Requirements for substances formed or released during the evaporation of e-liquids used in electronic cigarettes

Study commissioned by:
The Consumer Council at the Austrian Standards Institute
the Austrian Ministry of Labour, Social Affairs and Consumer Protection

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Final report

03 November 2017

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Summary

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 e-cigarettes cannot be considered safe with respect to health effects. An important risk factor is posed through inhalation of nicotine, however, additional ingredients in the e-liquids such as solvents (propylene glycol, glycerine), various scent and aroma substances (e.g. menthol, linalool) and contaminants etc. can pose health risks as well.

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 for 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.

The purpose of this study was to develop a proposal for requirements for selected substances that are formed from substances in the e-liquids or are released from e-cigarettes hardware during use based on relevant existing threshold values for different chemical substances. The focus will be on the substances formed or released during the evaporation of e-liquids and not the substances contained in the e-liquids. Substances used as ingredients in e-liquids are dealt with in another project. Furthermore, the purpose of the study is to review existing standards on e-cigarettes, focussing on requirements for substances formed during evaporation of the e-liquids.

This project is carried out as a desk-top study and includes a description of existing legislation regarding chemical substances formed from substances in the e-liquids or released from e-cigarettes hardware and a review of the chemical requirements in existing standards on e-cigarettes. Furthermore, a screening (an internet search) for substances formed or released during the evaporation of e-liquids has been prepared and relevant existing threshold limit values (TLVs) for these substances were identified. Finally, 12 substances were selected for which a proposal for limit values of these substances formed or released during evaporation of e-liquids has been calculated based on the identified TLVs and based on simple ‘worst-case’ calculations. The proposed preliminary calculated limit values for the 12 selected substances formed or released from e-liquids are presented in chapter 8 “Preliminary proposal for limit values of selected substances”.

It must be emphasised that the calculations performed in this report are made on a screening level, i.e. that a simple ‘worst-case’ calculation has been made. This means that it is assumed that all the substance contained in the e-liquid is evaporated, and all the substance evaporated is inhaled, and finally that all of the inhaled substance is absorbed in the body. Absorption of the substances in the body may therefore be overestimated and the proposed limit values may therefore be lower than necessary. However, in case of missing information regarding absorption a precautionary principle should be used. Furthermore, it can also be discussed which limit values that should be used for the individual substances. In

this report, the lowest limit values found have generally been used, unless newer assessments on limit values have been carried out. The proposed preliminary limit values in this report should therefore be considered as a first approximation and the risk assessment presented needs further refinement in order to establish limit values for substances formed or released during the evaporation of e-liquids.

The calculated proposed limit values for the 12 selected substances formed or released during the evaporation of e-liquids lie between 0.04 µg (for nickel) and 3,200 mg (for acetone) for 500 puffs.

For all 12 substances where limit values in vapours are proposed, information about the actual concentration in vapours from e-cigarettes has been identified in this review. In 4 of the 12 cases, the actual identified maximum concentration in vapours from e-cigarettes is higher than the proposed limit value. In some cases, the maximum concentrations found in e-liquids are a factor of 9-12 times higher than the proposed limit values in this report. For formaldehyde, the maximum concentration found in vapours exceeds the proposed limit value by a factor of about 40 – and in one case (for acrolein) even by a factor of 150. These facts suggest that limit values may be needed.

However, as the available information about the actual minimum concentrations measured in vapours from e-liquids reveals, it will be possible for some of the e-liquids examined in the literature to meet the proposed limit values for substances formed or released for all 12 selected substances. For example, acrolein was identified in vapours from 9 out of 13 e-liquids where its content was measured. This suggests that it will be possible for some of e-liquids on the market to meet the suggested limit value for acrolein in the vapour.

For five of the substances (acetaldehyde, acetone, elemental chromium, toluene and xylene), the actual measured concentrations in vapour from e-cigarettes are all well below the proposed limit values set for the vapour in this report. This would imply that no risk of health effects is to be expected from these five substances.

However, the fact that 4 of the proposed limit values are exceeded by actual measured maximum concentration in vapours from e-cigarettes suggests that vaping on e-cigarettes (heavy vapourers of 500 puffs/day) cannot be considered as safe in all cases, i.e. long term (or acute) health effects may occur for these 4 substances in some situations.

According to the Tobacco Directive, it is only allowed to use substances in e-cigarettes and e-liquids which do not pose a risk to human health in heated and unheated form. Furthermore, it is a requirement to notify toxicological data regarding both ingredients and emissions when heated. This review and other reviews on the subject illustrate that substances formed or released during the evaporation of e-liquids are evaporated in concentrations which cannot be considered as safe. This fact emphasises the need for limit values for several of the substances formed or released during the evaporation of e-liquids.

Neither the GPS Directive nor the Tobacco Directive contains specific requirements (limit values) for substances used in e-cigarettes and e-liquids or substances formed or released during the evaporation of e-liquids. It is therefore important that the standards developed set the necessary chemical requirements (for all the necessary chemical substances formed or released during the evaporation of 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. BfR, the German Federal Institute for Risk Assessment, prepared in 2012 an opinion on liquids in e-cigarettes (BfR, 2012) and concluded that even though e-cigarette vapourers 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 often remains unclear.

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.

1.2 Purpose

The purpose of this study was to develop a proposal for requirements for selected substances that are formed from substances in the e-liquids during use based on relevant existing threshold values for different chemical substances. The focus will be on the substances formed or released during the evaporation of e-liquids and not the substances contained in the e-liquids. Furthermore, the purpose of the study is to review existing standards on e-cigarettes, focussing on requirements for e-liquids formed during evaporation of the e-liquids.

1.3 Definitions

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: “means 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).

The **substances formed or released** during the evaporation of e-liquids are defined as substances, which are either reaction or degradation products of substances contained in the e-liquid or substances leaching from hardware components. Some of the substances may also be contained in the e-liquids e.g. impurities. Some metals may for example be present in the liquid (impurities). The vapour resulting from heating the e-liquid is emissions in the form of an aerosol consisting of both gas and liquid phase components (BSI, 2015).

2 Project methodology used

This project is carried out as a desk-top study and includes the following tasks:

1. Description of existing legislation regarding chemical substances formed during the evaporation of e-liquids including identical substances released from e-cigarettes themselves.
2. Review of existing standards on e-liquids in electronic cigarettes – with a focus on the chemical requirements concerning substances formed or released during the evaporation of e-liquids including identical substances released from e-cigarettes themselves.
3. Screening of existing knowledge regarding chemical substances formed or released during evaporation of e-liquids including identical substances released from e-cigarettes themselves.
4. Identification of relevant existing threshold values for the substances formed or released during the evaporation of e-liquids.
5. Prioritisation and selection of substances formed or released during the evaporation of e-liquids for which a proposal for limit values will be set.
6. Proposal for requirements for selected substances formed or released during evaporation of e-liquids including identical substances released from e-cigarettes themselves.
7. Discussion, conclusion and recommendation.

The methodology used for the different tasks is described briefly below.

Description of existing legislation regarding substances formed or released during evaporation of the e-liquids
The legislation relevant for chemical substances formed or released during the evaporation of the e-liquids is described and reviewed in chapter 3. The legislation reviewed is the CLP Regulation, the General Product Safety Directive and the Tobacco Directive.

Review of existing standards on e-liquids in electronic cigarettes
Currently, standards are under development in relation to CEN/TC 437 “Electronic cigarettes and e-liquids”, which was established in 2015. However, no standards are available so far (June 2017). For this reason, national standards on e-cigarettes have been reviewed in chapter 4. The focus will be on requirements regarding substances formed or released during the evaporation of e-liquids.

Screening of substances formed or released during evaporation of e-liquids
A screening of chemical substances formed or released during the evaporation of e-liquids was performed by searching for articles on the subject on the internet. Furthermore, the project advisor contributed with a list of articles found on the internet on the subject. Only articles addressing the substances formed or substances evaporating from e-cigarettes were used. A list of ingredients evaporating from e-liquids is presented in chapter 5.

Proposal for requirements for selected substances formed or released during evaporation of the e-liquids
In chapter 5 relevant existing threshold values for the listed identified substances formed or released during the evaporation of the e-liquids have been identified as well. This information has been used to prioritise (chapter 6), which ingredients

that should be selected for the main task of this report, i.e. to propose requirements for the selected substances formed or released during the evaporation of e-liquids (chapter 8).

Discussion, conclusion and recommendation
The results of the report are discussed and conclusions made in chapter 9.

3 Legislation

The following relevant legislation is described regarding substances formed or released during the evaporation of e-liquids used in e-cigarettes:

- General Product Safety Directive (GPSD)
- Tobacco Directive

This legislation is described and discussed below, but mainly with the focus on requirements for substances formed or released during the evaporation of e-liquids when using e-cigarettes.

3.1 Tobacco Directive

The Tobacco Directive (EU Directive no. 40, 2014) lays down the rules for ingredients and emissions of tobacco products including e-cigarettes, as well as rules for labelling. Both e-cigarettes and refill containers (e-liquids) are covered by the Tobacco Directive, but only nicotine-containing e-cigarettes and e-liquids. The legislation concerning e-cigarettes and e-liquids in the Tobacco Directive was valid from November 20, 2016.

The legislation concerning e-cigarettes is described in Article 20 “Electronic cigarettes” and contains the following elements:

- Notification to competent authorities of the Member States
- Requirements concerning nicotine
- General requirements concerning ingredients
- Requirements concerning child- and tamper-proof refill containers
- Labelling, instructions for use and health warnings
- Requirements concerning submission of sales volumes and other information to the competent authorities of the Member States
- General requirements concerning the Member States and gathering of information on the use of e-cigarettes

Only the rules concerning chemical requirements to ingredients in e-liquids will be described in detail below, and with a focus on requirements for substances formed or released during the evaporation of e-liquids.

All manufactures and importers of e-cigarettes and refill containers (e-liquids) must submit a **notification** to the competent authorities of the Member States with the following information:

- Name and contact details of the manufacturer/importer.
- A list of all ingredients contained in and emissions resulting from the use of the product, including quantities.
- Toxicological data regarding the ingredients and emissions including when heated. In particular the health effects of the ingredients when inhaled by consumers and taking into account any addictive effect.
- Information on nicotine doses and absorption, when consumed under normal or reasonably foreseeable conditions.
- A description of the components of the product, including a description of the opening and refill mechanism.

- A description of the production process.
- A declaration stating that the manufacturer and importer bear full responsibility for the quality and safety of the product, when placed on the market and used under normal or reasonably foreseeable conditions.

Requirements concerning nicotine are:

- Nicotine-containing liquids must not contain more than 20 mg/ml nicotine.
- The e-cigarettes must deliver the nicotine doses at consistent levels under normal conditions of use.

Besides requirements for nicotine, some **general requirements concerning the ingredients** are listed:

- Only ingredients of high purity must be used in the manufacturing of the nicotine-containing e-liquids.
- Only trace levels of other ingredients than listed for the e-liquid are allowed and only if technically unavoidable during manufacture.
- Except for nicotine, only ingredients which do not pose a risk to human health in heated or unheated form must be used.
- Nicotine-containing liquids must not contain the following additives:
    - Vitamins or other additives that create the impression that the product has a health benefit
    - Caffeine or taurine or other additives and stimulant compounds that are associated with energy and vitality
    - Additives having colouring properties for emissions
    - Additives that have CMR[1] properties in unburnt form

According to the **labelling instructions**, the outside packaging of e-cigarettes and refill containers must contain a list of all ingredients contained in the product in descending order of weight. Furthermore, it must be indicated, what the nicotine content is and the delivery per dose. Health warnings concerning nicotine must be listed on the outside packaging of e-cigarettes and e-liquids.

Finally, **the Member States must ensure**:

- That these requirements also apply to cross-border distance sales of e-cigarettes and e-liquids.
- That a system for collecting information about all suspected adverse effects on human health of these products are established and maintained.
- Products which are not safe or could present a serious risk to human health or not of good quality are withdrawn (and perhaps recalled) from the market.

3.2 General Product Safety Directive (GPSD)

The General Product Safety Directive (EU Directive no. 95, 2001) is intended to ensure product safety for EU consumer products not covered by specific other legislation, by stating that “producers shall be obliged to place safe products on the market”.

Safe products are defined as “any product, which under normal or reasonably foreseeable conditions of use… does not present any risk… considered to be acceptable with a high level of protection for the safety and health of persons…”. Products are presumed safe:

[1] CMR = Carcinogenic, Mutagenic or toxic to Reproduction

1. If they follow specific Community provisions concerning safety of the product. This means that the General Product Safety Directive does only apply to risks or categories of risks not covered by the specific European product legislation if specific European product legislation, such as the Tobacco Directive applies. However, article 5 to 18 of the GPSD (concerning e.g. market surveillance from Member States, RAPEX notifications as well as producers' and distributors' obligation to inform consumers of risks, i.e. by use of appropriate warnings) still apply even though the Tobacco Directive also applies.
2. If they follow specific national legislation concerning safety of the product.
3. If they follow European standards, the references which have been published by the Commission in the Official Journal of the European Communities.
4. If they follow other European Standards.
5. If they follow relevant national standards (which do not transpose European standards).
6. If, in the absence of product specific legislation or relevant national standards, they follow:
    - Commission recommendations setting guidelines on product safety,
    - product safety codes of good practice in force for the sector concerned,
    - the state of art and technology
    - and reasonable consumer expectations concerning safety.

Furthermore, producers must inform consumers of the risks associated with the products they supply.

The Tobacco Directive only applies for nicotine containing e-cigarettes, whereas e-cigarettes not containing nicotine are not covered. For such products, only the GPS Directive applies. The safety assessment of the ingredients in accordance with the GPS Directive may rely on requirements set in existing standards (which currently (June 2017) are under development).

3.3 Discussion on legislation regarding chemical substances formed or released during the evaporation of e-liquids

The Tobacco Directive contains specific requirements for nicotine-containing e-cigarettes and e-liquids, but the actual chemical requirements are limited and are on a more general level. The chemical requirements listed specifically for e-liquids concern mostly the content on nicotine itself or are general requirements for the ingredients in the e-liquids. However, a few general requirements are listed specifically for the chemical substances formed or released during the evaporation of e-liquids. These are:

- Except for nicotine, only ingredients which do not pose a risk to human health in heated or unheated form, must be used.
- A list of all ingredients contained in and emissions resulting from the use of the product, including quantities, must be notified to the competent authorities of the Member States.
- Toxicological data regarding the ingredients and emissions including when heated must be notified to the competent authorities of the Member States. In particular the health effects of the ingredients when inhaled by consumers and taking into account any addictive effect.

This means that in general no specific chemical requirements are set for substances formed or released during the evaporation of e-liquids. There is only the general statement, that the producers most know of and notify, which chemical substances that are formed during use – as well as their quantities, and that these chemical substances must not pose a risk to human health in heated or unheated form.

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).

Even though the Tobacco Directive contains chemical requirements, these requirements are on a very general level and are rather vague, as it is debatable how to interpret phrases such as "consistent levels", "high purity", "trace levels" and "do not pose a risk to human health".

In practice, this means that it is difficult for the producers of e-liquids (and e-cigarettes) to ensure 'safe' products on the market, as the general vague requirement of 'must not pose a risk to human health' requires risk assessment expertise. From a producer's point of view, it would be easier to follow limit values of substances formed or released during the evaporation of e-liquids or limit values for ingredients in e-liquids.

Currently (June 2017), standards are under development in relation to CEN/TC 437 "Electronic cigarettes and e-liquids", which was established in 2015. It is important that these standards address the health aspects (chemical safety) of the ingredients used in e-liquids as well as the substances formed or released during the evaporation of e-liquids as the products may be considered safe when European Standards are followed.

4 Standards

Currently, standards are under development in relation to CEN/TC 437 “Electronic cigarettes and e-liquids”, which was established in 2015. So far (June 2017), no standards have been published on the website of CEN[2] under this committee – neither drafts nor standards under approval. However, some national standards on e-cigarettes and e-liquids do exist, which are also used in the CEN/TC 437 committee as a basis of their standardization work:

- The British document PAS 54115:2015 “Vaping products, including electronic cigarettes, e-liquids, e-shisha and directly-related products – Manufacture, importation, testing and labelling – Guide” (BSI, 2015).
- The French standard XP D 90-300:
    - XP D 90-300-1: “Electronic cigarettes and e-liquids – Part 1: Requirements and test methods for electronic cigarettes” (Afnor, 2015a).
    - XP D 90-300-2: “Electronic cigarettes and e-liquids – Part 2: Requirements and test methods for e-liquids” (Afnor, 2015b).
    - XP D 90-300-3: “Electronic cigarettes and e-liquids – Part 3: Requirements and test methods for emissions” (Afnor, 2016).

These standards are described and reviewed in this chapter.

4.1 British document PAS 54115

It is written in PAS 54115 that the document is not to be regarded as a British Standard. The PAS document is a guidance document and contains recommendations, and it is emphasised that claims of compliance cannot be made to the document as well as compliance with the PAS document does not imply immunity from legal requirements (BSI, 2015).

The PAS document covers the following areas:

- Purity of e-liquid ingredients in manufacture
- Contaminants arising from device materials and potential emissions from device operations
- Electrical safety
- Metals and carbonyls in emissions

Only the recommendations/requirements that are relevant for the chemical substances formed or released during the evaporation of e-liquids are described below, i.e. neither the recommendations for good manufacture practice nor the specific requirements for substances contained in the e-liquids are described here.

Concerning the **quality of the ingredients**, the PAS document describes the following recommendations:

- The diluent solvents making up the base liquid (that dilutes the concentration of nicotine and/or flavourings) should be of a pure technical grade (European Pharmacopoeia/United States Pharmacopeia Standard (Ph. Eur./USP) grade).

[2] https://standards.cen.eu/dyn/www/f?p=204:105:0:::::

- Propylene glycol should be tested to ensure that the level of di-ethylene glycol (potential contaminant) does not exceed 0.1%.
- Flavouring ingredients should be of Ph. Eur./USP grade or of food grade.
- Regularly monitoring should be carried out in order to ensure that any contaminants are minimised.

The PAS document contains a list of recommendations concerning product toxicological risk assessment (TRA) of the substances contained in the e-liquids as well as a list of ingredients which should not be added to e-liquids. These recommendations are, however, not described here, as the focus in this report is on the substances formed or released during the evaporation of e-liquids.

The PAS document contains the following recommendations regarding emissions from e-liquids:

- The emission from e-liquids should be tested as proportionate to and justified by a documented risk-based compliance check for the production of inhalation of toxicants produced during the vaporisation process.
- Where e-liquids are sold separately from devices, their emissions can be measured using a commercially available refillable e-cigarette or other test device.
- New emissions testing should be carried out when there are substantial modifications in base liquids and/or substantial additions of new flavourings.
- If toxic substances are generated by an e-liquid (i.e. formed during the evaporation of e-liquids) at levels higher than accepted in the TRA, the e-liquids should not be sold and the e-liquid recipes should be reformulated.
- Emission testing may be carried out only once for each e-liquid product, unless the e-liquid is subject to a substantial modification.
- An analysis of emissions should be carried out for every specific model of atomiser or hardware product which includes an atomiser. The emissions measured should be evaluated in a TRA. If emissions of toxicological concern are identified the source of these should be identified, and attempts should be made to alter the structure components or design to reduce the levels present to a level that is toxicologically supportable.
- Nicotine delivery to vapour should be measured and expressed as mass per puff.

Furthermore, the PAS document contains a list of substances which should be monitored for emissions by the hardware during the use of vaping products. These are:

- Acetaldehyde (CAS 75-07-0)
- Acrolein (CAS 107-02-8)
- Formaldehyde (CAS 50-00-0)
- Metals such as Al, Cr, Fe, Ni and Sn
- Silica particles

4.2 French standard XP D-90-300

The French standard XP D-90-300 consists of three parts dealing with requirements and test methods for:

- Part 1: Electronic cigarettes
- Part 2: E-liquids
- Part 3: Emissions

4.2.1 XP D 90-300 Part 1: Electronic cigarettes

Part 1 of the French standard (Afnor, 2015a) only deals with aspects concerning the e-cigarette and not the e-liquids or emissions from e-liquids. This means that this part of the standard does not set requirements concerning chemical substances in e-liquids or substances formed or released from e-liquids, but is limited to physical mechanical and thermal requirements of the e-cigarettes, and requirements for leakage of e-liquids from the e-cigarette. Furthermore, this part of the standard sets chemical requirement regarding the content of allergenic and toxic substances for the e-cigarette materials used for the mouthpiece, tank and coatings of the e-cigarette. This part of the standard is therefore not described further.

4.2.2 XP D 90-300 Part 2: E-liquids

Part 2 of the French standard (Afnor, 2015b) only deals with contents of the e-liquids and is therefore not described in detail here, as the focus of this report is on the substances formed or released during evaporation of e-liquids[3].

This part 2 sets different requirements for ingredients in e-liquids, such as requirements for purity of the ingredients, only use of flavouring compounds of food grade quality, general requirements for ingredients that must not be used (e.g. no use of CMR classified substances), and specific requirements for specific ingredients such as nicotine, preservatives, diluents, contaminants etc.

4.2.3 XP D 90-300 Part 3: Emissions

Part 3 of the French standard (Afnor, 2016) deals with emissions of the e-cigarettes and sets different requirements for the specific substances emitting from e-cigarettes, including a requirement for a constant delivery of nicotine from the e-cigarettes. Finally, this standard sets requirements concerning the thermal risks in order to prevent the user to burn the lips or the mouth during use.

The chemical requirements concerning emissions from e-cigarettes are:

- The operation of e-cigarettes with e-liquids (in test performance conditions described in the standard) shall not cause the emission of the following substances beyond the technical unavoidable concentrations – with the exception of nicotine:
    - Solid particles
    - Carcinogenic substances
    - Potentially toxic substances
- Substances specifically described to be measured in emissions during use (test performance conditions described in the standard) are:
    - Nicotine
    - Diacetyl (limit value: 490 µg/200 puffs)
    - Formaldehyde (limit value: 200 µg/200 puffs)
    - Acetaldehyde (limit value: 3200 µg/200 puffs)
    - Acrolein (limit value: 16 µg/200 puffs)
    - Metals and inorganic substances
        - Pb (limit value: 5 µg/200 puffs)
        - Sb (limit value: 20 µg/200 puffs)
        - As (limit value: 2 µg/200 puffs)

[3] However, in another report ("Requirements for substances in e-liquids used in electronic cigarettes") the focus will be on substances contained in e-liquids.

    - Ni (limit value: 5 µg/200 puffs)
    - Cr (limit value: 3 µg/200 puffs)
    - Cd (limit value: 2 µg/200 puffs)
- Nicotine emissions shall be constant, i.e. the nicotine concentration measurement for each of the three series shall be within a range of ± 25% of the mean value of the three series.

4.3 Summary and discussion regarding chemical requirements in standards for substances formed or released during the evaporation of e-liquids

Currently, no standards have been published by CEN/TC 437 "Electronic cigarettes and e-liquids", which was established in 2015. However, a British guidance document does exist, but is not to be considered as a standard. Furthermore, a French standard in three parts sets requirements for the physical appearance of the e-cigarettes (part 1), the e-liquids (part 2) and the emissions from the e-liquids (part 3).

Both the British guidance document (BSI, 2015) and the French standard (Afnor, 2016) set some chemical requirements for substances formed or released during the evaporation of e-liquids. Both documents set requirements for the purity of the ingredients and both standards set requirements for certain specific substances (mostly metals). However, where the French standard sets specific limit values, the British guidance document only requires that these substances should be measured in the vapour.

The British guidance document sets a general requirement for toxic substances, that these should not be generated by any e-liquid above the levels accepted by a toxicological risk assessment (TRA). The French standard contains a similar requirement saying that carcinogenic substances and potentially toxic substances shall not be emitted beyond the technical unavoidable concentrations. The specific substances restricted by the two documents are listed in Table 1 below.

The rest of the requirements in the British guidance document is mostly connected to when measurements should be carried out (i.e. when new modifications to the e-liquid are made, for every specific atomizer model etc.).

Table 1: Overview of emission related requirements in existing national standards

Chemical substance in emissions from e-cigarettes	**CAS no.**	**Limit value**	
		British PAS guidance document	**French Afnor standard (part 3)**
Nicotine	54-11-5	Nicotine delivery should be measured (mass/puff)	Nicotine emissions should be measured and be constant (±25%)
Diacetyl (2,3-butadione)	431-03-8		490 µg/200 puffs
Formaldehyde	50-00-0	Emission should be measured	200 µg/200 puffs
Acetaldehyde	75-07-0	Emission should be measured	3200 µg/200 puffs
Acrolein	107-08-8	Emission should be measured	16 µg/200 puffs
Al		Emissions should be measured	

Chemical substance in emissions from e-cigarettes	CAS no.	Limit value	
		British PAS guidance document	French Afnor standard (part 3)
Cd			2 µg/200 puffs
Cr		Emissions should be measured	3 µg/200 puffs
Fe		Emissions should be measured	
Pb			5 µg/200 puffs
Ni		Emissions should be measured	5 µg/200 puffs
As			2 µg/200 puffs
Sb			20 µg/200 puffs
Sn		Emissions should be measured	
Silica particles		Emissions should be measured	
Solid particles			No emission beyond technical avoidable concentrations
Carcinogenic substances			No emission beyond technical avoidable concentrations
Toxic or dangerous substances in general		No substances must be emitted above the toxicological value as defined by TRA	No emission beyond technical avoidable concentrations

As described in the previous chapter on “Legislation”, neither the GPS Directive nor the Tobacco Directive contains specific requirements for e-cigarettes, e-liquids and substances formed or released during the evaporation of e-liquids – both directives contain a general statement regarding ‘products must be safe’ or ‘ingredients must not pose a risk to human health in heated or unheated form’. It is therefore important that the standards developed set the necessary chemical requirements (for the necessary chemical substances formed or released during the evaporation of the e-liquids) and the correct limit values to protect the consumer from unwanted health effects from substances formed or released during the evaporation of e-liquids.

Similarly, it is important to set chemical requirements for the substances contained in e-liquids, but this aspect is addressed in another report concerning requirements for substances in e-liquids (Poulsen et al., 2017).

5 Screening of chemical substances formed or released from e-liquids

In this chapter, a screening of chemical substances formed or released during the evaporation of e-liquids has been performed by searching for articles on the subject on the internet.

5.1 Internet search for substances formed or released during the evaporation of e-liquids

The search has been carried out by searching for articles and reports on the subject. The articles are not described in detail, but have been used to create the table below (Table 2), which is an overview of substances evaporating from e-liquids.

A total of 12 different articles was used as source and the underlying purpose, method of analysis, type of reported data etc. varies a lot between the articles. However, the majority of the articles have been published in scientific magazines. The oldest article used is from 2012, but most of the articles are not older than 2014.

The included substances are on a list, which does not distinguish between substances which were identified in few or several studies.

It should also be noted that it is not all references that distinguish between substances being formed during the evaporation of e-liquids or ingredients already present in the e-liquids which evaporate. In Table 2 all substances mentioned in the different references have been listed irrespective of the substances evaporating from e-liquids or being formed during the evaporation. Instead the substances have been marked in bold typing, if they were also identified as ingredients in e-liquids (according to the ongoing project Poulsen et al., 2017).

The total number of substances identified to be formed during the evaporation of e-liquids counts 33. However, two of the entries are groups of substances (aldehydes and tobacco specific nitrosamines) with no CAS number. The substances identified in the vapour of e-liquids can be divided into five categories (where there is some overlap between the last category and the other categories):

- Aldehydes (7)
- Volatile organic substances (11)
- Elements (8)
- Tobacco specific nitrosamines (2)
- Ingredients also present in the e-liquids (8)

According to some references (e.g. BMA, 2012), the presence of metals is not necessarily because they are impurities in the e-liquids, but more likely because these metals originate from the heating elements or batteries in the e-cigarettes.

The internet search illustrates that substances such as xylene, toluene, acetone and aldehydes such as formaldehyde, acetaldehyde, propionaldehyde and o-methyl

benzaldehyde are identified as being formed during the evaporation of e-liquids according to several sources. All in all, not many substances have been identified as being formed during the evaporation of e-liquids, as some of the 33 substances listed also are present in e-liquids (according to Poulsen et al., 2017) and thereby merely seem to be ingredients evaporating and not substances formed. Furthermore, several of the 33 substances are heavy metals, which seem to originate from the electronic cigarette and not from the e-liquids.

It is expected that all ingredients present in the e-liquids also will be present in the vapour from the e-liquid, whereas not all substances found in the vapour will be present in the e-liquids (i.e. the substances formed). In Table 2 those evaporated substances, which were also identified as ingredients in the e-liquids, have been marked in bold (Poulsen et al., 2017).

5.2 Existing threshold values for ingredients

The purpose of this study is to develop a proposal for requirements for selected substances, which are formed during the evaporation of e-liquids. The proposal for requirements will be based on relevant existing threshold values for different chemical substances. It has therefore been examined if the identified substances formed or released during the evaporation of e-liquids are on different lists of existing threshold values for different chemical substances. The following schemes with existing threshold values have been examined and compared with the substances identified as formed during the evaporation of e-liquids:

- EU-LCI Group
- The German AgBB scheme
- German indoor air guide values
- REACH DNEL values for registered substances
- ATSDR Minimal Risk Levels (MRLs)
- US EPA Reference Concentration (RfC) and Reference Dose (RfD) values
- WHO Air Quality Guidelines
- ANSES Indoor Air Quality Guidelines

5.2.1 EU-LCI Group

The EU LCI concept[4] was developed as part of a basic scheme for the evaluation of VOC emissions from building products. The objective of the European LCI Group is to elaborate and establish a common European list of chemicals and their associated toxicological thresholds relevant to human health. The relevant chemicals are identified via indoor air monitoring programs and emission testing of building products by EU countries.

The LCI values (Lowest Concentration of Interest) were originally based on either air quality guideline values (AQG) or occupational exposure limits, but a detailed framework for assessing chemicals emitted has now been developed, which involves a comprehensive data compilation (from sources like the REACH registration system, RIVM, Health Canada, US-EPA, WHO indoor air quality guidelines etc.) and data evaluation (JRC, 2013).

The EU-LCI Group defines EU-LCI in the following way:

[4] https://ec.europa.eu/growth/sectors/construction/eu-lci/about_en

- EU-LCIs are health-based values used to evaluate emissions after 28 days from a single product during a defined laboratory test chamber procedure.
- EU-LCIs are applied in product safety assessment with the ultimate goal to avoid health risks from long-term exposure for the general population.
- EU-LCI values are usually expressed as µg/m^3.
- Only values derived by application of the process established by the EU-LCI WG and described herein and ratified by the EU-LCI WG shall be called EU-LCIs.

The identified substances formed or released during the evaporation of e-liquids have been looked up in the EU-LCI Group list and the values are listed in Table 2. However, only a few of the identified substances formed or released during the evaporation of e-liquids were found on the list of EU-LCI values (5 out of 33 substances). Many of the more 'cigarette specific substances' are not found emitting from building products.

5.2.2 The German AgBB scheme

The German AgBB[5] (the Committee for Health-related evaluation of Building Products) scheme is a scheme for VOC emissions from construction products. The AgBB scheme was reviewed and edited the last time in February 2015.

The AgBB scheme (AgBB, 2015) consists of a health-related evaluation of emissions from building products based on substance specific values – the so-called LCI values (Lowest Concentration of Interest). The LCI values are derived by specialists using existing health-based evaluations of substances in the workplace as a starting point. The AgBB scheme takes among others the following values into consideration when establishing LCI values:

- Indicative and binding occupational exposure limit values set by the European Commission.
- National occupational exposure limits such as German, American and values applied in other EU member states.
- DNEL (derived no-effect level) values determined for inhalative occupational exposure or DNEL values determined for long-term inhalative consumer exposure under the REACH Regulation.
- Values or recommendations from the European Scientific Committee on Occupational Exposure Limits (SCOEL).
- And may also include in individual cases WHO indoor air quality guidelines.

It is written in the document which describes the AgBB scheme that the European LCI values (EU-LCI) are more elaborate and based on a comprehensible rationale. The AgBB scheme therefore adopts published EU-LCI values into the German LCI list. However, the AgBB scheme has LCI values for more substances compared to the EU-LCI list.

For carcinogenic substances, specific LCI values are only established if the carcinogenicity threshold is above the non-carcinogenic endpoints. Otherwise no LCI values are derived for carcinogenic properties according to EU categories 1A and 1B, as these substances are dealt with separately within the AgBB scheme: No carcinogen belonging to EU categories 1A and 1B may exceed a concentration of 0.01 mg/m³ after 3 days and the value of 0.001 mg/m³ after 28 days.

[5] http://www.eco-institut.de/en/certifications-services/national-marks-of-conformity/agbb-scheme/

The German AgBB LCI list consists of about 190 different chemical substances in total (February 2015), compared to the EU-LCI values that exist for about 110 substances (December 2016). This means that the German AgBB LCI list (from 2015) has adopted the EU-LCI values existing in 2015 and LCI values are developed for other substances.

The identified substances formed or released during the evaporation of e-liquids have been looked up in the German AgBB LCI list and the values are listed in Table 2. The LCI values are usually measured in µg/m^3. However, only a few of the identified substances formed or released during the evaporation of e-liquids were found on the list of AgBB LCI values (6 out of 33 substances). Many of the more 'cigarette specific substances' are not found emitting from building products.

5.2.3 German indoor air guide values

The German Environment Agency (UBA – Umwelt Bundesamt) has established the German Committee on Indoor Guidelines, which has prepared indoor air guide values for 47 individual substances (UBA, 2016). Guide Value I and II have been established:

- Guide Value I represents the concentration of a substance in indoor air which is not expected to cause adverse health effects in sensitive persons even in the case of lifelong exposure (according to current knowledge and when considered individually).
- Guide Value II is an effect-related value based on toxicological and epidemiological knowledge of the effect threshold of a substance. Guide Value II is usually a long-term value. Guide Value II represents the concentration of a substance in indoor air at and above the value where action needs to be taken immediately because this concentration could endanger the health of sensitive persons including children, when they stay indoor constantly for long periods of time.

The guide values apply for individual substances and provide no indication of any possible combined effects with different substances. The guide values are given in mg/m^3 for the concentration of specific substances in indoor air. Guide Value I figures are in all cases lower than Guide Value II figures and are therefore used for the calculations.

A total of 10 of the substances identified to be formed during the evaporation of e-liquids was found on the German indoor air guide value list and is listed in Table 2.

5.2.4 REACH DNEL values for registered substances

Toxicological as well as physical data delivered to ECHA in connection with a REACH registration is listed in the database of the REACH-registered substances. In this database DNEL (Derived No-Effect Level) values can be found for different exposures (oral, inhalation, dermal) and for different populations (workers or consumers). These values are frequency dependent (short-term exposure or long-term exposure) and have different effects (local or systemic). A DNEL value is defined as an external exposure level below which an adverse effect on human health is not expected. This means that a lower DNEL value implies a more toxic substance. DNEL values are based on a NOAEL (No Observed Adverse Effect Level) and are divided by a safety factor (size depending on data quality etc.).

The DNEL values in the database of REACH-registered substances are, however, derived by the companies who have registered the substances, and it may be difficult to evaluate the basis and the validity for these DNEL values.

The DNEL values for consumers and workers (long term exposure for systemic and local effects) have been looked up and are listed in Table 2 below, if the substances identified as being formed during the evaporation of e-liquids have been registered. Currently (March 2017), about 17,200 substances are listed in the ECHA database of registered substances. The DNEL values are measured in mg/m^3 for exposure via inhalation. It should be noted that only a few of the substances (6 out of 33 substances) were not registered and therefore no information was available. However, for several of the registered substances, no information on DNEL values was available (for 11 out of 33 substances), and for two of the substances identified, there was no CAS number to look up, as these were identified as group of substances. This means that all in all a DNEL value was identified for 14 of the 33 identified substances to be formed during the evaporation of e-liquids.

5.2.5 ATSDR Minimal Risk Levels

ATSDR (Agency for Toxic Substances & Disease Registry) is a federal public health agency of the U.S. Department of Health and Human Services. ATSDR has prepared Minimal Risk Levels (MRLs) for a number of prioritised substances that are considered to be hazardous for the human health or the environment. The MRLs are listed as "estimates, which are intended to serve as screening levels" for ATSDR health assessors and others in order to identify areas to investigate further[6].

The MRLs are derived by preparing a toxicological profile for the substances which includes an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. The MRLs are based on non-cancer health effects only and are not based on a consideration of cancer effects. ATSDR uses the no observed adverse effect level/uncertainty factor (NOAEL/UF) approach to derive the MRLs for hazardous substances. They are set below levels that, based on current information, might cause adverse health effects in the people most sensitive to such substance-induced effects. MRLs are derived for acute (1-14 days), intermediate (>14-364 days), and chronic (365 days and longer) exposure durations and for the oral and inhalation routes of exposure.

The MRL values for chronic exposure for inhalation have been looked up for the substances identified as being formed during the evaporation of e-liquids and are listed in Table 2 below. Furthermore, the MRL values for oral chronic exposure have been looked up. The used ATSDR MRL list is dated March 2016 and contains a total of 435 substances. Only 15 substances out of the 33 substances identified with CAS number as being formed during the evaporation of e-liquids were listed on the ATSDR MRL list. The MRL values are measured in either mg/m^3 or ppm for the inhalation values or mg/kg bw/day for oral values.

[6] https://www.atsdr.cdc.gov/mrls/index.asp

5.2.6 US EPA Reference Concentration (RfC) and Reference Dose (RfD)

The US EPA (Environmental Protection Agency) has established the IRIS Program (Integrated Risk Information System) in order to protect the human health and the environment. Through the IRIS program, health hazards of chemicals found in the environment are identified and characterised. IRIS assessments provide the following toxicity values for health effects resulting from chronic exposure to chemicals[7]:

- Inhalation reference concentration (RfC), which is the concentration of a chemical that a person can inhale every day for a lifetime and which is not anticipated to cause harmful non-cancer health effects. The RfC can be compared to an exposure estimate concentration in mg/m^3.
- Oral reference dose (RfD), which is the amount of a chemical that a person can ingest every day for a lifetime and which is not anticipated to cause harmful non-cancer health effects. The RfD can be compared to an exposure estimate in mg/kg bw/day.

Currently (March 2017), the IRIS database[8] contains 511 substances. However, neither the RfC nor the RfD has been evaluated for all 511 substances. Both the RfC and the RfD have been looked up in the database for the substances identified to be formed during the evaporation of e-liquids. For only 7 of the 33 substances identified to be formed during the evaporation of e-liquids, a RfC was identified. For 8 of the 33 substances, a RfD was identified. In all, either a RfC or RfD value was identified for 12 of the 33 substances. The values are listed in Table 2 below.

5.2.7 WHO Air Quality Guidelines

WHO (World Health Organisation) has established limit values for 35 chemical air pollutants based on a chemical risk assessment (WHO, 2000). For the organic pollutants, the WHO Guidelines have been used to establish limit values by both the EU-LCI Group and the German AgBB scheme (AgBB, 2015; JRC, 2013). However, the WHO Guidelines also set limit values for inorganic compounds (elements), which are not addressed in the mentioned schemes concentrating on construction products.

For substances with carcinogenic effects, the conclusion by WHO is most often that no safe threshold limit value can be set, but limit values are then set for e.g. an excess life time risk of 1/10,000, 1/100,000 or 1/1,000,000 for a specific type of cancer. In these cases, the life time risk values of both 1/10,000 and 1/1,000,000 have been listed.

The WHO Air Quality Guidelines contain limit values for 8 of the 33 substances identified to be formed during the evaporation of e-liquids. Most of these are elements, but limit values were also found for formaldehyde and toluene. These values are listed in Table 2 below.

5.2.8 ANSES Indoor Air Quality Guidelines

ANSES[9], the French Agency for Food, Environmental and Occupational Health & Safety, has been working since 2004 to develop Indoor Air Quality Guidelines

[7] https://www.epa.gov/iris
[8] https://cfpub.epa.gov/ncea/iris/search/index.cfm?keyword=101-48-4
[9] https://www.anses.fr/en/content/indoor-air-quality-guidelines-iaqgs

(IAQGs). IAQGs are based exclusively on health criteria and have been defined for 9 substances and particulate matter. IAQGs are defined as airborne concentrations of a chemical substance below which no health effects or harm with an impact on health is expected for the general population at the current state of knowledge.

IAQGs (ANSES, 2013a) exist for 2 of the 33 substances identified to be formed during the evaporation of e-liquids. These are formaldehyde and acetaldehyde. These values are listed in Table 2 below.

Table 2: Overview of substances identified evaporating from e-liquids (substances in bold have been identified in e-liquids (see Poulsen et al., 2017) and substances marked with green shading have been selected for further review)

Only threshold values found are listed in the last right column "Threshold value"

Substance name	**CAS no.**	**Concentration (if mentioned)**	**Comment in literature**	**Reference/source**	**Threshold value (measured in mg/m^3)**
Acetaldehyde (ethanal)	75-07-0	11 mg/m3 (BfR), up to approx 8 µg per puff (Hutzler), up to 120 µg/10 puffs (Bekki), up to 1.36 µg/ 15 puffs (Drummond)	More concentration results can be found in Hutzler (2014), Bekki (2014) and Cheng (2014). Highest values are listed here.	BfR, 2012; Pisinger, 2014; Hutzler, 2014; Bekki, 2014; Drummond, 2014; and more	EU-LCI: 1.2; AgBB LCI: 1.2; US EPA RfC: 0.009; German IA GV II: 1; German IA GV I: 0.1; ANSES IAQG: 0.160
Acetone	67-64-1	2.9 mg/m3 aerosol and 0.16 ppm/38 mL puff (Cheng)	Varlet (2015) reported as present in the liquid of 1 out of 42 samples. The rest as present in vapour.	Pisinger, 2014; Cheng, 2014; Varlet 2015	REACH DNEL Inh. Cons.: 200; DNEL Inh. Work.: 1210; AgBB LCI: 1.2; ATSDR MRL (inh.): 13 ppm; ATSDR MRL (oral): 2.0; US EPA RfD: 0.9
Acrolein (propenal)	107-02-8	9.3 mg/m3 (BfR), up to approx.. 3 µg per puff (Hutzler), up to 40 µg/10 puffs (Bekki), up to 4.19 µg/ 15 puffs (Drummond)	Thermodegradation of glycerol. More concentration results can be found in Hutzler (2014), Bekki (2014) and Cheng (2014).	BfR, 2012; Pisinger, 2014; Hutzler, 2014; Bekki, 2014; Drummond, 2014; and more	REACH DNEL Inh. Work.: 0.2; ATSDR MRL (inh.): 0.00004 ppm; ATSDR MRL (oral): 0.004; US EPA RfC: 0.00002; US EPA RfD: 0.0005
Aldehydes	-			Hutzler, 2014	*No information available*
Aluminium	7429-90-5	47.28 ug/1200 puffs (Farsalinos), not detected in emissions (Saffari) A 'real-life' study showed a 2-fold increase of aluminum in indoor air after vaping – but no concentration listed (Pisinger)	Farsalinos study only list result of 1 measurement, otherwise Al was not measured.	Pisinger, 2014; Saffari, 2014; Farsalinos, 2015	REACH DNEL Inh. Work.: 3.72; ATSDR MRL (oral): 1.0
Anthracene	120-12-7	7 ng/cartridge	PAH	Cheng, 2014	ATSDR MRL (oral): 10.0; US EPA RfD: 0.3; German IA GV II: 0.03; German IA GV I: 0.01

Substance name	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Cadmium	**7440-43-9**	Between 0 and 1.6 µg/1200 puffs (Farsalinos), up to 0.22 µg/150 puffs (Cheng), detected in lower concentrations compared to normal cigarettes (Schraufnagel), 0.48 ng/h (Saffari)	Farsalinos study based on measurements of 12 e-cigarettes. Detected in 9 of 12 e-cigarettes.	Pisinger, 2014; Cheng, 2014; Schraufnagel, 2014; Farsalinos, 2015	REACH DNEL Inh. Work.: 0.004; ATSDR MRL (inh.): 0.00001; ATSDR MRL (oral): 0.0001; US EPA RfD: 0.001 (food); WHO AQ: 0.000005
Chloromethane	74-87-3	Identified, but no value given		Herrington, 2015	REACH DNEL Inh. Work.: 12.5; ATSDR MRL (inh.): 0.05 ppm; US EPA RfC: 0.09
Chromium (elemental)	**7440-47-3**	Same as cigarettes (Pisinger), 0.007 µg/10 puffs (Cheng), 0.84 µg Cr(III)/1200 puffs (Farsalinos)	Chromium (III) only detected in 1 out of 13 e-cigarettes in Farsalinos study.	Pisinger, 2014; Cheng, 2014; Farsalinos, 2015	REACH DNEL Inh. Cons.: 0.027; DNEL Inh. Work.: 0.5; WHO AQ: based on Cr(VI): 0.0000025 (1/10,000 risk) and 0.000000025 (1/1,000,000 risk)
Cresol (hydroxytoluene)	1319-77-3	0.16 ppm/38 mL puff	PAH, methylphenol	Cheng, 2014	REACH DNEL Inh. Work.: 3.5; ATSDR MRL (oral): 0.1; German IA GV II: 0.03; German IA GV I: 0.01
Formaldehyde	50-00-0	8.3 mg/m3 (BfR), up to approx.. 5 µg per puff (Hutzler), up to 140 µg/10 puffs (Bekki), up to 5.61 µg/ 15 puffs (Drummond)	More concentration results can be found in Hutzler (2014), Bekki (2014) and Cheng (2014). Carcinogenic acc. to IARC. BfR limit says below 0.124 mg/m^3 (0.1 ppm) is safe for indoor air (023/2006).	BfR, 2012; Pisinger, 2014; Hutzler, 2014; Bekki, 2014; Drummond, 2014; and more.	REACH DNEL Inh. Cons.: 3.2; DNEL Inh. Work.: 9; EU-LCI: 0.10; AgBB LCI: 0.10; ATSDR MRL (inh.): 0.008 ppm; ATSDR MRL (oral): 0.2; US EPA RfD: 0.2; German IA GV I: 0.1; WHO AQ: 0.1; ANSES IAQG: 0.010
Glycerin	**56-81-5**	Up to 15 µg/puff and up to 610 mg/m3 (Cheng)		Cheng, 2014	REACH DNEL Inh. Work.: 56
Glyoxal	107-22-2	Up to 23 µg/10 puffs (Bekki)	More concentration results can be found in Bekki (2014)	Bekki, 2014	REACH DNEL Inh. Cons.: 1.3; DNEL Inh. Work.: 5.29
Lead	**7439-92-1**	Same as cigarettes (Pisinger), 0.017 µg/10 puffs (Cheng), 0.08 to 4.4 µg/1200 puffs - average 0.7 µg/1200 puffs (Farsalinos)	Lead detected in all 13 e-cigarettes measured in Farsalinos study.	Pisinger, 2014; Cheng, 2014; Schraufnagel, 2014; Farsalinos, 2015	WHO AQ: 0.0005

Substance name	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Mercury	7439-97-6	Trace quantities (Pisinger)		Pisinger, 2014	REACH DNEL Inh. Cons.: 0.004; DNEL Inh. Work.: 0.02; ATSDR MRL (inh.): 0.0002; US EPA RfC: 0.0003; German IA GV II: 0.00035; German IA GV I: 0.000035; WHO AQ: 0.001
o-Methyl benzaldehyde	529-20-4	Up to 7.1 µg/150 puffs (Cheng)	Flavour, which was found in aerosol, but unclear if it was in the liquid?	Cheng, 2014; Goniewicz, 2013	*No information available*
1-Methyl phenanthrene	832-69-9	5 ng/cartridge	PAH	Cheng, 2014	German IA GV II: 0.03; German IA GV I: 0.01
3-Methylbutyl-3-methylbutanoate	659-70-1	Up to 1.1 µg/puff		Cheng, 2014	*No information available*
Methylglyoxal (pyruvaldehyde or 2-oxopropanal)	1186-47-6	Up to 21 µg/10 puffs (Bekki)	More concentration results can be found in Bekki (2014)	Bekki, 2014	*No information available*
Nickel	**7440-02-0**	100 times more than cigarettes (Prev), 0.005 µg/10 puffs (Cheng), 0 to 0.96 µg/1200 puffs - average of 0.32 µg/1200 puffs (Farsalinos)	Detected in 7 out of 13 e-cigarettes in Farsalinos study	Pisinger, 2014; Cheng, 2014; Schraufnagel, 2014; Farsalinos, 2015	REACH DNEL Inh. Cons.: 0.020; DNEL Inh. Work.: 0.05; ATSDR MRL (inh.): 0.00009; WHO AQ: 0.00025 (1/10,000 risk) and 0.0000025 (1,000,000 risk)
NNK (4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone)	64091-91-4	Up to 28.3 ng/150 puffs	Tobacco-specific nitrosamine	Goniewicz, 2013	*No information available*
NNN (N'-nitrosonornicotine)	**16543-55-8**	Up to 4.3 ng/150 puffs	Tobacco-specific nitrosamine. IARC classification - Group 1 carcinogen.	Goniewicz, 2013	*No information available*
Phenanthrene	85-01-8	48 ng/cartridge	PAH	Cheng, 2014	German IA GV II: 0.03; German IA GV I: 0.01
Propionaldehyde (propanal)	**123-38-6**	Up to approx 1 µg per puff (Hutzler). Up to 46 µg/10 puffs (Bekki)	More concentration results can be found in Hutzler (2014) and Bekki (2014).	Hutzler, 2014; Bekki, 2014	REACH DNEL Inh. Work.: 6.1; US EPA RfC: 0.008
Propylenglycol (Propylene Glycol)	**57-55-6**	32-5000 ppm (99-15550 mg/m^3) (BfR), up to 5525 µg/puff and up to 1660 mg/m3 and up to 32 ppm/38 mL puff (Cheng)		BfR, 2012; Cheng, 2014	REACH DNEL Inh. Cons.: 50; DNEL Inh. Work.: 168; EU-LCI: 2.1; AgBB LCI: 2.5; ATSDR MRL (inh.): 0.009 ppm
Pyrene	129-00-0	36 ng/cartridge	PAH	Cheng, 2014	German IA GV II: 0.03; German IA GV I: 0.01

Substance name	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
Silicate beads (silicone dioxide)	112926-00-8	Significant amounts	Found in one study	Pisinger, 2014	REACH DNEL Inh. Work.: 4
Silver	7440-22-4	Vapour contains silver (Pisinger), silver detected in a bit higher concentration in vapour compared to normal cigarettes 20.91 ng/h (Saffari)		Pisinger, 2014; Saffari, 2014	REACH DNEL Inh. Cons.: 0.04; DNEL Inh. Work.: 0.1; US EPA RfD: 0.005
Tin	**7440-31-5**	4.44 µg/1200 puffs (Farsalinos), tin detected (Pisinger), not detected (Saffari)	Tin only measured in 1 out of 13 e-cigarettes in Farsalinos study.	Pisinger, 2014; Farsalinos, 2015; Saffari, 2014	REACH DNEL Inh. Cons.: 17; DNEL Inh. Work.: 71; ATSDR MRL (oral): 0.3
Toluene (VOC)	108-88-3	Up to 6.3 µg/150 puffs (Cheng), up to 0.63 µg/ 15 puffs (Drummond)		Pisinger, 2014; Cheng, 2014; Drummond, 2014; Goniewicz, 2013	REACH DNEL Inh. Cons.: 56.5; DNEL Inh. Work.: 192; EU-LCI: 2.9; AgBB LCI: 2.9; ATSDR MRL (inh.): 1 ppm; ATSDR MRL (oral): 0.2; US EPA RfC: 5; US EPA RfD: 0.08; German IA GV II: 3; German IA GV I: 0.3; WHO AQ: 0.26
TSNAs (tobacco specific nitrosamines)	-	From trace level to "higher than in tobacco"		Pisinger, 2014	*No information available*
Vanadium	7440-62-2	Up to 0.11 ng/puff		Visser, 2015	REACH DNEL Inh. Cons.: 6460 (no hazard identified); DNEL Inh. Work.: 13098 (no hazard identified); ATSDR MRL (inh.): 0.0001; ATSDR MRL (oral): 0.01; WHO AQ: 0.001

Substance name	CAS no.	Concentration (if mentioned)	Comment in literature	Reference/source	Threshold value (measured in mg/m^3)
p,m-xylene (VOC)	1330-20-7	Up to 0.2 µg/150 puffs and 0.18 ppm/38mL puff (Cheng)		Pisinger, 2014; Cheng, 2014	REACH DNEL Inh. Cons.: 14.8; DNEL Inh. Work.: 77; EU-LCI: 0.5; AgBB LCI: 0.5; ATSDR MRL (inh.): 0.05 ppm; ATSDR MRL (oral): 0.2; US EPA RfC: 0.1; US EPA RfD: 0.2; German IA GV II: 0.8; German IA GV I: 0.1

6 Selection of substances formed or released

In the selection of substances formed or released during the evaporation of e-liquids for calculation of proposals for limit values, the following criteria have been used:

- Substances which according to more than one reference have been identified as formed or released during the evaporation of e-liquids have been prioritised first.
- Mainly substances with an identified threshold value have been selected for further review.
- Substances with the lowest threshold values have been selected.

Not much information has been available concerning concentration levels. For this reason, the measured concentration has not been used as a selection parameter in all cases.

A total of 12 substances formed or released during the evaporation of e-liquids was selected for further review. These have been marked with green shading in Table 2 above, and these are:

1. Formaldehyde
2. Acetaldehyde
3. Acrolein
4. Nickel
5. Chromium (elemental)
6. Aluminium
7. Lead
8. Cadmium
9. Xylene
10. Glyoxal
11. Toluene
12. Acetone

It seems that the substances formaldehyde, acetaldehyde and acrolein are identified in the highest concentrations in the vapour from e-cigarettes according to the review carried out in this report. These three substances were therefore selected for further review. These three substances are also listed in the British PAS document and in the French Afnor standard as substances of relevance for emission measurements (BSI, 2015; Afnor, 2016).

Furthermore, the elements nickel, chromium, aluminium, lead and cadmium have been selected for further review, as:

- According to two studies, nickel is emitted in much higher concentrations in vapour compared to ordinary cigarettes (Saffari, 2014; Pisinger, 2014). Furthermore, nickel is one of the main elements measured in vapour from e-cigarettes (Pisinger, 2014).
- According to one study, chromium is measured in higher concentrations in vapour compared to ordinary cigarettes (Saffari, 2014).
- According to one study, aluminium is measured in higher indoor concentrations after vaping (Pisinger, 2014). Furthermore, aluminium is

one of the main elements measured in vapour from e-cigarettes (Pisinger, 2014).

- Lead is detected in all e-cigarettes measured in a study by Farsalinos (2015) and as lead is one of the most critical elements according to a risk assessment carried out in this study.
- Cadmium is detected in most (9 of 12) e-cigarettes measured in a study by Farsalinos (2015) and as cadmium is one of the most critical elements according to a risk assessment carried out in this study.

The elements nickel, chromium and aluminium are also three of five elements that according to the British PAS document are relevant for emissions from e-cigarettes hardware. The other two elements listed in the British PAS documents are iron and tin (BSI, 2015). In comparison, the French Afnor standard describes limit values for the following elements: antimony, nickel, chromium, cadmium, lead and arsenic (Afnor, 2016).

Other elements such as mercury and tin seem to be measured at trace levels (detected in some studies, but not in others). Therefore, these elements are not selected for further review regarding proposal for limit values.

The last four substances selected for calculation of a proposal for limit values are xylene, glyoxal, toluene and acetone. These four substances have been chosen because they all have low limit values and because they have been measured in higher concentrations than for example the PAHs such as anthracene and pyrene.

7 Exposure calculation

For the selected substances formed or released during the evaporation of e-liquids (see chapter 6), a proposal for limit values in the vapour from e-cigarettes is calculated. The calculation is based on the identified existing threshold limit values for the selected substances. This means that in this report it is not assessed whether the limit values are “correct”, but the limit values are used directly in the calculations.

The proposals are calculated as a concentration of the substances in the vapour from the e-cigarettes and are based on assumptions and worst-case scenarios regarding e-cigarette use. However, it should be emphasised that even though the term ‘worst-case scenarios’ is used, this does not prevent that a few individuals in extreme cases will be exposed to larger amounts than used in the ‘worst-case scenarios’.

In this chapter, the calculation method is described and the worst-case values used are described and discussed.

Existing threshold limit values in the form of e.g. ECHA DNEL values or US Reference Concentration values are assumed to be derived in a similar way by use of appropriate safety and uncertainty factors. In practice, the differences between values may occur as a function of the size of the safety and uncertainty factors used, and perhaps also as a function of the date of establishing the threshold value, as the most recent values may be based on newer/better data on toxicity. The main difference between the values is, however, that ECHA DNEL values are calculated by industry and based on registrations to ECHA by companies producing these chemicals whereas Reference Concentration or Dose values are prepared by independent scientists (toxicologists). For this reason, the ECHA DNEL values are only used if other values are not available.

In some situations, only threshold limit values set for indoor air/construction products are available. In these situations, these limit values are used.

The 12 substances selected in chapter 6 ”Selection of substances formed” were selected on the basis of the first preliminary search for threshold limit values irrespective of the limit value being based on local or systemic effects. Afterwards, a search has been made for the 12 substances in order to determine the critical effect (i.e. the effect caused by the lowest dosage (threshold value)). This search and the threshold limit values identified are described in more details in section 8.1 “Identification of threshold values”. The proposal for limit values in the vapour from e-cigarettes is therefore calculated based on the lowest identified threshold limit value for either local and/or systemic effects including acute effects (such as e.g. irritation) or long-term effects (such as e.g. cancer).

7.1 Calculation method

The core information to be established is which concentration of a substance in the vapour from an e-cigarette (formed during the evaporation of the e-liquid) can be assumed to be safe (“*the safe concentration”*) using a conservative approach. This

concentration is calculated by use of conservative assumptions regarding daily inhalation of vapour from e-cigarettes. The basic unit for this *safe concentration* will be mg/m^3 (or µg/m^3).

This *safe concentration* in the vapour from the e-cigarette is calculated on the basis of information about the *safe daily dose or safe daily total amount of a substance*, which it is possible to inhale or take in the body each day without the risk of health effects.

It has been decided for this report only to use threshold values (given in mg/m^3) based on inhalation (in contrast to threshold limit values given in mg/kg bw/day, which are based on intake of the substance) – simply because the exposure pathway for e-cigarettes is by inhalation.

For local effects, such as e.g. irritation, the identified threshold limit value is used directly as a limit value for the selected substance. The motivation for this is that it most often is the concentration rather than the total amount causing the critical effect.

For systemic effects, the *safe dose or safe daily total amount* of substance to be inhaled can be established from DNEL or Reference Concentration-values in mg/m^3 or other threshold limit values in mg/m^3, where the DNEL/RfC value is multiplied by the assumed daily (i.e. 24 hours) volume of inhaled air. However, if a threshold limit value in the working environment is used, the value should be multiplied by the volume of air inhaled during a working day, i.e. eight hours.

This *safe daily total amount* of inhaled substance is then subsequently distributed on the total volume of vapour inhaled per day during vaping on e-cigarettes, using a conservative approach. The amount of vapour inhaled per day is calculated as the vapour volume of each puff multiplied by the worst-case number of puffs taken per day on the e-cigarette. This method is based on the assumptions that all the inhaled e-liquid will be absorbed in the body and that all vapour from the e-cigarette is inhaled.

Regarding the amount of vapour inhaled from e-cigarettes (i.e. the consumption of e-liquid) per day, it is important to notice that this daily consumption could strongly depend on the nicotine level in the e-liquid (ranging from no nicotine to highest allowed nicotine level of 20 mg/ml). Several discussion forums can be found debating the typical consumption of e-liquids per day[10]. It is therefore important that the proposed limit values for substances in e-liquids will be valid for all e-liquids irrespective of nicotine content (from 0 to 20 mg/ml). As a worst-case, a consumer may “chain smoke” on an e-cigarette with a low or no content of nicotine, i.e. getting a low level of nicotine or no nicotine, but a high level of other ingredients.

The concentration of a substance inhaled in each puff will be diluted in the lung, as the lung is already filled with air. However, this dilution of the concentration may only be relevant to consider for acute local sensory irritation effects, where the concentration in the lung rather than the amount of substance absorbed is of relevance. Whether a dilution may be relevant to look at, has not been addressed in this screening project.

[10] https://www.e-cigarette-forum.com/forum/threads/average-daily-e-liquid-consumption.414565/; https://www.nicvape.com/About-Nicotine-Strengths; https://www.planetofthevapes.co.uk/forums/ecig-discussion/general-chat/threads/common-misunderstanding-1-ml-liquid-can-not-be-compared-with-a-cigarette.52078/

Where long-term effects are considered, the important aspect is to look at the *total* amount of substance inhaled/absorbed into the body. The formula below shows how to calculate the maximum concentration of a substance in vapour from an e-cigarette by use of the *safe dose or daily total amount of a substance* given in mg/m^3. The *safe dose* is the maximum amount of a substance which may be included in the vapour inhaled per day.

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

$C_{Substance\_in\_vapour}$	Is the maximum concentration of the substance in the vapour from e-cigarettes (mg/m^3) that will not result in adverse effects, when inhaled on a daily basis for a long time, i.e. the limit value that should be set for the substance
V_{air_daily}	Is the volume of air typically inhaled per day (24 hours) for a human or per eight hours where occupational limits are used (m^3)
$RfC_{substance}$	Is the DNEL or Reference Concentration (existing threshold limit values available) for the substance (mg/m^3)
$abs_{substance}$	Is the absorption coefficient (%) of the substance, i.e. how large a part 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.
$V_{Vapour\_per\_puff}$	Is the volume of e-liquid vapour inhaled (vaporised) per puff (m^3/puff)
n_{puffs}	Is the total number of puffs per day (puffs/day)

The proposed limit values are hence calculated in mg/m^3 (or $\mu g/m^3$). However, this may not be an operational limit value in practice. Some limit values have been set in the Afnor (2016) standard for formaldehyde, acrolein, acetaldehyde, diacetyl and some metals. The limit values are in the Afnor (2016) standard given in µg/200 puffs, i.e. a measurement of the total amount of substance measured in the vapour from 200 standard puffs and where a standard puff is defined as 55.0 mL ± 0.3 mL (Afnor, 2016). For comparison reasons, the calculated limit values are given in µg/x puffs as well.

7.2 Assumptions used

The following values are used in the calculations:

$\underline{abs_{substance}}$
As described above, it is assumed that the entire amount of the substance being inhaled will be absorbed in the body. This means that a factor of 1 is used for $abs_{substance}$.

V_{air_daily}

As a worst-case value for daily inhaled volume of air (also called inhalation rate), the value of 16 m^3 is used. ECHAs "Guidance document for consumer exposure" (ECHA, 2016) refers to among others the US EPA "Exposure Factors Handbook" (US EPA, 2011) and RIVM "General default parameters for estimating consumer exposure" (RIVM, 2014) for default values on inhalation rates. However, in an earlier ECHA Guidance document (ECHA, 2012), a default inhalation of 18 m^3 was suggested for long term daily inhalation rate for adults (age 20-75).

According to the US EPA (2011), the inhalation rate differs across age and gender. Adults have a higher inhalation rate compared to children, young adults have a higher inhalation rate compared to average adults, and males have a higher inhalation rate compared to females. The male daily inhalation rate lies between 19.3 m^3 for 16 to <21 year olds and 16.5 m^3 for > 60 year olds. The same values for females are 14.6 m^3 and 12.9 m^3. The daily inhalation rate for a weighted combination of gender has values between 17.0 and 14.7 m^3 across the different age groups.

According to RIVM (2014), the long-term inhalation rate for adults is 16 m^3 (based on Human Exposure Expert Group opinion (2013)) or 18 m^3 (based on ECHA (2012) value).

For this reason, a value of 16 m^3 is used as the worst-case value (the lowest value will result in the lowest *safe dose* and thereby the lowest calculated limit value in the e-liquids). For comparison, the Afnor (2016) uses a default value of 20 m^3/day.

In the cases where the threshold limit values used are based on occupational limit values, i.e. an eight-hour working day, the inhaled volume will be one third of an entire day's (24 hours) inhaled volume, corresponding to 5.33 m^3.

$V_{Vapour\_per\_puff}$

This value is the volume of air being inhaled for one puff on an e-cigarette. The value used by BfR (2015) of 0.055 litre/puff (55 mL/puff) is also used in the calculations in this report, as this value seems to be generally accepted for one puff – the same value is also used in the French Afnor standard (Afnor, 2016). However, other sources may use other values. In Cheng (2014), the puff volume has been reported from different sources, and this puff volume varies between 35 and 498 ml. The actual puff volumes listed in Cheng (2014) are: 35 ml, 38 ml, 50 ml, 55 ml, 58 ml, 70 ml, 100 ml and 498 ml.

n_{puffs}

Of course, the number of puffs per day depends on how heavy an e-cigarette vapourer the individual vapourer is. Several studies[11] indicate that the number of puffs per day also is dependent on the concentration of nicotine in the e-liquid, i.e. if the nicotine concentration is too low, the e-cigarette vapourer will typically puff more on the e-cigarette during the day to get the amount of nicotine wanted/needed – or in the case of e-liquids without nicotine, the consumer may assume that it is safe and will therefore not limit their vaping on non-nicotine containing e-cigarettes.

[11] https://www.e-cigarette-forum.com/forum/threads/average-daily-e-liquid-consumption.414565/; https://www.nicvape.com/About-Nicotine-Strengths; https://www.planetofthevapes.co.uk/forums/ecig-discussion/general-chat/threads/common-misunderstanding-1-ml-liquid-can-not-be-compared-with-a-cigarette.52078/

In a report on the health risk of e-cigarettes, RIVM (2015b) has made a questionnaire for a representative group of 456 daily or weekly users of e-cigarettes in the Netherlands. Based on this study, they divide the e-cigarette vapourers into the following categories:

- Light vapourer: 15 inhalations (puffs) per day
- Average vapourer: 60 inhalations (puffs) per day
- Heavy vapourer: 500 inhalations (puffs) per day

The light vapourer category mentioned in RIVM (2015b) could be vapourers only vaping a couple of times per week (i.e. weekly users and not daily users) or vapourers just vaping once a day.

Other studies/articles use an average of 150 puffs per day (e.g. Burstyn (2014) and BfR (2015)). As an example, user input to a debate forum varies between about 200 puffs (1.3 mL e-liquid) and > 400 puffs (2.6 mL e-liquid) per day (with different nicotine levels)[12], but people have reported up to 10 mL (=1500 puffs) per day, and many seem to use about 3-5 mL of e-liquid per day (i.e. 450-750 puffs/day). According to BfR (2015), 150 puffs equal 1 mL of e-liquid.

In this project, the RIVM value of 500 puffs per day is used as a high value – it is, however, not considered to be a worst-case value, as different forums illustrate that even higher number of puffs per day are used by extremely heavy vapourers. According to the values used by BfR (2015), 500 puffs per day would equal a consumption of 3.3 mL e-liquid per day. It should be emphasised that in extreme cases the calculated limit values (in chapter 8) still may not be sufficient because more heavy vapourers do exist.

To summarise the following values are used in the calculations:

$abs_{substance}$	1
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 eight-hour working day, the inhaled volume will be one third of the inhaled volume of an entire day, corresponding to 5.33 m^3.
$V_{Vapouor\_per\_puff}$	Is the volume generated for one puff, i.e. 0.000055 m^3, because this amount is used in the existing French standard Afnor (2016).
n_{puffs}	500 puffs per day, because this number represents a "heavy" e-cigarette vapourer.

[12] https://www.e-cigarette-forum.com/forum/threads/how-many-puffs-a-day-do-you-take.388452/

8 Preliminary proposal for limit values of selected substances

In this chapter, calculations for a preliminary proposal for limit values have been made for the 11 substances selected in chapter 6 “Selection of substances formed”. The limit values are considered as a preliminary proposal considering the limitations in this screening project. The limitations are discussed in chapter 9 “Discussion and recommendations”.

8.1 Identification of threshold values

For the 12 selected substances, which are formed or released during the evaporation of e-liquids, the first step has been to identify the threshold values for both short-term and long-term exposure for the selected ingredients – and if possible also the critical effects of the substances. The effect with the lowest threshold value is the critical effect for the substance.

The threshold values for short-term and long-term exposure (or the critical effects) have been identified by searches in the ECHA database of registered substances in combination with different toxicological reports of the 12 selected substances, such as OECD toxicological reports, toxicological reports from US EPA, EU Risk Assessment Reports etc.

The no effect levels (NOEL or DNEL) or threshold limit values (TLVs) identified and their references used for the calculations are presented in Table 3 below. In general, the lowest threshold limit values have been used in the calculations of the proposed limit values of the selected substances, which are formed or released during the evaporation of e-liquids. However, in some cases a higher limit value was used, if the lowest limit values e.g. are very old and newer more up-to-date limit values are found.

In cases where the lowest identified threshold limit values are based on e.g. indoor air limit values, a critical effect is not necessarily identified, as the documentation behind the established limit values has not been available or has not been examined in details.

It should be noted that this project is a screening project and therefore all relevant literature has not necessarily been identified and reviewed. Hence, it may be possible that more up-to-date threshold limit values/DNEL values may be found compared to the values identified in this report.

From Table 3, it can be seen that for almost all substances, the lowest identified threshold limit value is based on long-term exposure. Only for glyoxal the lowest identified TLV is based on short-term exposure.

Furthermore, it should be noted that for aluminium and toluene, the threshold limit values used are based on a workday (eight hours) and not a 24-hour inhalation exposure. This has been taken into consideration in the calculations.

Regarding the release of chromium, it should be noted that the identified literature (such as Saffari et al. (2014), Pissinger (2014) and RIVM (2015b)), which describe the release of chromium does not specify in which form the chromium is released, i.e. Cr(III) or elemental chromium. One article (Farsalinos, 2015) has measured the release of soluble Cr (III). Whether Cr(VI) is relevant here needs further research, as well as identification of the most relevant form of chromium. In this project, the limit values are calculated for elemental chromium and chromium(III).

Table 3 Threshold limit values identified and used in the calculations of limit values for selected substances

Substance	CAS no.	Lowest identified TLV (mg/m^3)	Comments
Acetaldehyde (ethanal)	75-07-0	Short-term exposure: 3.0 mg/m^3 (ANSES, 2013a) Long-term exposure: 0.160 mg/m^3 (ANSES, 2013a)	No information in ECHA (2017). ANSES (2013a) lists IAQG for short-term exposure (1 h) at 3.0 mg/m^3 (irritation of airways, bronchoconstriction) and long-term exposure (> 1 y) at 0.160 mg/m^3 (damage of epithelium, possibly carcinogenic). US EPA IRIS (1991) lists a RfC of 0.009 mg/m^3 (degeneration of olfactory epithelium (long-term effect)). They use conservative safety factors, which are not supported by current ECHA guidelines. For this reason, this value is not used even though it is the lowest value. EU-LCI (2013) is set at 1.2 mg/m^3.
Acetone	67-64-1	Short-term exposure: 511 mg/m^3 (ACC, 2003) Long-term exposure: 200 mg/m^3 (ECHA, 2017)	American Chemistry Council (ACC, 2003) lists a RfC of 29 ppm (74.2 mg/m^3) based on a NOAEL of 2200 ppm for developmental toxicity by inhalation. A value for short term exposure is set at 200 ppm (511 mg/m^3), which is NOAEL for throat irritation. ECHA (2017) lists a limit value for consumers of 200 mg/m^3 based on long term inhalation. An overall assessment factor of 2 is used with the EU OEL of 1210 mg/ m^3 as the basis, which has been corrected for 24 hours exposure instead of eight hours working exposure. ATSDR MRL(1994) sets a limit of 13 ppm (33.2 mg/m^3) for chronic exposure and 26 ppm for acute exposure based on neurological effects. An uncertainty factor of 100 is used. AgBB (2015) sets a limit of 1.2 mg/m^3, which, however, is the German or EU OEL of 1210 mg/m^3 divided by a safety factor of 1000. For long-term exposure for the general population, the ECHA DNEL value of 200 mg/m3 is used, as the other values seem of older date and use conservative safety factors, which are not supported by current ECHA guidelines.
Acrolein (propenal)	107-02-8	Short-term exposure: 0.0069 mg/m^3 (ANSES, 2013b) Long-term exposure: 0.0008 mg/m^3 (ANSES, 2013b)	US EPA (2003) sets a RfC of 0.02 $\mu g/m^3$ (sub-chronic effects in nose). ATSDR MRL (2007) for inhalation is 0.00004 ppm (0.0987 $\mu g/m^3$). ANSES (2013b) sets a short-term limit value (1 hour) at 3 ppb or 6.9 $\mu g/m^3$ and a long-term (> 1 year) at 0.35 ppb or 0.8 $\mu g/m^3$. No information for consumer inhalation in ECHA (2017). However, DNEL value for long-term inhalation for workers is 0.2 mg/m^3. The ANSES long-term value is used in the calculations even though it is not the lowest value (US EPA). The ANSES value is, however, the most recent value.
Aluminium	7429-90-5	Short-term exposure: 50 mg/m^3 (Krewski et al., 2007) Long-term exposure: 0.0055 mg/m^3 (Michigan DEQ, 2015)	In a risk assessment, Krewski et al. (2007) has determined the relevant exposure level of concern for irritation following inhalation to be 50 mg/m^3. Long-term exposure for inhalation not described. Michigan DEQ (2015) has set a RfC of 0.0055 mg/m^3 based on human data of a long-term occupational exposure with a critical effect of psychomotor and cognitive impairment. No information for consumer inhalation in ECHA (2017). However, DNEL value for long-term inhalation for workers is 3.72 mg/m^3.

Substance	CAS no.	Lowest identified TLV (mg/m^3)	Comments
Cadmium	7440-43-9	Short-term exposure: 0.00003 mg/m^3 (ATSDR, 2012) Long-term exposure: 0.00001 mg/m^3 (ATSDR, 2012)	ATSDR (2012) MRL for inhalation is 0.03 $\mu g/m^3$ (acute, short-term exposure – an uncertainty factor of 300 is used) and 0.01 $\mu g/m^3$ (chronic, long-term exposure – an uncertainty factor of 9 is used). US EPA IRIS has not listed a RfC for inhalation for cadmium. ECHA (2017) lists a DNEL value for workers for long-term exposure of 4 $\mu g/m^3$. WHO (2000) sets an air quality guideline at 5 ng/m^3 in order to prevent any further increase of Cd in agricultural soils likely to increase the dietary intake of future generations. The values from ATSDR are used for the calculations as they are from recent years and because the WHO air quality guideline is set low in order to prevent accumulation of Cd in soils.
Chromium (elemental)	7440-47-3	Short-term exposure: *none for elemental Cr* Long-term exposure: 0.027 mg/m^3 (ECHA,2017) 3 µg/day (EMA, 2016)	ECHA (2017) lists a DNEL value for consumers for long-term exposure of 0.027 mg/m^3. WHO (2000) air quality guideline is 0.025 ng/m^3, based on a risk of 1/1,000,000 of cancer by inhalation. However, this value is for Cr (VI) and not chromium itself. US RAIS (1992a) lists a nasal irritation inhalation value of 0.01 mg/m^3, and a long-term inhalation limit value of 0.012 $\mu g/m^3$ for carcinogenic effects – but again this limit value is for Cr (VI). US EPA (1998) has not established a RfC for elemental chromium, only for chromium VI, which is 0.000008 mg/m^3 based on respiratory effects in humans. Based on risk assessments, EMA (2016) has defined PDE (Permitted Daily Exposure) values for elemental impurities in drugs. PDE for inhalation of elemental chromium is 3 µg/day, which can be used as the *safe daily total amount*.
Chromium (III)		Intermediate-term exposure: 0.0001 mg/m^3 Long-term exposure: *none*	ATSDR (2012) MRL for inhalation of soluble chromium (III) is 0.1 $\mu g/m^3$ for intermediate exposure – an uncertainty factor of 300 is used. US EPA (1998) has not established a RfC for chromium (III) (insoluble salts) as data are considered to be inadequate.
Formaldehyde	50-00-0	Short-term exposure: 0.05 mg/m^3 (ANSES, 2013a) Long-term exposure: 0.01 mg/m^3 (ANSES, 2013a)	ANSES (2013) lists IAQG for short-term exposure (2 h) at 0.050 mg/m^3 and long-term exposure (> 1 y) at 0.010 mg/m^3. Critical effect is nasal irritation. The limit value is also low enough to protect against local nasal carcinogenic effects. ECHA (2017) lists a DNEL value of 0.1 mg/m^3 for the general population (inhalation route) for local effects (long term exposure). Most critical effect in humans seems to be sensory irritation of the eyes (OECD, 2002) with a threshold of 0.1 ppm (Golden, 2011) or 0.08 ppm (Naya & Nakanishi, 2005). However, effect may not be relevant for inhalation of e-liquid. Golden (2011) lists a TLV of 0.1 ppm (0.13 mg/m^3) for nasal cancer as a result of inhalation.

Substance	CAS no.	Lowest identified TLV (mg/m^3)	Comments
Glyoxal	107-22-2	Short-term exposure: 0.006 mg/m^3 (WHO, 2004) Long-term exposure: 0.1 mg/m^3 (NICNAS, 2014)	NICNAS (2014) has listed different occupational TLV's for glyoxal around the world. Lowest TLV for short-term exposure is 0.3 mg/m^3 and 0.1 mg/m^3 for long-term exposure. WHO (2004) has used a NOEL value for local effects in the larynx of 0.6 mg/m^3 to establish a tolerable concentration limit value of 0.006 mg/m^3 for local effects for short-time exposure. ECHA (2017) has listed the following DNEL values for consumers for inhalation: local effects (0.01 mg/m3) and long-term exposure (1.3 mg/m3).
Lead	7439-92-1	Short-term exposure: *None* Long-term exposure: 0.0005 mg/m^3 (WHO, 2000)	US EPA (2004) has not evaluated a RfC for lead based on the available data. WHO (2000) air quality guideline for lead is 0.5 $\mu g/m^3$, which is an annual average lead level in air that should not be exceeded (i.e. long-term exposure).
Nickel	7440-02-0	Short-term exposure: 0.8 mg/m^3 (ECHA, 2017) Long-term exposure: 0.0000025 mg/m^3 (WHO, 2000)	ECHA (2017) has listed the following DNEL values for consumers for inhalation: long-term exposure (0.020 mg/m^3), local effects (0.8 mg/m^3). WHO (2000) calculates a value of 0.0000025 mg/m3 (or 2.5 ng/m3) associated with a cancer risk of 1/1,000,000 inhalation.
Toluene	108-88-3	Short-term exposure: 150 mg/m^3 (EU RAR, 2003) Long-term exposure: 0.26 mg/m^3 (WHO, 2000)	ECHA (2017) has listed the following DNEL values for consumers for inhalation: short-term exposure (226 mg/m^3) and long-term exposure (56.5 mg/m^3), local effects. WHO (2000) sets a limit value of 0.26 mg/m^3 as guideline value for potential effects on the developing central nervous system (long term effects).
Xylene	1330-20-7	Short-term exposure: 174 mg/m^3 (ECHA, 2017) Long-term exposure: 0.1 mg/m^3 (US EPA)	ECHA (2017) has listed the following DNEL values for consumers for inhalation: inhalation short-term exposure (174 mg/m^3), local effects (260 mg/m^3), long-term exposure (14.8 mg/m^3). German AgBB and EU-LCI list the limit value of 0.5 mg/m^3. ATSDR lists a MRL value of 0.05 ppm corresponding to 0.234 mg/m^3 with a molecular weight of 106.16 g/mol for xylene. US EPA RfC and German Indoor Value I is 0.1 mg/m^3. NICNAS (2013) lists different occupational exposure limits in different countries between 25-100 ppm (108-435 mg/m^3). Critical effect is neurobehavioural effects.

8.2 Proposal for limit values of selected ingredients

In Table 4 on the next pages, a proposal for limit values has been made for the 12 selected substances based on the calculation method and values presented in chapter 7. Please note that the calculations are made for a daily intake of 500 puffs, as described in chapter 7. However, the *safe daily total amount* of inhaled substance is also listed for comparison reasons, as this amount is used in e.g. the French Afnor (2016) standard, where it, however, is listed for 200 puffs, as this is used as 'a reasonable estimation of a day of vaping' (Afnor, 2016).

It should be noted that most information found regarding toxicity for chromium is not for elemental chromium, but for chromium (VI), which is considered more toxic compared to elemental chromium. However, in the calculations information regarding the toxicity of elemental chromium and chromium (III) is used. Many articles measuring chromium do not state in which form chromium is found and is therefore assumed to be elemental chromium. One article measures the soluble form of chromium (III), (Farsalinos, 2015). For this reason, the proposed limit values are calculated for elemental chromium and chromium (III). However, further investigation regarding the possibility of release and relevance of chromium (VI) is needed.

Use of the toxicological values identified for Cr (elemental) and Cr(III) results in a *safe daily total amount* of inhaled chromium (elemental) and chromium (III) of 3 and 1.6 µg respectively. For elemental chromium, it has been decided in this report to use the limit value established by Europeans Medicines Agency, EMA (2016). The EMA value is based on a risk assessment defined PDE (Permitted Daily Exposure) values for elemental impurities in drugs. PDE for inhalation of elemental chromium is 3 µg/day, which in this report is used directly as the limit value (for 500 puffs). For chromium (III), the ATSDR (2012) MRL value for inhalation of soluble chromium (III) of 0.1 $\mu g/m^3$ is used.

In Table 4 it is indicated with a light red background colour if the proposed limit values are exceeded by existing maximum levels of evaporating substance identified in this review. Similarly, it is indicated with a light green background colour if the proposed limit values are *not* exceeded by existing maximum levels identified for the substances in the vapour from e-cigarettes.

For all of the 12 substances where limit values are proposed for substances formed or released during the evaporation of e-liquids, information about the actual concentration measured in vapours has been identified in this review. In 6 of 12 cases, the actual identified maximum concentration in vapours is higher than the proposed limit values, which indicates that there may be a need for limit values.

However, as the available information about the actual minimum concentrations measured in e-liquids reveals, it will be possible for some of the examined e-cigarettes to meet the proposed limit values for substances formed or released during the evaporation of e-liquids for all the 12 substances where measurements have been carried out. For all the 12 selected substances, measurements on e-cigarettes do exist where the selected substances have not been detected. This means that e-cigarettes which can meet the proposed limit values are available on the market.

Table 4: Proposal for limit values for 12 selected substances which are formed during the evaporation of e-liquids.
Limit values marked with light red background are exceeded by existing maximum levels found evaporating from e-liquids.
Limit values marked with light green background are not exceeded by existing maximum levels found in this review evaporation from e-liquids.

Substance	**CAS no.**	**Values used**	**Limit value µg/500 puffs (equal to safe dose)**	**Limit value µg/m³ (based on 500 puffs)**	**Comments / comparison with AFNOR standard value or actual measurements**
Acetaldehyde	75-07-0	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.160 mg/m³	2,560	93,091	Found in concentrations up to 8 µg/puff (Hutzler, 2014) and in concentrations up to 120 µg/10 puffs (Bekki, 2014), corresponding to a total of 6,000 µg for 500 puffs. In Bekki (2014), 13 brands of e-cigarettes were analysed, where acetaldehyde was detected in 9 of 13 brands. Lowest concentration measured (if detected) was 0.2 µg/10 puffs, i.e. 10 µg/500 puffs. No LOD or LOQ is listed. In comparison Afnor (2016) calculates a total acceptable amount of 3200 µg (and relates this amount to 200 puffs).
Acetone	67-64-1	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 200 mg/m³	3,200,000	116,363,636	Present in most vapours (Varlet, 2015). Found in concentrations between 0.16 and 2.9 mg/m³ or 2,900 µg/m³ (Cheng, 2014). No information regarding how often acetone is identified from evaporation of e-liquids.
Acrolein	107-02-8	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.0008 mg/m³	12.8	465.5	Found in concentrations up to 3 µg/puff (Hutzler, 2014) and in concentrations up to 40 µg/10 puffs (Bekki, 2014). This corresponds to a total of 2,000 µg for 500 puffs. In Bekki (2014), 13 brands of e-cigarettes were analysed, where acrolein was detected in 9 of 13 brands. Lowest concentration measured (if detected) was 0.6 µg/10 puffs, i.e. 30 µg/500 puffs. No LOD or LOQ is listed. BfR (2012) found acrolein in concentrations up to 9.3 mg/m³. In comparison Afnor (2016) calculates a total acceptable amount of 16 µg (and relates this amount to 200 puffs).

Substance	CAS no.	Values used	Limit value µg/500 puffs (equal to safe dose)	Limit value µg/m^3 (based on 500 puffs)	Comments / comparison with AFNOR standard value or actual measurements
Aluminium	7429-90-5	V_{air_daily} = 5.33 m^3 (TLV 8h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.0055 mg/m^3	29	1,067	A 'real-life' study showed a 2-fold increase of aluminium in indoor air after vaping (Pisinger, 2014). No actual level stated. According to Saffari (2014) aluminium is not detected in emissions. Measured in 1 e-cigarette in a concentration of 47.28 µg/1200 puffs corresponding to 19.7 µg/500 puffs (Farsalinos, 2015).
Cadmium	7440-43-9	V_{air_daily} = 16 m^3 (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.00001 mg/m^3	0.16	6	Found in concentrations from not detected and up to 0.22 µg/150 puffs (Cheng, 2014), corresponding to a total of 0.73 µg per 500 puffs. No LOD or LOQ is listed. Farsalinos (2015) detected cadmium from 9 of 12 e-cigarettes. Concentrations were between 0.08 and 1.6 µg/1200 puffs, i.e. up to 0.67 µg per 500 puffs. No LOD or LOQ is listed.
Chromium (elemental)	7440-47-3	V_{air_daily} = 16 m^3 (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 3 µg/day	3	109	Found in concentrations of 0.7 ng/puff, corresponding to a total of 0.350 µg (per 500 puffs)), (Cheng, 2014). In another study cited by Cheng (2014), chromium was not detected. No LOD or LOQ is listed. Saffari (2014) states that higher concentrations are measured compared to normal cigarettes (28.1 ng/h). In comparison Afnor (2016) calculates a total acceptable amount of 3 µg (and relates this amount to 200 puffs) – based on EMA (2016).
Chromium (III)		V_{air_daily} = 16 m^3 (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.0001 mg/m^3	1.6	58	Found in concentrations up to 0.84 µg/1200 puffs (Cr(III)), equal to 0.35 µg/500 puffs. However, Cr(III) was only detected in 1 out of 13 e-cigarettes (Farsalinos, 2015). No LOD or LOQ is listed.

Substance	CAS no.	Values used	Limit value µg/500 puffs (equal to safe dose)	Limit value µg/m³ (based on 500 puffs)	Comments / comparison with AFNOR standard value or actual measurements
Formaldehyde	50-00-0	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.01 mg/m³	160	5,818	Found in concentrations up to 5 µg/puff (Hutzler, 2014) and up to 140 µg/10 puffs (Bekki, 2014) corresponding to a total maximum amount of 7,000 µg for 500 puffs. In Bekki (2014), 13 brands of e-cigarettes were analysed, where formaldehyde was detected in 9 of 13 brands. Lowest concentration measured (if detected) was 0.7 µg/10 puffs, i.e. 35 µg/500 puffs. No LOD or LOQ is listed. BfR (2012) found formaldehyde in concentrations up to 8.3 mg/m³ (8,300 µg/m³). In comparison Afnor (2016) calculates a total acceptable amount of 200 µg (and relates this amount to 200 puffs).
Glyoxal	107-22-2	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.006 mg/m³	96	3,491	Found in concentrations up to 23 µg/10 puffs corresponding to a total amount of 1,150 µg for 500 puffs (Bekki, 2014). In Bekki (2014), 13 brands of e-cigarettes were analysed, where glyoxal was detected in 9 of 13 brands. However, in 12 out of 13 brands glyoxal was not detected for some of the tests performed for the specific e-cigarettes. Lowest concentration measured (if detected) was 0.7 µg/10 puffs, i.e 35 µg/500 puffs. No LOD or LOQ is listed.
Lead	7439-92-1	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.0005 mg/m³	8	291	Found in concentrations from 0.8 to 4.4 µg/1200 puffs with an average of 0.7 µg/1200 puffs and was detected in all 13 e-cigarettes examined (Farsalinos, 2015). These values correspond to between 0.33 to 1.8 µg/500 puffs with an average of 0.3 µg/500 puffs.
Nickel	7440-02-0	V_{air_daily} = 16 m³ (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.0000025 mg/m³	0.04	1.5	Found in concentrations between 2 and 7 ng/10 puffs (Cheng, 2014) corresponding to between 0.1 and 0.35 µg for 500 puffs. In another study cited by Cheng (2014), nickel was not detected. No LOD or LOQ is listed. According to Saffari (2014), nickel is measured in higher concentrations compared to normal cigarettes (130.5 ng/h). In comparison Afnor (2016) calculates a total acceptable amount of 5 µg (and relates this amount to 200 puffs) – based on EMA (2016).

Substance	CAS no.	Values used	Limit value µg/500 puffs (equal to safe dose)	Limit value µg/m^3 (based on 500 puffs)	Comments / comparison with AFNOR standard value or actual measurements
Toluene	108-88-3	V_{air_daily} = 5.33 m^3 (TLV 8h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.26 mg/m^3	1387	50,424	Found in concentrations between not detected and up to 6.3 µg/150 puffs (Cheng, 2014) and up to 0.63 µg/15 puffs (Drummond, 2014) corresponding to a total amount of 21 µg for 500 puffs. No LOD or LOQ is listed.
Xylene	1330-20-7	V_{air_daily} = 16 m^3 (TLV 24h) V_{per_puff} = 0.055 L n_{puffs} = 500 puffs Used TLV = 0.1 mg/m^3	1,600	58,182	Found in concentrations between not detected and up to 0.2 µg/150 puffs (Cheng, 2014) corresponding to a total amount of 0.7 µg for 500 puffs. No LOD or LOQ is listed.

9 Discussion and recommendations

In chapter 8 (Table 4), a preliminary proposal has been made for a limit value for the concentration in the vapour from e-cigarettes for 12 selected substances formed or released during the evaporation of e-liquids.

The limit values are given as two different figures:

- As a total amount of substance that must be inhaled per day (per 500 puffs), which is measured in µg (equal to the *safe daily total amount*).
- As a concentration in the vapour based on the value above and the assumption of a heavy vapourer of 500 puffs per day (of 55 mL). This concentration is measured in µg/m^3.

The limit values have been calculated based on existing threshold limit values for such as occupational exposure, outdoor concentrations for air, indoor emissions for building products etc. In most cases, the existing threshold limit values are based on long term systemic exposure, as these were the lowest identified limit values. Only for the substance glyoxal, a limit value for short-term exposure has been used.

As discussed in chapter 7, it may be relevant to use a factor for dilution of the concentration inhaled, as each puff will be diluted in the lung, as the lung already is filled with air. However, this dilution of the concentration may only be relevant to consider for acute local sensory irritation effects, where the concentration in the lung rather than the amount of substance absorbed is of relevance. Whether a dilution may be relevant to look at, has not been addressed in this screening project.

In general, the lowest existing threshold limit values were used for the calculation of proposed limit values for concentration in the vapour – unless newer limit values had been set/assessed and therefore seemed more valid. 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 – even though in the high end, as different chat forums for e-cigarette vapourers indicate that even heavier vapourers can be found.

It should be stressed that the calculations performed in this report are made on a screening level, i.e. that a simple 'worst-case' calculation has been made. This means that it is assumed that all the substance contained in the e-liquid is evaporated, and all 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 12 selected substances formed or released during the evaporation of e-liquids lie between 0.04 µg (for nickel) and 3,200 mg (for acetone) for 500 puffs, and between 1.5 µg/m^3 (for nickel) and 116,000 mg/m^3 (for acetone).

For all 12 substances where limit values in vapours are proposed, information about the actual concentration in vapours from e-cigarettes has been identified in this review. In 6 of the 12 cases, the actual identified maximum concentration in vapours from e-cigarettes is higher than the proposed limit value (marked with red

shading in Table 4). For formaldehyde, the maximum concentration found in vapours exceeds the proposed limit value by a factor of about 40 – and in one case (for acrolein) even by a factor of 150. These facts suggest that limit values may be needed.

However, as the available information about the actual minimum concentrations measured in vapours from e-liquids reveals, it will be possible for some of e-liquids examined in literature to meet the proposed limit values for substances formed or released for almost all of the 12 selected substances. For example, acrolein was identified in vapours from 9 out of 13 e-liquids where its content was measured. This suggests that it will be possible for some of e-liquids on the market to meet the suggested limit value for acrolein in the vapour. It is, however, unclear whether this applies to nickel as well, as the proposed limit value of 0.04 µg/m^3 is lower than the lowest value measured of 0.1 µg/m^3, and there is no indication of level of detection (LOD) for the study.

For nickel and glyoxal, the actual identified maximum concentration in vapours from e-cigarettes exceeds the proposed limit value by a factor of 9 and 12 respectively. It must, however, be noted that for nickel the value associated with a lifetime cancer risk of 1/1,000,000 was used.

For cadmium, the actual identified maximum concentration in vapours from e-cigarettes exceeds the proposed limit value by a factor of about 4. However, in some cases, cadmium was not detected in vapours from e-cigarettes and in some cases cadmium was detected in concentrations below the proposed limit value. This means that it is possible for vapours in e-cigarettes to apply with the proposed limit value.

For glyoxal, the limit value for short-time exposure based on local effects was used directly without any dilution factor. As discussed earlier, it may be relevant to use a dilution factor for local effects. It is, however, assumed that dilution is not relevant as the inhaled concentration will affect the larynx directly when the local effect for glyoxal is in the larynx. It should, however, be investigated and discussed further, if a dilution factor is relevant here. Use of a dilution factor will result in a higher limit value proportional with the dilution factor.

For five of the substances (acetaldehyde, acetone, elemental chromium, toluene and xylene), the actual measured concentrations in vapour from e-cigarettes are all well below the proposed limit values set for the vapour. This would imply that no risk of health effects is to be expected from these five substances.

The French Afnor standard (Afnor, 2016) contains some restrictions concerning the total amount of substances emitted from e-cigarettes. The limit values are listed as so-called ‘target values’ and represent the amount of substance, which should not be exceeded per day (equal to ‘*the safe daily total amount’* used in this report). Where a daily amount of 500 puffs has been used in this report, a daily amount of 200 puffs has been used in the Afnor (2016) standard. The limit value (per 500 puffs) from this report can be compared with the ‘target value’ in the Afnor standard – however, the limit values proposed in this report are stricter, as they represent the total volume of 500 puffs compared to only 200 puffs in the Afnor standard.

When comparing with Afnor limit values set for vapour from e-cigarettes (Afnor, 2016), most of the limit values proposed in this report are lower than the Afnor limit values and in one case identical. The limit values set in the Afnor (2016)

standard are as listed below [with the proposed limit values calculated in this report in squared brackets]:

- Formaldehyde – 200 µg as maximum inhaled amount (per 200 puffs); [160 µg (per 500 puffs)]
- Acetaldehyde – 3,200 µg as maximum inhaled amount (per 200 puffs); [2,5600 µg (per 500 puffs)]
- Acrolein – 16 µg as maximum inhaled amount (per 200 puffs); [12.8 µg (per 500 puffs)]
- Nickel – 5 µg as maximum inhaled amount (per 200 puffs); [0.04 µg (per 500 puffs)]
- Cadmium – 2 µg as maximum inhaled amount (per 200 puffs); [0.16 µg (per 500 puffs)]

The fact that 6 of the proposed limit values are exceeded by actual measured maximum concentration in vapours from e-cigarettes suggests that vaping on e-cigarettes (heavy vapourers of 500 puffs/day) cannot be considered as safe, i.e. long term (or acute) health effects may occur for these 6 substances.

As mentioned earlier, the proposed limit values are calculated by use of scenarios of high use of e-cigarettes as well as assumptions of a full intake of the substances contained in the e-liquids. This result is most likely an overestimation of the absorption of the substances in the e-liquids into the human body by vaping e-cigarettes, resulting in proposed limit values that may be too conservative. Calculation of higher limit values may therefore be 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 also be discussed which limit values that should be used for the individual substances. In this report, the lowest limit values found have generally been used. However, in some cases, the lowest limits were not considered appropriate, as a new assessment of the substances had been carried out and higher limit values were proposed. Generally, the limits values were chosen from the low end of the available options.
The proposed preliminary limit values in this report should be considered as a first approximation and the risk assessment presented needs further refinement in order to establish limit values for substances in vapours from e-liquids.

However, there is no doubt that vaping on e-cigarettes is not risk-free, which has also been proven in a large study by Pissinger, who has carried out several reviews on the subject (Pissinger, 2014; Pissinger, 2015). In a letter to the Danish Parliament, Jørgensen and Pissinger (2016) argued against the sale of e-cigarettes in Denmark or at least a restriction of public vaping on of e-cigarettes in line with ordinary cigarettes/tobacco. Jørgensen & Pissinger (2016) state that the use of e-cigarettes should never have been allowed as a new product on the market because of the content of carcinogenic, toxic and addictive substances. It may be a safer alternative compared to smoking of ordinary cigarettes/tobacco, but it is a huge problem if non-smokers take up the habit of vaping e-cigarettes, if they consider it to be safe. This is, however, also a political discussion and will not be addressed further in this report.

According to the Tobacco Directive, it is only allowed to use substances in e-cigarettes and e-liquids which do not pose a risk to human health in heated and unheated form. Furthermore, it is a requirement to notify toxicological data regarding both ingredients and emissions when heated. This review and the reviews by Pissinger (Pissinger, 2014; Pissinger, 2015; Jørgensen & Pissinger, 2016) illustrate that substances formed or released during the evaporation of e-liquids are

evaporated in concentrations which cannot be considered as safe. This fact emphasises the need for limit values for several of the substances formed or released during the evaporation of e-liquids.

Neither the GPS Directive nor the Tobacco Directive contains specific requirements (limit values) for substances used in e-cigarettes and e-liquids or substances formed or released during the evaporation of e-liquids. It is therefore important that the standards developed set the necessary chemical requirements (for all the necessary chemical substances formed or released during the evaporation of the e-liquids) as well as the correct limit values to protect the consumer from unwanted health effects from vaping on e-cigarettes.

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