TOX/2019/58

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). Paper 10d: Toxicity assessment of flavourings used in E(N)NDS: Menthone

Background

1. The COT is reviewing the potential human health effects of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (which, overall, are referred to as E(N)NDS).

2. A number of flavourings are used in E(N)NDS liquids, the toxicity of which has been fully evaluated via the oral route. However, toxicity via inhalation is less widely understood. Two flavourings, vanillin and cinnamaldehyde (TOX/2019/24 and TOX/2019/25) were reviewed at the May 2019 COT meeting and a third, menthol (TOX/2019/48) was reviewed at the September 2019 COT meeting. This paper reviews published data on the toxicity via inhalation exposure of menthone, a further flavouring chemical.

Introduction

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

lithium-ion batteries and are highly customisable (different coil options, power settings, tank sizes). In addition, highly advanced 'fourth generation' E(N)NDS (innovative regulated mods) are now being described.

4. Constituents that have been identified in E(N)NDS liquids and/or aerosols include PG, VG, water, nicotine, carbonyls, volatile organic compound (VOCs), tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), metals, ethanol, ethylene glycol, di-ethylene glycol, flavouring compounds, flavour enhancers, sweeteners and phenolics.

5. Over 7000 unique flavours of E(N)NDs liquids are reportedly available (Erythropel *et al.*, 2018; Zhu and Bonnevie, 2014), such as green apple, strawberry mint, or caramel cafe.

6. The primary concern about the use of flavouring compounds is that whilst they are approved food flavourings for ingestion in the EU, few have undergone acute or chronic toxicity testing via the inhalation route (Fowles and DiBartolomeis, 2017; Gerloff *et al.*, 2017).

7. Menthone (5-methyl-2-propan-2-ylcyclohexanone; is a constituent in peppermint. Due to its asymmetric carbon centres, there are cis- and trans-isomers, which are known as isomenthone and menthone, respectively. (Trans-)menthone (CAS 89-80-5) exists as L-menthone (CAS 14073-97-3) and D-menthone (CAS 3391-87-5) (figure 1). Only menthone (isomer unspecified in the database) and L-menthone appear to be used in e-liquids (Centre for Tobacco Regulatory Science and Lung Health website https://eliquidinfo.org/).

L-Menthone
(CAS 14073-97-3)

D-Menthone
(CAS 3391-87-5)

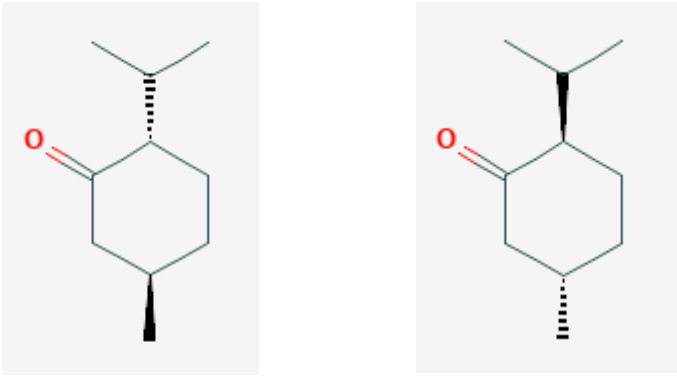

Figure 1 Structure of L-menthone and D-menthone

8. The following sections summarise data relevant to the inhalation toxicity of the E(N)NDS flavouring compound menthone, including human epidemiological and clinical data and experimental studies in animals.

Search strategies

9. The following search strategies were combined to identify literature relevant to the inhalation toxicity of menthone: 1) Scopus and PubMed databases were searched using combinations of terms as described in Annex A. 2) Reports from authoritative bodies that have reviewed the toxicity and human health effects of exposure to menthone were evaluated and relevant literature cited within these reports was identified. 3) Reference lists within the literature citations identified from 1 and 2, above, were inspected for further relevant literature.

Toxicity evaluation

Authoritative reviews

10. Menthone and L-menthone have been registered under the Registration, Evaluation, Authorisation and restriction of CHemicals (REACH) regulations. Menthone is classified as acutely toxicity (category 4) (H302: harmful if swallowed). Human and animals data are lacking on carcinogenicity and aspiration hazard. It is not classified for any other toxicological endpoint, including acute inhalation toxicity.

11. L-Menthone is classified as a skin irritant (category 2) (H315: causes skin irritation) and a skin sensitiser (category 1B) (H317: may cause an allergic skin reaction). Data are lacking for acute toxicity via inhalation, respiratory sensitisation, carcinogenicity and specific target organ toxicity following a single exposure (STOT SE). It is not classified for any other endpoint.

12. Under the Classification, Labelling and Packing (CLP) scheme, industry has notified ECHA that menthone should be classified according to the following categories: skin and eye irritation (category 2) (H315: causes skin irritation and H319: causes eye irritation); skin sensitisation (H317: may cause an allergic skin reaction); carcinogenicity (H351: suspected for causing cancer); and acute toxicity (category 4) (H302: harmful if swallowed). Similarly, L-menthone was notified for skin irritation (category 2) (H315: causes skin irritation); skin sensitisation (H317: may cause an allergic skin reaction); and acute toxicity (category 4) (H302: harmful if swallowed).

13. Menthone is used as a food flavouring and has been designated as Generally Regarded as Safe (GRAS) for use in food by the US Flavor and Extract Manufacturers Association (FEMA).

14. The European Food Safety Authority (EFSA) and the Australia Department of Health evaluated the toxicity of menthone via ingestion but did not assess the toxicity via inhalation (EFSA, 2015; NICNAS, 2018).

Acute toxicity

15. No data were available regarding the acute toxicity of menthone or L-menthone.

Irritation and corrosion

16. Menthone was tested in two studies in rabbits. In the first study, 100 % menthone was administered onto abraded and intact skin under occlusive conditions for 24 hours. Mild irritation was noted (no further information available) (Opdyke, 1979a). In a similar study by the same author, 8 % menthone in petrolatum did not cause any irritation when applied to abraded and intact skin of rabbits (no further information available) (Opdyke, 1979b) .

17. Menthone was also non-irritating when applied to 20 guinea pigs for 30 seconds once daily for five consecutive days under non-occlusive conditions. No signs of skin lesions were observed during the 14 days post-exposure observation period (OECD HPV Chemicals programme, 2003 cited in ECHA, 2019b).

18. In humans, a maximisation test with 8 % menthone in petrolatum was carried out in 25 volunteers. No signs of skin irritation were reported (no further details available) (Opdyke, 1976)

19. Skin irritation was modelled using Quantitative Structural Analysis Relationship (QSAR) models including Battery, Leadscope, SciQSAR and CASE Ultra used within the Danish QSAR database. Based on estimations from all models, no severe skin irritation effects were expected when menthone was exposed to rabbit skin. Hence, it was considered not irritating to skin by the REACH registrants (ECHA, 2019b).

20. A read-across approach was used in an *in vitro* study performed according to OECD 439 (In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method), 10 µL of a mix of 76 % L-menthone and 23.5 % isomenthone was applied to reconstructed human epidermis for 15 min. After a 42 hour incubation period, the mean tissue viability was 10.4 % therefore the mixture was considered a skin irritant by the authors (ECHA, 2019a).

21. Menthone was tested for eye irritation in New Zealand white rabbits (6/sex/group) (NTRL report, 1982 cited in ECHA, 2019b), with 0.1 ml of a 100 % solution being administered to the left eye without rinsing. Reactions were scored at one, 24, 48 and 72 hours and at 4 and 7 days after treatment according to the Draize system. Some conjunctival redness was observed in a few rabbits (number not given) which was reversible within 7 days. Overall the test chemical was considered not to be irritating to the eye by the authors.

22. In an *in vitro* study conducted according to OECD 437 (Bovine Corneal Opacity and Permeability Test), 3 bovine corneas isolated from donor cattle were treated with an undiluted mix of menthone and isomenthone (ratio not specified) for 10 min followed by washing with saline. A slight increase in corneal opacity was observed but there was no change in permeability. The calculated mean irritation score was 1.76 therefore, the mixture was not considered irritating to the eyes by the authors (ECHA, 2019a).

23. Respiratory irritants may be ranked according to their RD50, which is the concentration required to reduce the mouse respiratory rate by 50 %. The RD50 has been used to estimate sensory irritancy in animals by a number of authors (Costigan et al., 2014; Erythropel et al., 2018; Kuwabara et al., 2007; Tisserand and Young, 2014).

24. The extent of mucous membrane irritation can be directly related to physico-chemical parameters for chemicals that otherwise have poor toxicological data sets (ECETOC, 2006). For substances from a homologous series, an increased vapour pressure correlated with an increased RD_{50} (Alarie *et al.*, 1995 cited in ECETOC, 2006). A decrease in log octanol-air partition coefficient (K_{ow}) was related to a decrease in RD_{50}, thereby both could be used as a predictor of the severity of sensory irritation (ECETOC, 2006). The ECETOC Task Force derived a relationship to predict the RD_{50} from the air-water partition coefficient (K_{aw}) and the K_{ow} using the equation below.

$$\text{Log RD50} = b_0 + b_1 \times \log K_{ow} + b_2 \times \log K_{aw}$$

Where:

b0=6.346; b1=-0.8333; b2=0.7139

25. Using this equation, the calculated RD_{50} for menthone and L-menthone would be 745 and 175 ppm, respectively.

Sensitisation

26. An open repetitive dermal test was conducted on guinea pigs. The induction phase consisted of menthone (concentration not given) administration to the shaved skin of guinea pigs for 30 seconds once daily for 3x5 days (not further information available). Following full dose administration and a rest period of five days without application, menthone was rubbed into a previously untreated part of the skin and left under non-occlusive conditions for 24 hours. No skin lesions were observed after a period of 72 hours hence menthone was considered not to be sensitising to the skin by the authors (ECHA, 2019b).

27. In humans, a maximisation test with 8 % menthone in petrolatum was carried out in 25 volunteers. No positive reactions were reported (no further details available) (Opdyke, 1976).

28. Skin sensitisation was modelled using QSAR models including Battery, Leadscope, SciQSAR and CASE Ultra used within the Danish QSAR database. Based on estimation, no skin sensitisation effects were expected in guinea pigs. Hence, it was considered not a skin sensitiser by the REACH registrants (ECHA, 2019b).

29. Skin sensitisation was assessed by carrying out a local lymph node assay (LLNA) performed in accordance with OECD 429, female CBA/J mice (4/dose) received topical applications of 25, 50 or 100 % (v/v) of L-menthone in acetone/olive

oil on three consecutive days. The reported stmulation indexes were 1.3, 2.5 and 9 for concentrations of 25, 50 and 100 % respectively. The reported estimated concentration of a test substance needed to produce a stimulation index of three (EC3) was 54.2 % indicating weak sensitisation potential (ECHA, 2019a).

Repeat dose toxicity

30. No data were found regarding the repeated dose toxicity following inhalation exposure to menthone or L-menthone.

Mutagenicity/genotoxicity

31. Menthone was positive in an Ames test with *S. typhimurium* TA1537 at concentrations up to 32 µg/plate and TA97 at concentrations up to 160 µg/plate, without metabolic activation. With metabolic activation using S9 mix menthone was negative in both strains, and was also negative in TA1535, TA100, and TA98 when tested up to 800 µg/plate, with and without metabolic activation (Andersen and Jensen, 1984).

32. In an *in vitro* mammalian chromosome aberration test, carried out according to OECD 473 (In Vitro Mammalian Chromosomal Aberration Test) in Chinese hamster fibroblast cells, menthone (up to 0.2 mg/ml) did not induce chromosomal aberrations and hence was not classified for gene mutation *in vitro* (Ishidate et al., 1984 cited in EACH, 2019b). Menthone was also negative for chromosomal aberrations in human lymphocytes with and without metabolic activation using S9 mix (Murthy et al., 1991 cited in ECHA, 2019b).

33. L-Menthone was negative in an *in vivo* micronucleus test carried out according to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test). Male and female mice (12/dose) were treated with 50, 100 or 200 mg/kg bw/day L-menthone via gavage. No increase in micronucleated polychromatic erythrocytes was observed (Unnamed study report, 2009 cited in WCHA, 2019a).

34. An Ames test carried out according to OECD 473 (Bacterial Reverse Mutation Assay), *S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and E. coli WP2 was carried out with a mix of L-menthone and isomenthone, with and without S-9 mix. The mixture did not induce any mutations (Unnamed study report, 2012 cited in ECHA, 2019a).

35. L-menthone was also negative in an *in vitro* mammalian cell gene mutation test, carried out according to OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test) in Chinese hamster lung fibroblasts (V79 cells) with and without metabolic activation (Unnamed study report, 2013 cited in ECHA, 2091a).

Carcinogenicity

36. No experimental carcinogenicity studies were found relating to the inhalation of menthone or L-menthone.

37. The REACH dossier for L-menthone used a read across approach with DL-menthol for this endpoint. DL-menthol was not carcinogenic in Fischer 344 rats or B6C3F1 mice (50 animals per sex and dose) treated for 103 weeks with 3750 or 7500 ppm (188 and 375 mg/kg bw/day for rats and 334 and 667 mg / kg bw/day for mice) in feed. The study was carried out according to OECD 453 (Combined Chronic Toxicity/Carcinogenicity Studies) (NCI, 1979).

Reproductive and developmental toxicity

38. No inhalation route specific reproductive or developmental studies were found for menthone or L-menthone.

39. The REACH dossier for L-menthone used a read across approach with menthol (ECHA, 2019a). Various developmental studies have been carried out with L-menthol. No treatment related effects were reported following administration via oral gavage on gestation day 6 to 10, 15 or 18 (ECHA, 2019c).

Immnunotoxicity

40. A number of papers were identified that indicated anti-inflammatory effects of peppermint oils *in vivo* and *in vitro*, although few reported effects of menthone alone. Most studies identified were mechanistic papers or investigated the immunomodulatory effect of peppermint oils or menthone following endotoxin or bacterial stimulation.

41. Wang et al. (2017) reported that menthone had a protective effect on lipopolysaccharide (LPS)-induced inflammation in C5&BI/6J male mice, by inhibiting the release of a number of inflammatory cytokines, thereby reducing the inflammatory reaction and inhibiting the activation of NLRP3 inflammasome. In an earlier study in HaCat cells *in vitro*, Cheng et al., (2008) also reported that menthone suppressed lipopolysaccharide (LPS)-induced proinflammatory cytokines IL-1β and tumour necrosis factor-α (TNF-α) as well as nuclear factor κb (NF-κB).

42. In mice infected with Schistosoma mansoni, a herbal commercial medicine consisting of menthol (30-55 %) and menthone (12-32 %) decreased the number of Schistosoma mansoni eggs in the faeces, liver and intestine, reduced the number of hepatic granulomas, interleukin-4 (IL-4) and IL-10 and eosinophilia. Authors concluded that the herbal medicine had an immunomodulatory and anti-inflammatory action in the animal model for schistosomiasis, thereby contributing to the pathophysiological effects caused by the infection (Zaia et al., 2016).

43. Vimal et al., (2013) reported that menthone was highly active against Proteus mirabilis isolated from immunosuppressed cancer patients and concluded that essential oil compounds could be used for the prevention, control and treatment of opportunistic bacterial infections, particularly in cancer patients.

44. In primary mouse splenocytes, menthone did not markedly increase IL-10/IL-2 (Th2/Th1) cytokine secretion ratios, suggesting that it may have a relative Th1-inclination property, relative to other terpenoid compounds (Ku et al., 2013).

Thermal decomposition of menthone

45. During E(N)NDS use, the vaporisation temperature has been estimated to be above 40 °C. The heating period introduces the potential for pyrolysis of compounds. Therefore, thermal degradation and reaction products of flavourings should also be considered in the assessment of risk (Costigan and Meredith, 2015).

46. In their Final Opinion on Additives Used in Tobacco Products, SCENIHR (2016) noted that 'thermal decomposition or burning may release carbon monoxide or other hazardous gases, acrid smoke and irritating fumes' and concluded that 'data on pyrolysis of most of the individual additives are scant' and called for more pyrolysis studies on individual and complex flavour additives to be carried out. It should be noted that CCs generally reach higher temperatures compared to E(N)NDS, hence the pyrolysis profile may be different.

47. No data were found regarding the thermal degradation of menthone or L-menthone or reaction with other constituents of e-liquids.

Summary

48. There are many different varieties of E(N)NDs liquids on the market made up of a number of flavouring chemicals, as well as PG, VG, nicotine and water. Few of these flavourings have undergone acute or chronic toxicity testing via the inhalation route. Therefore, the potential toxicity via E(N)NDs use cannot currently be ascertained.

49. Menthone has been notified under CLP as a skin and eye irritant, skin sensitiser and a carcinogen and L-menthone as a skin irritant and skin sensitiser. The REACH dossier for L-menthone also classified it as a skin irritant and sensitiser. In contrast with the CLP notification, the REACH dossier for menthone did not classify it as an irritant, sensitiser or carcinogen. The reason for this discrepancy is unclear as data are not provided to support the CLP notification on the ECHA website.

50. The respiratory sensory irritation potential of menthone has been calculated based on physico-chemical parameters.

51. Menthone is not considered to be mutagenic.

52. No reproductive or developmental toxicity studies or carcinogenicity studies could be identified for menthone via the inhalation route.

Questions for the Committee

53. Members are asked to consider the information provided in this paper and in particular:

i. Are there any data gaps with respect to the risk assessment for menthone or other particular aspects of this paper which should be captured in the COT statement on E(N)NDS?

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
October 2019

Abbreviations/Glossary

CC	Conventional Cigarettes
CHL	Chinese Hamster Lung
CLP	Classification, Labelling and Packing
CTP	Centre for Tobacco products
E(N)NDS	Electronic Nicotine and Non-Nicotine Delivery Systems
ENDS	Electronic Nicotine Delivery Systems
ENNDS	Electronic Non-Nicotine Delivery Systems
EU	European Union
FDA	US Food and Drug Administration
FEMA	Flavour Extracts Manufacturers Association
GRAS	Generally Regarded As Safe
K_{aw}	Air-Water Partition Coefficient
K_{ow}	Octanol-Air Partition Coefficient
LED	Light-Emitting Diode
LLNA	Local Lymph Node Assay
NOAEC	No observed adverse effect concentration
PAH	Polycyclic Aromatic Hydrocarbon
PG	Propylene Glycol
RD_{50}	The concentration required to reduce the mouse respiratory rate by 50%
QSAR	Quantitative Structural Analysis Relationship
REACH	Registration, Evaluation, Authorisation and restriction of CHemicals
STOT SE	Specific target organ toxicity single exposure
TSNA	Tobacco-Specific Nitrosamine
VG	Vegetable glycerol
VOC	Volatile Organic Compound
WHO	World Health Organization

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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). Paper 10c Toxicity assessment of flavourings used in E(N)NDS: Menthone

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

Relevant literature was obtained from reviews published by authoritative bodies, as described in paragraph 4 of the main report. In addition, searches for further literature relating to toxicity of E(N)NDS aerosol were identified as described below. The following three sets of literature searches were performed by NCET at WRc/IEH-C under contract to PHE on xxx in Scopus and PubMed, with no limit of publication date.

Search 1: toxicity

Scopus

((CASREGNUMBER ("14073-97-3") OR CHEMNAME (menthone) OR TITLE-ABS-KEY (menthone))) AND ((TITLE-ABS-KEY (*toxic* OR acute OR irritation OR sensitization OR "repeat dose" OR carcin* OR mutagen*) AND TITLE-ABS-KEY (inhal*))):1PubMed

(((((“14073-97-3”[EC/RN Number]) OR menthone[Title/Abstract]))) AND (((*toxic* [Title/Abstract] OR acute [Title/Abstract] OR irritation [Title/Abstract] OR sensitization [Title/Abstract] OR "repeat dose" [Title/Abstract] OR carcin* [Title/Abstract] OR mutagen*[Title/Abstract])) AND inhal*[Title/Abstract]))) AND english[Language]: 0

((CASREGNUMBER ("14073-97-3" OR "89-80-5") OR CHEMNAME (menthone OR "isopropyl-5-methylcyclohexanone") OR TITLE-ABS-KEY (menthone OR "isopropyl-5-methylcyclohexanone"))) AND (TITLE-ABS-KEY (*toxic* OR acute OR irritation OR sensitization OR "repeat dose" OR carcin* OR mutagen*)) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (LANGUAGE , "Greek") OR EXCLUDE (LANGUAGE , "Portuguese") OR EXCLUDE (LANGUAGE , "Spanish")): 184

PubMed

((((“14073-97-3” [EC/RN Number] OR “89-80-5” [EC/RN Number]) OR menthone [Title/Abstract]))) AND (((*toxic* [Title/Abstract] OR acute [Title/Abstract] OR irritation [Title/Abstract] OR sensitization [Title/Abstract] OR "repeat dose"

[Title/Abstract] OR carcin* [Title/Abstract] OR mutagen*[Title/Abstract])) AND english[Language]: 58

Search 2: thermal degradation

Scopus

((CASREGNUMBER ("14073-97-3”) OR CHEMNAME (menthone) OR TITLE-ABS-KEY (menthone))) AND (TITLE-ABS-KEY ("thermal decomposition" OR "thermal breakdown" OR "thermal degradation" OR thermolysis)): 3PubMed

((("14073-97-3”[EC/RN Number]) OR (menthone[Title/Abstract]))) AND (("thermal decomposition" [Title/Abstract] OR "thermal breakdown" [Title/Abstract] OR "thermal degradation" [Title/Abstract] OR thermolysis[Title/Abstract])): 0

For completeness, the reference lists of selected papers were examined for further relevant publications, and additional *ad hoc* searches were carried out as considered appropriate.