Requirements for flavour substances in e-liquids used in electronic cigarettes

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Supervised by:
Dr. Franz Fiala

FORCE Technology
Department of Plastics, Composites and Surface characterisation
Group of Applied Environmental Assessment
Pia Brunn Poulsen
Charlotte Merlin
Mirko Miseljic

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Summary

Smoking by use of electronic cigarettes (e-cigarettes) is a new phenomenon. BfR, the German Federal Institute for Risk Assessment, prepared in 2012 an opinion on liquids in e-cigarettes and concluded that e-cigarettes cannot be considered safe with respect to health effects. An important risk factor is posed through inhalation of nicotine, however, additional ingredients of the liquids such as solvents, various scent and aroma (flavour) substances and contaminants can pose health risks (BfR, 2012).

Today, EU legislation exists concerning nicotine containing e-cigarettes (EU Directive no. 40, 2014), which among other things sets requirements for the purity of the ingredients used in e-liquids as well as a requirement of only using ingredients which do not pose a threat to human health. However, requirements for the total content of chemical substances in e-liquids are limited – except for a requirement of the level of nicotine in the e-liquids. Standards are now under development in relation to CEN/TC 437 "Electronic cigarettes and e-liquids", which was established in 2015.

During 2017, FORCE Technology carried out two projects for the Austrian Consumer Council at the Austrian Standards International:

- "Requirements for substances in e-liquids used in electronic cigarettes" (Poulsen et al., 2017a)
- "Requirements for substances formed or released during the evaporation of e-liquids used in electronic cigarettes" (Poulsen et al., 2017b)

The purpose of these two former projects was to look more closely at the substances used in e-liquids and the substances formed from e-cigarettes during the evaporation of e-liquids. Based on existing threshold limit values for inhalation for selected substances and a very rough calculation of the expected exposure to the ingredients and formed substances, a proposal for limit values for selected ingredients and substances formed was calculated based on risk assessment principles. In the former study on substances in e-liquids, 15 ingredients in all were selected for further review and a proposal for a limit value of these ingredients in e-liquids was calculated. Eight of these 15 ingredients were fragrances, aroma substances or flavour substances.

The purpose of this study is to go into more details with the flavour substances used in e-liquids for electronic cigarettes and develop a proposal for requirements for a selection of these substances in e-liquids based on available toxicological data for the substances or based on relevant existing threshold values for the selected substances. The focus will be on substances in e-liquids and not the substances formed by evaporation.

The study is based on and further elaborates on the information and work carried out in the former project "Requirements for substances in e-liquids used in electronic cigarettes" carried out for the Consumer Council at Austrian Standards International.

This project is carried out as a desk-top study and includes a summary of the former project on e-liquids "Requirements for substances in e-liquids used in

electronic cigarettes" (Poulsen et al., 2017a). As a starting point, the flavour substances identified in the former project on e-liquids were used (about 70 flavour substances). In addition, a screening (an internet search) for flavour substances used in e-liquids was carried out and resulted in a total list of about 170 different flavour substances. Furthermore, a search for used concentrations of the different flavour substances in e-liquids was performed. Based on this information, the flavour substances were prioritised and a search for toxicological information (existing relevant threshold limit values) for the first 55 flavour substances on the list was performed. Finally, a total of 35 flavour substances – for which existing threshold limit values were identified – was selected for a calculation of limit values (concentrations in e-liquids). The proposed preliminary calculated limit values for the 35 selected ingredients in e-liquids are presented in chapter 6 "Preliminary proposal for requirements for selected flavour substances".

It must be pointed out that the calculations performed in this report are made on a screening level, which means that a simple 'worst case' calculation has been made. In this worst-case calculation, it has been assumed that all of the substance contained in the e-liquid is evaporated, and all of the substance evaporated is inhaled, and finally that all of the inhaled substance is absorbed in the body. This result is most likely an overestimation of the actual absorption of the substances in the e-liquids into the human body by vaping on e-cigarettes and thereby calculation of lower limit values than actually necessary. However, if no information is available concerning absorption of the substance in the body (no search for this has been made in the preparation of this report), a full absorption (100%) must be used as a precautionary principle. Furthermore, it can of course be discussed whether the correct limit values (DNEL values, LCI values etc.) have been used for the individual substances. In this report, the limit value of the highest quality (i.e. it has been reviewed by experts) has been used and otherwise the lowest limit values identified have generally been used in the calculations. The proposed preliminary limit values in this report should therefore be considered as a first approximation and the risk assessment presented may need further refinement in order to establish limit values for ingredients in e-liquids.

The calculated proposed limit values for the 35 selected flavour substances in e-liquids lie between 28 µg/ml e-liquid (0.003%) for diacetyl and 180,000 µg/ml e-liquid (18%) for vanillin.

In all cases except for one, use concentrations have been identified for the 35 selected flavour substances. These use concentrations are primarily identified through safety data sheets on e-liquids, which means that most use concentrations are given as a concentration range. However, for 27 of the 35 flavour substances where limit values in e-liquids are proposed, the actual identified maximum concentration in an existing e-liquid on the market is higher than the proposed limit value. For additionally three flavour substances, the proposed limit value may be exceeded, but it is difficult to conclude based on the use information in a wide concentration range. This means that it is only for a total of four flavour substances of the 35 reviewed substances, where the maximum use concentration does not exceed the proposed limit value. In most cases, the maximum concentrations found in e-liquids are a factor of 2-10 times higher than the limit values proposed in this report. However, in some cases the maximum concentration identified may be up to 100-200 times higher than the proposed limit value (e.g. for benzaldehyde). This fact suggests that limit values may be needed for flavour substances in e-liquids.

Nevertheless, the available information about the actual minimum concentrations identified in e-liquids suggests that it will be possible for many of the examined flavour substances to meet the proposed limit values. Many of the flavour substances reviewed are only used in a few percentages of the e-liquids on the market. This suggests that it should be possible for many e-liquid products on the market to comply with the proposed limit values. However, in this report, it is not known and has not been discussed which concentrations that are needed for different flavour substances to provide the ‘correct’ flavour to the e-liquids; nor has it been discussed on which level the ‘needed’ concentration is compared to the proposed calculated limit values.

According to the Tobacco Directive, it is only allowed to use ingredients in e-cigarettes and e-liquids which do not pose a risk to human health in heated and unheated form. This review illustrates that flavour substances may be used in concentrations which cannot necessarily be considered as safe. The results of this report and the former report on ingredients in e-liquids emphasise the need for limit values for several of the ingredients used in e-liquids.

Neither the GPS Directive nor the Tobacco Directive contains specific requirements for e-cigarettes and e-liquids. Therefore, it is important that the standards developed set the necessary chemical requirements (for all the necessary ingredients contained in the e-liquids) as well as the correct limit values to protect the consumer from unwanted health effects from vaping on e-cigarettes.

1 Introduction

1.1 Background

Smoking by use of electronic cigarettes (e-cigarettes) is a new phenomenon. In 2012, BfR, the German Federal Institute for Risk Assessment, prepared an opinion on liquids in e-cigarettes and concluded that even though smokers of e-cigarettes do not inhale the characteristic carcinogenic combustion products and substances known to be present in tobacco smoke, e-cigarettes cannot be considered safe with respect to health effects. An important risk factor is posed through inhalation of nicotine. Moreover, additional ingredients of the liquids such as fumigation agents (propylene glycol, glycerine), chemical additives, added pharmacologically active compounds, various scent and aroma substances (e.g. menthol, linalool) and contaminants can pose health risks. Furthermore, BfR states that it is difficult to identify the pollutants that contribute to the contamination of indoor air, as the nature of the substances that are inhaled and exhaled are often unclear (BfR, 2012).

Today, EU legislation exists concerning nicotine containing e-cigarettes (EU Directive no. 40, 2014), which among other things sets requirements for the purity of the ingredients used in e-liquids as well as a requirement of only using ingredients which do not pose a threat to human health. However, requirements for the total content of chemical substances in e-liquids or to the substances being formed during use (evaporation of e-liquids) are limited – except for a requirement of the level of nicotine in the e-liquids. Standards are now under development in relation to CEN/TC 437 "Electronic cigarettes and e-liquids", which was established in 2015.

During 2017, FORCE Technology carried out two projects for the Austrian Consumer Council at Austrian Standards International:

- "Requirements for substances in e-liquids used in electronic cigarettes" (Poulsen et al., 2017a)
- "Requirements for substances formed or released during the evaporation of e-liquids used in electronic cigarettes" (Poulsen et al., 2017b)

The purpose of these two projects was to look more closely at the substances used in e-liquids and the substances formed from e-cigarettes during the evaporation of e-liquids. Based on existing threshold limit values for inhalation for selected substances and a very rough calculation of the expected exposure to the ingredients and formed substances, a proposal for limit values for selected ingredients and substances formed was calculated based on risk assessment principles.

1.2 Purpose

The purpose of this study is to go into more details with the fragrances/aroma/flavour substances used in e-liquids for electronic cigarettes and develop a proposal for requirements for a selection of these substances in e-liquids based on available toxicological data for the substances or based on relevant existing threshold values for the selected substances. The focus will be on substances in e-liquids and not the substances formed by evaporation.

The study will be based on and will further elaborate on the information and work carried out in the former project "Requirements for substances in e-liquids used in electronic cigarettes" carried out for the Consumer Council at Austrian Standards International.

1.3 Definitions

The same definitions as used in the former projects on e-liquids and e-cigarettes carried out for the Consumer Council at Austrian Standards International are used in this report:

According to the Tobacco Directive (EU Directive no. 40, 2014), 'electronic cigarettes' or '**e-cigarettes**', which is the term used in this report, is defined as: "a product that can be used for consumption of nicotine-containing vapour via a mouth piece, or any component of that product, including a cartridge, a tank and a device without cartridge or tank. Electronic cigarettes can be disposable or fillable by means of a refill container and a tank, or rechargeable with single use cartridges".

In this report, the term '**e-liquid**' means any liquid used in e-cigarettes intended for evaporation. The e-liquid may be with or without nicotine. In short, an e-cigarette is a device that is used to transform an e-liquid into an inhalable aerosol. When the e-cigarette user takes a puff on the e-cigarette product, a heating element is activated – and this converts the liquid into an aerosol, which is then taken into the mouth or inhaled, and subsequently exhaled (Colard et al., 2015).

According to the French standard XP D 90-300-2 on electronic cigarettes and e-liquids (Afnor, 2015b), an e-liquid intended for e-cigarettes comprises of the following **ingredients**:

1. A diluent (propylene glycol and/or glycerol and perhaps water)
2. Nicotine, CAS 54-11-5 (may be added)
3. A flavouring compound (may be added)
4. Other ingredients (may be added)

The diluent currently consists mainly of propylene glycol (CAS 57-55-6) and glycerol (CAS 56-81-5) (Afnor, 2015b). However, other diluents such as water or ethanol may be used. A typical composition could be about 80% glycerol and 10% water, or 20-25% glycerol, about 65% propylene glycol and 5-7% water (Tayyarah & Long, 2014). The maximum content of nicotine allowed is 2% if nicotine is added (nicotine-free e-liquids do exist). According to Hutzler et al., 2014, which carried out a chemical analysis of 28 different e-cigarettes, 10 out of 28 e-cigarettes were declared as being "free-of-nicotine", which means that nicotine-free e-cigarette products are on the market.

E-liquids often contain a high number of different **flavouring compounds**. Which flavouring compounds that are used differ a lot between the e-liquids. A specific flavour for e-liquids may for example be fruit such as kiwi, banana, strawberry etc. or coffee/tea flavours such as cappuccino, chai latte etc., or simply just menthol or tobacco flavour. A specific flavour may contain one or most often several flavouring compounds/flavour substances. Examples of flavour substances are vanillin (CAS 121-33-5), menthol (CAS 89-78-1) and trimethylpyrazine (CAS 14667-55-1) according to the findings in Poulsen et al. (2017a). Flavouring compounds are also described as **fragrances** or **aroma substances**, as these flavouring substances are found as fragrances and/or aroma substances in cosmetic products as well. In general, the term 'flavour substances' is used in this report.

Other ingredients can be either deliberately added ingredients such as the pharma ingredient rimonabant (CAS 158681-13-1) or it can be impurities such as tobacco-specific nitrosamines (TSNA) and different metals (elements).

1.4 Summary of the former project on e-liquids

The former project on e-liquids for the Consumer Council at Austrian Standards International ”Requirements for substances in e-liquids used in electronic cigarettes” (Poulsen et al., 2017a) was designed to develop a proposal for requirements for selected substances in e-liquids based on relevant existing threshold values for different chemical substances. The focus was on the substances in e-liquids and not the substances formed by the evaporation. Furthermore, the purpose of the study was to review existing legislation and standards on e-cigarettes, focusing on the requirements for e-liquids.

A review of existing literature listing actual ingredients in e-liquids was carried out. This review resulted in a list of more than 105 ingredients used in e-liquids of which more than 60 different flavour substances were identified as used in e-liquids.

The review of the relevant legislation for e-liquids used for e-cigarettes concluded that the Tobacco Directive is relevant for e-liquids and contains some requirements concerning ingredients in e-liquids. However, the actual chemical requirements are limited and on a more general level. The restrictions for chemical ingredients in e-liquids are limited to the following:

- a specific limit value for nicotine,
- no use of ingredient such as vitamins, caffeine and similar substances,
- no use of ingredients that colour the emissions from e-cigarettes,
- and a general requirement of no use of ingredients that pose a risk to human health (except for nicotine) or are classified as CMR.

The Tobacco Directive, however, only covers e-cigarettes that contain nicotine. Non-nicotine containing e-cigarettes are thereby only covered by the General Product Safety Directive, which only uses a general statement saying that products on the market ‘must be safe’ (including chemical safety).

The review of relevant standards for e-liquids used for e-cigarettes concluded that no standards have been published by the working group CEN/TC 437 “Electronic cigarettes and e-liquids”, which was established in 2015. However, while not considered a standard, a British guidance document exists (BSI, 2015) on this area. Furthermore, a French standard in three parts sets requirements for the e-liquids (part 2) (Afnor, 2015b). The French Afnor (2015b) standard sets specific requirement for five specific substances, elemental impurities as well as no use of specific preservatives, sugars, sweeteners, vitamins, radioactive substances etc. However, there is no general requirement concerning the content of flavour substances in this standard on e-liquids, but a general requirement of no use of substances classified as STOT 1 for the respiratory tract exists.

Therefore, it is concluded in the report that neither legislation nor existing standards are very specific concerning limit values for ingredients used in e-liquids.

In this former report, 15 ingredients were selected for which a proposal for limit values of these ingredients in e-liquids was calculated based on the identified existing TLVs (Threshold Limit Values) and based on simple ‘worst case’ calculations. The ‘worst case’ calculations were based on an assumption that all of the substance contained in the e-liquid has evaporated, and all of the substance evaporated has been inhaled, and finally that all of the inhaled substance has been absorbed in the body. Therefore, it is emphasised in the report that absorption of the substances in the body may be overestimated and the proposed limit values may be lower than necessary.

Seven of the 15 selected ingredients were flavour substances. For five of these flavour substances, no information on existing levels used in e-liquids was found and the calculated proposed limit values could therefore not be compared with actual levels. However, for benzaldehyde and menthol the calculated proposed limit values could be compared to existing levels, and this comparison illustrated that the proposed limit value for menthol has not been exceeded in existing products, but the proposed limit value for benzaldehyde may be exceeded by a factor of 100-200.

2 Project methodology used

This project was carried out as a desk-top study and included the following tasks:

1. Introduction with a summary of the former project on e-liquids "Requirements for substances in e-liquids used in electronic cigarettes". Including a list of about 70 flavour substances identified in the former project.
2. Search for additional relevant flavour substances in new literature, safety data sheets on e-liquids, etc.
3. Prioritising and selecting flavour substances for which a proposal for limit values was calculated (depending on the availability of toxicological data).
4. Identification of relevant toxicological data for selected flavour substances.
5. Proposal for requirements for the selected flavour substances in e-liquids.
6. Discussion, conclusion and recommendation.

3 Use of flavour substances

This chapter describes information on use of flavour substances in e-liquids. Overall information on flavourings of e-liquids for e-cigarettes is described in section 3.1, whereas information on which specific flavour substances that are used is described afterwards. The information is based on the review performed in the previous project carried out on e-liquids for the Consumer Council at Austrian Standards International (section 3.2) and is supplemented with new information (section 3.3).

3.1 Overall information on flavourings

Zhu et al. (2014) performed in 2012 and 2014 a comprehensive search on websites (with English language) for e-cigarettes and e-liquids. They illustrated that the market for e-cigarettes/e-liquids was growing and that the number of new brands as well as different types of flavours identified in 2014 compared to the search in 2012 was exploding. In 2014, Zhu et al. identified more than 460 different brands (each with their own website) and more than 7,700 unique flavours (identified by name). Today (2018) the market is most likely even bigger, and with many more unique flavours. The different e-liquids identified in the Zhu et al. (2014) survey were divided into the following flavours (the percentage of brands offering this type of flavour is listed in brackets):

- Tobacco (93.4%)
- Menthol (including flavours described as minty, icy and frosty) (92.1%)
- Tobacco-Menthol (24.8%)
- Fruit (84.2%)
- Dessert/Candy (79.9%)
- Alcohol/Drinks (77.5%)
- Snacks/Meals (25.7%)
- Others (like cinnamon, almonds, normal, mystery) (44.5%)

In 2016, Yingst et al. (2017) performed a survey amongst 3,700 e-cigarette smokers, where the smokers were asked to name their favourite flavour (i.e. only one answer per person). The answers were then classified into the following categories (the percentage preferring the listed flavour is listed in brackets):

- Tobacco (23.7%)
- Menthol/mint (14.8%)
- Dessert/sweets (20.7%)
- Fruit (20.3%)
- Coffee/tea (4.3%)
- Beverage (3.1%)
- Alcohol (2.8%)
- Nuts/spices (2.0%)
- Candy (2.1%)
- Unflavoured (0.4%)
- Don’t Know/Other (5.8%)

The survey performed by Yingst et al. (2017) also illustrates that most e-cigarette smokers use flavoured e-liquids (99.6%). A specific flavour may contain one or most often several different flavour substances.

However, in most cases, the flavour substances giving the e-liquids the different types of flavour are not included in the ingredients list, and it is only stated that e.g. ‘natural or artificial flavours’ are added. Little information is therefore available regarding which specific flavour substances that are used in e-liquids (National Academy of Sciences, 2018). Likewise, a Polish survey (Kucharska et al., 2016) has tested the content of 50 different e-liquids and found a good match between the measured ingredients and declared content in percentage for the solvents and nicotine, but a mismatch for the declared flavour substances (often not declared on the label).

The British company Nerudia Consulting Limited has prepared a list of more than 600 ingredients found in e-liquids and compounds found in e-cigarette emission. Some of these substances are of course solvents and compounds formed by the evaporation of e-liquids in e-cigarettes, but most of the substances on this list are likely to be different flavour substances. However, the function of the substances is not given on the list (Nerudia, 2017).

On the website of the British company Vape Inc. (2018), it is possible to buy toxicology reports for specific ingredients for e-liquids – and this is possible for about 140 specific CAS numbers, which means that at least 140 different ingredients can be found for the e-liquids they sell.

The information identified in the previous project on e-liquids for The Consumer Council at Austrian Standards International and in this project, is listed below and is supplemented with new information in section 3.3.

3.2 Information on use in the previous project

In the former report “Requirements for substances in e-liquids used in electronic cigarettes” (Poulsen et al., 2017a), more than 60 flavour substances were identified. In the present project, some of the ingredients for which no function was identified in the former project have been identified as flavour substances and are therefore included in the total table of flavour substances as such. The resulting list of flavour substances from the former project is therefore a list of about 70 flavour substances.
The flavour substances for which a proposal for a limit value was calculated in this former report are marked with grey shading in Table 1.

3.3 Search for new information

In this project, a search for new information regarding flavour substances being used in e-liquids for e-cigarettes has been performed in order to identify if other flavour substances could be relevant than those found in the previous report. The search has been performed as a general internet search with relevant search words like ‘e-liquids’, ‘fragrances’, ‘aroma’, ‘flavouring’, etc.

Some new articles were found, listing different flavour substances. Furthermore, some SDS (safety data sheets) for e-liquids list some of the flavour substances, but only those substances, which are considered as dangerous in the used concentrations. Finally, new flavour substances were identified, as some websites list the ingredients with chemical names and CAS numbers in connection to their web shops.

The search resulted in about 100 ‘new’ flavour substances, which have been added to the 70 flavour substances identified in the previous project. The total list of flavour substances is listed in Table 1.

3.4 Prioritisation of the flavour substances

The purpose of this report has been to develop a proposal for requirements for a selection of flavour substances in e-liquids based on available toxicological data for the substances or based on relevant existing threshold values for the selected substances. The selection of the flavour substances is limited to about 25 substances due to limitations on the extent of the work in this project. However, as more than 170 flavour substances have been identified, it was necessary to prioritise the flavour substances.

The flavour substances listed in Table 1 have been prioritised, i.e. the first mentioned flavour substance in the table has been given the highest priority. The flavour substances have been prioritised by use of the following information:

1. Flavour substances with the highest identified concentration in the e-liquids (listed in at least one reference) are given the highest priority. Concentrations above 5% in the e-liquids have been grouped together and have been given the highest priority. The flavour substances were divided into the following groups based on information about their highest identified concentration in e-liquids listed from different references:
    a. Concentration of 5% or above (46 flavour substances)
    b. Concentration of 1% to less than 5% (15 flavour substances)
    c. Concentration of 0.5% to less than 1% (21 flavour substances)
    d. Concentration of 0.1% to less than 0.5% (27 flavour substances)
    e. Concentrations of 0.01% to less than 0.1% (2 flavour substances)
    f. Flavour substances where no information regarding concentration was found (63 flavour substances)
2. Within each concentration group above, the flavour substances were then prioritised by how often they were identified in e-liquids in different surveys. This means flavour substances identified to be present in e.g. 74% of the examined e-liquids in a survey were given higher priority than flavour substances only identified in e.g. 5% of e-liquids based on information from another survey.
3. This final prioritisation criterion was only used when flavour substances were equal on prioritisation criteria number 1 and 2: The flavour substances were prioritised by the number of references/sources positively identifying the use of the flavour substance in e-liquids. If many different surveys have identified a use of a specific flavour substance, this was prioritised higher than a flavour substance only being identified to be used by one or fewer surveys.

In practise, this means that the flavour substances have been prioritised according to use, where the flavour substances used in the highest concentrations and used most often have been given the highest priority. Of course, this prioritisation depends on the information that has been found in this report. A more thorough search could of course result in more information that could change the prioritisation order.

In the search for relevant toxicological information for the ‘new’ flavour substances identified in this project (i.e. not marked with grey shading), this prioritisation list has been used. A search for relevant toxicological information has been carried out starting with the flavour substances listed first in the table (Table 1). If no information was found for a flavour substance, a search has been performed for the next substance in the list – until relevant toxicological information for at least 25 flavour substances was identified.

The 170 flavour substances identified and listed in Table 1 are listed in order of the priority for which the search has been made – with the substance of highest priority (here vanillin) listed in the top. This means that the search for threshold limit values in practise only has been carried out for the top about 55 substances in order to identify about 25 flavour substances for which information on threshold limit values could be identified.

In the right column “Threshold value” in Table 1, the threshold limit values identified have been listed. An empty field means either no limit values found or no search for limit values has been performed.

In Table 1 the flavour substances that were selected for further review and calculation of proposed limit values in the former project Poulsen et al. (2017a) are marked with grey shading. The flavour substances which have been selected for calculation of proposed limit values in this project are marked with yellow shading.

It should be noted that the flavour substances selected for review in the former project (Poulsen et al., 2017a) were selected because of their toxicity, i.e. they had the lowest threshold limit values (DNEL values, LCI values etc.) and not necessarily because of their use.

Table 1: Overview of flavour substances identified in e-liquids

The list includes both new flavour substances and flavour substances identified in the former report on ingredients in e-liquids (Poulsen et al., 2017a)

Threshold values identified are listed in the last right column "Threshold value".

Substances that were selected for further review and calculation of proposed limit values in the former project Poulsen et al. (2017a) are marked with grey shading. Substances marked with yellow shading are selected in this project for further review and calculation of proposed limit values.

Flavour substance	**CAS no.**	**Concentration (if mentioned)**	**Comment in literature**	**Reference/source**	**Threshold value (measured in mg/m^3)**
Vanillin (4-hydroxy-3-methoxybenzaldehyd)	121-33-5	Up to 33 mg/mL; Content < 1%; Content 0.2-1.2%; Content 2-12%; Content 5-6%; 0.13%; Content 8.48%; Content < 0.5%	In 22 out of 28 liquids (Hutzler) and 17 out of 30 samples (Tierney); In 11 out of 50 e-liquids (Kurcharska)	Hutzler, 2014; Tierny et al., 2015; Kucharska et al., 2016; Bengali, 2017; Gerloff, 2017; SDS Flavourart Nonnas cake, 2016; SDS Shenzhen Hangsen Star Technology, 2017a	Other relevant info.: OECD SIDS: no inh. Value; ADI = 10.0 mg/kg bw/day
Ethyl vanillin	121-32-4	Up to 8.4 mg/ml; Content < 1%; Content 4-4.5%; Content 0.07%; Content ≥ 1% and < 10%; ≤ 2.5%	In 14 out of 28 liquids; In 1 out of 50 e-liquids; In 8 out of 29 e-liquids (Nieuwesigaret)	Hutzler, 2014; Tierny et al., 2015; Kucharska et al., 2016; Bengali, 2017; Gerloff, 2017; SDS Flavourart Nonnas cake, 2016; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018; SDS Mount Bakor Vapor USA Blend Tobacco, 2016	REACH DNEL Inh. Cons.: 8.75; DNEL Inh. Work.: 49
Menthol (DL-menthol)	89-78-1	Up to 21.6 mg/mL; Content < 1%; Content 10%; Content 5%; Content 1.2-3%; Content 0.2-1.2%	In 12 out of 28 liquids; In 8 out of 50 e-liquids	BfR, 2012; Hutzler, 2014; Tierny et al., 2015; Kucharska et al., 2016; Bengali, 2017; Gerloff, 2017; SDS Eliquid Solutions, 2018a	REACH DNEL Inh. Cons.: 16.3; DNEL Inh. Work.: 66.28; Other relevant info.: OECD SIDS: but no inh. Value; ADI = 4 mg/kg bw/day
Benzyl alcohol	100-51-6	Content 1-1.5%; Content ≥ 1% and < 10%	In 3 out of 28 liquids; In 18 out of 50 e-liquids; In 6 out of 29 e-liquids; Regulated by European Cosmetics Directive	Hutzler, 2014; Kucharska et al., 2016; Gerloff, 2017; SDS Flavourart Nonnas cake, 2016; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 5.4; DNEL Inh. Work.: 22; EU-LCI: 0.440; AgBB LCI: 0.440; German Indoor air Guide Value I: 0.4; Other relevant info.: OECD SIDS: TLV 44 mg/m3
Isoamyl acetate	123-92-2	Content ≥0.05 ≤0.5%; Content ≥ 10%	In 6 out of 50 e-liquids; In 9 out of 29 e-liquids (Nieuwesigaret)	Kucharska et al., 2016; SDS Grupa Dynamic, 2017b; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 5.1; DNEL Inh. Work.: 20.8; NIOSH: TLV 50 ppm (270 mg/m3)

Flavour substance	**CAS no.**	**Concentration (if mentioned)**	**Comment in literature**	**Reference/source**	**Threshold value (measured in mg/m^3)**
Acetoin ((3-Hydroxy-2-butanone))	513-86-0	Up to 529 µg/e-cigarette; Content ≥ 1% and < 10%; Content ≤ 2.5%; Content ≥ 1% and < 10%	In 9 out of 29 e-liquids	Allen, 2015; Nieuwesigaret.nl, 2018; SDS Mount Baker Vapor Butterscotch, 2016	
n-Butyric acid	107-92-6	Content ≤ 2.5%; Content ≥ 1% and < 10%	In 8 out of 29 e-liquids	Gerloff, 2017; SDS Mount Baker Vapor Butterscotch, 2016; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 9.15; DNEL Inh. Work.: 36.8; EU-LCI: none; AgBB LCI: 0.37; Other relevant info.: OECD SIDS: only initial assessment
Trimethylpyrazine	14667-55-1	Content ≥ 1% and < 10%	In 6 out of 28 liquids; In 2 out of 29 e-liquids	Hutzler, 2014; Gerloff, 2017; Nieuwesigaret.nl, 2018	
Ethyl 2-methylbutyrate	7452-79-1	Content ≥ 1% and < 10%; > 10%; 0.2-1.2%	In 4 out of 50 e-liquids; In 6 out of 29 e-liquids (Nieuwesigaret)	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 12.95; DNEL Inh. Work.: 52.08
3-Methyl-1,2-cyclopentanedione (cyclotene)	765-70-8	Content ≥ 1% and < 10%	In 6 out of 28 liquids; In 4 out of 29 e-liquids	Hutzler, 2014; Nieuwesigaret.nl, 2018	
Hexyl acetate	142-92-7	Content ≥ 1% and < 10%; < 0.5%; 1-5%; <0.6%; ≤ 2.5%	In 8 out of 50 e-liquids; In 3 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018; SDS Perfumers Apprentice Green Apple, 2014; SDS Aquatic Tradework Kiwi, 2017; SDS Mount Baker Vapor USA Blend Tobacco, 2016	REACH DNEL Inh. Cons.: 12; DNEL Inh. Work.: 48
γ-decalactone (or gamma-decalactone)	706-14-9	Content > 1 ≤ 5%; Content ≥ 1% and < 10%	In 6 out of 50 e-liquids; In 4 out of 29 e-liquids	Kucharska et al., 2016; Gerloff, 2017; SDS Flavourart condensed milk, 2013; Nieuwesigaret.nl, 2018	
γ-undecalactone (or gamma-undecalactone or aldehyde C-14 or undecan-4-olide)	104-67-6	Content 0.26%; Content ≥ 1% and < 10%; Content < 0.5%; Content ≤ 2.5%; Content 2-12%	In 7 out of 50 e-liquids; In 4 out of 29 e-liquids (Nieuwesigaret)	Kucharska et al., 2016; Gerloff, 2017; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018; SDS Mount Bakor Vapor USA Blend Tobacco, 2016; SDS Mount Bakor Vapor Antarctic Ice, 2016	REACH DNEL Inh. Cons.: 4.68; DNEL Inh. Work.: 19
γ-Octalactone	104-50-7	Content ≥ 1% and < 10%	In 4 out of 28 liquids; In 3 out of 29-eliquids	Hutzler, 2014; Gerloff, 2017; Nieuwesigaret.nl, 2018	
Isoamyl isovalerate	659-70-1	Content ≥ 1% and < 10%	In 4 out of 50 e-liquids; In 4 out of 29-eliquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Acetylpyrazine (2-acetyl pyrazine)	22047-25-2	Content ≥ 1% and < 10%	In 3 out of 28 liquids; In 5 out of 50 e-liquids; In 1 out of 29 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Anisaldehyde (p-methoxy benzaldehyde)	123-11-5	Content ≥ 1% and < 10%; Content < 0.5%	In 3 out of 28 liquids; In 2 out of 29 e-liquids	Hutzler, 2014; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 4.35; DNEL Inh. Work.: 14.7; Other relevant info.: OECD SIDS: only initial assessment
2-Methyl butyric acid	116-53-0	Content ≥ 1% and < 10%	In 1 out of 50 e-liquids; In 3 out of 29 e-liquids (Nieuwesigaret)	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Isoamyl alcohol	123-51-3	Content ≥ 10%	In 5 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: no hazard identified; DNEL Inh. Work.: no hazard identified; EU-LCI: 0.730; AgBB LCI: 0.730; NIOSH: TLV 100 ppm (360 mg/m3)
Ethyl heptanoate	106-30-9	Content ≥ 10%; Content ≥ 1% and < 10%	In 3 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Carvone	99-49-0	Content 5%	In 4 out of 50 e-liquids	Kucharska et al., 2016; Bengali, 2017	
Hydrocoumarine	119-84-6	Content > 1 ≤ 5%; Content < 0.5%	In 2 out of 28 liquids; In 1 of 29 e-liquids	Hutzler, 2014; SDS FlavourArt Cappucino, 2015; Nieuwesigaret.nl, 2018	
n-Decanoic acid	334-48-5	Content > 1 ≤ 5%; Content 0.05%	In 2 out of 28 liquids	Hutzler, 2014; SDS Flavourart Condensed milk, 2013; SDS Shenzhen Hangsen Star Technology, 2017a	
Isobutyl acetate	110-19-0	Content ≥0.05 ≤0.5%; Content 0.2-1.2%; Content ≥ 1% and < 10%; ≤ 2.5%	In 2 out of 29 e-liquids	SDS Grupa Dynamic, 2017b; SDS Eliquid Solutions, 2018a; Nieuwesigaret.nl, 2018; SDS Mount Bakor Vapor USA Blend Tobacco, 2016	REACH DNEL Inh. Cons.: 35.7; DNEL Inh. Work.: 300; EU-LCI: 4.8; AgBB LCI: 4.8; NIOSH: MAK 100 ppm (480 mg/m3); Other relevant info.: OECD SIDS: only initial assessment
Triethyl citrate	77-93-0	Content ≥ 1% and < 10%; Content 2-12%	In 2 out of 50 e-liquids; In 2 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018; SDS Mount Bakor Vapor Antarctic Ice, 2016	REACH DNEL Inh. Cons.: 28.8; DNEL Inh. Work.: 73.5
Beta-pinene	127-91-3	Content ≥ 1% and < 10%; Content 0.1-0.9%	In 1 out of 50 e-liquids; In 2 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018; SDS Eliquids Solutions VM Lemon, 2018	REACH DNEL Inh. Cons.: 1; DNEL Inh. Work.: 5.69; EU-LCI: 1.4; AgBB LCI: 1.4

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Hexanal, aldehyde C6	66-25-1	Content ≥ 1% and < 10%; Content 1-5%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018; SDS Perfumers Apprentice Green Apple, 2014	REACH DNEL Inh. Cons.: no information; DNEL Inh. Work.: no information; EU-LCI: 0.9; AgBB LCI: 0.9
Beta-Damascone	35044-68-9	Content ≥ 1% and < 10%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Furfurylthiol acetate	13678-68-7	Content ≥ 1% and < 10%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Allyl heptanoate	142-19-8	Content ≥ 1% and < 10%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 0.73; DNEL Inh. Work.: 2.97
Alpha-terpineol	98-55-5	Content ≥ 1% and < 10%; Content 0.2-1.2%	In 3 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018; SDS Eliquids Solutions VM Lime Zinger, 2018	REACH DNEL Inh. Cons.: 2.25; DNEL Inh. Work.: 9.03
Methyl anthranilate	134-20-3	Content ≥ 1% and < 10%	In 2 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Gerloff, 2017; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 1.3; DNEL Inh. Work.: 5.28
Geranyl acetate	105-87-3	Content ≥ 1% and < 10%; Content 0.1-0.9%	In 2 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018; SDS Eliquids Solutions VM Take Two, 2018	REACH DNEL Inh. Cons.: 15.4; DNEL Inh. Work.: 62.59
2-Acetylpyridine	1122-62-9	Content ≥ 10%	In 2 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Furaneol (Strawberry furanone)	3658-77-3	Up to 7622.7 mg/l; Content < 3%; Content 0.1-0.9%; Content > 1 ≤ 5%; Content ≥ 1% and < 10%;	In 1 out of 29 e-liquids (Nieuwesigaret)	Schober, 2014; SDS FlavourArt Cappucino, 2015; Bengali, 2017; SDS Eliquid Solutions, 2017a; Nieuwesigaret.nl, 2018	
Sulfurol	137-00-8	Content > 1 ≤ 5%; Content 0.69%; Content < 0.5%	In 1 out of 29 e-liquids	SDS Flavourart Condensed milk, 2013; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018	
Hexanoic acid (or caproic acid)	142-62-1	Content ≥0.05 ≤0.15%; Content ≥ 1% and < 10%	In 1 out of 29 e-liquids	SDS Grupa Dynamic, 2017a; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 4.348; DNEL Inh. Work.: 17.632; EU-LCI: none; AgBB LCI: 0.49; NIOSH: no TLV established
Methyl cinnamate	1754-62-7	Content ≥ 1% and < 10%	In 1 out of 29 e-liquids	Gerloff, 2017; Nieuwesigaret.nl, 2018	
Veratraldehyde	120-14-9	Content ≥ 10%	In 1 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	

Flavour substance	**CAS no.**	**Concentration (if mentioned)**	**Comment in literature**	**Reference/source**	**Threshold value (measured in mg/m^3)**
Mentha x piperita (Peppermint essential oil)	8006-90-4	Content ≥ 10%; Content ≤ 2.5%; Content 2-12%; Content 2-12%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018; SDS Mount Baker Vapor Black Ice, 2016; SDS Mount Baker Vapor Spearmint, 2016; SDS Mount Baker Vapor Candy Cane, 2016	REACH DNEL Inh. Cons.: 8.7; DNEL Inh. Work.: 35.3
Benzyl butyrate	103-37-7	Content ≥ 1% and < 10%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Benzyl propionate	122-63-4	Content ≥ 1% and < 10%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 1.85; DNEL Inh. Work.: 12.3
2-Ethylpyrazine	13925-00-3	Content ≥ 1% and < 10%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Methyl propionate	554-12-1	Content ≥ 1% and < 10%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Allyl hexanoate (or allyl caproate)	123-68-2	Content < 1 %; Content 5.94%		SDS Flavourtec Jamaican fruits, 2015; SDS Shenzhen Hangsen Star Technology, 2017b	REACH DNEL Inh. Cons.: 3.7; DNEL Inh. Work.: 15
Propionic acid (or propanoic acid)	79-09-4	Content > 1 ≤ 5%		SDS Flavourart Condensed milk, 2013	REACH DNEL Inh. Cons.: 18.3; DNEL Inh. Work.: 73; EU-LCI: 1.5; AgBB LCI: 0.31; NIOSH: TLV 10 ppm (30 mg/m3); Other relevant info.: OECD SIDS: only initial assessment
Ethyl maltol (2-Ethyl-3-hydroxy-4-pyranone)	4940-11-8	up to 23.4 mg/mL; Content < 0.2%; Content 3.58%; Content 2.7%; Content < 1%; ≤ 2.5%	In 16 out of 28 liquids; In 28 out of 50 e-liquids; In 7 out of 29 e-liquids (Nieuwesigaret)	Hutzler, 2014; Tierny et al., 2015; Kucharska et al., 2016; Gerloff, 2017; SDS Eliquid Solutions, 2017a; SDS Shenzhen Hangsen Star Technology, 2017b; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018; SDS Mount Bakor Vapor USA Blend Tobacco, 2016	REACH DNEL Inh. Cons.: 17.4; DNEL Inh. Work.: 58.7
Ethyl butyrate	105-54-4	up to 11.1 mg/mL; Content 1.2-3%; Content ≤ 2.5%; Content 2.63%; Content < 0.5%	In 22 out of 50 e-liquids; In 8 out of 29 e-liquids (Nieuwesigaret)	Tierny et al., 2015; Kucharska et al., 2016; SDS Eliquid solutions, 2018a; SDS Mount Baker Vapor Butterscotch, 2016; SDS Shenzhen Hangsen Star Technology, 2017b; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 2.22; DNEL Inh. Work.: 14.8
Ethyl hexanoate (or ethyl caproate)	123-66-0	Content 2.49%; Content < 0.5%	In 5 out of 50 e-liquids; In 6 out of 29 e-liquids	Kucharska et al., 2016; SDS Shenzhen Hangsen Star Technology, 2017b; Nieuwesigaret.nl, 2018	

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Isoamyl butyrate	106-27-4	Content 2.91%; Content < 0.5%	In 2 out of 28 liquids; In 7 out of 50 e-liquids; In 1 out of 29 e-liquids	Hutzler, 2014; Kucharska et al., 2016; SDS Shenzhen Hangsen Star Technology, 2017b; Nieuwesigaret.nl, 2018	
Phenolethyl alcohol (phenethyl alcohol)	60-12-8	Content 0.2-1.2%; Content 0.31%; Content < 1%	In 3 out of 28 liquids; In 1 out of 29 e-liquids	Hutzler, 2014; SDS Eliquid Solutions, 2018a; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 17.7; DNEL Inh. Work.: 59.9
Cinnamaldehyde	104-55-2	Content 1.5%; Content <1%	In 2 out of 28 liquids; In 2 out of 50 e-liquids; In 1 out of 29 e-liquids; is an allergen	Hutzler, 2014; Kucharska et al., 2016; Bengali, 2017; Gerloff, 2017; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 2.4; DNEL Inh. Work.: 13.6
Vanillin propylene glycol acetal	68527-74-2	Content 0.2-1.2%; Content 0.32%	In 3 out of 50 e-liquids;	Kucharska et al., 2016; Gerloff, 2017; SDS Eliquid Solutions, 2017a; SDS Shenzhen Hangsen Star Technology, 2017b	
Propenyl guaethol	94-86-0	Content 1-1.5%; Content < 1%	In 1 out of 29 e-liquids	SDS Flavourart Nonnas cake, 2016; Nieuwesigaret.nl, 2018	
Cis-3-Hexen-1-yl acetate (or cis 3 hexenyl acetate)	3681-71-8	Content < 5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 2.9; DNEL Inh. Work.: 11.75
Ethyl acetate	141-78-6	Up to 7.1 mg/mL, Up to 253 ug/g (Varlet); Content > 1 ≤ 5%; Content ≤ 2.5%, Content 1-5%		Tierny et al., 2015; Varlet 2015; SDS FlavourArt Kiwi, 2013; SDS Mount Baker Vapor Butterscotch, 2016; SDS Perfumers Apprentice Green Apple, 2014	REACH DNEL Inh. Cons.: 367; DNEL Inh. Work.: 734; AgBB LCI: VVOC; US EPA RfC: not evaluated; German Indoor air Guide Value I: 0.6; NIOSH: TLV 400 ppm (1500 mg/m3); Other relevant info.: OECD SIDS: only initial assessment
(E)-Anethole	4180-23-8	Content ≥0.125 ≤0.5%; Content 1-2%		SDS Grupa Dynamic, 2017b; SDS Eliquid Solutions, 2018a	REACH DNEL Inh. Cons.: 6.5; DNEL Inh. Work.: 26.45
Ethyl propionate	105-37-3	Content < 0.2%; Content ≤ 2.5%		SDS Eliquid Solutions, 2018a; SDS Mount Baker Vapor Butterscotch, 2016	
Limonene-D (or p-Mentha-1,8-diene)	5989-27-5	Content 2.44%		SDS Shenzhen Hangsen Star Technology, 2017b	REACH DNEL Inh. Cons.: 16.6; DNEL Inh. Work.: 66.7; EU-LCI: 5.0; AgBB LCI: 5.0; NIOSH: MAK 20 ppm (110 mg/m3)

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Furfuryl alcohol	98-00-0	Content > 0.1 ≤ 1%		SDS FlavourArt Cappucino, 2015	REACH DNEL Inh. Cons.: 9.3; DNEL Inh. Work.: 31; NIOSH: TLV 10 ppm (40 mg/m3)
Acetyl propionyl (AP); (2,3-pentanedione)	600-14-6	20-432 µg/day (Farsalinos), Up to 64 µg/e-cigarette (NIH); Content < 1%	Found in 74,2% of 159 samples. In 4 out of 29 e-liquids. Approved for food use, but associated with respiratory disease when inhaled.	Farsalinos et al., 2015; Allen, 2015; Nieuwesigaret.nl, 2018	NIOSH document: 0.03808
Cis-3-Hexen-1-ol (or Leaf alcohol or cis-3-Hexanol)	928-96-1	Content 0.49%; Content < 0.5%	In 17 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; SDS Shenzhen Hangsen Star Technology, 2017b; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 2.9; DNEL Inh. Work.: 11.75
Piperonal	120-57-0	Content 0.58%; Content < 0.5%	In 7 out of 28 liquids; In 2 out of 50 e-liquids; In 1 out of 29 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Gerloff, 2017; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 4.3; DNEL Inh. Work.: 17.6
Linalool	78-70-6	Content 0.1-0.9%; Content < 0.5%	In 6 out of 28 liquids, Common Ingredient In perfumes; In 5 out of 50 e-liquids; In 5 out of 29 e-liquids	BfR, 2012; Hutzler, 2014; Kucharska et al., 2016; SDS Eliquid solutions, 2018a; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 0.7; DNEL Inh. Work.: 2.8; NIOSH: no TLV established; Other relevant info.: OECD SIDS: ADI 0.5 mg/kg bw/day; API (2015): 63
Eugenol	97-53-0	Content < 0.5%	In 5 out of 28 liquids; In 1 out of 50 e-liquids; In 1 out of 29 e-liquids; Regulated by European Cosmetics Directive	Hutzler, 2014; Kucharska et al., 2016; Gerloff, 2017; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 5.22; DNEL Inh. Work.: 21.2
Corylon (2-cyclopeten-1-one or methylcyclopentenolone)	80-71-7	Content < 1%	In 5 out of 28 liquids; In 6 out of 50 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Bengali, 2017	
Cis-3-Hexenyl butyrate	16491-36-4	Content < 1%	In 6 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
γ-Nonalactone	104-61-0	Content 0.5%; < 1%	In 2 out of 28 liquids; In 1 out of 50 e-liquids; In 1 out of 29 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Gerloff, 2017; SDS Shenzhen Hangsen Star Technology, 2017b; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 3.97; DNEL Inh. Work.: 16.1;

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Butyl butyryllactate	7492-70-8	Content < 1%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Pentyl alcohol	71-41-0	Content < 1%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: no hazard identified; DNEL Inh. Work.: no hazard identified; EU-LCI: 0.73; AgBB LCI: 0.73; NIOSH: MAK 20 ppm (73 mg/m3)
Ethyl lactate	97-64-3	Content < 1%; <0.5%	In 2 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Bengali, 2017; Nieuwesigaret.nl, 2018	
Ethyl laurate (or Ethyl dodecanoate)	106-33-2	Content < 1%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Citronellyl acetate	150-84-5	Content < 1%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 4.2; DNEL Inh. Work.: 17
Cinnamyl alcohol	104-54-1	Content < 1%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 1.19; DNEL Inh. Work.: 7.92
(E)-Hex-3-enyl acetatet	3681-82-1	Content < 1%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Delta-Dodecalactone	713-95-1	Content 0.2-1.2%; Content 0.56%		SDS Eliquid Solutions, 2017a; SDS Shenzhen Hangsen Star Technology, 2017a	REACH DNEL Inh. Cons.: 16667; DNEL Inh. Work.: 67
Hexenol cis.3	84961-46-6	Content 0.5%		Bengali, 2017	
Geranyl butyrate	106-29-6	Content 0.63%		SDS Shenzhen Hangsen Star Technology, 2017b	
Alpha, alpha-Dimethylphenethyl acetate	151-05-3	Content 0.62%		SDS Shenzhen Hangsen Star Technology, 2017b	
(2E,4E)-Hepta-2,4-Dienal	4313-03-5	Content < 1%		Bengali, 2017	
Cocoa Ext.	84649-99-0	Content < 1%		Bengali, 2017	
Maltol	118-71-8	Up to 6,2 mg/mL; Content < 0.5%	In 2 out of 50 e-liquids; In 7 out of 29 e-liquids (Nieuwesigaret)	Tierny et al., 2015; Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Citral	5392-40-5	Content < 0.5%	In 5 out of 28 liquids; In 2 out of 50 e-liquids; In 1 out of 29 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 2.7; DNEL Inh. Work.: 9

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Ethyl isovalerate	108-64-5	Content < 0.5%	In 6 out of 50 e-liquids; In 5 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Benzyl acetate	140-11-4	Content < 0.5%	In 3 out of 28 liquids; In 6 out of 50 e-liquids; In 3 out of 29 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 5.5; DNEL Inh. Work.: 21.9
Beta-Ionone	79-77-6	Content < 0.5%	In 5 out of 50 e-liquids; In 2 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Ethyl Nonanoate	123-29-5	Content < 0.5%	In 3 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Ethyl phenylacetate	101-97-3	Content 0.06%; Content < 0.5%	In 2 out of 28 liquids; In 2 out of 29 e-liquids	Hutzler, 2014; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018	REACH DNEL Inh. Cons.: 0.74; DNEL Inh. Work.: 4.9
Citronellol	106-22-9	Content < 0.5%	In 1 out of 50 e-liquids; In 2 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Guiacol	90-05-1	Content < 0.5%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Furfural	98-01-1	Content < 0.5%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Amyl isobutyrate	2445-72-9	Content < 0.5%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Coffie Furanone	3188-00-9	Content < 0.5%	In 2 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Methylhept-5-en-2-one	110-93-0	Content < 0.5%	In 3 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Delta-Decalactone	705-86-2	Content 0.07%; Content < 0.5%	In 1 out of 29 e-liquids	Gerloff, 2017; SDS Shenzhen Hangsen Star Technology, 2017a; Nieuwesigaret.nl, 2018	
Methyl N-Methylanthranilate	85-91-6	Content < 0.5%	In 1 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
2,6,6-Trimethylcyclohex-2-ene-1,4-dione	1125-21-9	Content < 0.5%	In 1 out of 50 e-liquids; In 1 out of 29 e-liquids	Kucharska et al., 2016; Nieuwesigaret.nl, 2018	
Ethyl Octanoate	106-32-1	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
5-Methylfurfural	620-02-0	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Cis-3-Hexenyl-2-methylbutyrate	53398-85-9	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Neryl Acetate	141-12-8	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Koolada-3	39711-79-0	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
6-Methyl Pyrazine	67952-65-2	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Lemon Oil	8008-56-8	Content 0.2-0.25%		SDS Flavourart Nonnas cake, 2016	
Methyl Amyl Ketone	110-43-0	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Linalyl Acetate	115-95-7	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Hex-3-en-1-ol	544-12-7	Content < 0.5%	In 1 out of 29 e-liquids	Nieuwesigaret.nl, 2018	
Buchu Oil	68650-46-4	Content ≥0.05 ≤0.125%		SDS Grupa Dynamic, 2017b	
Caprylic Acid (Octanoic Acid)	124-07-2	Content 0.03%		SDS Shenzhen Hangsen Star Technology, 2017a	
Delta-Nonalactone	3301-94-8	Content 0.06%		SDS Shenzhen Hangsen Star Technology, 2017a	
Diacetyl (DA)	431-03-8	26-278 µg/day (Farsalinos), Up to 239 µg/e-cigarette	Found in >74,2% of 159 samples in one study and in 39 out of 51 samples in another. Approved for food use, but associated with respiratory disease when inhaled. Is restricted by the Afnor standard.	Shraufnagel, 2014	NIOSH: no TLV established; NIOSH document: 0.01761 mg/m3
Acetic Acid	64-19-7		In 18 out of 50 e-liquids	Kucharska et al., 2016	
Damascenone (α or β)	23696-85-7		In 7 out of 28 liquids	Hutzler, 2014	
Limonene	138-86-3		In 2 out of 28 liquids; In 12 out of 50 e-liquids	Hutzler, 2014; Kucharska et al., 2016	REACH DNEL Inh. Cons.: no information; DNEL Inh. Work.: no information; EU-LCI: 5.0; AgBB LCI: 5.0
Hexyl Alcohol (Hexanol)	111-27-3		In 9 out of 50 e-liquids	Kucharska et al., 2016	
Terpineol	7785-53-7		In 5 out of 28 liquids	Hutzler, 2014	
Thujone	76231-76-0	6.7 mg/l on average.	Detected in 4% of studied samples. BMDL10 = 11 tested on clonic seizures on rats (see source table 5)	Hahn, 2014	
Benzyl benzoate	120-51-4		In 4 out of 28 liquids; In 2 out of 50 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Gerloff, 2017	REACH DNEL Inh. Cons.: 1.25; DNEL Inh. Work.: 5.1
Benzaldehyde	100-52-7	Up to 21.2 mg/mL	In 4 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 4.9; DNEL Inh. Work.: 9.8; US EPA RfC: not evaluated; German Indoor air Guide Value I: 0.02
Melonal	106-72-9		In 7 out of 50 e-liquids	Kucharska et al., 2016	

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Coumarin	91-64-5		Detected in 4 out of 28 samples. Prohibited in tobacco in Germany.	Hutzler, 2014	REACH DNEL Inh. Cons.: 0.183; DNEL Inh. Work.: 0.741
Anisaldehyde propylene glycol acetal	6414-32-0		In 4 out of 28 liquids	Hutzler, 2014	
Methyl cinnamate	103-26-4		In 2 out of 28 liquids; In 6 out of 50 e-liquids	Hutzler, 2014; Kucharska et al., 2016; Gerloff, 2017	REACH DNEL Inh. Cons.: 6.96; DNEL Inh. Work.: 28.8
Menthone	89-80-5		In 6 out of 50 e-liquids	Kucharska et al., 2016	
L-Menthone	14073-97-3		In 6 out of 50 e-liquids	Kucharska et al., 2016	
Pulegone	89-82-7		In 3 out of 28 liquids; In 4 out of 50 e-liquids	Hutzler, 2014; Kucharska et al., 2016	
Diisobutyl phthalate	84-69-5		In 3 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 0.72; DNEL Inh. Work.: 2.94
1,2-Hexanediol	629-11-8		In 3 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 8.7; DNEL Inh. Work.: 35
1,8-Cineol (eucalyptol)	470-82-6		In 2 out of 28 liquids; In 5 out of 50 e-liquids	Hutzler, 2014; Kucharska et al., 2016	REACH DNEL Inh. Cons.: 1.74; DNEL Inh. Work.: 7.05
Alpha-Pinene	80-56-8		In 5 out of 50 e-liquids	Kucharska et al., 2016	
p-Cymene	99-87-6		In 5 out of 50 e-liquids	Kucharska et al., 2016	
Geraniol (Geraniol Pur)	106-24-1		In 4 out of 50 e-liquids	Kucharska et al., 2016	
γ-Heptalactone	105-21-5		In 2 out of 28 liquids	Hutzler, 2014	
Miosmine (or myosmine)	532-12-7		In 2 out of 28 liquids(Arch), Impurities of anabasine, myosmine or beta-nicotyrint found in a majority of the samples (BMA)	Hutzler, 2014; BMA, 2012	
Anatabine	581-49-7		In 2 out of 28 liquids. Alkaloid.	Hutzler, 2014; Cheng, 2014	
Piperitone	89-81-6		In 2 out of 28 liquids	Hutzler, 2014	
Syringol	91-10-1		In 2 out of 28 liquids	Hutzler, 2014	
(2,2-Diethoxyethyl) benzene	101-48-4		In 2 out of 28 liquids	Hutzler, 2014	
Butyl carbitol	112-34-5		In 2 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 40.5; DNEL Inh. Work.: 67.5; EU-LCI:

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
					0.67; AgBB LCI: 0.67; German Indoor air Guide Value I: 0.4
Isobornyl acetate	125-12-2		In 2 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 13.04; DNEL Inh. Work.: 13.22
Ethyl mandelate	774-40-3		In 2 out of 28 liquids	Hutzler, 2014	
4-Methyl-2-pentyl-1,3-dioxolane	1599-49-1		In 2 out of 28 liquids	Hutzler, 2014	
Benzaldehyde propylene glycol acetal	2568-25-4		In 2 out of 28 liquids	Hutzler, 2014	
4-Chloro-2,5-dimethoxy-aniline	6358-64-1		In 2 out of 28 liquids	Hutzler, 2014	
Carvone	6485-40-1		In 2 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 0.289; DNEL Inh. Work.: 1175
Methyl dihydrojasmonate	14851-98-7		In 2 out of 28 liquids	Hutzler, 2014	
trans-Carane	18969-23-5		In 2 out of 28 liquids	Hutzler, 2014	
Diacetin	25395-31-7		In 2 out of 28 liquids	Hutzler, 2014	
α-Damascenone	57549-92-5		In 2 out of 28 liquids	Hutzler, 2014	
Piperonal propyleneglycol acetal	61683-99-6		In 5 out of 28 liquids	Hutzler, 2014	
p-Menthane-1,2-diol	336669-76-0		In 2 out of 28 liquids	Hutzler, 2014	
Dl-Menthol	1490-04-6		In 3 out of 50 e-liquids	Kucharska et al., 2016	
3-Octanol	589-98-0		In 3 out of 50 e-liquids	Kucharska et al., 2016	
Butyl acetate	123-86-4		In 2 out of 50 e-liquids	Shraufnagel, 2014; Kucharska et al., 2016	REACH DNEL Inh. Cons.: 35.7; DNEL Inh. Work.: 300; EU-LCI: 4.8; AgBB LCI: 4.8
Rheosmin (Raspberry ketone)	5471-51-2		In 1 out of 28 liquids	Hutzler, 2014	REACH DNEL Inh. Cons.: 59.5; DNEL Inh. Work.: 114.24
Nerol Special	106-25-2		In 2 out of 50 e-liquids	Kucharska et al., 2016	
γ -Dodecalactone	2305-05-7	Up to 0.6 mg/l	In 1 out of 50 e-liquids	Schober, 2014; Kucharska et al., 2016	
Acetylbenzene (Acetophenone)	98-86-2		In 1 out of 50 e-liquids	Kucharska et al., 2016	
Methyl butyl acetate 2	624-41-9		In 1 out of 50 e-liquids	Kucharska et al., 2016	
Tert-butyl alcohol	71-36-3		In 1 out of 50 e-liquids	Kucharska et al., 2016	

Flavour substance	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Ethyl Benzoate	93-89-0		In 1 out of 50 e-liquids	Kucharska et al., 2016	
Octanal	124-13-0		In 1 out of 50 e-liquids	Kucharska et al., 2016	
Beta-Ionone	14901-07-6			Gerloff, 2017	
Anisyl alcohol	105-13-5		Regulated by European Cosmetics Directive	Hutzler, 2014	REACH DNEL Inh. Cons.: 5.248; DNEL Inh. Work.: 21.284
6-Methylcoumarin	92-48-8			Gerloff, 2017	
p-Propenylansiole (Anethole)	104-46-1	Up to 13.4 mg/l		Schober, 2014	
p-Dimethoxybenzene	150-78-7	Up to 15.6 mg/l		Schober, 2014	
p-Tolualdehyde	14-87-0	Up to 2.8 mg/mL		Tierny et al., 2015	
Sucralose	56038-13-2			-	

4 Identification of relevant toxicological data for selected flavour substances

In this chapter, it is described how the search for relevant toxicological data/threshold limit values for the selected flavour substances was performed and the results of this search.

4.1 Search for relevant data

A search was made for relevant toxicological data for selected flavour substances. The search was made for existing threshold limit values in the same schemes, reports and databases that were used in the previous project on e-liquids, i.e. the following schemes/databases:

- **EU-LCI Group**, which has established LCI (Lowest Concentration of Interest) values for VOC emissions for building products. It was not expected that many LCI values for flavour substances would be found on the list, as this type of substances is normally not found emitting from building products (EU LCI, 2016).
- **The German AgBB scheme**, which has established LCI values for VOC emissions from construction products. It was not expected that many LCI values for flavour substances would be found on the list, as this type of substances is normally not found emitting from construction products (AgBB, 2015).
- **The German Environment Agency (UBA)**, which has established German indoor air guide values for relevant substances for the indoor climate (UBA, 2017). The list has been updated since the preparation of the former e-liquids report, and therefore the former identified flavours have been looked up in this new list as well, if new values should have been set.
- **ECHA database of REACH registered substances**, which lists DNEL (Derived No Effect Level) values (ECHA, 2018). DNEL values are calculated by use of NOEL (No Observed Effect Level) values and assessment factors (uncertainty factors). The main search for DNEL values was carried out in the last half of April 2018, where about 19,000 unique substances were registered. However, after the REACH registration deadline of May 31, 2018, a new search was made in order to see if non-registered substances had been registered (in June 2018 about 20,800 unique substances were registered). Furthermore, the substances listed with 'no information' in the ECHA database of registered substances were looked up in the database again to see whether new information was available after the registration deadline. Flavour substances identified in the former report on e-liquids have also been looked up once again in the ECHA database of registered substances, as new information may be available for some substances.

- **ATSDR (Agency for Toxic Substances & Disease Registry, USA)**, which has prepared Minimal Risk Levels (MRLs) for about 4-500 substances (ATSDR, 2017). The list only concerns non-cancer effects. The list has been updated (in June 2017) since the preparation of the former e-liquids report, and therefore the former identified flavours have been looked up in this new list as well to see if new values have been set.
- **US EPA IRIS (Integrated Risk Information System) database**, which lists Reference Concentration (RfC) and Reference Dose (RfD) values for 511 substances (US EPA IRIS, 2018). The list does not seem to have been updated since the preparation of the former e-liquids report, as it still contains the same number of substances.
- **WHO** has established **Air Quality Guidelines** for 35 chemical air pollutants (WHO, 2000). However, these pollutants are well-known air pollutants such as carbon monoxide, nitrogen dioxide, PAHs, elements etc. Therefore, the WHO list on air quality does not contain limit values for flavour substances and has not been used in this project.
- **NIOSH** (the American National Institute for Occupational Safety and Health) has prepared so-called International Chemical Safety Cards (ICSC) for several substances where threshold limit values (TLVs) are listed (NIOSH, 2018). The list was last updated in 2014.
- **OECD** has published several assessment reports on chemicals. These are published as an OECD SIDS (Screening Information Data Sheets). In some of these reports, relevant inhalation threshold limit values may be found.

4.2 Results of the search

The search was performed from the top in Table 1 (the flavour substances with the highest priority). However, for many of the flavour substances no information regarding threshold values for inhalation was found. Therefore, the search was in practice performed for the first about 55 prioritised flavour substances in order to find data on inhalation limit values for about 25 new flavour substances. In general, the ECHA database of registered substances is the database where most inhalation threshold values were found. The information search was performed in the last half of April 2018, however, it was checked in June 2018, whether more substances had been registered after the last REACH registration deadline of May 31, 2018.

In the following text, the new information found is summarised and covers the results for a search among the first about 55 prioritised flavour substances:

- **EU-LCI Group:** Threshold level data was found for 5 new flavour substances.
- **German AgBB scheme:** Threshold level data was found for 7 new flavour substances.
- **The German Environment Agency (UBA):** No new information was found, i.e. none of the first about 55 flavour substances was on the list.
- **ECHA database of registered substances:** Threshold level data was found for 24 new flavour substances.
- **ATSDR:** No new information was found, i.e. none of the about 55 flavour substances was in the database.

- **US EPA IRIS:** No new information was found. One new substance was in the database, but the substance had not been evaluated.
- **NIOSH:** 10 new flavour substances were listed in their database, but only four of them were listed with threshold limit values. However, no new information was obtained, as threshold limit values were already found in other lists/databases.
- **OECD:** 5 new flavour substances were found in their database, but in most cases only initial assessment reports were performed, and no inhalation threshold values were available.

In practice, this means that the ECHA database of registered substances is the best source of information for inhalation threshold values for the flavour substances, as most inhalation threshold values are found here (24 out of the first about 55 flavour substances had information on inhalation threshold values). Threshold limit values are found for much fewer flavour substances in the lists prepared by the EU-LCI Group (5 new flavour substances) and the German AgBB scheme (7 new flavour substances), and it is typically for the same substances. However, the data of the EU-LCI Group and the German AgBB scheme is of higher quality, as the threshold limit values are set after a risk assessment carried out by experts, whereas the DNEL values listed in the ECHA database of the registered substances are listed by the companies registering their substances. For this reason, the LCI values set by the EU-LCI Group or the German AgBB scheme is almost always lower than the long-term DNEL value set for consumers. Actually, the LCI values are usually a factor of 3 to 60 lower than the corresponding DNEL value for consumers. Only in one case, the LCI value is higher (a factor of 1.4) than the corresponding DNEL value. In this case, the limit value set by the EU-LCI Group has been used instead of the DNEL value, i.e. the worst-case approach was deviated in order to use data of higher quality.

For the worst-case calculations of the proposed limit values for the flavour substances in the e-liquids, the threshold limit values of the highest quality are used (i.e. LCI values reviewed by experts) and the lowest threshold limit values found have been used. In principle, this means that the LCI value will be used, if such a value exists, otherwise the DNEL value will be used, unless another lower threshold limit value has been found in another source.

It should be noted that the threshold limit values are used directly in the calculations without assessing their validity. Actually, this means that the proposed limit values are guiding values and should be used as a starting point for the necessity of setting limit values for the individual fragrances. There may be a need for a thorough risk assessment of the threshold limit values used, especially if these are based on REACH DNEL values or threshold limit values set for the working environment (which may be a politically determined limit value).

5 Selection of flavour substances

A proposal for concentration limit values for about 25 selected flavour substances in e-liquids is calculated in this report based on available toxicological data for the substances. The about 25 flavour substances have been selected by prioritising the identified used flavour substances (see section 3.4 “Prioritisation of the flavour substances”) and searching for toxicological information for the flavour substances with the highest priority. If no toxicological information was available for use in the calculation of the limit values, the search was performed for the next prioritised flavour substance on the list.

The result was that toxicological information was identified for the flavour substances listed in Table 2 below. Table 2 includes the about 25 selected flavour substances in this report as well as the 8 flavour substances (marked with grey shading) where a suggestion for a limit value was calculated in the former project (Poulsen et al., 2017a). In the table below, it has also been noted which priority number the different flavour substances have in Table 1. Only substances, where a threshold limit value has been identified, are selected for calculation of a proposed limit value in e-liquids.

No inhalation threshold limit value was found for vanillin (the flavour substances prioritised as no. 1). Instead the accepted daily intake (ADI) value identified was used in the calculations.

Table 2: Selected flavour substances in this project

Flavour substances selected for priority in the former Austrian Standards International project (Poulsen et al., 2017a) are marked with grey shading.

Priority no. in Table 1	Flavour substance	CAS no.
1	Vanillin (4-hydroxy-3-methoxybenzaldehyd)	121-33-5
2	Ethyl vanillin	121-32-4
3	Menthol (DL-menthol)	89-78-1
4	Benzyl alcohol	100-51-6
5	Isoamyl acetate	123-92-2
7	n-Butyric acid	107-92-6
9	Ethyl 2-methylbutyrate	7452-79-1
11	Hexyl acetate	142-92-7
13	γ-undecalactone (or gamma-undecalactone or aldehyde C-14 or undecan-4-olide)	104-67-6
17	Anisaldehyde (p-methoxy benzaldehyde)	123-11-5
19	Isoamyl alcohol	123-51-3
24	Isobutyl acetate	110-19-0
25	Triethyl citrate	77-93-0
26	Beta-pinene	127-91-3
27	Hexanal, aldehyde C6	66-25-1
30	Allyl heptanoate	142-19-8
31	Alpha-terpineol	98-55-5
32	Methyl anthranilate	134-20-3
33	Geranyl acetate	105-87-3
37	Hexanoic acid (or caproic acid)	142-62-1
40	Mentha x piperita (Peppermint essential oil)	8006-90-4
42	Benzyl propionate	122-63-4
45	Allyl hexanoate (or allyl caproate)	123-68-2

Priority no. in Table 1	Flavour substance	CAS no.
46	Propionic acid (or propanoic acid)	79-09-4
47	Ethyl maltol (2-Ethyl-3-hydroxy-4-pyranone)	4940-11-8
48	Ethyl butyrate	105-54-4
51	Phenolethyl alcohol (phenethyl alcohol)	60-12-8
52	Cinnamaldehyde	104-55-2
55	Cis-3-Hexen-1-yl acetate (or cis 3 hexenyl acetate)	3681-71-8
61	Acetyl propionyl (AP); (2,3-pentanedione)	600-14-6
64	Linalool	78-70-6
111	Diacetyl (DA)	431-03-8
119	Benzaldehyde	100-52-7
121	Coumarin	91-64-5
146	Carvone	6485-40-1

6 Preliminary proposal for requirements for selected flavour substances

In this chapter, the calculated preliminary proposal for requirements for the selected flavour substances is calculated based on existing threshold limit values for inhalation.

6.1 Exposure calculation

The same method for exposure calculation as used in the former project “Requirements for substances in e-liquids used in electronic cigarettes” (Poulsen et al., 2017a) is used in this project. Therefore, the rationale behind the exposure calculation is not described in detail, only a summary of the assumptions used and the calculation method used are given. For a detailed description of the assumptions, calculation method and references, please refer to the former project (Poulsen et al., 2017a).

6.1.1 Assumptions

The assumptions used in the exposure calculations are (see the former project Poulsen et al. (2017a) for details):

- The proposed limit values are calculated based on existing threshold limit values for the specific substances. These values are used directly in the calculations and have not been reviewed/assessed for their validity. This means that the proposed limit values are guiding values and should be used as a starting point for the necessity of setting limit values for the individual fragrances. There may be a need for a thorough risk assessment of the threshold limit values used,
- The used existing threshold limit values for the calculations are based on long-term local or systemic effects of the inhaled substances. This means that short-term effects like irritation are not necessarily considered.
- The proposed limit values are based on worst-case scenarios regarding e-cigarette use, i.e.:
  - The entire amount of a substance in the e-liquids is assumed to be vaporised.
  - All substances in the e-liquids are vaporised without being chemically changed or without undergoing a chemical reaction during the vaporisation process.
  - The entire amount of the substance being vaporised for each puff is assumed to be inhaled by the user.
  - Each puff contains the same quantity of a substance in the e-liquid, i.e. it is assumed that the e-cigarette will deliver a constant concentration of substances for each puff.
  - The entire amount of the substance being inhaled is assumed to be absorbed in the human body, which means that $abs_{substance} = 1$.

6.1.2 Calculation method

The calculation method used is the same as used in the former project (Poulsen et al., 2017a). See this project for a more detailed description.

$$C_{Substance\_in\_e\_liquid} = \frac{V_{air\_daily} \times RfC_{substance}}{abs_{substance} \times V_{Liquid\_per\_puff} \times n_{puffs}}$$

$C_{Substance\_in\_e\_liquid}$	Is the maximum concentration of the substance in the e-liquid (mg/ml) that will not result in adverse effects, i.e. the limit value that should be set for the substance
V_{air_daily}	Is the volume of air inhaled per day (24 hours) or per 8 hours where occupational limits were used (m^3)
$RfC_{substance}$	Is the Reference Concentration (existing threshold limit values available) for the substance (mg/m^3), e.g. a DNEL value
$abs_{substance}$	Is the absorption coefficient (%) of the substance, i.e. how large an amount of the substance that will be absorbed in the body, when inhaling e-cigarette vapour. It is assumed that by default in this screening project 100% of the substance will be absorbed in the body (worst case). By default, this absorption coefficient will then be 1
$V_{Liquid\_per\_puff}$	Is the volume of e-liquid used (vaporised) per puff (ml/puff)
n_{puffs}	Is the total number of puffs per day (puffs/day)

Almost all existing threshold limit values used for the selected flavour substances are inhalation values, except for vanillin where no inhalation value could be found. Here the ADI value (Accepted Daily Intake) is used in the calculations instead. In this case the equation below is used for the calculations:

$$C_{Substance\_in\_e\_liquid} = \frac{BW \times RfD_{substance}}{abs_{substance} \times V_{Liquid\_per\_puff} \times n_{puffs}}$$

$C_{Substance\_in\_e\_liquid}$	Is the maximum concentration of the substance in the e-liquid (mg/ml) that will not result in adverse effects, i.e. the limit value that should be set for the substance
BW	Is the bodyweight of a typical human (kg)
$RfD_{substance}$	Is the ADI (Acceptable Daily Intake) or Reference Dose (existing threshold limit values available) for the substance (mg/kg bw/day)

$abs_{substance}$	Is the absorption coefficient (%) of the substance, i.e. how large an amount of the substance that will be absorbed in the body, when inhaling e-cigarette vapour. It is assumed that by default in this screening project 100% of the substance will be absorbed in the body (worst case). By default, this absorption coefficient will then be 1
$V_{Liquid\_per\_puff}$	Is the volume of e-liquid used (vaporised) per puff (ml/puff)
n_{puffs}	Is the total number of puffs per day (puffs/day)

6.1.3 Values used in the calculations

The values used in the calculations are discussed in detail in the former project on e-liquids "Requirements for substances in e-liquids used in electronic cigarettes" (Poulsen et al., 2017a). The values used are summarised below (for details, please see the former project Poulsen et al. (2017a)). However, in the calculation for vanillin (where no inhalation value was identified), a value for body weight of 60 kg (small adult) has been used, as a low body weight will result in a lower concentration in the e-liquids.

V_{air_daily}	16 m^3/day, because this value is used in exposure calculations by ECHA. However, when the used threshold values are based on an 8-hour working day, the inhaled volume will be one third of an entire day's inhaled volume, corresponding to 5.33 m^3
BW	60 kg, because e-cigarettes only are for adult use. The lowest adult body weight is used as a worst case.
$abs_{substance}$	1
$V_{Liquid\_per\_puff}$	150 puffs equal 1 mL, because this value seems to be used in several sources.
n_{puffs}	500 puffs per day, because this number represents a "heavy" e-cigarette smoker. However, the calculations based on 200 puffs per day are performed as well, as this unit is used in e.g. the Afnor standard for calculation of limit values.

6.2 Threshold limit values used

The threshold limit values (TLVs) identified for the flavour substances and their references used for the calculations are presented in Table 3 below. In general, the threshold limit values of highest quality, i.e. TLVs that have been reviewed and set by experts such as EU-LCI values have been used. Otherwise the lowest threshold limit values have been used in the calculations of the proposed limit values of the selected ingredients.

It should be noted that the 8 flavour substances for which a proposal for limit values was calculated in the former project (Poulsen et al., 2017a), are also included in this report (and are marked with grey shading). No newer data has been used for these substances, as no new data was available for these substances.

Therefore, the calculated limit values are identical with the data presented in the former project.

The flavour substances are listed in their prioritised order with their priority number listed in the outer most left column.

Table 3: Threshold limit values used in the calculations of proposed limit values for selected flavour substances

Pri. No.	Substance	CAS no.	Used TLV (mg/m^3)	Comments	Reference used
1	Vanillin (4-hydroxy-3-methoxybenzaldehyd)	121-33-5	10 mg/ kg bw/day	ADI (Acceptable Daily Intake) value listed in mg/kg bw/day	OECD SIDS, 1996
2	Ethyl vanillin	121-32-4	8.75	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
3	Menthol	89-78-1	16.3	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
4	Benzyl alcohol	100-51-6	0.4	German Indoor Air, Guide Value I: conc. in indoor air not expected to cause adverse health effects in sensitive persons in case of lifelong exposure. Similar value by EU-LCI (2016)	UBA, 2016 (EU-LCI, 2016)
5	Isoamyl acetate	123-92-2	5.1	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
7	n-Butyric acid	107-92-6	0.37	German evaluation procedure for VOC emissions from construction products. LCI value established	AgBB, 2015
9	Ethyl 2-methylbutyrate	7452-79-1	12.95	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
11	Hexyl acetate	142-92-7	12	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
13	γ-undecalactone (or gamma-undecalactone or aldehyde C-14 or undecan-4-olide)	104-67-6	4.68	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
17	Anisaldehyde (p-methoxy benzaldehyde)	123-11-5	4.35	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
19	Isoamyl alcohol	123-51-3	0.73	LCI value set concerning VOC emissions from construction products based on detailed assessment of data	EU-LCI, 2016
24	Isobutyl acetate	110-19-0	4.8	LCI value set concerning VOC emissions from construction products based on detailed assessment of data	EU-LCI, 2016
25	Triethyl citrate	77-93-0	28.8	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
26	Beta-pinene	127-91-3	1.4	LCI value set concerning VOC emissions from construction products based on detailed assessment of data	EU-LCI, 2016

Pri. No.	Substance	CAS no.	Used TLV (mg/m^3)	Comments	Reference used
27	Hexanal, aldehyde C6	66-25-1	0.9	LCI value set concerning VOC emissions from construction products based on detailed assessment of data	EU-LCI, 2016
30	Allyl heptanoate	142-19-8	0.73	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
31	Alpha-terpineol	98-55-5	2.25	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
32	Methyl anthranilate	134-20-3	1.3	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
33	Geranyl acetate	105-87-3	15.4	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
37	Hexanoic acid (or caproic acid)	142-62-1	0.49	German evaluation procedure for VOC emissions from construction products. LCI value established	AgBB, 2015
40	Mentha x piperita (Peppermint essential oil)	8006-90-4	8.7	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
42	Benzyl propionate	122-63-4	1.85	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
45	Allyl hexanoate (or allyl caproate)	123-68-2	3.7	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
46	Propionic acid (or propanoic acid)	79-09-4	0.31	German evaluation procedure for VOC emissions from construction products. LCI value established	AgBB, 2015
47	Ethyl maltol (2-Ethyl-3-hydroxy-4-pyranone)	4940-11-8	17.4	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
48	Ethyl butyrate	105-54-4	2.22	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
51	Phenolethyl alcohol (phenethyl alcohol)	60-12-8	17.7	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
52	Cinnamaldehyde	104-55-2	2.4	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
55	Cis-3-Hexen-1-yl acetate	3681-71-8	2.9	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
61	Acetyl propionyl (AP)	600-14-6	0.03808	Occupational threshold limit value (8-hour average, 40 hours, 45 years) based on 1/1,000 excess risk of lung function below normal	NIOSH, 2016
64	Linalool	78-70-6	0.7	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
111	Diacetyl (DA)	431-03-8	0.01761	Occupational threshold limit value (8-hour average, 40 hours, 45 years) based on 1/1,000 excess risk of lung function below normal	NIOSH, 2016
119	Benzaldehyde	100-52-7	0.02	German Indoor Air, Guide Value I: conc. in indoor air not expected to cause adverse health effects in sensitive persons in case of lifelong exposure	UBA, 2016
121	Coumarin	91-64-5	0.183	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value
146	Carvone	6485-40-1	0.289	DNEL for consumers based on long term inhalation	ECHA, 2018 DNEL value

6.3 Preliminary proposal for limit values

In this chapter, calculations for a preliminary proposal for limit values have been carried out for 27 selected flavour ingredients, including the 8 flavour ingredients where limit values were calculated in the former project. The limit values are considered as a preliminary proposal bearing in mind the limitations in this screening project. The limitations are discussed above in section 6.1.1 “Assumptions”.

In Table 4 on the next pages, the proposal for limit values has been listed for the selected ingredients based on the calculation method and values presented above. Please note that the calculations are made for a daily intake of 200 as well as 500 puffs, as described above.

In Table 4, it is indicated with a light red background colour (in the columns “Limit value”) if the proposed limit values are exceeded by an existing maximum level of the substance identified in this review in e-liquids. The cell in the table with the limit value is marked red if at least one example of a higher concentration above the calculated proposed limit value has been found in literature or an SDS for an e-liquid. Similarly, it is indicated with a light green background colour (in the columns “Limit value”) if the proposed limit values are *not* exceeded by existing maximum levels of the substance identified in e-liquids. Some cells are marked with a light yellow background colour instead. This is used in situations where it is uncertain whether the calculated limit value is exceeded or not. For example, where a limit value is calculated to be 5.8% and most concentrations identified for the flavour substances are around 1-2%, but on one safety data sheet (SDS) a concentration range of 1-10% has been listed. The use of concentration ranges in safety data sheets is most often due to confidentiality reasons and not necessarily because a concentration of 10% is used in the e-liquid.

A comprehensive search has been performed in order to identify values for concentrations of the selected flavour substances used in e-liquids. However, for one flavour substance – coumarin, which was reviewed in the former Austrian Standards International project (Poulsen et al., 2017a), it has not been possible to identify a source listing this flavour substance as used in e-liquids. This may be due to the fact that coumarin is found naturally in a wide variety of plants and thereby may be found naturally in small amounts in a wide variety of fragrances/flavours. The source, which identified coumarin in four out of 28 examined e-liquids (Hutzler et al., 2014), did so by use of chemical analysis of 28 different e-liquids on the market in 2014. No safety data sheets for e-liquids have been identified where it is noted that coumarin is added deliberately as an ingredient. Hutzler et al. (2014) only describes that coumarin has been identified in four of 28 e-liquids, but does not list the concentrations measured.

For all other listed flavour substances where a proposed limit value has been calculated, it was possible to identify a use concentration or a use concentration range. When comparing the maximum identified use concentration with the proposed calculated limit values, the maximum use concentration is actually higher than the limit value for 27 of the 35 flavour substances (when using 500 puffs for the calculation of the limit value). This indicates that there may be a need for limit values for flavour substances used in e-liquids. However, as the available information about the actual minimum use concentrations reveals, it will be possible for some of the examined e-liquid products to meet the proposed limit values in most cases.

It should be noted that the prioritisation of the flavour substances discussed in the former project is low mainly because of few or no data concerning the content (concentrations used). The data (in Table 4 below) has been identified after the prioritisation process and may therefore be given another priority for the flavour substances marked with grey shading, if the priority had been given after the more thorough search for further data regarding use concentrations.

Table 4: Proposal for limit values for 35 selected ingredients in e-liquids.
Limit values marked with light red background are exceeded by one or more existing levels found in e-liquids.
Limit values marked with light green background are not exceeded by existing levels found in this review in e-liquids.
Limit values marked with light yellow background indicate that it is uncertain whether the calculated limit values are exceeded by existing levels found in this review in e-liquids.
Substance names marked with light grey background are the 8 flavour substances also described in the former Austrian Standards International project (Poulsen et al., 2017a)

Pri. No.	Substance	CAS no.	Values used	Limit value µg/mL e-liquid (500 puffs)	Limit value µg/mL e-liquid (200 puffs)	Comments / comparison with AFNOR standard value or actual measurements
1	Vanillin (4-hydroxy-3-methoxybenzaldehyd)	121-33-5	BW = 60 kg $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used ADI = 10 mg/kg w/day	180,000 (180 mg/ml or 18%)	450,000 (450 mg/ml or 45%	Found in concentrations up to 33 mg/ml (Tierney, 2015). Found in the following concentrations in SDSs: < 1%; 0.2-1.2%; 2-12%; 5-6%; 0.13%; 8.48%; < 0.5%. In 22 out of 28 liquids (Hutzler, 2014); In 17 out of 30 samples (Tierney, 2015); In 11 out of 50 e-liquids (Kurcharska, 2016).
2	Ethyl vanillin	121-32-4	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 8.75 mg/m^3	42,000 (42 mg/ml or 4.2%)	105,000 (105 mg/ml or 10.5%)	Found in concentrations up to 8.4 mg/ml (Tierney, 2015). Found in the following concentrations in SDSs: < 1%; 4-4.5%; 0.07%; ≥ 1% and < 10%; ≤ 2.5%. In 14 out of 28 liquids (Hutzler 2014); In 1 out of 50 e-liquids (Kurcharska, 2016); In 8 out of 29 e-liquids (Nieuwesigaret, 2018).
3	Menthol	89-78-1	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 16.3 mg/m^3	78,240 (78.2 mg/mL or 7.8%)	195,600 (195.6 mg/mL or 19.6%)	Found in concentrations up to 21,600 µg/mL (i.e. 2.2%), (Hutzler, 2014). Found in the following concentrations in SDSs: < 1%; 10%; 5%; 1.2-3%; 0.2-1.2%. Identified in 12 out of 28 e-liquids examined (Hutzler, 2014). In 8 out of 50 e-liquids ((Kurcharska, 2016).
4	Benzyl alcohol	100-51-6	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.4 mg/m^3	1,920 (0.2%)	4,800 (0.5%)	Found in the following concentrations in SDSs: 1-1.5%; ≥ 1% and < 10%. In 3 out of 28 liquids (Hutzler, 2014); In 18 out of 50 e-liquids (Kurcharska, 2016); In 6 out of 29 e-liquids (Nieuwesigaret, 2018).
5	Isoamyl acetate	123-92-2	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 5.1 mg/m^3	24,480 (2.5%)	61,200 (6.1%)	Found in the following concentrations in SDSs: ≥0,05 ≤ 0,5%; ≥ 10%. In 6 out of 50 e-liquids (Kurcharska, 2016); In 9 out of 29 e-liquids (Nieuwesigaret, 2018).

Pri. No.	Substance	CAS no.	Values used	Limit value µg/mL e-liquid (500 puffs)	Limit value µg/mL e-liquid (200 puffs)	Comments / comparison with AFNOR standard value or actual measurements
7	n-Butyric acid	107-92-6	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.37 mg/m^3	1,776 (0.2%)	4,440 (0.4%)	Found in the following concentrations in SDSs: ≤ 2.5%; ≥ 1% and < 10%. In 8 out of 29 e-liquids (Nieuwesigaret, 2018).
9	Ethyl 2-methylbutyrate	7452-79-1	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 12.95 mg/m^3	62,160 (6.2%)	155,400 (15.5%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; > 10%; 0.1 - 1.2%. In 4 out of 50 e-liquids (Kurcharska, 2016); In 6 out of 29 e-liquids (Nieuwesigaret, 2018).
11	Hexyl acetate	142-92-7	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 12 mg/m^3	57,600 (5.8%)	144,000 (14.4%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; < 0.5%; 1-5%; < 0.6%, ≤ 2.5%. In 8 out of 50 e-liquids (Kurcharska, 2016); In 3 out of 29 e-liquids (Nieuwesigaret, 2018).
13	γ-undecalactone (or gamma-undecalactone or aldehyde C-14 or undecan-4-olide)	104-67-6	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 4.68 mg/m^3	22,464 (2.2%)	56,160 (5.6%)	Found in the following concentrations in SDSs: 0.26%; ≥ 1% and < 10%; < 0.5%; ≤ 2.5%; 2-12%. In 7 out of 50 e-liquids (Kurcharska, 2016); In 4 out of 29 e-liquids (Nieuwesigaret, 2018).
17	Anisaldehyde (p-methoxy benzaldehyde)	123-11-5	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 4.35 mg/m^3	20,880 (2.1%)	52,200 (5.2%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; < 0.5%; 0.2-1.2% In 3 out of 28 liquids (Hutzler, 2014); In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
19	Isoamyl alcohol	123-51-3	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.73 mg/m^3	3,504 (0.4%)	8,760 (0.9%)	Found in the following concentrations in SDSs: ≥ 10% In 5 out of 50 e-liquids (Kurcharska, 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
24	Isobutyl acetate	110-19-0	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 4.8 mg/m^3	23,040 (2.3%)	57,600 (5.8%)	Found in the following concentrations in SDSs: ≥ 0.05 ≤ 0.5%; 0.2-1.2%; ≥ 1% and < 10%; ≤ 2.5%. In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
25	Triethyl citrate	77-93-0	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 28.8 mg/m^3	138,240 (13.8%)	345,600 (34.6%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 2-12% In 2 out of 50 e-liquids (Kurcharska, 2016); In 2 out of 29 e-liquids (Nieuwesigaret, 2018).

Pri. No.	Substance	CAS no.	Values used	Limit value µg/mL e-liquid (500 puffs)	Limit value µg/mL e-liquid (200 puffs)	Comments / comparison with AFNOR standard value or actual measurements
26	Beta-pinene	127-91-3	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 1.4 mg/m^3	6,720 (0.7%)	16,800 (1.7%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 0.1-0.9%. In 1 out of 50 e-liquids (Kurcharska, 2016); In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
27	Hexanal, aldehyde C6	66-25-1	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.9 mg/m^3	4,320 (0.4%)	10,800 (1.1%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 1-5%. In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
30	Allyl heptanoate	142-19-8	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.73 mg/m^3	3,504 (0.4%)	8,760 (0.9%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%. In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
31	Alpha-terpineol	98-55-5	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 2.25 mg/m^3	10,800 (1.1%)	27,000 (2.7%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 0.2-1.2% In 3 out of 50 e-liquids (Kurcharska, 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
32	Methyl anthranilate	134-20-3	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 1.3 mg/m^3	6,240 (0.6%)	15,600 (1.6%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%. In 2 out of 50 e-liquids (Kurcharska, 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
33	Geranyl acetate	105-87-3	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 15.4 mg/m^3	73,920 (7.4%)	184,800 (18.5%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 0.1-0.9%. In 2 out of 50 e-liquids (Kurcharska, 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
37	Hexanoic acid (or caproic acid)	142-62-1	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.49 mg/m^3	2,352 (0.2%)	5,880 (0.6%)	Found in the following concentrations in SDSs: ≥ 0.05 ≤ 0.15%; ≥ 1% and < 10%. In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
40	Mentha x piperita (Peppermint essential oil)	8006-90-4	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 8.7 mg/m^3	41,760 (4.2%)	104,400 (10.4%)	Found in the following concentrations in SDSs: ≥ 10%; ≤ 2.5%; 2-12% In 1 out of 29 e-liquids (Nieuwesigaret, 2018).

Pri. No.	Substance	CAS no.	Values used	Limit value µg/mL e-liquid (500 puffs)	Limit value µg/mL e-liquid (200 puffs)	Comments / comparison with AFNOR standard value or actual measurements
42	Benzyl propionate	122-63-4	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 1.85 mg/m^3	8,880 (0.9%)	22,200 (2.2%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%. In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
45	Allyl hexanoate (or allyl caproate)	123-68-2	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 3.7 mg/m^3	17,760 (1.8%)	44,400 (4.4%)	Found in the following concentrations in SDSs: < 1 %; 5.94%.
46	Propionic acid (or propanoic acid)	79-09-4	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.31 mg/m^3	1,488 (0.1%)	3,720 (0.4%)	Found in the following concentrations in SDSs: > 1 ≤ 5%.
47	Ethyl maltol (2-Ethyl-3-hydroxy-4-pyranone)	4940-11-8	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 17.4 mg/m^3	83,520 (8.4%)	208,800 (20.9%)	Found in concentrations up to up to 23.4 mg/ml, i.e. 23,400 µg/ml (Hutzler, 2014). Found in the following concentrations in SDSs: < 0.2%; 3.58%; 2.7%; < 1%; ≤ 2.5%. In 16 out of 28 liquids (Hutzler, 2014); In 28 out of 50 e-liquids (Kurcharska, 2016); In 7 out of 29 e-liquids (Nieuwesigaret, 2018).
48	Ethyl butyrate	105-54-4	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 2.22 mg/m^3	10,656 (1.1%)	26,640 (2.7%)	Found in concentrations up to 11.1 mg/mL, i.e. 11,100 µg/ml (Tierney, 2015). Found in the following concentrations in SDSs: 1.2-3%; ≤ 2.5%; 2.63%; < 0.5%; 0.2-1.2%. In 22 out of 50 e-liquids (Kurcharska, 2016); In 8 out of 29 e-liquids (Nieuwesigaret, 2018).
51	Phenolethyl alcohol (phenethyl alcohol)	60-12-8	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 17.7 mg/m^3	84,960 (8.5%)	212,400 (21.2%)	Found in the following concentrations in SDSs: 0.2-1.2%; 0.31%; < 1%. In 3 out of 28 liquids (Hutzler, 2014); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
52	Cinnamaldehyde	104-55-2	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 2.4 mg/m^3	11,520 (1.2%)	28,800 (2.9%)	Found in the following concentrations in SDSs: 1.5%; <1%. In 2 out of 28 liquids (Hutzler, 2014); In 2 out of 50 e-liquids (Kurcharska, 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).

Pri. No.	Substance	CAS no.	Values used	Limit value µg/mL e-liquid (500 puffs)	Limit value µg/mL e-liquid (200 puffs)	Comments / comparison with AFNOR standard value or actual measurements
55	Cis-3-Hexen-1-yl acetate (or cis 3 hexenyl acetate)	3681-71-8	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 2.9 mg/m^3	13,920 (1,4%)	34,800 (3,5%)	Found in the following concentrations in SDSs: < 5%; < 1.1%. In 1 out of 29 liquids (Nieuwesigaret, 2018).
61	Acetyl propionyl (AP)	600-14-6	V_{air_daily} = 5.33 m^3 (TLV 8h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.03808 mg/m^3	61 (0.006%)	152 (0.015%)	Found in concentrations from 20 to 432 µg/day (Farsalinos, 2015), i.e. 6 to 130 µg/mL assuming use of 3.3 mL/day (equals 500 puffs). Found in the following concentrations in SDSs: < 1%. Found in 74.2% out of 159 samples (Farsalinos, 2015). In 4 out of 29 e-liquids (Nieuwesigaret, 2018). Approved for food use, but associated with respiratory disease when inhaled.
64	Linalool	78-70-6	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.7 mg/m^3	3,360 (0.3%)	8,400 (0.8%)	Found in the following concentrations in SDSs: 0.1-0.9%; < 0.5%. In 6 out of 28 liquids (Hutzler, 2014); In 5 out of 50 e-liquids (Kurcharska, 2016); In 5 out of 29 e-liquids (Nieuwesigaret, 2018). Common ingredient in perfumes, where it is regulated by European Cosmetics Directive.
111	Diacetyl (DA)	431-03-8	V_{air_daily} = 5.33 m^3 (TLV 8h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.01761 mg/m^3	28 (0.003%)	70 (0.007%)	Found in concentrations from 26 to 278 µg/day (Farsalinos et al., 2015), i.e. 8 to 84 µg/mL assuming use of 3.3 mL/day (equals 500 puffs). Is restricted by the Afnor standard by no use as ingredient. Afnor (2015b) standard target value: 22 mg/L, i.e. 22 µg/mL. Found in >74.2% of 159 samples (Farsalinos, 2015); In 39 out of 51 samples (Allen, 2015). Approved for food use, but associated with respiratory disease when inhaled (Shraufnagel, 2014).
119	Benzaldehyde	100-52-7	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.02 mg/m^3	96 (0.01%)	240 (0.02%)	Found in concentrations up to 21,200 µg/mL (Hutzler, 2014). Found in the following concentrations in SDSs: < 0.5%; ≥ 1% and < 10%; In 4 out of 28 e-liquids (Hutzler, 2014); In 7 out of 29 e-liquids (Nieuwesigaret, 2018).

Pri. No.	Substance	CAS no.	Values used	Limit value µg/mL e-liquid (500 puffs)	Limit value µg/mL e-liquid (200 puffs)	Comments / comparison with AFNOR standard value or actual measurements
121	Coumarin	91-64-5	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.183 mg/m^3	878 (0.09%)	2,196 (0.2%)	*No indication on concentration levels found in this review* In 4 out of 28 e-liquids (Hutzler, 2014), but no concentrations listed. Prohibited in tobacco in Germany (Hutzler, 2014)
146	Carvone	6485-40-1	V_{air_daily} = 16 m^3 (TLV 24 h) $V_{Liquid\_per\_puff}$ = 150 puffs/mL n_{puffs} = 500/200 puffs Used TLV = 0.289 mg/m^3	1,387 (0.1%)	3,468 (0.3%)	Found in the following concentrations in SDSs: $> 1 \leq 5\%$; $\geq 0,5 \leq 0,75\%$. In 2 out of 28 e-liquids (Hutzler, 2014).

7 Discussion and recommendations

A preliminary proposal for limit values for the concentration of 35 selected flavour substances used in e-liquids has been calculated (see Table 4). The limit values have been calculated based on existing threshold limit values such as REACH DNEL values, indoor emissions for construction products etc. The existing threshold limit values used for the calculations have been based on effects for long term systemic exposure and will therefore not consider short term effects like e.g. irritation effects.

In general, the lowest existing threshold limit values were used for the calculation of proposed limit values for concentration in the e-liquids. Furthermore, a high number of puffs per day (500) has been used in the calculations. It should, however, be emphasised that the number of 500 puffs per day is not considered as worst case – although in the high end, as different chat forums for e-cigarette vapours indicate that even heavier vapours can be found. Furthermore, a limit value for 200 puffs per day has been calculated to compare the calculated limit values with the limit values for some substances set in the existing standards.

It must be pointed out that the calculations performed in this report are made on a screening level, which means that a simple 'worst-case' calculation has been made. In this worst-case calculation, it has been assumed that all of the substance contained in the e-liquid is evaporated, and all of the substance evaporated is inhaled, and finally that all of the inhaled substance is absorbed in the body.

The calculated proposed limit values for the 35 selected flavour substances in e-liquids lie between 28 µg/ml e-liquid (0.003%) for diacetyl and 180,000 µg/ml e-liquid (18%) for vanillin.

In most cases – except for coumarin – use concentrations have been identified for the 35 selected flavour substances. These use concentrations are primarily identified through safety data sheets on e-liquids, which means that most use concentrations are given as a concentration range. However, for 27 of the 35 flavour substances where limit values in e-liquids are proposed, the actual identified maximum concentration in an existing e-liquid on the market is higher than the proposed limit value (when using the value of 500 puffs per day). For additionally three flavour substances, the proposed limit value may be exceeded, but it is difficult to conclude based on the use information in a wide concentration range. This means that it is only for a total of four flavour substances of the 35 reviewed substances, where the maximum use concentration *does not* exceed the proposed limit value. In most cases, the maximum concentrations found in e-liquids are a factor of 2-10 times higher than the limit values proposed in this report. However, in some cases the maximum concentration identified may be up to 100-200 times higher than the proposed limit value (for benzaldehyde). This fact suggests that limit values may be needed for flavour substances in e-liquids.

Of course, when only using the vaping value of 200 puffs per day, the proposed limit values will be higher and more flavour substances will be able to meet the proposed limit values (10 out of 35 flavour substances, compared to four out of 35 when using the value of 500 puffs per day).

It should, however, be emphasised that the search for actual used amounts of the flavour substances in e-liquids has mainly been based on concentration ranges listed in safety data sheets found on the internet. Furthermore, the search has not been very extensive and only a couple of examples of concentrations have been identified for each selected flavour substance. This means that the identified concentrations do not necessarily reflect the actual usage in e-liquids but must simply be viewed as examples. However, as the actual content is often classified information the best available information is through safety data sheets or scientific articles measuring the used concentrations in e-liquids.

Nevertheless, the available information about the actual minimum concentrations identified in e-liquids suggests that it will be possible for many of the examined flavour substances to meet the proposed limit values. Many of the flavour substances reviewed are only used in a few percentages of the e-liquids on the market. This suggests that it should be possible for many e-liquid products on the market to comply with the proposed limit values. However, it is not known and has not been discussed in this report which concentrations that are needed for different flavour substances to provide the ‘correct’ flavour to the e-liquids. It is not known whether for example cis-3-Hexen-1-yl acetate (CAS 3681-71-8) is needed in a concentration above the calculated limit value of 1.4% in order to provide the ‘correct’ strawberry flavour to an e-liquid.

As stated in the former Austrian Standards International report (Poulsen et al., 2017a), the British guidance document PAS (BSI, 2015) and the French Afnor standard (Afnor, 2015b) both contain some restrictions concerning ingredients in e-liquids, but no normal restrictions for flavour substances. However, for diacetyl (DA) both documents restrict the substance, which is also the ingredient with the lowest calculated limit value in this report. The British guidance document PAS states that diacetyl should not be used, but no limit value is given, and the French Afnor standard sets a limit value of 22 µg/ml, which is in line with the proposed limit value in this and the former Austrian Standards International report of 28 µg/ml.

The fact that most of the proposed limit values are exceeded by the maximum identified use concentrations in e-liquids suggests that smoking e-cigarettes (heavy vapours of 500 puffs/day) for some e-liquids cannot necessarily be considered as safe, because long-term health effects are likely to occur. However, the minimum identified use concentrations found in literature or in safety data sheets for e-liquids illustrate that the proposed limit values are not exceeded for every e-liquid on the market, but that it is possible to produce e-liquids that will comply with the proposed limit values.

The proposed limit values are, as earlier mentioned, calculated by use of worst-case scenarios involving a high use of e-liquids as well as assumptions of full intake of the substances contained in the e-liquids. This result is most likely an overestimation of the actual absorption of the substances in the e-liquids into the human body by vaping on e-cigarettes and thereby calculation of lower limit values than actually necessary. However, if no information is available concerning absorption of the substance in the body (no search for this has been made in the preparation of this report), a full absorption (100%) must be used as a precautionary principle. Furthermore, it can of course be discussed whether the correct limit values (DNEL values, LCI values etc.) have been used for the individual substances. In this report, the limit value of the highest quality (i.e. has been reviewed by experts) has been used and otherwise the lowest limit values identified. The proposed preliminary limit values in this report should therefore be considered as a first approximation and the risk assessment presented may need further refinement in order to establish limit values for ingredients in e-liquids.

However, there is no doubt that smoking e-cigarettes is not risk-free, which was also discussed in the former Austrian Standards International report (Poulsen et al., 2017a). According to the Tobacco Directive, it is only allowed to use ingredients in e-cigarettes and e-liquids which do not pose a risk to human health in heated and unheated form. This review illustrates that flavour substances may be used in concentrations in some e-liquids which cannot be considered as safe. This fact emphasises the need for limit values for several of the flavour substances used in e-liquids.

Neither the GPS Directive nor the Tobacco Directive contains specific requirements for e-cigarettes and e-liquids. It is therefore important that the standards developed set the necessary chemical requirements (for all the necessary chemical substances contained in the e-liquids) as well as the correct limit values to protect the consumer from unwanted health effects from ingredients contained in e-liquids.

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