).

Proposed cause of the outbreak and potential mechanism(s) of pathology

20. As described in the preceding paragraphs, a strong link has been identified between the development of EVALI and exposure to VEA, which is used as a diluent in THC-containing e-liquids. The potential role of VEA in causation of EVALI has not been fully established, but some preliminary theories have been postulated and some early experimental data are available.

21. CDC conducted a study to evaluate effects of exposure to inhaled VEA on BAL fluid and lung histology in mice. Groups of ten mice were whole-body exposed to aerosols of either VEA, PG/glycerol (50:50 v/v), or air, five hours per day, five

[7] Limonene is found in flavoured nicotine solutions.
[8] For THC and nicotine, results for control samples were reported as percentages in the narrative text, but numbers of samples tested were not indicated.

days per week for two weeks[9]. Exposure doses were calculated to be in the same range as those for a human E(N)NDS user consuming 0.52 to 1.13 mL per day vaping product containing 88% VEA. Analytical studies of aerosols (e.g. for thermal degradation products) were not performed. In the VEA group, BAL fluid analyses indicated delivery of VEA to the lungs. Markers of pulmonary injury, including increased levels of albumin in BAL fluid (indicating epithelial damage) and total leukocyte numbers, were significantly higher in VEA than PG/glycerol exposed mice (levels were also reported to be significantly higher in PG/glycerol exposed mice than in air controls). BAL fluid cells from VEA-exposed mice contained numerous lipid-laden macrophages, consistent with those seen during clinical evaluations in EVALI patients. Tissue sections of mouse lung showed alveolar macrophages with abundant oil red O-stained lipid, often in clusters, residing with pneumocytes lining the alveoli. In PG/glycerol-exposed mice, BAL cells contained fewer macrophages and tissue staining showed tiny oil red O-stained granules in the cytoplasm of cells lining the alveoli. Authors concluded that these findings, coupled with previous research identifying VEA in BAL fluid from EVALI patients and in samples of case-associated product liquids, provide additional evidence to support a possible role for VEA in the development of EVALI (Bhat et al. 2020).

22. A review article on radiological, pathologic, clinical, and physiologic findings in EVALI patients commented that although oil red O-positive lipid-laden macrophages in BAL fluid has been described in a number of cases, this is a non-specific finding that can be seen in various forms of lung injury. It is not known whether the lipid-laden macrophages seen in EVALI cases are filled with VEA or other lipid, and in addition if VEA or other lipids are acting as a toxin or are just markers of exposure. Histopathologic studies of human cases have suggested that the basis of EVALI is not simply lipid accumulation in the lung, and cases have not shown evidence of exogenous lipoid pneumonia (Kligerman et al. 2020).

23. Wu and O'Shea (2020) postulated that pyrolysis of VEA during use of E(N)NDS devices may lead to production of toxic ketene gas, via thermal activation of the aryl acetate group present. The authors noted that pyrolysis of the same functional group in phenyl acetate – the simplest aryl acetate – occurs at 625 ^{o}C. They obtained experimental evidence that ketene formation from VEA can occur, using atomic pressure chemical ionisation mass spectrometry (APCI-MS), density-functional theory (DFT) calculations, and trapping experiments of vaped product. However, they pointed out that their experiments were not designed to replicate a user's experience of vaping, but rather to determine the effect of pyrolysis on VEA,

[9] The exposure procedure was "Separate CE4 topcoil clearomizers with a 1.6 milliliter capacity polycarbonate tanks were refilled with each tested solvent and output voltage of 4.8 volts was used for all exposure conditions. Aerosols from each compound were generated using a puffing protocol intended to mimic vaping behavior of experienced nicotine vapers. Clusters of 10 puffs were taken every 15 seconds. A single puff had volume of 55 milliliter and was generated over 3 seconds. The interval between clusters was 7.5 minutes with 240 puffs per day. The time-weighted average concentrations of aerosol inside chambers during exposure to VEA and PG:VG were 322.1±2.0 and 302.1±15.7 mg/m^3, respectively. Control air exposures were also performed similarly without generation of any aerosol" (Bhat et al. 2020, supplementary appendix).

thus their findings could not be directly extrapolated to indicate a causal relationship with EVALI.

24. In an editorial commentary on the publication of Wu and O'Shea (2020), Strongin (2020) noted that ketene has been reported to cause severe, acute lung damage in animal models (species not defined) at the alveolar level within 24 hours of exposure, with a 10-min acute exposure guideline level (lethal) (AEGL-3) for ketene in air of 0.24 ppm. Strongin (2020) also emphasised that there has been a tendency to dismiss the findings from chemical/laboratory studies indicating the formation of reactive intermediates during vaping. For example, some commentators have asserted that reactive aldehyde breakdown products of PG and glycerol detected in laboratory vaping experiments would not lead to human exposure during use of E(N)NDS, due to avoidance of inhalation of the acrid product by the user. In addition, the author also suggested that in the absence of the ability to identify the instable ketene in human EVALI patient samples, 'biological footprints', for example post-translationally modified proteins and characteristic reaction products could be measured in its place.

25. Strongin (2020) also noted, however, that the formation of ketene has a very high activation energy (over 500 ^{o}C). Nevertheless, although such temperature would only be expected to occur during 'dry puffing'[10], it has been shown that E(N)NDS filament wires exhibit strong catalytic effects that modulate aerosol toxin formation at low temperatures[11] (Saliba et al. 2018, *cited in* Strongin, 2020). It has been speculated that this could be a mechanism by which ketene may be formed under normal E(N)NDS usage conditions (Narimani and Silva, 2020, *cited in* Strongin, 2020). Strongin (2020) also noted that as VEA is very viscous, more heat is required for aerosolization than with the use of PG/glycerol-based products. Indeed, this has been noted to sometimes lead to combustion of cotton wick materials during vaping of THC. In addition, vaping of illicit or counterfeit products is noted to be more often associated with the use of E(N)NDS devices of poor overall quality (e.g. products of uncertain production origin or that have been modified).

26. Lanzarotta et al. (2020) reported that VEA and THC are present as a hydrogen-bonded complex, linked by THC hydroxyl and VEA carbonyl groups, in the unvaped liquid mixture, aerosol, and aerosol condensate, as indicated by spectral analyses[12]. The authors noted that identification of the presence of such complex in aerosol indicates that it would likely be delivered to the lung and thus could, in theory, be implicated in lung injury.

27. In an editorial commentary on the publication of Blount et al. (2020), Gordon and Fine (2020) noted that although VEA and THC are the only chemicals that have

[10] Heating of the coil in the absence of an adequate supply of e-liquid.
[11] Typical temperatures attained during the heating process in the presence of e-liquid are reported in the range of 40 and 180 °C.
[12] Infra-red (IR), nuclear magnetic resonance (NMR), and direct analysis in real-time ionization coupled to high-resolution mass spectrometry (DART-HRMS).

been consistently observed in EVALI cases, further research is required. For example, it needs to be determined whether VEA and THC are simply surrogates for other toxic agents produced during high-temperature vaping, or whether illicit e-liquids contain chemicals with unknown properties, distribution kinetics, and metabolism.

Summary

28. An outbreak of severe respiratory illness linked to recent use of E(N)NDS products was signalled to the US CDC in the second part of 2019. Case numbers peaked in September 2019 and subsequently declined. As at mid-February 2020, a total of 2807 hospitalised cases had been recorded by the CDC, of which 68 had resulted in death of the patient.

29. Many of the EVALI cases were young adults who reported recent use of THC-containing E(N)NDS products. In many cases the products had been obtained from informal sources.

30. CDC and FDA concluded that the presence of VEA in E(N)NDS products is strongly linked to the EVALI outbreak. VEA has been found in product samples tested by FDA and state laboratories and was identified in BAL fluid samples taken from 48 of 51 EVALI patients. VEA was not identified in BAL fluid from a control set of 99 subjects without EVALI, including 18 who were E(N)NDS users.

31. CDC note that the evidence is not strong enough to rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC products, in some of the EVALI cases.

32. CDC and FDA recommend that THC-containing E(N)NDS products, particularly those obtained from informal sources, should not be used. In addition, VEA and/or other substances not intended by the manufacturer to be present, should not be added to E(N)NDS products.

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Abbreviations

AEGL-3	Acute exposure guideline level (lethal)
BAL	Bronchoalveolar lavage
CBD	Cannabidiol
CC	Conventional cigarette
CDC	US Centers for Disease Control and Prevention
E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ENDS	Electronic nicotine delivery system
ENNDS	Electronic non-nicotine delivery system
EVALI	E-cigarette, or vaping, product use – associated lung injury
FDA	US Food & Drug Administration
PG	Propylene glycol
THC	Tetrahydrocannabinol

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