TOX/2019/37

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 11: Decision tree for risk assessing flavouring compounds in E(N)NDS

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 be referred to as E(N)NDS).

2. A number of flavourings are used in E(N)NDS liquids, the toxicity of which has been evaluated via the oral route as many are used to flavour food. However, their toxicity via inhalation has been less well studied and hence few data are available on which to assess the toxicity of flavouring compounds via this route.

3. Two flavouring compounds were considered at the May 2019 COT meeting (TOX/2019/24 and 25), and it was agreed that it would be helpful to develop a decision tree to best utilise the available information for such compounds and focus on potential for toxicity specifically following use in E(N)NDS. This paper provides a draft of such a decision tree that could be used in the risk assessment of flavouring compounds following inhalation.

Introduction

4. 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). 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 conventional

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.

5. 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.

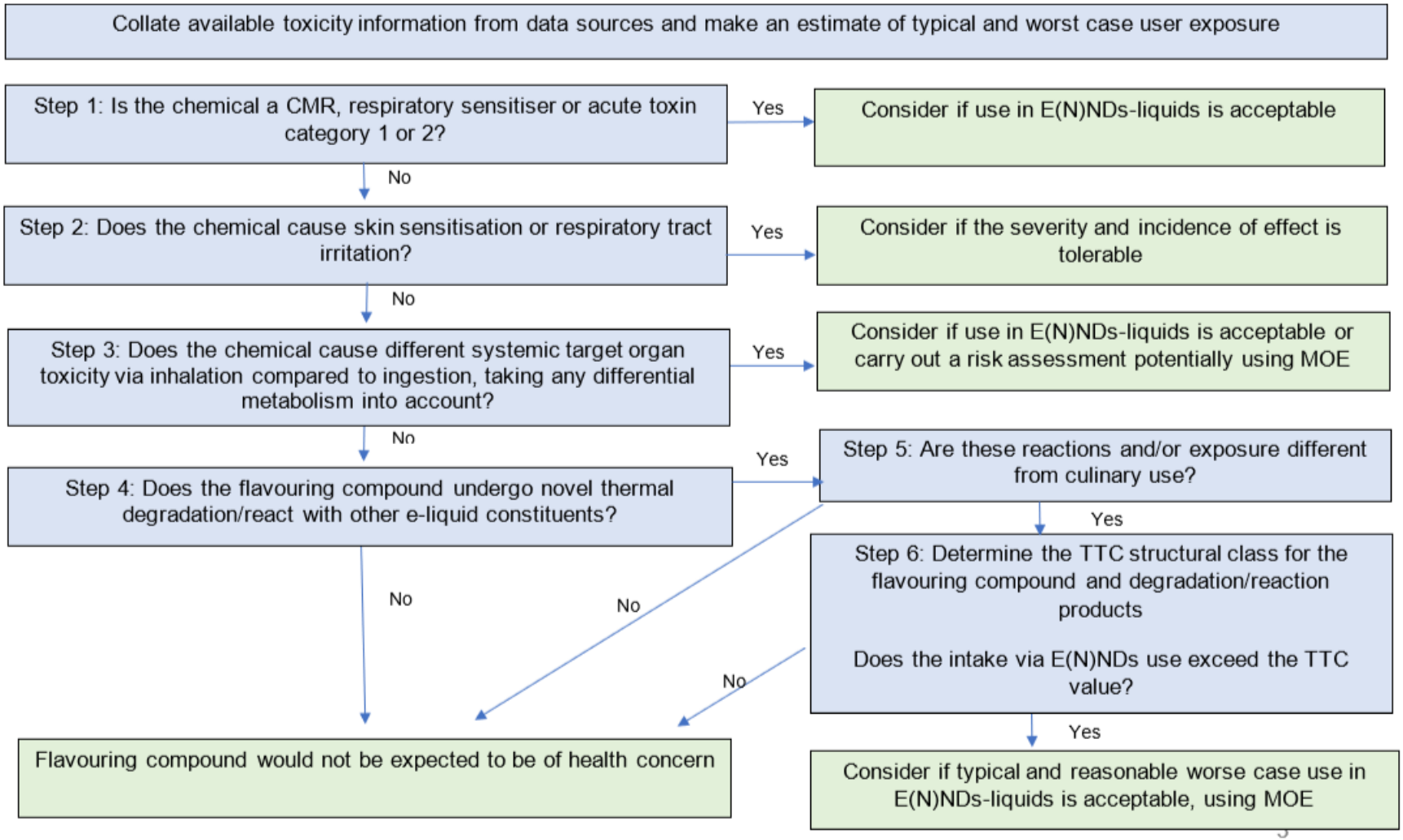
6. Flavouring compounds are one of the five most commonly listed ingredients in E(N)NDS liquids, along with PG, VG, nicotine and water. Over 7000 unique flavours are reportedly available (Erythropel et al., 2018; Zhu and Bonnevie, 2014) although information is not available on the dominant compounds on the UK market.

7. 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 inhalation route (Fowles and DiBartolomeis, 2017).

Decision tree

8. The draft decision tree 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. Decision tree for the risk assessment of flavouring compounds via inhalation exposure



Carcinogenicity / Mutagenicity / Reproductive and developmental toxicity

Description

9. In general food flavouring compounds should already be assessed for carcinogenicity, mutagenicity and reproductive and developmental toxicity (CMR) (Costigan et al., 2014). However, as different regions may have different classification criteria some exceptions may exist. Therefore, chemicals 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 C+L classification[2]

10. 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 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. Annex A gives an overview of the classification categories.

11. 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

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

flavouring compounds. Results from the classification and labelling (C+L) notifications may be used in a weight of evidence approach, along with read across predictions and data from QSAR modelling.

Outcome

12. Depending on the MOA and other relevant information, flavouring compounds would be undesirable in E(N)NDs liquids if they are classed as being carcinogenic by IARC or if they have a Harmonised classification for CMR. Compounds may also be undesirable based on a weight of evidence and expert judgement i.e. if other data described above indicate the possibility of the flavouring compounds exerting CMR effects.

Acute toxicity

Description

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

Data sources

- Harmonised classification
- Self-notified C+L classification

14. Acute toxicity data such as LC50 values via the inhalation route should be noted. It should also be documented if the flavouring compound has been classified on Specific Target Organ Toxicity following a single exposure (STOT SE) via oral or inhalation exposure (see irritation section). Annex A gives an overview of the classification categories. If a risk-based approach is applied, potency should be considered as well as the effect.

Outcome

15. Flavouring compounds would be undesirable in E(N)NDs liquids if they have a Harmonised classification for acute toxicity via the inhalation route.

Respiratory Sensitisation

Description

16. Respiratory sensitisation refers to hypersensitivity of the airways after inhalation of a substance (GHS, 2017). Based on the 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 (2017)). Inhalation of e-liquids containing respiratory sensitisers (i.e. type I allergens and causative agents of immediate hypersensitivity) could, over time, lead to IgE-

mediated responses, similar to hay fever and occupational asthma (e.g. perennial rhinitis, eczema, breathing difficulties and bronchoconstriction). This may ultimately lead to anaphylactic responses (Costigan et al., 2014).

Data sources

- Harmonised classification
- Candidate list of SVHCs
- Self-notified C+L classification
- Clinical reports and observations

17. There are currently no recognised and validated animal or in vitro models for testing respiratory hypersensitivity (ECHA, 2017; GHS, 2017). Annex A gives an overview of the classification categories.

18. 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 structural relationship analysis (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, 2017). 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, 2017).

19. 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. Identification of structural alerts for respiratory sensitisation using QSAR models and a possible prediction via read-across should be carried out. The Read Across Assessment Framework (RAAF) published by ECHA in 2017 can be used as guidance for carrying out read across.

Outcome

20. Flavouring compounds would be undesirable in E(N)NDs liquids if they have a harmonised European classification for respiratory sensitisation or are on the Candidate list based on respiratory sensitisation. Compounds may also be undesirable based on a weight of evidence and expert judgement i.e. if other data described above indicate the possibility of the flavouring compounds exerting respiratory sensitisation effects.

Skin Sensitisation

Description

21. 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
- QSARs
- Self-notified C+L classification
- Clinical reports and observations

22. 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 RAAF guidance, 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, 2017). Annex A gives an overview of the classification categories.

Outcome

23. Flavouring compounds would be undesirable in E(N)NDs liquids if they have a Harmonised classification for skin sensitisation. Compounds would also be considered undesirable based on a weight of evidence and expert judgement.

24. 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).

Respiratory tract irritation

Description

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

26. 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, resulting repeated episodes of cell proliferation in the affected tissues, may increase the risk of local tumour development.

27. In contrast, sensory irritation refers to the local interaction of a substance with the autonomic nerve receptors that widely distributed in the mucosal tissues of the upper respiratory tract. Sensory irritation leads to pain, burning, pungency, 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, 2017). It should be noted that sensory irritation is not the same as local irritation, and does not progress to any pathological outcome.

28. To date there are no recognised tests for acute respiratory tract irritation. Acute inhalation studies including histopathological evaluation of the respiratory tract and/or examinations of nasal or bronchioalveolar lavage 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. Annex A gives an overview of the classification categories.

29. In rodents, sensory irritation leads to a reduction in respiratory rate, which can be determined experimentally by measuring the RD_{50} (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, and is a standard measure of sensory irritation for humans.

30. In vitro tests quantifying the capability of a chemical to activate transient receptor potential (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 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)).

31. As well as determining the RD_{50} 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 RD_{50} and 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). An ECETOC Task Force, set up to formulate appropriate guidance for data-poor substances, 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

32. $0.03 \times RD_{50}$ 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.

Data sources

- RD_{50} (in vivo data/in vitro data/physchem data)
- Clinical reports and observations

Outcome

33. The respiratory tract irritation potential should be used in a weight of evidence with data on any other endpoints, based on expert judgement.

Repeat dose toxicity

Description

34. A chemical may induce local or systemic effects. A local effect, such as respiratory tract irritation described above, is one that is observed at the site of contact, irrespective of whether the chemical is systemically available. 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, 2017; Kuwabara et al., 2007).

35. 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, few data are available on the toxicity via inhalation.

Data sources

- Harmonised classification

- Candidate list of SVHCs
- Self notified C+L classification
- ADME data
- Evaluations for use as food flavouring
- Clinical reports and observations

36. 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) (Article 57(f)) and those that have a Harmonised classification should be identified. Annex A gives an overview of the classification categories. Those that have been self-notified as causing target organ toxicity after repeated exposure should be noted. If systemic toxicity is observed via the oral route of exposure, it must be determined if the toxic effects would also occur via inhalation. First pass metabolism may occur following ingestion which will not occur following inhalation. In some cases this may result in a reactive metabolite that may not occur following inhalation. Conversely, metabolism may deactivate the flavouring compound hence exposure via inhalation may result in greater systemic toxicity.

37. 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. Read across may also be used 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 data from QSAR modelling (ECHA, 2017).

38. Kinetic data such as absorption, metabolism, distribution and excretion (ADME) should be collated to assess if the chemical is likely to reach the systemic circulation. It is important to understand the metabolism of the flavouring compound. First pass metabolism may occur following ingestion which will not occur following inhalation.

Outcome

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

Thermal degradation or reaction products

Description

40. During E(N)NDS use, the vaporisation temperature has been estimated to vary between 40 and 180 °C. The heating period, influenced by the temperature, length of puff, air flow of the individual puff and how recently the coil was changed introduces 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 in their risk assessment (Costigan and Meredith, 2015).

Data sources

41. 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).

42. These reactions are not specific to E(N)NDs liquids as 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.

43. 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 discussed above.

Outcome

44. If degradation or reaction products are formed, they should undergo a toxicological risk assessment following the steps in the decision tree.

Threshold of toxicological concern

Description

45. The Threshold of Toxicological Concern (TTC) is a principle that refers to the establishment of a generic exposure level 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 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).

46. Although the TTC approach has traditionally been used to assess the risk from oral exposure to chemicals, Carthew et al. (2009) and Escher et al. (2010) adapted the TTC approach for the inhalation exposure of chemicals. Carthew et al. (2009) suggested that not all classes of chemicals are suitable for such an approach, but for chemicals with a predictable low potential toxicity, and very low levels of exposure, the TTC approach could be used. Consideration should be made over whether user exposure to a flavouring compound in an E(N)NDs liquid will result in exposure above the relevant TTC level. If this is the case, a substance specific evaluation would be required.

47. Escher determined TTC values of 71 and 4 µg/day for Cramer class 1 and 3[4], respectively, based on data from 203 chemicals in the RepDose database for industrial chemicals. When genotoxins and organophosphates were excluded, TTC values were 180 and 4 µg/day for Cramer class 1 and 3, respectively. These inhalation values are significantly lower that the oral thresholds originally derived (1800 and 90 µg/day). Authors suggested that the difference could be due to the high sensitivity of the respiratory tract to local effects.

48. In contrast, based on 92 rat inhalation studies on consumer aerosol products Carthew et al. (2009) derived TTC values for systemic effects of 980 and 170 µg/day and 1400 and 470 µg/day for localised effects, for Cramer class 1 and 3 respectively (excluding genotox carcinogens). The authors stated that it was reassuring that there were not large differences between the TTC values derived from oral and inhalation studies and that the values for inhalation systemic TTCs lie within the range of 1800–90 µg/day for the oral Cramer classes 1 and 3 TTC values.

49. 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 may be also considered (SCCS/SCHER/SCENIHR., 2012). In such cases, bioavailability from the different routes of exposure should be taken into account.

Outcome

50. Flavouring compounds, degradation and/or reaction products without sufficient information for a full assessment using the decision tree should be

[4] Chemicals are designated to Cramer class I, II or III depending on their chemical structure. Class I: Substances of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity. Class II: Substances that are intermediate. They possess structures that are less innocuous than those in Class 1 but they do not contain structural features that are suggestive of toxicity like those in Class 3 Class III: Substances with chemical structures that permit no strong initial impression of safety and may even suggest a significant toxicity.

assessed using the TTC approach using inhalation values or using route to route extrapolation from oral values. TTC should be used as a weight of evidence for the use of the flavouring in E(N)NDs liquids. Those compounds that exceed the TTC value would be undesirable in E(N)NDs liquids.

Summary

51. 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 decision tree 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.

52. A number of toxicological endpoints have been included in the decision tree. 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 listed, it would be undesirable to include the flavouring compound in E(N)NDs liquids.

Questions for the Committee

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

i. Can the Committee comment on each step and the design of the decision tree?

ii. Should a hazard- or risk-based approach be adopted?

iii. Are the included steps sufficient to aid assessment of flavouring compounds?

iv. If a TTC approach is included, which threshold values should be recommended?

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

ADME	Absorption, metabolism, distribution and excretion
C+L	Classification and labelling
CC	Conventional cigarette
CEL	Consumer estimated worst case exposure level
CMR	Carcinogenic, mutagenic, reproductive toxin
DST	Dermal sensitisation threshold
E(N)NDS	Electronic Nicotine and Non-Nicotine Delivery Systems
EFSA	European Food Safety Authority
ENDS	Electronic Nicotine Delivery Systems
FDA	US Food and Drug Administration
GRAS	Generally Regarded As Safe
IARC	International Agency on Research on Cancer
IFRA	International Fragrance Association
JECFA	Joint FAW/WHO Expert Committee on Food Additives
K_{aw}	Air-Water Partition Coefficient
K_{ow}	Octanol-Air Partition Coefficient
LED	Light-Emitting Diode
LOAEL	Lowest observed adverse effect levels
MHRA	Medicines and Healthcare Products Regulatory Agency
NESILS	No expected sensitisation induction levels
PAH	Polycyclic Aromatic Hydrocarbon
PG	Propylene Glycol
QSAR	Quantitative structural relationship analysis
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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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Decision tree for risk assessing flavouring compounds in E(N)NDS

Annex A

The following tables describe the hazard categories for the endpoints discussed in the document according to Guidance to Regulations (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5).

Tables include:

Table 3.6.1: Hazard categories for carcinogens

Table 3.5.1: Hazard categories for germ cell mutagens

Table 3.7.1 (a): Hazard categories for reproductive toxicants

Table 3.1.1: Acute toxicity hazard categories and acute toxicity estimates (ATE) defining the respective categories

Table 3.4.1. Hazard category and sub-categories for respiratory sensitisers

Table 3.4.2. Hazard category and sub-categories for skin sensitisers

Table 3.8.1. Categories for specific target organ toxicity-single exposure

Table 3.9.1. Categories for specific target organ toxicity-repeated exposure

These tables are provided; for copyright reasons the content of this Annex is not included in the published version on the COT website.