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Reducing attractiveness of e-liquids: proposal for a restrictive list of tobacco-related flavourings

Jeroen L A Pennings ,[1] Anne Havermans ,[1] Erna J Z Krüsemann,[1] Dion Zijtveld,[2] Eva H W Huiberts,[2] Peter M J Bos,[2] Erna Schenk,[1] Wouter F Visser ,[1] Ingrid M E Bakker-'t Hart ,[1] Yvonne C M Staal ,[1] Reinskje Talhout[1]

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[1]Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, Netherlands
[2]Centre for Safety of Substances and Products, National Institute for Public Health and the Environment, Bilthoven, Netherlands

Correspondence to
Dr Jeroen L A Pennings, National Institute for Public Health and the Environment, Bilthoven 3721 MA, Netherlands; jeroen.pennings@rivm.nl

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ABSTRACT

Objective Electronic cigarettes are addictive and harmful, and flavour is a key factor determining their abuse liability. Both adult smokers and young non-smokers like sweet and fruity flavours in particular. In order to discourage e-cigarette use among youth, the Dutch government announced in 2020 to only allow tobacco flavours in e-liquids. We propose a restrictive list of flavourings that will only enable the production of e-liquids with a tobacco flavour.

Methods We used e-liquid ingredient data notified via the European Common Entry Gate system before the government's announcement. First, we classified all e-liquids into flavour categories, and continued with the set of flavourings present in tobacco e-liquids. Five selection criteria related to prevalence of use, chemical composition, flavour description and health effects were defined to compile a restrictive list of tobacco flavourings.

Results E-liquids marketed as having tobacco flavour contained 503 different flavourings, some with tobacco flavour, but also other (such as sweet) flavours. We excluded (1) 330 flavourings used in <0.5% of e-liquids, (2) 77 used less frequently in tobacco than in all e-liquids, (3) 13 plant extracts, (4) 60 that are sweet or not associated with a tobacco flavour and (5) 7 flavourings with hazardous properties. This resulted in a final list of 16 flavourings.

Conclusions Implementing this restrictive list will likely discourage e-cigarette use among youth, but could also make e-cigarettes less attractive as smoking cessation aid.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Worldwide, countries implemented bans for e-liquid flavours other than tobacco to discourage e-liquid use among youth. However, to the best of our knowledge, methods to implement such a flavour ban in practice are lacking.

WHAT THIS STUDY ADDS

⇒ This paper is the first to propose a list of flavouring additives in e-liquids that will only enable the production of e-liquids with a tobacco flavour.

⇒ We developed an approach using several criteria to exclude flavouring additives that are not tobacco related, or are harmful for health, and applied these criteria to ingredient data for all e-liquids notified by manufacturers for the Dutch market. Out of the 503 different flavourings used in Dutch tobacco-flavoured e-liquids, 16 passed all criteria.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Implementing this restrictive list will discourage young people and non-smokers to use e-cigarettes.

⇒ Regulators should consider that users may add non-tobacco flavourings not marketed for use in e-liquids as an alternative.

INTRODUCTION

Although e-cigarettes are less harmful than conventional tobacco cigarettes, the use of e-cigarettes is nevertheless addictive and harmful to health. In addition, evidence suggests that e-cigarettes are potentially a gateway for young people to smoking cigarettes.[1–3] Although only weak to moderate evidence exists for the effectiveness of e-cigarettes in helping smokers to quit or smoke less,[4] smokers indicate using e-cigarettes mainly to stop smoking or to smoke less.[5–7] Younger and young adult non-smokers are more likely to cite the novelty of the product and curiosity as reasons for using e-cigarettes.[6–8]

One of the main aspects that make e-cigarettes attractive to both young people and adults is the diversity of flavours available.[9–11] Flavours reduce product risk perception and increase willingness to try.[12] Both smokers and non-smokers, regardless of their age, like sweet and mint-like flavours much more than tobacco flavours.[13 14] Thus, it is not surprising that the majority of e-liquids have a sweet flavour.[11] For example, almost 20 000 different e-liquids were registered for sale on the Dutch market in 2017 in 245 different flavours. Only 16% of these e-liquids had a tobacco flavour; most e-liquids had sweet or fruity flavours.[15] To impart such flavours, manufacturers mainly add flavourings with a sweet, fruity flavour to e-liquids (such as vanillin, ethyl maltol and ethyl butyrate[16 17]).

E-cigarettes are becoming increasingly popular among young people.[11 14] In recent years, prevalence of ever use of e-cigarettes among high school students in the Netherlands has increased to more than 25%.[18] According to the signatories of the Dutch National Prevention Agreement, to achieve a smoke-free generation by 2040, youth e-cigarette use should be discouraged.[19] Therefore, a ban on all e-liquid flavours other than tobacco was announced, to further reduce the attractiveness of e-cigarettes, in particular for young people.[19]

In the European Union, some countries already regulate flavours in e-liquids, enabled by the Tobacco Products Directive that leaves the responsibility of regulating flavours of vaping products to the member states. Hungary prohibits all flavouring agents in vaping products.[20] Finland and Estonia prohibit vaping products with flavours other than tobacco, and Denmark prohibits those with a flavour other than tobacco or menthol. Flavour bans can be based on the flavour as perceived by users of the product (sensory information) and/or based on the flavouring ingredients in the e-liquid that impart the perceived flavour.[21] The Dutch government decided to use the latter option and announced that a restrictive list of flavour-determining additives in e-cigarettes will be established based on data notified by manufacturers via the European Common Entry Gate (EU-CEG) system. This is a database in which manufacturers and importers are legally obliged to provide information about the composition and other properties of the tobacco and related products they market in each European country.[19] The Dutch government decided that protecting young people against the harmful effects of e-cigarettes outweighs the attractiveness of the product as a smoking cessation tool.[22] Thus, the restrictive list should be composed in such a way as to minimise the possibility that an e-liquid with a sweet or fruity flavour can still be made with the list of allowed substances. As already stated in the European Tobacco Products Directive, substances should not have carcinogenic, mutagenic or reproduction (CMR) toxic properties (article 7.6) in unburnt form and should not be hazardous for health in heated or non-heated condition (article 20.3).[23]

This paper describes our approach for compiling a restrictive list of flavourings. We formulated selection criteria based on prevalence of use, chemical composition, flavour description and health effects. Flavourings with a sweet flavour and flavourings not associated with tobacco (flavour) were excluded. The purpose of these criteria is to exclude all flavourings that can also be used to make e-liquids with a flavour other than tobacco.

METHODS

Data set and analyses

Data in the Dutch part of the EU-CEG system were used as data source. As of 20 June 2020, just before the Dutch government's decision to ban e-cigarette flavours other than tobacco was announced,[24] 28 556 e-liquids were registered for the Dutch market. These products, together with their EU-CEG product data, were used for compiling our proposal for a restrictive list. Data were exported as tab-delimited text and further processed using R software.

Manufacturers are not required to provide a flavour description of their products in EU-CEG. To categorise the e-liquids in flavour categories, we therefore used the information from the database fields 'BrandName', 'BrandSubtypeName', 'ProductIdentification', 'GeneralComment' (comments to accompany submission) and 'NationalComment' (comments to accompany national market notification). With this information, e-liquids were classified into one of the 16 main categories of the e-liquid 'flavor wheel'.[25] The category 'tobacco flavor' was subdivided into two groups: a group with a secondary flavour and a group without. E-liquids with a secondary flavour have an additional flavour, such as menthol, besides tobacco flavour.[25] If the information in EU-CEG was not sufficient to assign the e-liquid to a flavour category, we performed a web search for the e-liquid using Google. If the e-liquid could not be found, or the information available was too unspecific to perform a search, the e-liquid was assigned to the category 'unclassifiable'. We found that 15 344 out of the 28 556 e-liquids were already registered for the Dutch market in 2017. For those e-liquids, the previously carried-out flavour categorisation by our institute was reused.[15] The other 13 212 e-liquids that had been registered since then had to be newly classified in a flavour category. This product flavour overview was compiled in Microsoft Excel.

Next, using R code, we made a list of all ingredients and the number of e-liquids in each flavour category in which they occurred. For this purpose, we used the Chemical Abstracts Service Registry (CAS) number to avoid confusion due to different spellings or translations of substance names (eg, etanol, ethyl alcohol, ethyl alkohol, alcool éthylique, EtOH). For each ingredient, we determined whether or not it is a flavouring. Usually manufacturers indicate this in EU-CEG; in case of doubt, we used the Leffingwell database, which contains flavour data relevant to the food, beverage and tobacco industry.[26] Next, we calculated three values for each flavouring: the percentage of e-liquids with a tobacco flavour (without a secondary flavour) in which the flavouring occurred, the percentage of all e-liquids in which it occurred and the ratio between these two percentages. Subsequent data handling was done in Microsoft Excel.

Selection criteria

To draft a proposal for a list of allowed flavourings (from now on: proposed list), we applied these selection criteria:

- Prevalence in more than 0.5% of all tobacco-flavoured e-liquids. We assume that flavourings that are important for tobacco flavour will be used in a high percentage of tobacco-flavoured e-liquids. Flavourings rarely used in tobacco-flavoured e-liquids are not expected to be essential for creating a tobacco flavour, even if they are needed to create the specific tobacco flavour in which they are used. Therefore, flavourings used in less than 0.5% of tobacco-flavoured e-liquids were excluded.
- The flavouring must be used more frequently (a higher percentage) in e-liquids with tobacco flavour compared with all e-liquids. This means that the ratio between the percentage of tobacco-flavoured e-liquids and the percentage of all e-liquids in which a specific flavouring is used is at least 1. This criterion makes it more difficult to make non-tobacco-flavoured e-liquids.
- Flavouring ingredients that are mixtures defined as a distillation or extraction product from plant material are excluded. The composition of such substances, for example, cocoa extract, is not consistent as it depends on the composition of the plant source material used (subject to seasonal influences, etc) and the extraction or distillation process. It is therefore not possible to establish conclusively through analytical chemical research whether an e-liquid contains a particular extract. This would hinder the monitoring of manufacturers' compliance with the restrictive list of flavourings.
- Flavourings associated with tobacco (flavour) were selected using the following sequential stepwise approach:
  A. We determined whether the flavouring has a tobacco flavour using the flavour descriptions found in the Leffingwell database.[26] Flavourings with a flavour description containing the word 'tobacco' or a related term (eg, 'roll-your-own') were added to the proposed list (even if their flavour descriptions also contained words mentioned in step 4B).
  B. For the flavourings that were not added to the proposed list in step 4A, we determined whether they have a sweet or fruity flavour. Flavourings with a flavour description

Table 1 Distribution of e-liquids across flavour categories

Category	Total number of e-liquids	% total (n=28 556)
Tobacco (without secondary flavour)	3366	11.8
Tobacco (with secondary flavour)	855	3.0
Menthol/mint	2001	7.0
Nuts	215	0.8
Spices	259	0.9
Coffee/tea	706	2.5
Alcohol	419	1.5
Other beverages	1313	4.6
Fruits (berries)	3510	12.3
Fruit (citrus)	920	3.2
Fruit (tropical)	1946	6.8
Fruit (other)	3904	13.7
Dessert	2212	7.7
Candy	991	3.5
Other sweets	1036	3.6
Other flavours	303	1.1
Unflavoured	459	1.6
Unclassifiable	4141	14.5
Total	28 556	100.0

containing one or more of the following words were excluded: 'sweet', 'honey', 'vanilla', 'caramel', 'chocolate', 'fruit(y)', 'butter(y)', 'popcorn'. Also, derived words or types of fruit (eg, 'cherry' or 'banana') were excluded.

C. For the flavourings not added in step 4A and not excluded in step 4B (ie, without tobacco-like, sweet or fruity flavour), we determined whether their flavour is part of tobacco aroma or whether they are present in tobacco or smoke. First, their Leffingwell flavour descriptions were compared with the attributes of tobacco aroma as described by the EU Independent Advisory Panel (IAP) on characterising flavours in tobacco products.[27] Flavourings with a flavour description containing any of the attributes IAP associates with tobacco aroma (ie, green pepper, potato skin, citronella, cedar, black tea, rotted dry wood, violet, saffron, cardboard, cucumber, freshly cut grass, hay, cheese, sweetcorn, vinegar, smoky, burnt coffee, dried leaves, prune, raisin) were added to the proposed list. Second, flavourings that were identified in tobacco or tobacco smoke according to a comprehensive analysis of tobacco industry documents[28] were added to the proposed list to complement those already added in step 4A. All remaining flavourings were excluded.

- Flavourings with a health hazard, as apparent from screening publicly available databases (IARC, ECHA, US EPA, JECFA), were excluded.

A. Information on how consumers used a product served as input to determine the quantity of e-liquid exposure. Previously published information on prevalence of use and topography was supplemented with information from users' forums on the daily e-liquid usage and with information on e-liquid evaporation per puff (see online supplemental file 1). Four exposure scenarios were defined from low to high exposure, for the median and maximum concentration found for the 23 flavourings in e-liquids in the EU-CEG. The systemic dose was calculated by assuming that 70% of the inhaled dose reaches the alveoli and 100% of that quantity will be absorbed.[29] This absorbed quantity was used to determine the systemic concentration for a 70 kg person.

B. All substances were checked for possible CMR toxic properties. For substances with no CMR toxic properties, dose–response information was searched to find the highest dose that did not result in adverse effects, which is the point of departure (PoD) (see online supplemental file 2 for details). Information was obtained from the most relevant toxicity tests; for example, inhalation studies were preferred over oral studies. For substances where a PoD could be determined, this was used to calculate the margin of exposure (MoE) (see online supplemental file 3). For each of these substances, a safe MoE was calculated based on the available information (see online supplemental file 2). For the remaining substances (no CMR toxic properties and not sufficient information for a PoD), the threshold of toxicological concern (TTC) approach was used (see online supplemental file 4).

C. To determine whether a substance in e-liquids at the concentrations used in e-liquids could result in a health hazard, the exposure (5A) was compared with the hazard (5B).

Substances were removed from the list:

- If a substance has CMR toxic properties or properties that did not allow determination of a safe level of exposure.
- If the MoE for a substance was lower for one or more exposure scenarios than the MoE that was considered safe (more details on this approach can be found in RIVM report 2022-0050[30]).
- If the TTC approach resulted in a possible concern for a substance.

RESULTS

Flavour overview of e-liquids registered in EU-CEG

Table 1 gives an overview of the flavour distribution of the e-liquids based on the e-liquid 'flavor wheel' categories.[25] Out of the 28 556 e-liquids registered for the Dutch market, 3366 (11.8%) had a tobacco flavour without a secondary flavour and 855 (3.0%) a tobacco flavour with a secondary flavour. Of the other flavour categories, the largest categories were menthol (7.0%), berries (12.3%), tropical fruit (6.8%), other fruit (13.7%) and dessert (7.7 %). For 14.5% of the e-liquids, insufficient information was available to assign them to a category (ie, those assigned to 'unclassifiable'). These e-liquids were, however, included in further calculations that involved the full set of e-liquids.

All e-liquids of all flavours together contained 1981 different ingredients. The tobacco-flavoured e-liquids (without a secondary flavour) contained 630 different ingredients. Of these, 503 were flavourings with a valid CAS number. With these flavourings, all e-liquids with a tobacco flavour can still be made.

Applying selection criteria

Figure 1 shows a flow chart of the application of the selection criteria.

After applying criterion 1, prevalence of use in more than 0.5% of all e-liquids with a tobacco flavour, 173 flavourings remained. Because only rarely used flavourings were excluded, for tobacco-flavoured e-liquids most of the flavourings (on average 94% of the ingredients per product) remained available, so the impact of this step on tobacco-flavoured e-liquids is small. After application of criterion 2 (ie, the flavouring must be more frequently used in e-liquids with tobacco flavour compared with all e-liquids), 96 flavourings were left.

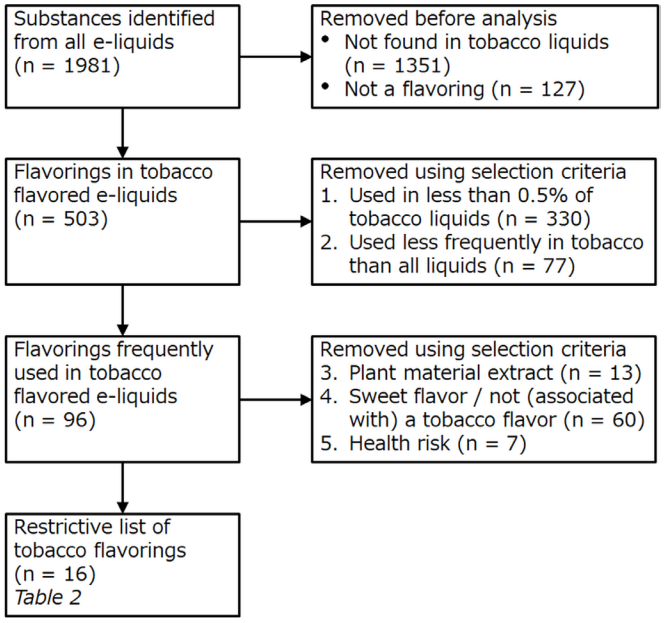

Figure 1 Flow chart for the stepwise application of selection criteria to obtain a proposed list of allowed flavourings.

In figure 2, the prevalence percentage ratio (criterion 2) is plotted against the prevalence percentage (criterion 1). The top right quadrant shows the 96 flavours that remained after applying both criteria. Many of these flavourings have a tobacco-like flavour, such as tobacco extract, tabanone and ketoisophorone. There are also a number of flavourings with other flavours such as guaiacol (smoke, vanilla), ethyl maltol (sweet, fruit-caramel-like) and cyclotene (caramel).

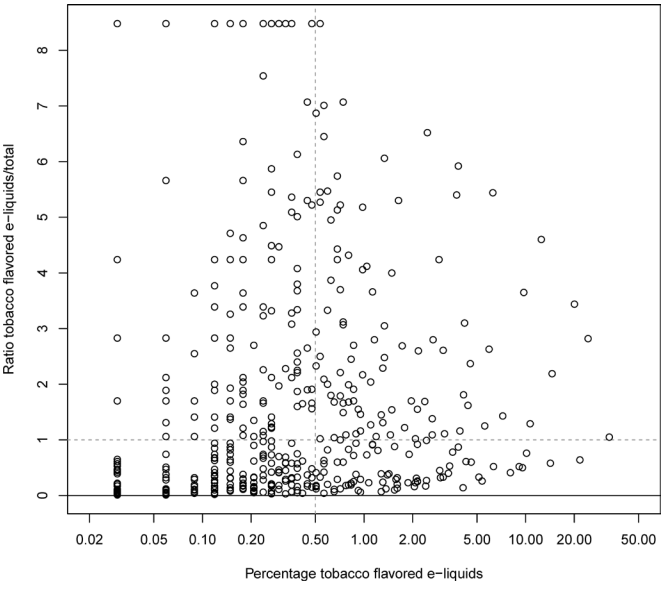

Figure 2 Flavouring prevalence percentage and ratio. The horizontal axis indicates the flavouring prevalence as a percentage of the tobacco-flavoured e-liquids (criterion 1), the vertical axis indicates the ratio between the prevalence in tobacco-flavoured e-liquids and the prevalence in all e-liquids (criterion 2). Dots indicate individual flavourings. Criterion threshold values are indicated by dotted lines. This divides the graph into four quadrants of which the flavourings in the upper right quadrant were assessed by additional criteria.

To illustrate the consequences of applying these criteria, some examples of flavourings in other quadrants are given. The top left quadrant lists 146 flavourings, including dill oil (dill), licorice extract (licorice), lovage oil (celery), glucose syrup (sweet) and phenol (medicinal). The lower left quadrant lists 184 flavours, including limonene (citrus/turpentine), ginger oil (ginger), butyl acetate (banana, pear, pineapple), diacetyl (butter) and 6-methylcoumarin (sweet, hay). Flavourings in these two quadrants were excluded by criterion 1. The lower right quadrant lists 77 flavourings, such as menthol (mint), cinnamaldehyde (cinnamon), vanillin (vanilla), ethyl butyrate (pineapple, banana) and *cis*-3-hexenol (fresh, grassy). These flavourings, many of which have a high prevalence of use in tobacco-flavoured e-liquids and an attractive but non-tobacco-related flavour, were excluded by criterion 2.

Thirteen of the 96 ingredients that remained after applying criteria 1 and 2 consist of extracts or distillates from plant materials, which were removed after applying the third selection criterion. This included substances such as cocoa extract, carob extract and tobacco leaf extract. Subsequently, applying the fourth criterion, the flavour of the remaining 83 flavourings was assessed. This resulted in the removal of 60 flavourings from the proposed list because they possess a sweet flavour or because the flavouring is not associated with tobacco (flavour). Finally, we excluded seven flavourings with sufficient information to conclude that they could result in a health hazard at the concentrations used in e-liquids.

Proposal for a list of allowed flavourings

Table 2 lists the flavouring ingredients that remain after applying all five criteria.

DISCUSSION

This paper presents a proposal for a list of flavourings to be allowed in e-cigarette e-liquids. The applied approach yields a list of 16 flavourings that have a tobacco(-like) flavour and/or are present in tobacco smoke.

Impact of the different selection criteria

Because the aim of the proposed Dutch legislation is to allow tobacco-flavoured e-liquids, step 4A allowed flavourings that smell like tobacco, even if their description also contains sweet or fruity attributes. In step 4B, non-tobacco sweet and fruity flavours were excluded to reduce the attractiveness of e-liquid flavours to young people. As the Dutch Prevention Agreement aims to achieve that e-liquids are not attractive to young people, it was decided to prioritise step 4B over step 4C. This way, sweet flavourings with no tobacco(-like) flavour are excluded from the proposed list. Of the remaining flavourings that have neither a sweet nor a tobacco(-like) flavour, only those associated with the aroma of tobacco or that are present in tobacco smoke are included on the proposed list. The proposed list therefore includes (1) flavourings that have a tobacco flavour and (2) flavourings which do not have tobacco flavour and that are not sweet or fruity, but whose flavour is part of tobacco aroma, or that occurs in tobacco smoke.

In most cases, this approach resulted in an unambiguous choice for or against inclusion on the proposed list. In three cases, however (2-ethyl-3-methylpyrazine, caryophyllene and isovaleric acid), the decision whether or not to include the flavouring on the proposed list was not clear-cut. Isovaleric acid does not have a tobacco(-related) flavour description. The description mentions 'fruity', but only in the phrase 'fruity on dilution'. Hence, we do

Table 2 Proposal for a list of allowed flavourings in e-cigarette e-liquids

CAS No	Flavouring name	Flavour description	Association with tobacco
35044-68-9	beta-Damascone	Complex odour of blackcurrant, plum, rose, honey and **tobacco**	Tobacco-like flavour
23726-91-2	(E)-beta-Damascone	Complex odour of blackcurrant, plum, rose, honey and **tobacco**	Tobacco-like flavour
23726-92-3	(Z)-beta-Damascone	Complex odour of blackcurrant, plum, rose, honey and **tobacco**	Tobacco-like flavour
23696-85-7	Damascenone	Fruity floral with apple-plum-raisin-prune, tea, rose, **tobacco notes**	Tobacco-like flavour
23726-93-4	(E)-beta-Damascenone	Fruity floral with apple-plum-raisin-prune, tea, rose, **tobacco notes**	Tobacco-like flavour
1125-21-9	Ketoisophorone	**Tobacco-like**, hay straw, tea notes, honey	Tobacco-like flavour
4883-60-7	2-Hydroxy-3,5,5-trimethyl-2-cyclohexenone	Sweet, musty tea, caramellic odour; musty, tea, nutty, **tobacco taste**	Tobacco-like flavour
536-78-7	3-Ethylpyridine	Strong **tobacco**, roasted, nutty, smoky notes odour; **tobacco-like flavour**	Tobacco-like flavour
350-03-8	3-Acetylpyridine	Strong, burnt roasted, nutty, **cigar tobacco-like**	Tobacco-like flavour
91-10-1	2,6-Dimethoxyphenol	Phenolic-**woody**-medicinal, smoky odour; a tarry, spicy, **smoky** (bacon) taste	Attribute of tobacco aroma
67-47-0	5-(Hydroxymethyl)-2-furfural	Herbaceous winey hay-like odour, sweet herbaceous hay and **tobacco-like** taste	Tobacco-like flavour
591-12-8	alpha-Angelica lactone	Sweet, bread, molasses, coumarin, **tobacco odour**; nut-like taste	Tobacco-like flavour
503-74-2	Isovaleric acid	Very sour, 'sweaty', **cheesy**, odour; fruity on dilution	Attribute of tobacco aroma
1139-30-6	(−)-Caryophyllene oxide	Dry, woody, faint cedar, **tobacco-like notes**	Tobacco-like flavour
3738-00-9	Ambroxide	Intense velvety ambergris notes	Present in tobacco smoke
564-20-5	(3aR)-(+)-Sclareolide	Cedary; **impact compound of certain tobaccos**; fish and berry flavour improver	Tobacco-like flavour

Terms associated with tobacco or tobacco smoke are indicated in bold.

not expect the flavouring to have a (strong) sweet flavour. Isovaleric acid is found in tobacco smoke, and the 'cheese' attribute is listed by the IAP. Thus, because overall evidence indicates that this flavouring has an association with tobacco, it was included on the proposed list. Both 2-ethyl-3-methylpyrazine and caryophyllene were excluded from the list in a later step because they are associated with health hazards.

The last selection criterion was the toxicity of the substances. Although substances that may be hazardous for health are not allowed in e-liquids, still seven substances were omitted due to possible health effects. For none of the remaining 16 substances literature data on the effects on inhalation were available. This means that local effects in the mouth and respiratory tract, the first site of contact for e-cigarette vapour, could not be assessed. Furthermore, the systemic effects after inhalation may be different from those after oral exposure, since the route of the compound in the body is different when inhaled. It could be argued that the remaining 16 substances should be prohibited due to a lack of toxicity data, as it cannot be concluded that their use is safe. However, as the e-cigarette is also used by tobacco smokers who would like to switch to a less harmful product, we propose to carefully monitor possible adverse effects in e-cigarette users, for example, by poison control centres or analysing trends on social media, until more toxicological data on these 16 substances are available. Additionally, toxicological studies may be carried out to provide a better knowledge basis for risk assessment of these substances.

Similar approaches

In June 2021, Health Canada published a proposal to limit e-cigarette flavours through the use of a restrictive list.[31] Canada would still allow tobacco and mint/menthol flavours. The Canadian list contains 40 tobacco flavourings. Eight flavourings on our proposed restrictive list are also on the Canadian list. A number of factors may help explain the differences between both lists. For example, the Dutch list is overall stricter in that it only allows tobacco-flavoured e-liquids, whereas the Canadian list also allows mint/menthol-flavoured e-liquids. Additionally, Health Canada based their list on analytical chemical measurements in 825 e-liquids[17] obtained from the Canadian market, whereas we based our list on data provided by manufacturers through the EU-CEG system for all e-liquids notified for the Dutch market. Moreover, both institutes did not use exactly the same inclusion and exclusion criteria; for example, we excluded substances with health risks. Finally, e-liquids with tobacco flavours could have a different composition in Canada than in the Netherlands.

The Chinese government also published a list of allowed additives including flavourings, the latter with the aim to ban flavours other than tobacco flavour. However, this list also contains sweet flavourings such as ethyl maltol and vanillin.[32] Although the list indicates upper limits for use, meaning that it is possible that the additives in such amounts will not impact a sweet flavour, such flavour information is not included in the document. To the best of our knowledge, no other countries use a restrictive list of allowed flavourings in e-liquids.

A main strength of our approach is that it is based on data for all e-liquids notified for the Dutch market, thus avoiding the need for analytical measurements or sensory studies on a large set of samples. However, this also implies a potential weakness because we can not be completely sure that all product composition data are submitted correctly in EU-CEG.

Potential impact of proposal on manufacturers and users

If the proposed list is implemented in legislation, this may have several potential consequences. As many flavoured tobacco e-liquids also contain flavourings with a flavour other than tobacco, such as ethyl maltol (sweet, fruit-caramel-like), not all tobacco-flavoured e-liquids currently on the market will remain available with their current ingredients. We found that for 0.2% of the tobacco-flavoured e-liquids without secondary flavours, all of their flavourings used are on the proposed list. Therefore, these products would be allowed to remain on the market with their current composition. 77.3% of the tobacco-flavoured e-liquids contain one or more flavourings that are not on the proposed list. For these liquids, manufacturers would have the option to adapt the composition using only (combinations of) the allowed flavourings. For the remaining 22.5%, the manufacturer has provided no, insufficient, or unclear information and we cannot say with certainty whether or not all of the flavourings used in these liquids are on the proposed list.

Overall, e-cigarettes will probably become less attractive if all flavours except tobacco are prohibited. This would support the intended goal of the National Prevention Agreement, that is, discouraging young people and non-smokers to use e-cigarettes. On the other hand, e-cigarettes could also become a less attractive alternative for smokers who want to quit smoking.[21] Although in general only weak to moderate evidence exists for the effectiveness of e-cigarettes,[4] it has been reported that smokers who use e-cigarette flavours other than tobacco, such as sweet flavours and fruity flavours, are more likely to quit smoking using the e-cigarette.[33–35]

Although it is not possible to predict how exactly the Dutch market for e-cigarettes will change in response to the flavour ban, it can be anticipated that the overall number of available e-liquids will decrease and that manufacturers will change the composition of some of their tobacco-flavoured e-liquids. Such market changes will influence e-cigarette use by young people as well as by smokers trying to quit. Follow-up research will be needed to determine how legislative as well as market changes work out on the overall protection of public health.

One possible unintended consequence of the intended ban is that users will add flavourings to their e-liquids themselves. With this proposed list, manufacturers can still produce unflavoured 'base e-liquids'. Numerous aromas are already for sale to add to such e-liquids. Flavours that are marketed as e-liquid for e-cigarettes fall under the Dutch Tobacco and Smoking Products Act. However, this regulation does not apply to flavourings presented as a liquid for other purposes, such as for the preparation of food. Furthermore, flavouring accessories are on the market to use in combination with e-cigarettes, for example, mouthpieces with a flavour capsule that the user can crush.[36] Such products still enable consumers to use a desired flavour, which may diminish the impact of the intended ban.

Enforcement of the proposed list

After the proposed list would come into effect in legislation, one of the possibilities that may be conducted is a check of EU-CEG data for the use of non-allowed flavourings. However, because EU-CEG files may be incomplete or contain inaccuracies, compliance can additionally be checked by chemical analysis. An advantage of a restrictive list is that it leaves no ambiguity about which substances are allowed. A disadvantage, however, is that the number of forbidden substances is essentially infinite. Thus, it can be challenging to ensure the detection of non-allowed ingredients by chemical analyses. Non-targeted screening methods can maximise the chance of detection. Because most flavourings are volatile, gas chromatography coupled to mass spectrometry is a common and suitable technique for flavour analysis that has previously been used for e-liquids.[17 37 38] Mass spectra can also provide information about the identity of unknown (non-allowed) flavourings. Combining different techniques will give the best possibilities to determine which—if any—non-allowed flavourings an e-liquid contains.

CONCLUSIONS

This paper proposes a restrictive list of 16 flavourings to be allowed in the production of e-liquids. We expect that with these flavourings, only e-liquids with a tobacco flavour can be produced. Implementing this proposed list in legislation will likely discourage e-cigarette use among youth, but also make e-cigarettes less attractive as smoking cessation aid. Regulators should also consider that users may add non-tobacco flavourings not marketed for use in e-liquids as alternative. After implementation, it will be useful to evaluate whether this proposed list achieves the final objective of only tobacco-flavoured e-liquids on the market. A comparison with other countries, such as Canada should they also implement a restrictive list, can be helpful, as can be the monitoring of commercially available e-liquids.

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ORCID iDs
Jeroen L A Pennings http://orcid.org/0000-0002-9188-6358
Anne Havermans http://orcid.org/0000-0003-2874-6560
Wouter F Visser http://orcid.org/0000-0003-1129-262X
Ingrid M E Bakker-'t Hart http://orcid.org/0000-0001-6632-783X
Yvonne C M Staal http://orcid.org/0000-0002-7187-0121

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Correction: *Reducing attractiveness of e-liquids: proposal for a restrictive list of tobacco-related flavourings*

Pennings JLA, Havermans A, Krüsemann EJZ, *et al*. Reducing attractiveness of e-liquids: proposal for a restrictive list of tobacco-related flavourings. *Tob Control* 2023. doi: 10.1136/tc-2022-057764

The authors have brought out attention to an error in their manuscript, which has been published as an online first article in *Tobacco Control*.

The error appears in the Discussion under subheading 'Potential impact of proposal on manufacturers and users'. The revised text should have read as follows:

We found that for 0.2% of the tobacco-flavoured e-liquids without secondary flavours, all of their flavourings used are on the proposed list. Therefore, these products would be allowed to remain on the market with their current composition. 77.3% of the tobacco-flavoured e-liquids contain one or more flavourings that are not on the proposed list. For these liquids, manufacturers would have the option to adapt the composition using only (combinations of) the allowed flavourings. For the remaining 22.5%, the manufacturer has provided no, insufficient, or unclear information and we cannot say with certainty whether or not all of the flavourings used in these liquids are on the proposed list.

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Supplementary file 1: Exposure scenarios

The exposure scenario to determine daily e-liquid consumption was based on a previously published RIVM report (1), information from users fora (https://damp-e.nl/blog/hoe-lang-doe-je-met-een-flesje-e-liquid# , https://www.esigaretsolutions.nl/service/ , https://dampforum.nu/topic/9925-hoeveel-liquid-gebruik-je-ongeveer/ , consulted on 27th of January 2022), and data related to the use of e-liquid per puff as measured with a VC1 smoking machine and with a clearomizer (1,6 Ω, puff volume of 55 ml/puff, puff duration of 3 seconds). The average weight of e-liquid per puff was 12.41 mg.

The assumptions to determine the exposure of a user are:

- No pyrolysis occurs and no chemical reactions of the compounds in e-liquid occur. Currently data on such reactions is too limited for the chemicals listed to be considered for exposure assessment.
- The composition of the e-liquid is representative for the vapor. This means that the e-liquid constituents transfer to the vapor proportionally.
- The vapor will consist of e-liquid constituents only, no substances from other sources, such as the device, will evaporate.
- The ratio of propylene glycol:glycerol in the liquid is 1:1. This ratio is used to calculate the e-liquid weight to a volume (density of the mixture is 1148 mg/ml).

We have used four exposure scenarios, from low to high exposure level:

1. Weekly user: 8 puffs/session, 7 sessions/day, 1 day/week
2. Daily user: 7 puffs/session, 16 sessions/day, 7 days/week
3. Daily user with a higher e-liquid consumption: 8 puffs/session, 16 sessions/day, 7 days/week
4. Daily user with the highest e-liquid consumption: 10 puffs/session, 20 sessions/day, 7 days/week

Scenarios 3 and 4 assume that the users have a higher e-liquid consumption, for example by adapting the device setting to vaporize more e-liquid. These scenarios were selected since the quantity of e-liquid use per puff was measured at a relatively mild scenario, whereas user information from fora indicated a daily e-liquid use of 10 ml/day (as in scenario 4). This means that even the most intense scenario is considered relevant and also higher exposure levels may be realistic. Table S1.1 shows the total e-liquid exposure.

Table S1.1: Exposure to the total volume of e-liquid per day, according to different exposure scenarios.

Scenario	Average quantity of e-liquid per puff	Number of puffs per session	Number of sessions per day	E-liquid consumption per day (in weight)	E-liquid consumption per day (in volume)	Systemic exposure
	mg/puff	number	number	mg/day	ml/day	ml/day
1	12.41	8	7	695	0.61	0.42
2	12.41	7	16	1390	1.21	0.85
3	24.81	8	16	3176	2.77	1.94
4	57.40	10	20	11480	10.00	7.00

The systemic exposure to the total volume of e-liquid per day (Table S1.1) was used to calculate the systemic exposure to each of the flavorings. Results are shown in Table S1.2). The method used for this calculation is described in the materials and methods section of the main text.

For evaluation of health effects, the most intense scenario was assessed first. If a possible health risk was found, further assessments were done for scenarios 3, 2 and finally 1.

Table S1.2: Absorbed dose of the 23 flavorings according to 4 exposure scenarios, for the median and maximum concentration found in e-liquids in the EU common entry gate (EU-CEG).
Bw = body weight

	Daily dose (µg/kg bw/day) median				Daily dose (µg/kg bw/day) maximum			
Substance name	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 1	Scenario 2	Scenario 3	Scenario 4
2,3,5-Trimethylpyrazine	1.00	1.99	4.55	16.46	140.94	281.88	644.30	2328.77
Damascenone	0.16	0.31	0.72	2.60	223.85	447.69	1023.29	3698.63
Isophorone	0.24	0.47	1.08	3.92	167.04	334.07	763.59	2759.96
beta-Damascone	3.27	6.54	14.94	54.00	66.23	132.47	302.79	1094.40
(E)-beta-Damascone	0.85	1.71	3.90	14.09	50.81	101.62	232.26	839.50
(Z)-beta-Damascone	0.63	1.26	2.88	10.40	5.58	11.16	25.50	92.16
Keto-isophorone	0.18	0.36	0.83	3.00	4.34	8.68	19.84	71.73
Tabanone	0.83	1.66	3.79	13.72	35.23	70.47	161.07	582.19
beta-Caryophyllene	0.31	0.63	1.44	5.20	279.44	558.89	1277.46	4617.30
(E)-beta-Damascenone	0.70	1.40	3.20	11.55	25.54	51.08	116.75	422.00
Isovaleric acid	0.01	0.02	0.05	0.18	9.57	19.15	43.77	158.20
2-Hydroxy-3,5,5-trimethyl-2-cyclohexenone	3.15	6.29	14.38	51.98	24.82	49.64	113.46	410.09
Pyridine	0.10	0.21	0.47	1.70	140.94	281.88	644.30	2328.77
3-Acetylpyridine	0.50	1.01	2.30	8.31	2.20	4.40	10.07	36.38
2-Ethyl-3-methylpyrazine	0.04	0.07	0.17	0.60	2.42	4.84	11.07	40.00
2,6-Dimethoxyphenol	0.11	0.22	0.49	1.78	2.79	5.58	12.75	46.10
p-Cresol	0.02	0.04	0.08	0.30	0.85	1.69	3.87	14.00
(-)Carophyllene oxide	0.06	0.11	0.26	0.94	0.31	0.62	1.41	5.10
alpha-Angelica lactone	0.01	0.02	0.04	0.14	0.13	0.27	0.61	2.19
Ambroxide	0.02	0.03	0.07	0.26	1.94	3.87	8.85	31.99

	Daily dose (µg/kg bw/day) median				Daily dose (µg/kg bw/day) maximum			
Substance name	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 1	Scenario 2	Scenario 3	Scenario 4
3-Ethylpyridine	0.00	0.01	0.01	0.05	1.21	2.42	5.53	20.00
5-(Hydroxymethyl)-2-furfural	0.01	0.02	0.06	0.20	0.11	0.21	0.49	1.76
(3aR)-(+)-Sclareolide	0.01	0.01	0.03	0.10	1.51	3.03	6.92	25.00

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Supplementary file 2: Points of Departure (PoD)

Table S2: Overview of the available toxicological data of the flavorings.

Substance name	Reference	Limit value	Remarks
2,3,5-Trimethylpyrazine	JECFA, 2002[1]	NOAEL: 18 mg/kg bw/day	90-day oral study with rats (diet, 1 dose). No observed effects.
Damascenone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Isophorone	ECHA, 2022a[3] and NTP, 1986[4]	CMR	Harmonised classification Carc. 2 (H351; suspected of causing cancer)
beta-Damascone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
(E)-beta-Damascone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
(Z)-beta-Damascone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Ketoisophorone	EFSA, 2015[2]	TTC: 540 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Tabanone	JECFA, 2011[5]	NOAEL: 40 mg/kg bw/day	14-day oral study with rats (gavage, 0, 40, 200 and 1000 mg/kg bw/day). Based on increased liver weight and decreased spleen weight.
Beta-Caryophyllene	ECHA, 2022b[6]	(potentially) sensitizing	Notified classification Skin. Sens. 1B (H317; may cause allergic skin reaction). Based on studies with mice and guinea pigs and a clinical study.
(E)-beta-Damascenone	EFSA, 2015[2]	TTC: 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Isovaleric acid	EFSA, 2012[7]	TTC: 1800 µg/person/day	Evaluated as part of a group of branched-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing branched-chain alcohols and acetals containing branched-chain aldehydes.
2-Hydroxy-3,3,5-trimethyl-2-cyclohexanone	EFSA, 2015[2]	TTC: 540 µg/ person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.

Substance name	Reference	Limit value	Remarks
Pyridine	IARC, 2019[8]	CMR	IARC Classification 2B; possibly carcinogenic to humans.
3-Acetylpyridine	EFSA, 2018[9]	TTC: 540 µg/person/day	Evaluated as part of a group of pyridine, pyrrole and quinoline derivatives.
2-Ethyl-3-methylpyrazine	JECFA, 2002[1]	NOAEL: 5.2 mg/kg bw/day	90-day oral study with rats (diet, 1 dose). No observed effects.
2,6-Dimethoxyphenol	EFSA, 2008[10]	TTC: 1800 µg/person/day	Evaluated as part of a group of phenol derivatives containing ring-alkyl, ring-alkoxy and side-chains with an oxygenated functional group.
p-Cresol	ECHA, 2022c[11]	DNEL of 3.5 mg/m^3 based on an oral NOAEL of 50 mg/kg bw/day	90-day oral study (gavage, 0, 50, 175 or 600 mg/kg bw/day).
(-)-Caryophyllene-oxide	EFSA, 2014[12] and Bauter, 2013[13]	NOAEL: 109 mg/kg bw/day	90-day oral study with rats (diet, 0, 109, 672 and 1398 mg/kg bw/day). Based on mesenteric lymph node pathology.
alpha-Angelica lactone	JECFA, 1998[14]	NOAEL: 17.4 mg/kg/day	90-day oral study with rats (drinking water, highest dose). No observed effects.
Ambroxide	EFSA, 2010[15]	TTC: 90 µg/person/day	Evaluated as part of a group of aliphatic and aromatic ethers.
3-Ethylpyridine	EFSA, 2018[9]	TTC: 540 µg/person/day	Evaluated as part of a group of pyridine, pyrrole and quinoline derivatives.
5-(Hydroxymethyl)-2-furfural	EFSA, 2011[16] derived from NTP, 2010[17]	BMDL: 14.4 mg/kg bw/day	90-day oral study with mice (gavage, 0, 47, 94, 188, 375 or 750 mg/kg). Corrected for dose regimen of 5 days/week to continuous daily administration). Based on cytoplasmic alterations in renal proximal tubule epithelium.
(3aR)-(+)-Sclareolide	EFSA, 2014[12]	TTC: 90 µg/person/day	Evaluated as part of a group of epoxides.

Abbreviations

BMDL: benchmark dose level
CLP: Classification, Labelling and Packaging
CMR: Carcinogenic, Mutagenic, Reprotoxic
DNEL: derived no effect level
ECHA: European Chemicals Agency
EFSA: European Food Safety Authority
IARC: International Agency for Research on Cancer
JECFA: Joint FAO/WHO Expert Committee on Food Additives
NOAEL: no-observed adverse effect level
NTP: National Toxicology Program
TTC: threshold of toxicological concern

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Supplementary file 3: Margin-of-Exposure (MoE)

Table S3.1: MoEs at the median and maximum exposure concentration for each exposure scenario, based on reported PoDs and the concentrations in e-liquids according to EU-CEG

			Substance concentration in e-liquids according to EU-CEG (mg/mL)		Daily dose scenario 4 (µg/kg bw/day)				Daily dose scenario 3 (µg/kg bw/day)			
Substance name	NOAEL/BMDL (µg/kg bw/day)	Minimum MoE	Median	Maximum	Median	MoE	Maximum	MoE	Median	MoE	Maximum	MoE
2,3,5-Trimethylpyrazine	18000	400	0.16	23.29	16.46	1094	2328.77	**8**	4.55	3954	644.30	**28**
Tabanone	40000	1200	0.14	5.82	13.72	2916	582.19	**69**	3.79	10540	161.07	**248**
2-Ethyl-3-methylpyrazine	5200	400	0.01	0.40	0.60	8667	40.00	**130**	0.17	31325	11.07	470
p-Cresol	50000	400	0.00	0.14	0.30	168350	14.00	3571	0.08	608491	3.87	12909
(-)-Carophylleen oxide	109000	400	0.01	0.05	0.94	116453	5.10	21379	0.26	420912	1.41	77272
alpha-Angelica lactone	17400	400	0.00	0.02	0.14	121800	2.19	7931	0.04	440238	0.61	28665
5-(Hydroxymethyl)-2-furfural	14400	700	0.00	0.02	0.20	72120	1.76	8182	0.06	260674	0.49	29573

The MoEs in bold indicate a possible health risk for that scenario and concentration of the substance in e-liquids.
NOAEL = No-Observed Adverse Effect Level
BMDL = Bench Mark Dose Level

Table S3.1. continued

			Substance concentration in e-liquids according to EU-CEG (mg/mL)		Daily dose scenario 2 (µg/kg bw/day)				Daily dose scenario 1 (µg/kg bw/day)			
Substance name	NOAEL/BMDL (µg/kg bw/day)	Minimum MoE	Median	Maximum	Median	MoE	Maximum	MoE	Median	MoE	Maximum	MoE
2,3,5-Trimethylpyrazine	18000	400	0.16	23.29	1.99	9037	281.88	**64**	1.00	18075	140.94	**128**
Tabanone	40000	1200	0.14	5.82	1.66	24092	70.47	**568**	0.83	48184	35.23	**1135**
2-Ethyl-3-methylpyrazine	5200	400	0.01	0.40	0.07	71600	4.84	1074	0.04	143200	2.42	2148
p-Cresol	50000	400	0.00	0.14	0.04	1390836	1.69	29506	0.02	2781672	0.85	59011
(-)-Carophyllene oxide	109000	400	0.01	0.05	0.11	962084	0.62	176623	0.06	1924168	0.31	353245
alpha-Angelica lactone	17400	400	0.00	0.02	0.02	1006259	0.27	65520	0.01	2012518	0.13	131040
5-(Hydroxymethyl)-2-furfural	14400	700	0.00	0.02	0.02	595827	0.21	67595	0.01	1191654	0.11	135189

MoE was calculated by dividing the NOAEL or BMDL by the daily dose. A possible health risk could occur for cases where the calculated MoE was lower than the minimum MoE.

The minimum MoE was calculated according to commonly used assessment factors:

- For differences between species
  - Factor 10 for translation from rat to human
  - Factor 17.5 for translation from mouse to human
  - Factor 10 for interspecies differences
- For differences in exposure duration
  - Factor 6 for subacute (14 of 28 day studies) to chronic exposure
  - Factor 2 for subchronic (90 day studies) to chronic exposure
- For differences in exposure rout
  - Factor 2 for oral studies to inhalation

Supplementary file 4: Threshold of Toxicological Concern (TTC)

Table S4: TTC approach for the 13 flavorings with insufficient toxicological data to apply an MoE approach

			Substance concentration in e-liquids according to EU-CEG (mg/mL)		Daily dose scenario 4 (µg/kg bw/dag)		Daily dose scenario 3 (µg/kg bw/dag)		Daily dose scenario 2 (µg/kg bw/dag)		Daily dose scenario 1 (µg/kg bw/dag)	
Substance name	TTC (µg/person /day)	TTC [1] (µg/kg bw/day)	Median	Maximum	Median	Maximum	Median	Maximum	Median	Maximum	Median	Maximum
Damascenone	1800	25.71	0.03	36.99	2.60	**3698.63**	0.72	**1023.29**	0.31	**447.69**	0.16	**223.85**
beta-Damascone	1800	25.71	0.54	10.94	**54.00**	**1094.40**	14.94	**302.79**	6.54	**132.47**	3.27	**66.23**
(E)-beta-Damascone	1800	25.71	0.14	8.40	14.09	**839.50**	3.90	**232.26**	1.71	**101.62**	0.85	**50.81**
(Z)-beta-Damascone	1800	25.71	0.10	0.92	10.40	**92.16**	2.88	25.50	1.26	11.16	0.63	5.58
Keto-isophorone	540	7.71	0.03	0.72	3.00	**71.73**	0.83	**19.84**	0.36	**8.68**	0.18	4.34
(E)-beta-Damascenone	1800	25.71	0.12	4.22	11.55	**422.00**	3.20	**116.75**	1.40	**51.08**	0.70	25.54
Isovaleric acid	1800	25.71	0.00	1.58	0.18	**158.20**	0.05	**43.77**	0.02	19.15	0.01	9.57
2-Hydroxy-3,5,5-trimethyl-2-cyclohexenone	540	7.71	0.52	4.10	**51.98**	**410.09**	**14.38**	**113.46**	6.29	**49.64**	3.15	**24.82**
3-Acetylpyridine	540	7.71	0.08	0.36	**8.31**	**36.38**	2.30	**10.07**	1.01	4.40	0.50	2.20
2,6-Dimethoxyphenol	1800	25.71	0.02	0.46	1.78	**46.10**	0.49	12.75	0.22	5.58	0.11	2.79
Ambroxide	90.00	1.29	0.00	0.32	0.26	**31.99**	0.07	**8.85**	0.03	**3.87**	0.02	**1.94**
3-Ethylpyridine	540	7.71	0.00	0.20	0.05	**20.00**	0.01	5.53	0.01	2.42	0.00	1.21
(3aR)-(+)-Sclareolide	90.00	1.29	0.00	0.25	0.10	**25.00**	0.03	**6.92**	0.01	**3.03**	0.01	**1.51**

[1] The daily dose is used to calculate a dose relative to body weight (bw) by using an average body weight of 70 kg.
Numbers in bold indicate for which scenario, substance and concentration in the e-liquid there may be a health risk concern.