TOX/2019/24

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 10a: Toxicity assessment of flavourings used in E(N)NDS: Vanillin

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, may also referred to as E(N)NDS). A summary of publications describing the chemical constituents of E(N)NDS liquids and aerosols (excluding metals and flavourings) (TOX/2018/16) was presented at the COT meeting in March 2018. A review of published data on the toxicity of the major constituents of E(N)NDS liquids such as propylene glycol (PG) and glycerol (VG) (TOX/2018/19) was presented at the COT meeting in May 2018, and a paper reviewing published data on the toxicity of E(N)NDS aerosols (TOX/2018/24) and nicotine (TOX/2018/25) were presented at the July 2018 COT meeting.

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. This paper reviews published data on the toxicity of one such flavouring chemical, vanillin, via inhalation exposure.

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. E(N)NDS liquids are comprised of flavouring chemical, such as vanillin or cinnamaldehyde, with PG, VG, nicotine and water, hence flavouring compounds are one of the five most commonly listed ingredients in E(N)NDS liquids, along with PG, VG, nicotine and water. The primary concern about the use of flavouring compounds is that whilst they are approved food flavourings for ingestion and have been deemed 'generally regarded as safe (GRAS)' by the US Food and Drug Administration (FDA) or World Health Organization (WHO), few have undergone acute or chronic toxicity testing via the inhalation route (Fowles and DiBartolomeis, 2017).

6. Vanilla is a popular flavouring agent used in E(N)NDS liquids and cigarette tobacco (Erythropel et al., 2018). Vanillin (4-hydroxy-3-methoxybenzaldehyde, CAS 121-33-5) is the primary component of the extract of the vanilla bean. Natural vanilla is a complex extract and is expensive therefore companies report using synthetic vanilla flavour substances, vanillin and ethyl vanillin (3-ethyoxy-4-hydroxybenzaldehyde, CAS 121-32-4) to reduce costs (SCENIHR, 2016).

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

Search strategies

8. The following search strategies were combined to identify literature relevant to the inhalation toxicity of vanillin: 1. Scopus and PubMed databases were searched using combinations of terms as described in Annex A. Reports from authoritative bodies that have reviewed the toxicity and human health effects of exposure to vanillin were appraised 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

9. Vanillin has been registered under the Registration, Evaluation, Authorisation and restriction of CHemicals (REACH) regulations. It is classified as an eye irritant (category 2) and has the hazard statement H319: causes serious eye irritation. It was not classified for any other endpoint, including acute inhalation toxicity. However, the Russian study[1] on which the acute inhalation classification was based in the registration dossier was deemed unreliable by the authors of the dossier due to major methodological deficiencies and was therefore disregarded by the authors. The study was also cited by the European Food Safety Authority (EFSA), although the report only gave an LD_{50} via the oral route. No inhalation data were presented by EFSA (EFSA, 2005) and as the study is written in the Russian language, data cannot be checked for inclusion here.

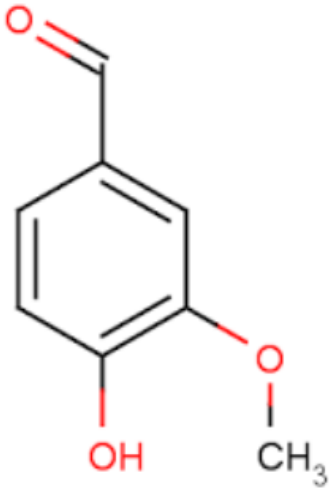
10. Several other authoritative bodies have evaluated the toxicity of vanillin via ingestion, including the Scientific Committee on Consumer Safety (SCCS, 2012), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2016), EFSA (2008), United States Environment Protection Agency (US EPA, 2010) and Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA, 2001). However, none assessed the toxicity of vanillin via inhalation.

Acute toxicity

11. US EPA cited an LC_{50} of >0.32 mg/L for vanillin in rats, based on a read across approach using 4-methoxy-benzaldehyde (CAS 123-11-5) as the surrogate chemical. During exposure, snout wiping and attempts to escape were observed amongst the animals. No further information was provided and the authors concluded that ‘acute inhalation (vapour) toxicity of CASRN 123-11-5 in rats is high’ (US EPA, 2010). No justification for the read-across approach was provided. The structures for vanillin (2-methoxy-4-hydroxybenzaldehyde) and the read across chemical 4-methoxy-benzaldehyde are given in figure 1. It is hypothesised that the position of the methoxy group at the meta position and the inclusion of the hydroxyl group in the para position may alter the reactivity of vanillin compared with 4-methoxy-benzaldehyde.

[1] Makaruk, MI (1980). Problem of the toxicity of vanillin/On the toxicity of vanilla. Gig Sanit, 6, 78-80. (in Russian)

Vanillin
(2-methoxy-4-hydroxybenzaldehyde)
CAS 121-33-5



Read across chemical
(4-methoxy-benzaldehyde)
CAS 123-11-5

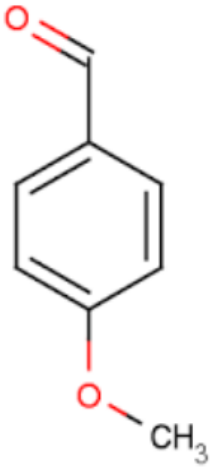


Figure 1 Structure of vanillin and read across chemical, 4-methoxy-benzaldehyde

Irritation and corrosion

12. In a double blind study, an asthmatic patient was administered vanillin via inhalation two or three times, at intervals of 1.5 hours. There was some evidence that vanillin reduced lung function 'at oral doses of 0.24 and 1 mg'. Itching of the ears and throat was also described (OECD SIDS, 1996).

13. Respiratory sensory irritation is the first sign of potential toxicity of an inhaled chemical, which is induced by chemical activation of chemosensory receptors in airway-innervating nerves (Erythropel et al., 2018). In a paper addressing the toxicological concerns of food flavourings following inhalation in E(N)NDS aerosols, Fowles and DiBartolomeis (2017) suggested it was necessary to determine the relative irritancy of inhaled flavourings and the potential to cause local irritation to understand the relative toxicity.

14. Respiratory irritants may be ranked according to their RD_{50}, which is the concentration required to reduce the mouse respiratory rate by 50 %. The RD_{50} 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). Tisserand and Young (2014) reported that RD_{50} values correlate well with log lowest observed adverse effect levels (LOAELs) in humans, suggesting that RD_{50} is a useful predictor of safe public exposure levels. The RD_{50} has been successfully correlated with irritant thresholds in occupational and general population settings (Alarie 1986; Alarie et al., 1995 and Kuwabara et al., 2007 cited in ECETOC, 2006) and is accepted as a standard measure of sensory irritation.

15. As well as determining the RD_{50} from animal data, 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 the 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. b0, b1 and b2 were estimated by multiple regression.

16. Using the equation above, the calculated RD_{50} for vanillin would be 2.00 ppm.

17. 0.03 x RD_{50} may be considered to be the threshold for irritation in humans (Fowles and DiBartolomeis, 2017; Kuwabara et al., 2007; Tisserand and Young, 2014). Fowles and DiBartolomeis (2017) suggested that flavourings, many of which are found in E(N)NDS liquids, would qualify as “moderate” irritants if the RD_{50} was <1000 ppm and concluded that ‘it may be useful to establish a mechanism to classify and categorise the flavouring chemicals for their potential respiratory irritancy whether or not specific respiratory irritation data exist for each individual chemical. The use of the calculated RD_{50} based on physical properties of the individual chemical [as presented in this paper], may be one way to accomplish this’.

18. In vitro tests quantifying the capability of a chemical to activate TRP irritant receptors are currently being considered as replacements for the animal studies to determine the RD_{50}. Recent studies identified TRP ion channels TRPA1 and TRPV1 to be the receptors for irritant aldehydes in airway-innervating nerves. They are activated by flavour aldehydes such as vanillin, eliciting irritation responses, pain, and cardiovascular reflexes increasing stress and inflammation (Bautista et al., 2006; Richards et al., 2010; Achanta et al., 2017 and Pozsgai et al., 2010 cited in Erythropel et al. (2018)). Vanillin activated TRPA1 but not TRPV1 receptors in HEK-293T cells suggesting that it may act as an airway irritant in e-cigarette users (Erythropel et al., 2018).

19. Vanillin was tested in a number of human patch test studies, with both healthy participants as well as those with skin conditions such as dermatitis or dermatoses. In one test, the skin of health subjects was made permeable by prior application of sodium lauryl sulphate. All tests reported no signs of irritation. No references were cited in the OECD SIDS document for inclusion here (OECD SIDS, 1996).

20. Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS) and US EPA both cited two in vivo skin irritation studies in rabbits and guinea pigs. OECD SIDS reported a rabbit study in which six animals were administered ground vanillin on the skin for 24 hours, and a guinea pig closed patch test in which five animals were administered 1, 2, 5 or 10 % vanillin for

48 hours. Both studies were negative, but were deemed of low reliability because limited details of the studies were available (OECD SIDS, 1996).

21. US EPA also cited two skin irritation studies in rabbits and guinea pigs although the data were considered of low reliability as no details of the studies were available (US EPA, 2010). Rabbits were administered 500 mg/kg bw vanillin for 24 hours after which moderate skin irritation was reported. Slight to moderate irritation was reported in guinea pigs administered 1.0-10 ml/kg bw vanillin for 24 hours. No further details on the studies were provided. The document concludes that 'the SIDS Initial Assessment Profile (SIAP) states that 4-methoxy-benzaldehyde is irritating to rabbit and guinea pig skin' and references the human health data in the SIAP document for 4-methoxy-benzaldehyde described below (US EPA, 2010). It is therefore unclear whether the data are related to vanillin or 4-methoxy-benzaldehyde, or if 4-methoxy-benzaldehyde is being used as a surrogate chemical in a read-across approach.

22. The SIAP cited a dermal irritation study in three rabbits, carried out according to a protocol similar to Federal Register 38 No 187, 1500.41. The study reported 4-methoxy-benzaldehyde to be slightly irritating after application for four hours under occlusive conditions, which was fully reversible within eight days in two of the three animals. The document concluded that 4-methoxy-benzaldehyde 'is considered to be non irritating to the skin' (SIDS Initial Assessment Profiles, 2009).

23. A rabbit eye irritation test, carried out in six rabbits with 55 mg finely ground vanillin powder, showed a slight irritant effect that was reversed within 168 hours. The authors considered the effect was due to the mechanical stress of the crystals (OECD SIDS, 1996).

Sensitisation

24. A number of sensitisation studies have been reported with vanillin. SCCS (2012) cited various sensitisation studies in healthy humans (n=744) or patients with suspected contact allergy to fragrance ingredients (n=747). In both studies, 1 (0.1 %) positive reaction was observed. In a later study carried out by Information Network of Departments of Dermatology (IVDK) (2010), 10 out of 4377 (0.19 %) of patients reacted to vanillin. In contrast, no reactions to vanillin were seen in patients that had previously showed a reaction to myroxylon pereirae resin, a commonly known allergen.

25. The sensitisation potential of vanillin was also investigated in a local lymph node assay (LLNA). Authors cited an EC3 value (concentration required to provoke a 3-fold increase in lymph node cell proliferative activity compared with controls) of >50 % indicating low sensitisation potential (Basketter et al., 2001 cited in SCCS, 2012).

26. Safford et al. (2015) looked at a number of fragrance allergens, including vanillin, and used the Dermal Sensitisation Threshold (DST) to determine the

potency of the allergens. The DST 'applies the same principles as those used to develop the Threshold of Toxicological Concern (TTC) to define the level of skin exposure where there is no appreciable risk of skin sensitisation to an untested chemical'. The LLNA EC3 value for vanillin was <12,500 µg/cm^2 hence authors concluded it did not fall within the potent category.

Repeat dose toxicity

27. No repeat dose inhalation toxicity tests on vanillin per se were found in animals or humans.

28. Lemus et al. (2007) carried out an inhalation study in rats using mainstream smoke from four experimental cigarettes containing differing concentrations of vanillin (V0, control; VL, low inclusion rate; VM, medium inclusion rate; VH, high inclusion rate). The target inclusion rates for addition of vanillin to the tobacco of V0, VL, VM and VH cigarettes was 0, 250, 250 and 5000 ppm, respectively, whilst the actual concentrations achieved were 0, 67, 1233 and 3109 ppm, respectively, representing 27, 49 and 55 % of the target values. The 'specific activity' was assessed for each dose group by using the same concentration of total particulate matter (TPM) in the smoke the rats were exposed to. A target TPM concentration of 150 mg/m^3 for 6 h/day and 7 days/week was selected since it represents a dynamic response range producing mild histopathological changes in the respiratory tract, based on increased and decreased effects reported in previous publications. No further information was provided.

29. In the study, male and female Sprague-Dawley rats (10-24 per group) were exposed by nose-only inhalation to diluted mainstream smoke containing different vanillin concentrations, 6 hours/day for 90 days (largely conforming to OECD guideline 413), after which systemic toxicity and histopathology of the respiratory tract were assessed. Body weight, feed consumption and respiratory physiology were measured throughout the study. Haematology and blood chemistry were measured at the end of the inhalation phase and organ weights were measured at necropsy including lungs with larynx and trachea attached, liver, kidney, testes, adrenals, thymus, brain and spleen. Histopathology was carried out on the skin, lower jaw, brain and lungs.

30. Authors reported that respiratory rates and tidal volumes were unaffected by exposure to smoke containing vanillin compared to controls, no toxicologically meaningful differences related to haematology, blood chemistry gross pathology and organ weights and few histopathological changes were observed in any groups exposed to vanillin compared with controls. In level 4 of the male rat nasal passages, squamous metaplasia was reported in VL (2.1±0.3) and VH (2.2±0.3), but not VM (0.8±0.3) or V0 (1.4±0.2). Overall, the authors concluded that 'there was no

difference between toxicological profiles of the three cigarettes with added vanillin and with the cigarette containing no such addition' (Lemus et al., 2007)[2].

Mutagenicity/genotoxicity

31. A number of assays have been carried out including Ames test, mouse lymphoma assay in L5178Y cells, unscheduled DNA synthesis in rat hepatocytes, micronucleus assay in human hepatoma HepG2 cells, chromosomal aberrations in Chinese hamster V79 cells, B241 cells and human lymphocytes, and sister chromatic exchange in several Chinese hamster cell lines and human lymphocytes (EFSA, 2005; EFSA, 2008; OECD SIDS, 1996; US EPA, 2010).

32. Overall, mixed results were obtained. Chromosomal aberrations in Chinese hamster and human cell lines were equivocal. Vanillin was negative in the forward mutation assay in L5178Y mouse lymphoma cells, both with and without metabolic activation. It did not induce unscheduled DNA synthesis in rat hepatocytes and weakly induced micronuclei in human Hep G2 cells, as only a moderate response at the highest concentration tested. An in vivo micronucleus test has been carried however mice were administered vanillin via oral gavage which is not of interest here.

33. Overall, EFSA concluded 'that the hydroxy- and alkoxy-substituted benzyl derivatives do not have genotoxic potential in vivo' (EFSA, 2008). US EPA (2010) also concluded that vanillin was not mutagenic in bacteria and mouse lymphoma cells in vitro and stated '121-33-5 induced chromosomal aberrations in human lymphocytes but not in Chinese hamster ovary (CHO) cells or Chinese hamster fibroblasts in vitro. It induced sister chromatid exchanges in human lymphocytes but not in CHO cells in vitro and did not induce unscheduled DNA'. No further information was provided but the document referred the reader to OECD SIDS (OECD SIDS, 1996). OECD SIDS concluded 'that the present use and production of vanillin represent little risk for genotoxicity' (OECD SIDS, 1996).

34. As part of the study described in paragraph 28, Lemus et al. (2007) carried out an Ames test with cigarettes containing varying concentrations of vanillin. The assay was conducted in Salmonella strains TA98, 100, 102, 1535 and 1537, with and without metabolic activation, largely in accordance with OECD test guideline 471. It deviated from the standard protocol in that few and lower doses were used to take into account that TPM is mutagenic. There were no differences in revertant colonies between cigarettes containing vanillin and controls, with or without metabolic activation (Lemus et al., 2007).

2 This study was carried out by Philip Morris Research Laboratories.

Reproductive and developmental toxicity

35. No inhalation route reproductive studies were found for vanillin in animals or humans.

Carcinogenicity

36. No inhalation route carcinogenicity studies were found for vanillin in animals or humans.

Thermal decomposition of vanillin

37. During E(N)NDS use, the vaporisation temperature has been estimated to vary between 40 and 350 °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)[3].

38. 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'. No further details were provided. It should be noted that CCs generally reach higher temperatures compared to E(N)NDS, hence the pyrolysis profile may be different.

39. An early study in cigarettes reported that vanillin would probably transfer intact to mainstream smoke at 200 °C with only approximately 0.1% degradation but at higher temperatures (200-800 °C) vanillin decomposes to phenol (6.6 %), 2-methyoxyphenol (6.2 %), o-cresol (5.6 %), 2-hydroxy benzaldehyde (3.0 %) and toluene (2.7 %) (Stotesbury et al., 2000). Authors stated that since such compounds were not produced from pyrolysis experiments conducted at lower relative temperatures, there is evidence of some degradation occurring at above the transfer temperature of the additives. The toxicity of these degradation products was not discussed by the authors and has not been included in this paper[4].

40. Aldehydes and alcohols can undergo chemical reactions to form aldehyde PG acetal. Therefore, Erythropel et al. (2018) hypothesised that vanillin could react with PG and VG, commonly found in E(N)NDs liquids, to form vanillin propylene glycol acetal. Experiments demonstrated that vanillin rapidly reacted with PG after mixing, and <40% was converted to vanillin propylene glycol acetal. This was measured in E(N)NDs liquids and E(N)NDs vapour. Costigan et al. (2014) also reported that vanillin propylene glycol acetal was present in e-cigarette aerosol of an experimental flavoured formulation that was not present in the ambient flavour[5].

3 This study was carried out by British American Tobacco
4 This study was carried out by Imperial Tobacco Limited and British American Tobacco.
5 This study was carried out by British American Tobacco

41. Other studies have also demonstrated the presence of flavour acetals in E(N)NDS liquids, in the headspace above E(N)NDS liquids and in E(N)NDS vapour (Geiss et al., 2015; Hutzler et al., 2014 and Behar et al., 2018 cited in Erythropel et al. (2018) and suggested that that E(N)NDs liquids can be unstable post-preparation (Erythropel et al., 2018).

42. Vanillin propylene glycol acetal activated both TRPA1 receptors with higher EC50 values compared with vanillin. Authors also reported that it was more efficacious at activating the TRPA1 receptor than equivalent concentrations of vanillin. Moreover, whilst vanillin only weakly activated TRPV1 at high concentrations (>3 mM), vanillin propylene glycol acetal activated the receptor at lower concentrations and with higher efficacies (Erythropel et al., 2018).

43. The analytical studies did not report the concentrations of the flavour aldehyde acetals in the respective e-liquids, and it remains unclear how frequently and how rapidly these compounds form and whether they remain stable during heating and vaporization in e-cigarettes (Erythropel et al., 2018). Costigan et al. (2014) estimated that the estimated exposure to vanillin propylene glycol acetal from the use of two devices was 477 µg/day[6].

Summary

44. There are many different flavours of E(N)NDs liquids on the market made up of a number of flavouring chemicals, as well as PG, VG, nicotine and water. Although such flavourings are considered to be GRAS by the US Food and Drug Administration (FDA) or World Health Organization (WHO) via ingestion, few have undergone acute or chronic toxicity testing via the inhalation route. Therefore, the potential toxicity via E(N)NDs use cannot be ascertained. There is, however, some evidence that vanillin may be a respiratory irritant following inhalation.

45. The respiratory irritation potential of vanillin was investigated using a number of approaches. The RD_{50} was calculated based on physico-chemical parameters as well as in mice. Moreover, vanillin activated TRP receptors in vitro. Such receptors are responsible for eliciting irritation responses in vivo. Overall, data suggest that vanillin may act as an airway irritant in E(N)NDs users. Some skin irritation was reported in animals although it is unclear if they were exposed to vanillin or 4-methoxy-benzaldehyde in a read-across approach. Eye irritation was also reported but was due to the mechanical effect of the crystals. Although mixed results were obtained regarding the mutagenicity of vanillin, overall, it is not considered to be mutagenic. There were no repeat dose, reproductive or carcinogenicity studies carried out with vanillin via the inhalation route.

6 This study was carried out by British American Tobacco

Questions for the Committee

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

i. Does vanillin in e-liquid pose a risk to E(N)NDs users, including as a result of degradation during heating?

ii. Is read-across from 4-methoxy-benzaldehyde reasonable?

iii. Are there any data gaps with respect to the risk assessment for flavouring chemicals 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
May 2019

Abbreviations/Glossary

CC	Conventional Cigarettes
CHO	Chinese Hamster Ovary
DST	Dermal Sensitisation Threshold
E(N)NDS	Electronic Nicotine and Non-Nicotine Delivery Systems
EC3	Concentration required to provoke an 3-fold increase in lymph node cell proliferative activity compared with controls
EFSA	European Food Safety Authority
ENDS	Electronic Nicotine Delivery Systems
ENNDS	Electronic Non-Nicotine Delivery Systems
EU	European Union
FAO	Food and Agriculture Organization
FDA	US Food and Drug Administration
GRAS	Generally Regarded As Safe
IVDK	Information Network of Departments of Dermatology
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{aw}	Air-Water Partition Coefficient
K_{ow}	Octanol-Air Partition Coefficient
LC_{50}	The concentration that is lethal to 50 % of a test population
LD_{50}	The dose that is lethal to 50 % of a test population
LED	Light-Emitting Diode
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PAH	Polycyclic Aromatic Hydrocarbon
PG	Propylene Glycol
RD_{50}	The concentration required to reduce the mouse respiratory rate by 50%
REACH	Registration, Evaluation, Authorisation and restriction of CHemicals
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SIAP	SIDS Initial Assessment Profile
SIDS	Screening Information Dataset
TPM	total particulate matter
TSNA	Tobacco-Specific Nitrosamine
TTC	Threshold of Toxicological Concern
US EPA	United States Environment Protection Agency
USA	United States of America
V0	Control
VG	Vegetable Glycerol
VH	High Inclusion Rate
VL	Low Inclusion Rate
VM	Medium Inclusion Rate
VOC	Volatile Organic Compound
WHO	World Health Organization

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TOX/2019/24- Annex A

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). Toxicity assessment of flavourings used in E(N)NDS: Vanillin

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 ("121-33-5") OR CHEMNAME (vanillin OR "vanillic aldehyde" OR "Benzaldehyde, 4-hydroxy-3-methoxy-") OR TITLE-ABS-KEY (vanillin OR "vanillic aldehyde" OR "Benzaldehyde, 4-hydroxy-3-methoxy-"))) AND ((TITLE-ABS-KEY (*toxic* OR acute OR irritation OR sensitization OR "repeat dose" OR carcin* OR mutagen*) AND TITLE-ABS-KEY (inhal*))) : 7

PubMed

(((("121-33-5"[EC/RN Number]) OR (vanillin [Title/Abstract] OR "vanillic aldehyde" [Title/Abstract] OR "Benzaldehyde, 4-hydroxy-3-methoxy-"[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]): 7

Search 2: thermal degradation

Scopus

((CASREGNUMBER ("121-33-5") OR CHEMNAME (vanillin OR "vanillic aldehyde" OR "Benzaldehyde, 4-hydroxy-3-methoxy-") OR TITLE-ABS-KEY (

vanillin OR "vanillic aldehyde" OR "Benzaldehyde, 4-hydroxy-3-methoxy-"))) AND (TITLE-ABS-KEY ("thermal decomposition" OR "thermal breakdown" OR "thermal degradation" OR thermolysis)) AND (EXCLUDE (LANGUAGE , "Chinese")): 68

PubMed

(("121-33-5"[EC/RN Number]) OR (vanillin [Title/Abstract] OR "vanillic aldehyde" [Title/Abstract] OR "Benzaldehyde, 4-hydroxy-3-methoxy-"[Title/Abstract])) AND (("thermal decomposition" [Title/Abstract] OR "thermal breakdown" [Title/Abstract] OR "thermal degradation" [Title/Abstract] OR thermolysis[Title/Abstract])): 3

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.