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

Framework for risk assessment of flavouring compounds in electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)

Introduction

1. E(N)NDS are battery-powered devices containing a liquid (E(N)NDS liquid or ‘e-liquid’) that is heated during use to produce an aerosol, which is inhaled by the user (‘puffing’, ‘vaping’).

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

3. Flavouring compounds are one of the five most commonly listed ingredients in E(N)NDS liquids, along with PG, VG, nicotine and water. Over 7000 unique flavours are reportedly available (Erythropel *et al.*, 2018; Zhu and Bonnevie, 2014) although detailed information is not available on the dominant specific compounds on the UK market. Overall, tobacco, fruit and menthol flavour types are popular (McNeill et al., 2019)

4. The primary concern about the use of flavouring compounds is that whilst many have been evaluated and approved for use in food, few have undergone acute or chronic toxicity testing via the inhalational route (Fowles and DiBartolomeis, 2017).

Framework for risk assessment of flavouring compounds

5. The framework for risk assessment of flavouring compounds provides a number of steps designed as a set of principles to guide the risk assessment process for a flavouring compound in E(N)NDS. It assumes some level of expertise of the assessor. Existing data or non-animal approaches should be used to inform each step where possible. The steps are illustrated in Figure 1.

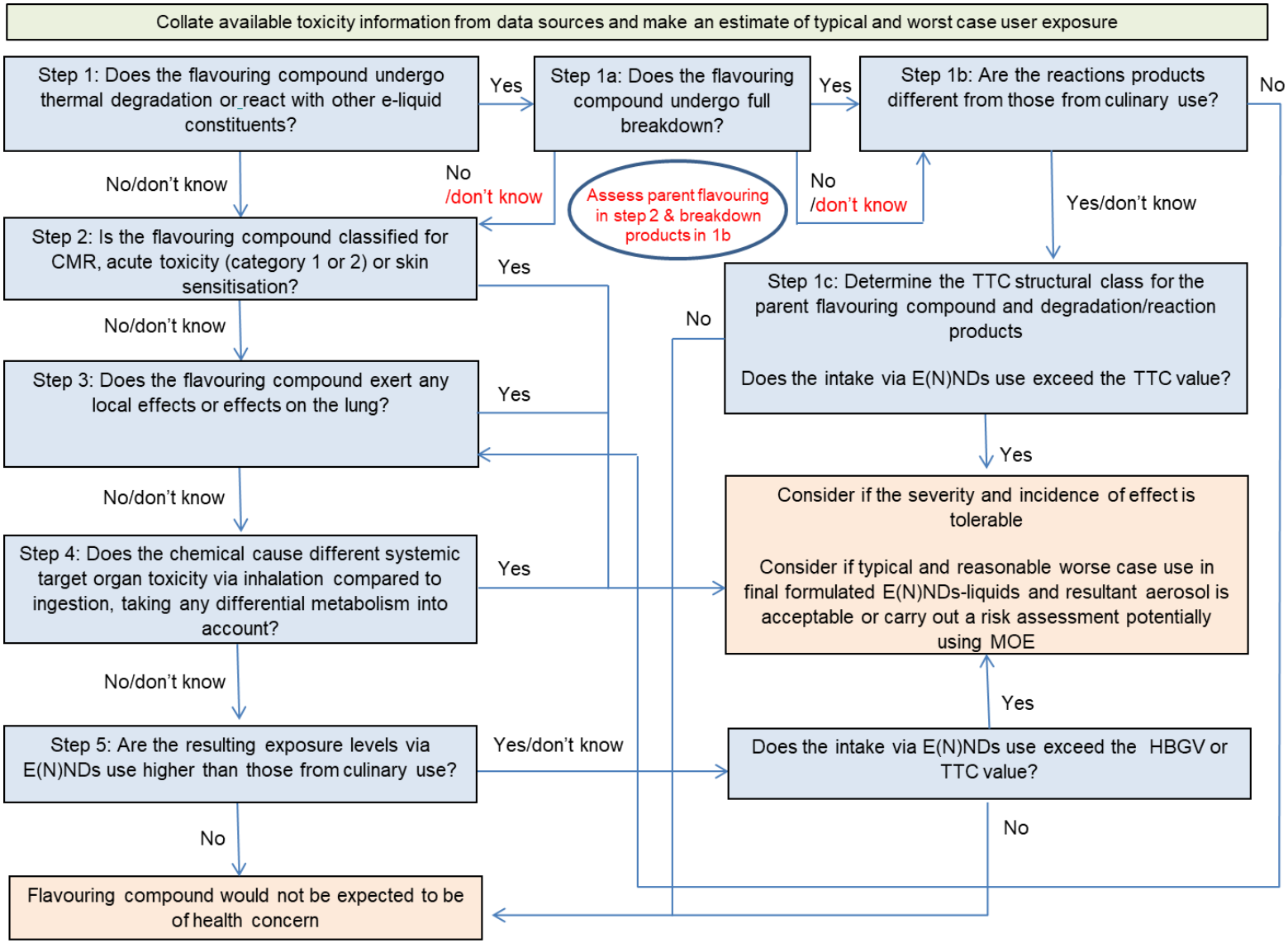

Figure 1. Framework for risk assessment of flavouring compounds via inhalation exposure

Step 1 Does the flavouring compound undergo thermal degradation or react with other e-liquid constituents?

Description

6. During E(N)NDS use, the vaporisation temperature has been estimated to vary between 40 and 180° C. The heating period, the temperature, length of puff, air flow of the individual puff and how recently the coil was changed affects the potential for thermal degradation of the compounds. Flavouring compounds may also react with other constituents of e-liquids. Therefore, thermal degradation and reaction products of flavouring compounds should also be considered as part of their risk assessment (Costigan and Meredith, 2015).

Data sources

7. Literature should be searched to identify if thermal degradation products are formed on heating of the flavouring compound and if possible, the concentration formed. Some flavouring compounds, namely, aldehydes and alcohols can undergo chemical reactions with PG, a main constituent of e-liquids, at room temperature to form PG acetals, and ketones for PG ketals (Elmore et al., 2014; Erythropel et al., 2018). Flavouring compounds that form acetals include vanillin, furfural, benzaldehyde, strecker aldehydes, cinnamaldehyde and citral, whilst acetoin, raspberry ketone (4-[4-hydroxyphenyl]-2-butone), and menthone form PG ketals (Elmore et al., 2014).

8. Acetals are sensitive to hydrolysis and may hydrolyse into the parent flavouring compound and PG in the high humidity environment in the respiratory tract or as part of the metabolic pathway (Costigan et al., 2014). Nevertheless, an indication of whether this reaction is likely to occur should be sought in the literature. If new degradation or reaction products are identified, then such products should be assessed using the steps described above.

Step 1a Does the flavouring compound undergo full breakdown?

Description

9. It is expected that different flavouring compounds with undergo thermal degradation or react with other constituents of e-liquids to different degrees. If 100 % breakdown does not occur then the parent flavouring compound will also need to be assessed for its toxicity as well as breakdown products.

Data sources

10. Literature should be searched to identify if the flavouring compound undergoes full or partial thermal degradation at temperatures similar to those reached by E(N)NDS. Similarly, does it fully react with other constituents of e-liquids or is the parent flavouring compound still expected to be present?

Step 1b Are the reaction products different from those from culinary use?

Description

11. Reactions between flavouring compounds and PG are not specific to E(N)NDs liquids. Elmore *et al.* (2014) reported that under acidic or basic conditions, PG can react with food flavourings to give rise to new compounds. Hence, if the use of flavouring compounds in E(N)NDS results in degradation products (thermal or otherwise), information should be sought on whether they are also formed on culinary use of the flavouring. If so, an estimate of systemic exposure by the respective routes should be obtained.

Data sources

12. Literature should be searched to identify if thermal degradation products formed on heating the flavouring compound are different from those formed on culinary use.

Step 1c Determine the TTC structural class for the flavouring compound and degradation/reaction products. Does the intake via E(N)NDs use exceed the TTC value?

Description

13. The Threshold of Toxicological Concern (TTC) approach utilises generic exposure levels for chemicals, below which the probability that they would cause adverse health effects is low. The TTC approach integrates data on exposure, chemical structure, metabolism, and toxicity consistent with chemical risk assessment principles (EFSA/WHO, 2016). The TTC is intended to provide a health-protective approach in situations where it is not feasible to obtain chemical-specific data, such as impurities and breakdown or reaction products, or where evaluation of a large number of compounds with low exposure is required, such as for flavouring compounds. The TTC approach has been used to evaluate flavouring substances by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the EC Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA), albeit via the oral route of exposure (EFSA/WHO, 2016).

14. Carthew et al. (2009) and Escher et al. (2010) have adapted the oral TTC approach for the inhalation exposure of chemicals. However, due to the limited number of chemicals included in the databases on which the proposed TTC values are based, route-to-route extrapolation from the oral values is currently considered more appropriate. In such cases, bioavailability from the different routes of exposure should be taken into account. As a default, 100 % bioavailability on inhalation should be assumed (ECHA, 2017a).

Outcome of step 1

15. Flavouring compounds, degradation and/or reaction products that are different to those produced from culinary use, and that do not have sufficient information for application of the framework for risk assessment should be evaluated using the TTC approach with route to route extrapolation from oral values. TTC should be used as part of the weight of evidence assessment of the use of the flavouring in E(N)NDS liquids. Those compounds that exceed their appropriate TTC value should be evaluated for their suitability for use in E(N)NDS liquids. Those that do not exceed the TTC value would not be expected to be of health concern.

16. Flavouring compounds, degradation and/or reaction products that are not different than those produced from culinary use should be assessed with respect to the similarity or difference in the systemic toxicity via oral or inhalation exposure at Step 4 of the framework.

Step 2 Is the flavouring compound classified for CMR, acute toxicity (category 1 or 2) or skin sensitisation?

Carcinogenicity / Mutagenicity / Reproductive and developmental toxicity

Description

17. In general food flavouring compounds should already have been assessed for carcinogenicity, mutagenicity and reproductive and developmental toxicity (CMR) in determining their suitability for use in food (Costigan *et al.*, 2014). However, as different regions may have different classification criteria some exceptions may exist. Therefore, flavourings under consideration should initially be screened for CMR.

Data sources

- IARC
- Harmonised classification for CMR[1]
- Candidate list of substances of very high concern (SVHCs)
- QSARs
- Self-notified classification and labelling (C+L) classification for CMR[2]

18. Flavouring compounds that have been classified as being carcinogenic by the International Agency on Research on Cancer (IARC) and their mode of action should be identified. In addition, those that have a Harmonised classification for CMR and those which have been included on the Candidate list[3] of SVHCs under the

[1] A harmonised classification is a classification for a substance that has been agreed by independent experts at European level, and then made mandatory by law. A harmonised classification is legally binding and suppliers are obliged to use these classifications.

[2] Self-classification is the process through which the supplier classifies the chemicals directly, and where no harmonised classifications are available for the substances involved.

[3] Chemicals that are deemed to be substances of very high concern (SVHCs) based on their hazard are placed on the Candidate list. EU or EEA suppliers of articles which contain substances on the Candidate List in a

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations, based on carcinogenicity (Article 57a), mutagenicity (Article 57b) or toxic to reproduction (Article 57c) should be identified. Chemicals that have been self-notified as being CMR should also be listed.

19. Predictions using QSAR models should also be carried out. Other than DNA-reactivity, predictions should be used as part of an overall weight of evidence approach. Many statistical and mechanistic QSAR models are available to detect mutagenicity, mainly through DNA-reactivity, although fewer models are available for carcinogenicity and reproductive toxicity, due to the complexity of the mechanisms involved. Read across may also be used to predict the CMR potential of the flavouring compounds. Results from the C+L notifications may be used in a weight of evidence approach, along with read across predictions and data from QSAR modelling.

Acute toxicity

Description

20. Acute toxicity refers to serious adverse health effects occurring after a single or short-term oral, dermal or inhalation exposure to a substance (ECHA, 2017a; GHS, 2017).

Data sources

- Harmonised classification for acute toxicity
- Self-notified C+L classification for acute toxicity

21. Acute toxicity data such as LC50 values via the inhalation route should be noted.

Skin Sensitisation

Description

22. Skin sensitisation refers to an allergic response following skin contact to a substance. Following a subsequent re-exposure, an immunological mechanism resulting in adverse health effects on the skin (allergic contact dermatitis), can occur (GHS, 2017).

Data sources

- Harmonised classification for skin sensitisation
- QSARs
- Self-notified C+L classification for skin sensitisation
- Clinical reports and observations

concentration above 0.1% w/w have to provide sufficient information to allow safe use of the article to their customers.

23. Flavouring compounds that have a Harmonised classification for skin sensitisation should be identified. Chemicals that have been self-notified as being a skin sensitiser should be noted. Predictions using QSAR models should also be carried out. Many statistical and mechanistic QSAR models are available to detect skin sensitisation as the steps in the adverse outcome pathway are well understood and serve to describe the applicability domain of a QSAR model or form the basis for grouping substances into chemical categories. Therefore, read across following the Read Across Assessment Framework (RAAF) guidance (ECHA, 2017b), may, also be used to predict the skin sensitisation potential of the flavouring compounds. Results from the C+L notifications may be used in a weight of evidence approach, along with read across predictions and data from QSAR modelling (ECHA, 2017a).

Outcome of step 2

24. Flavouring compounds that have a harmonised European classification for CMR or acute toxicity (category 1 or 2) or skin sensitisation (category 1) should be evaluated for their suitability for use in E(N)NDs liquids. The severity and incidence of effect should be considered. A risk assessment should be carried out, potentially using a margin of exposure (MOE) approach.

25. Depending on the mode of action (MOA) and other relevant toxicological information, the suitability of flavouring compounds should also be considered for their use in E(N)NDs liquids if they are classed as being carcinogenic by IARC.

26. Compounds should be considered for risk assessment if other data sources described above or other available evidence based on weight of evidence and expert judgement indicate the possibility of the flavouring compounds exerting CMR, acute toxicity or skin sensitisation.

27. If flavouring compounds are not classified as CMR, an acute toxin or a skin sensitiser then local effects on the lung should be considered (step 3).

Step 3 Does the flavouring compound exert any local effects by inhalation or effects on the lung?

28. A chemical may induce local or systemic effects. A local effect, such as respiratory irritation, ciliary loss, mucous thickening and pneumonitis, is one that is observed at the site of contact, irrespective of whether the chemical is systemically available.

Respiratory irritation

<u>Description</u>

29. The term respiratory irritation is used to indicate two different toxicological effects, namely cytotoxic effects in the respiratory tract and sensory irritation (ECHA, 2017a; GHS, 2017).

30. Cytotoxic effects in the respiratory tract are comparable to dermal and eye irritation, consisting of inflammation (increased blood flow, local infiltration with white blood cells, swelling, oedema), haemorrhage, and eventual necrosis and other pathological changes. Such effects are potentially reversible, depending on the severity, which is dependent on the concentration and duration of exposure. However, chronic irritation can lead to progressive and ultimately irreversible effects such as fibrosis. In addition, the resultant repeated episodes of cell proliferation in the affected tissues, may increase the risk of local tumour development.

31. In contrast, sensory irritation refers to the local interaction of a substance with the autonomic nerve receptors that are widely distributed in the mucosal tissues of the upper respiratory tract. Sensory irritation leads to pain, burning sensation, and tingling, the severity depending on the airborne concentration of the irritant rather than duration of exposure. Sensory irritation is a receptor-mediated effect, and usually occurs almost immediately upon exposure to the inhaled irritant, leading to reflex involuntary responses such as sneezing, lacrimation, rhinorrhea, coughing, vasodilatation of blood vessels in the nasal passages, and changes in the rate and depth of respiration (ECHA, 2017a). It should be noted that sensory irritation is not the same as local irritation (see paragraph 30), and does not itself progress to any pathological outcome.

32. To date there are no recognised tests for acute respiratory irritation. Acute inhalation studies including histopathological evaluation of the respiratory tract and/or examinations of nasal or bronchioalveolar lavage fluid as well as repeated inhalation studies may provide some information. Substances that cause respiratory tract irritation via a local cytotoxic effect are classified as STOT SE category 3. Those that cause respiratory tract corrosion are classified as STOT SE category 1 or 2, depending on the dose level required to cause the toxicity.

33. In rodents, sensory irritation leads to a reduction in respiratory rate, which can be determined experimentally by measuring the RD50 (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). Tisserand and Young (2014) reported that RD50 values correlate well with log lowest observed adverse effect levels (LOAELs) in humans, and is a standard measure of sensory irritation for humans.

34. Recent studies identified transient receptor potential (TRP) ion channels TRPA1 and TRPV1 to be the receptors for irritant aldehydes in airway-innervating nerves. They are activated by flavour compounds, such as aldehydes, 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)). 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 RD50.

35. As well as determining the RD50 from animal data or in vitro data, the extent of mucous membrane irritation can be directly related to physico-chemical parameters (ECETOC, 2006). An increased vapour pressure was shown to be correlated with an increased RD50 and a decrease in log octanol-air partition coefficient (Kow) was related to a decrease in RD50. Thereby both could be used as a predictor of the severity of the sensory irritation (ECETOC, 2006). An ECETOC Task Force, set up to formulate appropriate guidance for data-poor substances, derived a relationship to predict the RD50 from the air-water partition coefficient (Kaw) and the Kow using the equation below.

Log RD50 = b0 + b1 x log Kow + b2 x log Kaw

Where:

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

36. 0.03 x RD50 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 RD50 was <1000 ppm.

Data sources

- Harmonised classification
- Self-notified C+L classification
- RD50 (in vivo data/in vitro data/physico-chemical properties)
- Clinical reports and observations

37. It should be documented if the flavouring compound has been classified on Specific Target Organ Toxicity following a single exposure (STOT SE) via the oral or inhalation route. If a risk-based approach is applied, potency should be considered as well as the effect.

Respiratory sensitisation

Description

38. Respiratory sensitisation refers to hypersensitivity of the airways after inhalation of a substance (GHS, 2017). Based on current knowledge, the induction of respiratory sensitisation can occur via inhalation or dermal exposure to the sensitising substance (Redlich, 2010 and Kimber et al., 2015 cited in ECHA (2017a)). Inhalation of e-liquids containing respiratory sensitisers could, over time, lead to IgE-mediated responses, similar to hay fever and occupational asthma. This may ultimately lead to anaphylactic responses (Costigan et al., 2014).

Data sources

- Harmonised classification for respiratory sensitisation
- Candidate list of SVHCs

- Self-notified C+L classification for respiratory sensitisation
- Clinical reports and observations

39. There are currently no recognised and validated animal or in vitro models for testing respiratory hypersensitivity (ECHA, 2017a; GHS, 2017).

40. Hazard identification and the derivation of tolerable doses are therefore usually based on a weight-of-evidence approach, predominantly from clinical and occupational data, both of which play an important role in identifying any potential hazards. A number of structural alerts for respiratory sensitisation have been identified. Various quantitative structure-activity relationship (QSAR) models contain alerts, including MCASE, Danish (Q)SAR database and Derek Nexus, although they are derived from chemical asthmagens rather than specific respiratory allergens (ECHA, 2017a). The OECD toolbox also contains a profiler (set of rules and structural alerts) for respiratory sensitisation. The profiler helps in grouping substances that share common structural alerts and possibly predicts the respiratory sensitisation potential via read-across (ECHA, 2017a). The RAAF published by ECHA in 2017 can be used as guidance for carrying out read across (ECHA, 2017b).

41. Flavouring compounds that have been included in the Candidate list of SVHC under REACH, based on respiratory sensitising properties (Article 57(f)) should be identified, and those that have been self-notified as being a respiratory sensitiser should be noted. Where the possibility of respiratory sensitisation has been identified using QSAR models or via read-across, this should also be noted.

Effects on the lung

Description

42. Flavouring compounds that have been included in the Candidate list as being a SVHC under REACH based on specific target organ toxicity after repeated exposure (STOT RE), citing the lung as the target organ, (Article 57(f)) and those that have a Harmonised classification should be identified. Those that have been self-notified as causing STOT RE should be noted.

Data sources

- Harmonised classification
- Candidate list of SVHCs
- Self-notified C+L classification

Outcome of step 3

43. Flavouring compounds that have a harmonised European classification for skin or respiratory sensitisation, respiratory irritation or STOT RE with the lung as a target organ should be considered for their suitability in E(N)NDs liquids. The severity and incidence of effect should be considered. A risk assessment should be carried out, potentially using a MOE approach.

44. Depending on the MOA and other relevant information, flavouring compounds should also be considered for their suitability in E(N)NDs liquids if they are on the Candidate list based on respiratory sensitisation.

45. Compounds may also be undesirable based on weight of evidence and expert judgement if other data indicate the possibility of the flavouring compounds exerting respiratory sensitisation effects.

46. For sensitisation effects, it may be possible to identify a threshold below which the risk of sensitisation would be very low using, for example, human no expected sensitisation induction levels (NESILS).

47. If flavouring compounds do not exert local effects on the lung then systemic effects via inhalation and ingestion should be assessed, taking into consideration differential metabolism, under Step 4.

Step 4 Does the chemical cause different systemic target organ toxicity via inhalation compared to ingestion, taking any differential metabolism into account?

Description

48. A chemical may induce local or systemic effects. A systemic effect is one that is observed distant to the site of contact as the chemical becomes systemically available. Secondary effects may occur as a consequence of local effects (ECHA, 2017a; Kuwabara et al., 2007). Local effects are described in paragraph 28.

49. As noted above, many E(N)NDS flavourings are food flavourings, and as such there is information on systemic repeat dose toxicity following oral exposure. However, in general few data are available on the toxicity following inhalation exposure.

Data sources

- Harmonised classification for STOT RE (any organ apart from lung)
- Candidate list of SVHCs
- Self notified C+L classification for STOT RE (any organ apart from lung)
- ADME data
- Evaluations for use as food flavouring
- Clinical reports and observations

50. Flavouring compounds that have been included in the Candidate list as being a SVHC under REACH based on STOT RE (Article 57(f)) and those that have a Harmonised classification should be identified. Those that have been self-notified as causing STOT RE should be noted.

51. If systemic toxicity is observed via the oral route of exposure, it must be determined if the toxic effects would also occur via inhalation. Kinetic data such as

absorption, metabolism, distribution and excretion (ADME) should be collated to assess if the chemical and/or metabolites are likely to reach the systemic circulation following inhalation and oral exposure and at what level. It is especially important to understand the metabolism of the flavouring compound as first pass metabolism may occur following ingestion which will not occur following inhalation. In some cases, this may result in a reactive metabolite that would not occur following inhalation. Conversely, metabolism may deactivate the flavouring compound hence exposure via inhalation may result in greater systemic toxicity.

52. Information relevant for repeated dose toxicity can also be obtained from data on other endpoints, route-to-route extrapolation from oral studies, structural analogues and physico-chemical properties. It might also be possible to use read across to predict the target organ toxicity via repeated exposure. Results from the C+L notifications may be used in a weight of evidence approach, along with read across predictions and results from QSAR modelling (ECHA, 2017a).

Outcome of step 4

53. The repeat dose toxicity potential should be used in a weight of evidence judgement with data on the other endpoints.

54. If flavouring compounds exert different toxicity via inhalation compared with ingestion, the severity and incidence of effect should be considered. A risk assessment should be carried out, potentially using a MOE approach.

55. If flavouring compounds exert similar toxicity via inhalation compared with ingestion, then the exposure levels via E(N)NDs use should be considered at Step 5.

STEP 5 Are the resulting exposure levels via E(N)NDs use higher than those from culinary use?

Description

56. Exposure to flavouring compounds via E(N)NDs use is important to assess the risk. If exposure is similar to or lower than that from culinary use, then the flavouring compound would not be expected to be of health concern.

Data sources

57. Exposure data would need to be gathered including the concentration of the flavouring compound in the aerosol and intake calculations made using generic assumptions regarding E(N)NDs use.

Outcome of step 5

58. If the exposure levels via E(N)NDs use are higher than those from culinary use, then levels should be compared against the relevant health-based guidance value (HBGV) or TTC value. Those compounds that exceed their appropriate HBGV/TTC value should be evaluated for their suitability for use in E(N)NDs liquids.

Those that do not exceed the HBGV/TTC value would not be expected to be of health concern.

59. If the exposure levels via E(N)NDs use are similar to or lower than those from culinary use, then the flavouring compound is not expected to be of health concern to the user. Assessment of risk to bystanders would require an appropriate estimate of exposure for comparison with the HBGV/TTC.

Summary

60. Flavouring compounds are commonly used in E(N)NDS liquids. Despite being approved for use in food, few have undergone acute or chronic toxicity testing via the inhalation route. Therefore, this framework aims to provide a number of steps designed as a set of principles to guide the risk assessment process for a flavouring compound in E(N)NDS.

61. A number of toxicological endpoints have been included in the framework. Data may be obtained from a number of sources, including evaluations by authoritative bodies such as IARC, EU Harmonised classifications or inclusion on the Candidate list for being an SVHC. Non-animal data may also be used in QSAR modelling and the TTC approach. Using all data available and expert judgement, if the flavouring compound shows the potential to cause any of the endpoints of specific concern, the inclusion of such a flavouring compound in E(N)NDs liquids would need to be justified in the consideration of other legitimate factors in the risk management process.

COT
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Abbreviations/Glossary

ADME	Absorption, metabolism, distribution and excretion
C+L	Classification and labelling
CMR	Carcinogenic, mutagenic, reproductive toxin
E(N)NDS	Electronic Nicotine and Non-Nicotine Delivery Systems
EFSA	European Food Safety Authority
HBGV	Health-based guidance value
IARC	International Agency on Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{aw}	Air-Water Partition Coefficient
K_{ow}	Octanol-Air Partition Coefficient
LOAEL	Lowest observed adverse effect levels
MOA	Mode of action
MOE	Margin of exposure
NESILS	No expected sensitisation induction levels
PAH	Polycyclic Aromatic Hydrocarbon
PG	Propylene Glycol
QSAR	Quantitative structural relationship analysis
RAAF	Read Across Assessment Framework
RD_{50}	The concentration required to reduce the mouse respiratory rate by 50 %
REACH	Registration, Evaluation, Authorisation and restriction of CHemicals
SCF	Scientific Committee on Food
STOT RE	Specific Target Organ Toxicity following a repeated exposure
STOT SE	Specific Target Organ Toxicity following a single exposure
SVHC	Substance of very high concern
TRP	Transient receptor potential
TSNA	Tobacco-Specific Nitrosamine
TTC	Threshold of Toxicological Concern
VG	Vegetable Glycerol

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