



Raising standards for consumers

POSITION PAPER

E-cigarettes and e-liquids - Limits for chemicals Basis for discussion



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Summary

The use of e-cigarettes spreads rapidly. The EU "Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) identified e-cigarettes as one of the "emerging health and environmental issues" in 2018. By contrast, the regulatory framework is not fit for the purpose and is hardly in the position to protect users ("vapers"). The EU Tobacco Directive (Directive 2014/40/EU) lays down some rules for ingredients and emissions of tobacco products including e-cigarettes, as well as rules for labelling. However, only nicotine-containing products are covered. Apart from nicotine and some generic bans (e.g. to use CMRs) it does not stipulate any substance specific limits of ingredients in e-liquids or in emissions.

Some national standards and guidelines on e-cigarettes and e-liquids exist (UK, FR) which do contain normative provisions regarding chemical substances including limits. These documents are a valuable starting point for establishing clear-cut protective substance specific rules. Currently, European normative documents are under development in a technical committee of CEN (CEN/TC 437 "Electronic cigarettes and e-liquids") which was established in 2015. At present it remains unclear whether it will define thresholds for substances or substance exclusions.

Against this background ANEC developed the present paper. Based on several studies commissioned by one of its members a proposal was prepared addressing substances in e-liquids (solvents, contaminants and flavours) as well as substances formed (degradation products) or released (from materials) during vaping. Suggested thresholds are based on existing air quality standards as well as appropriate "derived no-effect levels" (DNELs) for inhalation exposure notified by manufacturers or importers in the context of the registration procedure required by the European chemicals regulation REACH.

Literature data show that maximum measured data would often exceed the proposed limits. Conversely, it is also clear that many products could pass. Unfortunately, this does not hold true for the main solvents used (propylene glycol, glycerine) the measured values are considerably higher than the suggested limits. Even though the (known) associated health effects (essentially respiratory irritation) have been considered as mild and transient some risk assessors have warned that there is a risk of damage to the respiratory tract (particularly in heavy vapers). It must be borne in mind that there may be several ingredients present in e-liquids or substances formed during vaping with irritating effects. The (combined) long-term effects of such exposures are not known. This issue requires further thought and debate. Hence, ANEC does not propose thresholds for solvents at this stage.

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Apart from that the paper contains proposals for limits for 39 substances in e-liquids (3 metallic contaminants and 36 flavours). In addition, there are also limits for 7 substances in emissions (3 metallic contaminants and 4 degradation products).

The suggestions in the present paper are intended to stimulate a debate on the need to establish clear-cut substance specific rules for e-cigarettes and e-liquids (with or without containing nicotine). In the long run it may be preferable to adopt a positive list of allowed flavours rather than setting thresholds for hundreds or even thousands of substances (which might be a mission impossible).

1. Background

The use of e-cigarettes has spread rapidly in the last decade. The number of vapers increased globally from estimated 7 million in 2011 to 35 million in 2016 and will further grow. The global market volume amounts currently to \$22.6bn¹.

The "Special Eurobarometer 458" (May 2017) reported that 15% of the respondents have at least tried e-cigarettes and 2% use them regularly². Assuming that the latter figure is representative and that the EU population is of about 430 million >14 years (84% of a total population of about 511 million) this would mean that about 8,6 million EU citizens are regularly vaping.

In its report on "Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS)" published in August 2016 the WHO stated: "*Based mostly on the levels and number of toxicants produced during the typical use of unadulterated ENDS/ENNDS made with pharmaceutical-grade ingredients, it is very likely that ENDS/ENNDS are less toxic than cigarette smoke. However, ENDS/ENNDS are unlikely to be harmless, and long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer, and possibly cardiovascular disease as well as some other diseases also associated with smoking. The magnitude of these risks is likely to be smaller than from tobacco smoke although there is not enough research to quantify the relative risk of ENDS/ENNDS over combustible products*"³.

Along the same lines the "Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) identified e-cigarettes as one of the "emerging health and environmental issues" in 2018⁴. It characterizes the situation as follows: "*E-cigarettes, in their modern form, were introduced in the early 2000s as a means for smoking cessation. The e-cigarette liquid contains several chemicals, like nicotine, propylene glycol, glycerine, flavourings and others. Current research suggests that the e-cigarette aerosol contains substances that could be considered as harmful, including*

¹ <https://www.bbc.com/news/business-44295336>

² <https://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/ResultDoc/download/DocumentKy/79002>

³ <https://www.who.int/tobacco/communications/statements/electronic-cigarettes-january-2017/en>

⁴ https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_s_002.pdf

*flavouring chemicals, metals (like lead), and other cancer-causing chemicals. There is no consistent evidence regarding the effectiveness of e-cigarettes in helping people to quit smoking. Moreover, there is a tendency in people to start vaping (e-cigarettes), instead of smoking. Compared with "regular" cigarettes, e-cigarettes may be less harmful in terms of smoking-related chronic diseases, but regarding their use compared to no smoking, the health effects are not well understood or appreciated. Moreover, taking into account that e-cigarette use is increasingly prevalent and fashionable, especially among adolescents and younger people, it can be regarded as an emerging public health issue". Hence, an overall prioritisation score of 3 (= "high") was determined for this product group (the options are: *, 1,2,3 where *=uncertain and 3 is high).*

Subsequently, this Committee was requested by the European Commission to deliver a scientific opinion on risks associated with the use of e-cigarettes to be delivered in September/October 2019⁵.

E-cigarettes that can be used for consumption of nicotine-containing vapour and nicotine-containing e-liquids are covered by Article 20 of the Tobacco Products Directive (2014/40/EU, TPD). It contains some safety and quality provisions for such products but does not include any limit values on ingredients and emissions apart from nicotine (max. 20 mg/ml). However, e-liquids not containing nicotine or pre-filled e-cigarettes (or cartridges) without nicotine are not covered. A French "experimental standard" (XP D 90-300-1, -2, -3) and a British guidance document (PAS 54115) addressing chemicals are available. The applicable European regulatory provisions and available national voluntary normative documents are further discussed below. Currently, standards are under development in CEN/TC 437 "Electronic cigarettes and e-liquids", which was established in 2015. It remains unclear whether and to which extent these standards will contain chemical limits.

At present allowed concentrations of substances of concern in e-liquids and e-cigarette vapours are not defined. There is an urgent need to initiate a debate on acceptable levels which will hopefully result in a set of European regulatory and normative rules aimed at the protection of (millions of) consumers. This paper aims to promote a discussion in the relevant European fora.

The Consumer Council at Austrian Standards International commissioned several studies on this subject which constituted the basis for the elaboration of the present ANEC position paper:

⁵ https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_q_013.pdf

- Requirements for substances in e-liquids used in electronic cigarettes (October 2017)
[11a.pdf](#)
- Requirements for substances formed or released during the evaporation of e-liquids used in electronic cigarettes (November 2017)
<http://www.verbraucherrat.at/content/1-news/19-studien-zu-chemischen-substanzen-in-liquids-und-daempfen-von-e-zigaretten/chemicalproducts-11b.pdf>
- Requirements for substances in e-liquids and substances formed during evaporation of e-liquids - elaboration (October 2018)
<http://www.verbraucherrat.at/content/1-news/21-weitere-studien-ueber-e-zigaretten/chemicalproducts-11d.pdf>
- Requirements for flavour substances in e-liquids used in electronic cigarettes (September 2018)
<http://www.verbraucherrat.at/content/1-news/21-weitere-studien-ueber-e-zigaretten/chemicalproducts-11c.pdf>

All studies were performed by FORCE Technology, Denmark. It should be noted that the third study listed ("elaboration") reviews some aspects of the first two studies and contains complementary information as well as some corrections.

2. Relevant regulations and standards

2.1 Regulations

The **EU Tobacco Directive (Directive 2014/40/EU)** 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.

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

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- 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

All manufactures and importers of e-cigarettes and refill containers (e-liquids) must submit a **notification** to the competent authorities of the Member States 6 months before the intended placing on the market 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.

The main requirements concerning **nicotine** are:

- Nicotine-containing liquids must not contain more than 20 mg/ml nicotine (there are also volume limitations).
- 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 (carcinogenic, mutagenic or toxic to reproduction) 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.

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". This Directive does not foresee an instrument such as delegated acts to further detail the requirements and to establish thresholds for substances in liquids or emissions. So, the burden lies on the shoulder of the Member States to "take appropriate provisional measures" where electronic cigarettes or refill containers "could present a serious risk to human health". The Commission must check whether the provisional measure is justified. If so, other Member States must be informed. In addition, Member States are allowed to adopt rules on flavours (Recital 47). However, it is big burden for authorities to conduct proper risk assessments and to define test procedures and acceptable levels themselves. By contrast, it is also difficult for producers of e-liquids and e-cigarettes to demonstrate that their products are safe. Hence, the current situation is highly unsatisfactory.

Under Article 28, the European Commission has an obligation to present a report on the functioning of the Directive by 20 May 2021 and may propose amendments to the Directive. This gives ANEC an opportunity to call for improvements and to repair the

deficits of the legislation. In this context the scientific committee SCHEER was requested to deliver an opinion in September/October 2020 at the latest⁶.

Non-nicotine containing e-cigarettes and e-liquids are covered by the EU **General Product Safety Directive** (Directive 2001/95/EC), which only uses a general statement saying that products on the market 'must be safe' (including chemical safety). This piece of legislation also does not allow to set detailed product specific regulatory rules (such as chemical limits). The only option is to request European Standardisation Organisations (ESOs) to develop standards which could be referenced in the Official Journal of the EU and thus give a presumption of conformity to the general safety requirement of the Directive. However, it does not seem to be very practical to follow a different route for this kind of e-cigarettes and e-liquids. There does not seem to be an intention of the Commission to develop and to submit a standardisation request anyway.

Lastly, the **Regulation on Classification, Labelling and Packaging of substances and mixtures** (CLP Regulation (EC) No 1272/2008) applies to e-liquids whether or not containing nicotine. In principle, only chemical substances which contribute or lead to a classification need to be indicated on the label. However, certain substances (e.g. sensitizers) need to be labelled even though the mixture is not classified as dangerous.

2.2 Standards

European standardisation

Currently, European standards are under development in CEN/TC 437 "Electronic cigarettes and e-liquids", which was established in 2015. So far (May 2019), two normative documents have been already published by this committee of CEN⁷:

- CEN/TR 17236:2018 Electronic cigarettes and e-liquids - Constituents to be measured in the aerosol of vaping products
- CEN/TS 17287:2019 "Requirements and test methods for electronic cigarette devices"

The first document is a so-called "Technical Report" (TR) – an informative document which does not establish normative requirements (though its scope considers the

⁶ https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_q_013.pdf

⁷ <https://standards.cen.eu/dyn/www/f?p=204:105:0>

proposed constituents as "default minimum requirement"). The TR follows the basic approach *"to only measure constituents in aerosol that are created or affected by the aerosolisation process. Everything that is already present in the e-liquid, i.e. e-liquid ingredients and any contaminants of those ingredients as well as leachables from device materials, will be easier and more accurate to measure in the e-liquid"* (7.1). It recommends, for instance, to measure thermal degradation products from solvents, i.e. formaldehyde, acetaldehyde and acrolein and hardware-related emissions such as cadmium, chromium, iron, lead, mercury and nickel (and other elements depending on the constituents of the materials used) in the aerosol. The TR does not specify any limits.

The second document is a so-called "Technical Specification" – a normative document for which there is not yet sufficient support to be published as a standard. It just briefly touches upon the release of substances from materials used for e-liquid reservoirs of e-cigarettes or e-liquid containers and establishes some very general requirements to avoid a risk for consumers but does not provide any details including substances, measurement methods or limits.

Several other documents are in preparation.

National standardisation

Some national standards and guidelines on e-cigarettes and e-liquids exist, which do contain normative provisions regarding chemical substances:

- 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 below.

BSI PAS 54115

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The "Publicly Available Specification" (PAS) is not a standard but a guidance document containing recommendations. Hence, claims of compliance cannot be made.

For **e-liquids** the PAS recommends to undertake a toxicological risk assessment (TRA) by a competent, qualified and registered toxicology specialist "if justified by some form of novelty or anticipated risk".

Apart from some purity requirements it contains a list of ingredients which should be "controlled" in e-liquids:

- E-liquids should not contain ingredients that have been classified as carcinogenic, mutagenic or toxic to reproduction (CMRs).
- Ingredients that are classified as respiratory sensitizer should not be added to e-liquids.
- Diacetyl (or 2,3-butanedione, CAS 431-03-8) and 2,3-pentanedione (or acetyl propionyl, CAS 600-14-6), which have known inhalation risks and should not be used in flavourings. On the other hand it is recommended that producers should refer to regulatory and scientific literature on permissible exposure levels.
- Diethylene glycol (CAS 111-46-6) and ethylene glycol (CAS 107-21-1) should not be added as ingredients, but might be present as contaminants in glycerol and propylene glycol. If present, the maximum level should be 0.1%.
- Formaldehyde (CAS 50-00-0), acetaldehyde (CAS 75-07-0) and acrolein (CAS 107-08-8) should not be added as ingredient, but might be present. If present, they should not be present above toxicologically supportable levels as identified by a TRA.
- Metals (Cd, Cr, Fe, Pb, Hg, Ni) should not be added to the e-liquids as ingredients but might be present. They should not be present above toxicological supportable levels (as identified by TRA).

Under certain conditions testing of emissions from (separately sold) liquids is recommended using commercially available devices.

Also for emissions from **hardware** the PAS includes some recommendations for testing and a toxicological risk assessment. Empty and refillable devices should be assessed under the TRA with a specified test solution.

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

However, no thresholds are given.

AFNOR XP D 90-300-1

Part 1 of the French standard deals with e-cigarettes and addresses some chemical requirements in a rather general fashion, e.g. saying that coatings, mouthpiece and tank shall not release allergenic or toxic substances or saying that for some materials specific migration tests shall be performed. No details are given (substances, limits, test methods). These aspects are not relevant for the present ANEC paper.

AFNOR XP D 90-300-2

Part 2 of the French standard contains requirements for e-liquids. Apart from some purity requirements the following applies:

- Other ingredients shall comply with the requirements defined in EU Regulation 1333/2008 on food additives and EU Regulation 231/2012 concerning specifications for food additives, i.e. only approved additives for use in food as listed in Annex II and Annex III of the food additives Regulation 1333/2008 must be used.
- The following ingredients must not be used in e-liquids:
 - Substances classified as CMR (CMR 1 and 2)
 - Substances classified as STOT for the respiratory tract (STOT 1)
 - Oil or fat of plant or mineral origin (essential oils are not covered by this definition)
 - The following sugars: glucose, fructose, lactose, maltose, saccharose
 - The following sweeteners: acesulfame potassium, aspartame, sodium saccharinate, stevia
 - Vitamins and minerals
 - Pharmacologically active molecules (other than nicotine), i.e. medicinal, psychotropic, anabolic and narcotic substances, as well as stimulant additives such as caffeine or taurine

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- Preservatives liable to release formaldehyde
- Triclosan (CAS 3380-34-5)
- Phenoxyethanol (CAS 122-99-6)
- Long-chain parabens, i.e. isopropylparaben (CAS 4191-73-5), isobutylparaben (CAS 4247-02-3), phenylparaben (CAS 17696-62-7), benzylparaben (CAS 94-18-8), pentylparaben (CAS 6521-29-5)
- Isothiazolinone (CAS 1003-07-2)
- Radioactive substances
- Diacetyl (CAS 431-03-8)
- Ethylene glycol (CAS 107-21-1)
- If food allergens are used, they shall be specifically traced.
- The following limit values are listed for contaminants in e-liquids:
 - Diacetyl (22 mg/L)
 - Formaldehyde (22 mg/L)
 - Acrolein (22 mg/L)
 - Acetaldehyde (200 mg/L)
- The following limit values are listed for heavy metals in e-liquids, which are considered to be technically unavoidable trace levels:
 - Pb (10 mg/L)
 - As (3 mg/L)
 - Cd (1 mg/L)
 - Hg (1 mg/L)
 - Sb (5 mg/L)
- E-liquids must not constitute a microbiological risk.
- The information on the e-liquid product must contain a list of ingredients contained in the product in descending order of concentration. However, the flavouring compound does not need to be detailed.

AFNOR XP D 90-300-3

Part 3 of the French standard deals with emissions of e-cigarettes.

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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 and their informative "indicative target values" (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)
 - 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 $\pm 25\%$ of the mean value of the three series.

2.3 Conclusion on relevant regulations and standards

The current regulatory framework for chemicals in e-cigarettes and e-liquids is entirely inadequate. In essence, the EU Tobacco Directive contains mainly vague

provisions such as "ingredients of high purity must be used in the manufacturing of the nicotine-containing e-liquids" or "only ingredients which do not pose a risk to human health in heated or unheated form must be used". Although manufactures and importers of e-cigarettes and refill containers (e-liquids) must submit a notification to the competent authorities of the Member States which must include information e.g. on ingredients and emissions as well as related toxicological data and health effects it remains completely unclear what this means and how these data are evaluated in absence of any framework for assessment and precise restriction provisions. The Directive does also not foresee a systematic evaluation of chemicals associated with e-cigarettes or e-liquids resulting in the establishment of thresholds using e.g. delegated acts.

As regards products which do not contain nicotine the situation is even worse – only the very general safety provisions of the General Product Safety Directive apply.

Existing national standards and guidelines contain a limited number of clear-cut requirements or recommendations for e-liquid constituents and, to some extent, also for emissions. These specifications constitute a useful departure point for developing more detailed provisions. It is the aim of the present paper to stimulate a debate and to contribute to the elaboration of set of rules which allows safe vaping.

3. General approach to derive limit values for selected substances

In the following two proposals for limit values are presented – one for selected substances which are contained in e-liquids and one for substances which are released from parts of the device or formed from ingredients during vaping (i.e. where the concentration of a substance in the vapour phase is does not correspond to its concentration in the e-liquid). The present paper follows the recommendation of the CEN/TR 17236:2018 *"to only measure constituents in aerosol that are created or affected by the aerosolisation process. Everything that is already present in the e-liquid, i.e. e-liquid ingredients and any contaminants of those ingredients as well as leachables from device materials, will be easier and more accurate to measure in the e-liquid"*. Hence, the majority of the proposed limits fall in the latter category.

The proposal is largely based on the research projects conducted by FORCE Technology (Denmark) listed in section 1 of this paper. A literature review - mostly articles published in scientific magazines - identified relevant substances and, where available, their measured concentrations.

3.1 Sources for thresholds

Appropriate threshold values (mainly for inhalation) have been identified, where available, for the identified substances from following main sources:

- **EU-LCI Group** (LCI = Lowest Concentration of Interest) - a subgroup of the "Expert Group on Dangerous Substances" within the EC "Advisory Group on Construction Products" – dealing with health based evaluations of indoor emissions from construction products
- **German AgBB scheme** - a scheme developed by the German "Committee for Health-related Evaluation of Building Products" ("Ausschuss zur gesundheitlichen Bewertung von Bauprodukten") for VOC emissions from construction products
- **German Indoor Guide Values** – developed by the "German Committee on Indoor Guide Values" ("Ausschuss für Innenraumrichtwerte") hosted by the German Environment Agency (Umweltbundesamt – UBA)
- **REACH DNEL values** (Derived No-Effect Level) - indicated by industry for registered substances according to the REACH Regulation identified in the ECHA (European Chemicals Agency) database.
- **US ATSDR Minimal Risk Levels (MRLs)** – published by the "Agency for Toxic Substances & Disease Registry" (U.S. Department of Health and Human Services) for screening purposes
- **US EPA Reference Concentration (RfC) and Reference Dose (RfD) values** – developed under the IRIS ("Integrated Risk Information System") programme of the US Environmental Protection Agency
- **WHO Air Quality Guidelines for Europe** – published by the World Health Organisation
- **OECD SIDS (Screening Information Data Sheets)** - assessment reports on chemicals published by OECD (Organisation for Economic Co-operation and Development).
- **ANSES Indoor Air Quality Guidelines** – published by the French Agency for Food, Environmental and Occupational Health & Safety
- **NIOSH International Chemical Safety Cards (ICSC)** – published by the American National Institute for Occupational Safety and Health

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Limits for selected substances in e-liquids and substances released or formed during vaping using the most appropriate thresholds from the sources above were calculated as detailed below.

Priority was given to substances frequently found in screened literature, substances with highest measured concentrations and substances with identified (low) thresholds.

3.2 Assumptions and calculation methods

The general calculation formula for the maximum concentration of **substances in e-liquids** is as follows:

$$C_{\text{Substance_in_e_liquid}} = \frac{V_{\text{air_daily}} \times Rf C_{\text{substance}}}{abs_{\text{substance}} \times V_{\text{Liquid_per_puff}} \times n_{\text{puffs}}}$$

The general calculation formula for the maximum concentration of **substances in vapours** (released or formed during vaping) is as follows:

$$C_{\text{Substance_in_vapour}} = \frac{V_{\text{air_daily}} \times Rf C_{\text{substance}}}{abs_{\text{substance}} \times V_{\text{vapour_per_puff}} \times n_{\text{puffs}}}$$

The meaning of the terms used in the formula is as given in the table below.

Term	Meaning	Value used
$C_{\text{Substance_in_e_liquid}}$	Proposed maximum concentration of a substance in the e-liquid (mg/ml)	-
$C_{\text{Substance_in_vapour}}$	Proposed maximum concentration of a substance in the vapour from e-cigarettes (mg/m ³)	-
$V_{\text{air_daily}}$	Is the volume of air typically inhaled a) per day (24 hours) where thresholds for the general public are used or b) per eight hours where occupational thresholds are used (m ³). In the latter	a) 16 m ³ /day b) 5,3333 (=16/3) m ³ /day * 5/7 =

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	case a correction factor of 5/7 is used as occupational limits apply 5 days per week	3,80952 m ³ /day
RfC _{substance}	Applied inhalation threshold limit value for the substance (mg/m ³)	-
abs _{substance}	Proportion of inhaled substance which is absorbed	1 (complete absorption, default)
V _{Liquid_per_puff}	Is the volume of e-liquid used (vaporised) per puff (ml/puff)	150 puffs per ml e-liquid = 0.006666667 ml/puff
V _{Vapour_per_puff}	Is the volume of e-liquid vapour inhaled (vaporised) per puff (m ³ /puff)	55 mL/puff = 0.000055 m ³ /puff
n _{puffs}	Is the total number of puffs per day (puffs/day)	500 puffs per day

Explanations:

V_{air_daily}

16 m³/day – based on reference data in the ECHA “Guidance document for consumer exposure”⁸

RfC_{substance}

Wherever possible threshold concentrations in air for long-term inhalative consumer exposure (or exposure of the general public) for systemic effects were chosen. In exceptional cases (long-term) occupational exposure limits (OELs) were taken. In the latter case corrections were made for the different exposure time (5x8 hours per week versus 7x24 hours per week). It is acknowledged that the resulting limit values may not be sufficiently protective as OELs are set for healthy adults at work.

Please note that the term "RfC_{substance}" is used here for any relevant inhalation threshold and is not identical with the term RfC used by the US EPA.

V_{Liquid_per_puff}

150 puffs/ml e-liquid (1 ml e-liquid = 8,25 l aerosol = 150 puffs of 55 ml each) = 0.006666667 ml/puff - from a study by the German Institute for Risk Assessment (BfR)⁹

⁸ https://echa.europa.eu/documents/10162/13632/information_requirements_r15_en.pdf

$V_{\text{Vapour per puff}}$

55 mL/puff – used by BfR (see above) and AFNOR emission standard XP D 90-300-3 (see above)

n_{puffs}

500 puffs per day – from a study by the Netherlands National Institute for Public Health and the Environment (RIVM) – category "Heavy vaper" (five hundred inhalations per day, with a total daily vaping duration of 240 minutes) ¹⁰

Using 150 puffs/ml e-liquid (see above) a consumption of 500 puffs would equal 3.3 ml e-liquid per day. It should be noted that this is not the worst case given that values of up to 10 ml per day (= 1500 puffs) have been identified in e-cigarette user groups.

4. Substances in e-liquids

4.1 Substances and their inhalation thresholds

Below is a table containing the selected substances in e-liquids, their type and the relevant inhalation thresholds (RfC) including references.

Substance	CAS no.	Type	RfC (mg/m ³)	Comments	Reference
Glycerine (glycerol)	56-81-5	solvent	10	OEL	OECD SIDS, 2002
Propylene glycol (PG, propane-1,2-diol)	57-55-6	solvent	2.1	VOC emissions from building products – EU-LCI value	EU-LCI, 2018
Ethylene glycol	107-21-1	solvent	3.4	VOC emissions from building products – EU-LCI value	EU-LCI, 2018

⁹ <https://www.bfr.bund.de/cm/343/nikotinfreie-e-shishas-bergen-gesundheitliche-risiken.pdf>

¹⁰ <https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf>

Substance	CAS no.	Type	RfC (mg/m ³)	Comments	Reference
Cadmium	7440-43-9	impurity	0.000005	Air quality guideline for general population	WHO, 2000
Lead	7439-92-1	impurity	0.0005	Air quality guideline for general population	WHO, 2000
Nickel	7440-02-0	impurity	0.0000025	Based on cancer risk of 1/1,000,000 of by inhalation	WHO, 2000
Acetyl propionyl (2,3-pentanedione)	600-14-6	flavour	0.03808	OEL	NIOSH, 2016
Allyl heptanoate	142-19-8	flavour	0.73	DNEL for consumers based on long term inhalation	ECHA Registered substances
Allyl hexanoate (or allyl caproate)	123-68-2	flavour	3.7	DNEL for consumers based on long term inhalation	ECHA Registered substances
Anisaldehyde (p-methoxy benzaldehyde)	123-11-5	flavour	4.35	DNEL for consumers based on long term inhalation	ECHA Registered substances
Benzaldehyde	100-52-7	flavour	0.2	German Indoor Air Guide Value II	UBA, 2019
Benzophenone	119-61-9	flavour	0.17	DNEL for consumers based on long term inhalation	ECHA Registered substances
Benzyl alcohol	100-51-6	flavour	4	German Indoor Air, Guide Value II	UBA, 2019
Benzyl propionate	122-63-4	flavour	1.85	DNEL for consumers based on long term inhalation	ECHA Registered substances
n-Butyric acid	107-92-6	flavour	1.8	VOC emissions from building products - German LCI value	EU-LCI, 2018
Carvone	6485-40-1	flavour	0.289	DNEL for consumers based on long term inhalation	ECHA Registered substances
Cinnamaldehyde	104-55-2	flavour	2.4	DNEL for consumers	ECHA

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Substance	CAS no.	Type	RfC (mg/m ³)	Comments	Reference
				based on long term inhalation	Registered substances
Coumarin	91-64-5	flavour	0.183	DNEL for consumers based on long term inhalation	ECHA Registered substances
Diacetyl (DA)	431-03-8	flavour	0.01761	OEL	NIOSH, 2016
Ethyl butyrate	105-54-4	flavour	2.22	DNEL for consumers based on long term inhalation	ECHA Registered substances
Ethyl maltol (2-Ethyl-3-hydroxy-4-pyranone)	4940-11-8	flavour	17.4	DNEL for consumers based on long term inhalation	ECHA Registered substances
Ethyl 2-methylbutyrate	7452-79-1	flavour	12.95	DNEL for consumers based on long term inhalation	ECHA Registered substances
Ethyl vanillin	121-32-4	flavour	8.75	DNEL for consumers based on long term inhalation	ECHA Registered substances
Geranyl acetate	105-87-3	flavour	15.4	DNEL for consumers based on long term inhalation	ECHA Registered substances
Hexanal, aldehyde C6	66-25-1	flavour	0.9	VOC emissions from building products – EU-LCI value	EU-LCI, 2018
Hexanoic acid (or caproic acid)	142-62-1	flavour	2.1	VOC emissions from building products - German LCI value	EU-LCI, 2018
Cis-3-Hexen-1-yl acetate	3681-71-8	flavour	2.9	DNEL for consumers based on long term inhalation	ECHA Registered substances
Hexyl acetate	142-92-7	flavour	12.0	DNEL for consumers based on long term inhalation	ECHA Registered substances
Isoamyl acetate	123-92-2	flavour	5.1	DNEL for consumers based on long term inhalation	ECHA Registered substances
Isoamyl alcohol	123-51-3	flavour	0.73	DNEL for consumers based on long term	ECHA Registered

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Substance	CAS no.	Type	RfC (mg/m ³)	Comments	Reference
				inhalation	substances
Isobutyl acetate	110-19-0	flavour	4.8	VOC emissions from building products – EU-LCI value	EU-LCI, 2018
Linalool	78-70-6	flavour	0.7	DNEL for consumers based on long term inhalation	ECHA Registered substances
Mentha piperita oil (Peppermint essential oil)	8006-90-4	flavour	8.7	DNEL for consumers based on long term inhalation	ECHA Registered substances
Menthol	89-78-1	flavour	16.3	DNEL for consumers based on long term inhalation	ECHA Registered substances
Methyl anthranilate	134-20-3	flavour	1.3	DNEL for consumers based on long term inhalation	ECHA Registered substances
Phenylethyl alcohol (phenethyl alcohol)	60-12-8	flavour	17.7	DNEL for consumers based on long term inhalation	ECHA Registered substances
β-Pinene	127-91-3	flavour	1.4	VOC emissions from building products – EU-LCI value	EU-LCI, 2018
Propionic acid (or propanoic acid)	79-09-4	flavour	1.5	VOC emissions from building products - German LCI value	EU-LCI, 2018
α-Terpineol	98-55-5	flavour	2.25	DNEL for consumers based on long term inhalation	ECHA Registered substances
Triethyl citrate	77-93-0	flavour	28.8	DNEL for consumers based on long term inhalation	ECHA Registered substances
γ-Undecalactone (or aldehyde C-14 or undecan-4-olide)	104-67-6	flavour	4.68	DNEL for consumers based on long term inhalation	ECHA Registered substances
Vanillin (4-hydroxy-3-methoxybenzaldehyd)	121-33-5	flavour	10 mg/kg bw/day	ADI (Acceptable Daily Intake) value – no inhalation threshold found (ADI value used)	OECD SIDS, 1996

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Substance	CAS no.	Type	RfC (mg/m ³)	Comments	Reference
				instead of $V_{\text{air_daily}} \times RfC_{\text{substance}}$	

4.2 Calculated limits for substances in e-liquids

Using the assumptions and calculation methods described in 3.2 and the RfCs listed in 4.1 the following limits have been calculated for 500 puffs:

Substance	Limit value µg/mL (500 puffs)	Comparisons and remarks
Glycerine (glycerol)	11,429 (~11 mg/mL or ~1.1 %)	Found in concentrations from 7 to 42% (solvent) in 28 of 28 e-liquids. Average content was 26% (Hutzler et al., 2014).
Propylene glycol (1,2-Propandiol, PG)	10,080 (~10 mg/mL or ~1.0%)	Found in concentrations from 2 to 79% (solvent) in 28 of 28 e-liquids. Average content was 53% (Hutzler et al., 2014).
Ethylene glycol	16,320 (~16 mg/mL or 1.6%)	Found in concentrations from 1 to 76% (solvent) in 13 of 28 e-liquids. Average content was 26% (Hutzler et al., 2014). AFNOR XP D 90-300-2: no use PAS 54115: 0.1%
Cadmium	0.024	Found in concentrations up to 81 ng/ml, i.e. 0.081 µg/mL (Visser et al., 2015). However, only 6 of 183 samples above LOQ (1 ng/ml). AFNOR XP D 90-300-2: 1 mg/L, i.e. 1 µg/mL (200 puffs) PAS 54115: no use, trace levels (TRA)
Lead	2.4	Found in concentrations up to 4.93 µg/ml (Visser et al., 2015). However, only 16 of 183 samples above LOQ (5 ng/ml). AFNOR XP D 90-300-2: 10 mg/L (200 puffs) PAS 54115: no use, trace levels (TRA)
Nickel	0.012	Found in concentrations up to 225.9 µg/mL (Visser et al., 2015). However, only 27 of 183 samples above LOQ (10 ng/mL equalling 0.010 µg/mL). PAS 54115: no use, trace levels (TRA)
Acetyl propionyl (2,3-	44	Found in concentrations from 20 to 432 µg/day (Farsalinos et

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Substance	Limit value µg/mL (500 puffs)	Comparisons and remarks
pentanedione)		al., 2015a), i.e. 6 to 130 µg/mL assuming use of 3.3 mL/day (equals 500 puffs). Found in 74.2% out of 159 samples (Farsalinos et al., 2015a). In 4 out of 29 e-liquids (Nieuwesigaret, 2018). PAS 54115: no use
Allyl heptanoate	3,504 (0.4%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%. In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
Allyl hexanoate (or allyl caproate)	17,760 (1.8%)	Found in the following concentrations in SDSs: < 1 %; 5.94%.
Anisaldehyde (p- methoxy benzaldehyde)	20,880 (2.1%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; < 0.5%; 0.2-1.2% In 3 out of 28 liquids (Hutzler et al., 2014); In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
Benzaldehyde	960	Found in 4 out of 28 e-liquids (Hutzler et al., 2014), up to 21.2 mg/mL (Tierney, 2015)
Benzophenone	811	Found in 3 out of 28 e-liquids (Hutzler et al., 2014).
Benzyl alcohol	19,200 (~19 mg/mL or 1.9%)	Found in the following concentrations in SDSs: 1-1.5%; ≥ 1% and < 10%. Found in 3 out of 28 e-liquids (Hutzler et al., 2014).
Benzyl propionate	8,880 (0.9%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%. In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
n-Butyric acid	8,597 (0.9%)	Found in the following concentrations in SDSs: ≤ 2.5%; ≥ 1% and < 10%. In 8 out of 29 e-liquids (Nieuwesigaret, 2018).
Carvone	1,387 (~1.4 mg/mL or 0.14%)	Found in 2 out of 28 e-liquids (Hutzler et al., 2014).
Cinnamaldehyde	11,520 (1.2%)	Found in the following concentrations in SDSs: 1.5%; <1%. In 2 out of 28 liquids (Hutzler et al., 2014); In 2 out of 50 e-liquids (Kurcharska, 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Coumarin	878 (~0.9 mg/mL or 0.09%)	Found in 4 out of 28 e-liquids (Hutzler et al., 2014).
Diacetyl (DA)	20	Found in concentrations from 26 to 278 µg/day (Farsalinos et

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Substance	Limit value µg/mL (500 puffs)	Comparisons and remarks
		al., 2015a), i.e. 8 to 84 µg/mL assuming use of 3.3 mL/day (equals 500 puffs). AFNOR XP D 90-300-2: no use, limit: 22 mg/L, i.e. 22 µg/mL (200 puffs) PAS 54115: should not be used
Ethyl butyrate	83,520 (8.4%)	Found in concentrations up to up to 23.4 mg/ml, i.e. 23,400 µg/ml (Hutzler et al. , 2014). Found in the following concentrations in SDSs: < 0.2%; 3.58%; 2.7%; < 1%; ≤ 2.5%. In 16 out of 28 liquids (Hutzler et al., 2014); In 28 out of 50 e-liquids (Kurcharska et al., 2016); In 7 out of 29 e-liquids (Nieuwesigaret, 2018).
Ethyl maltol (2-Ethyl-3-hydroxy-4-pyranone)	83,520 (8.4%)	Found in concentrations up to up to 23.4 mg/ml, i.e. 23,400 µg/ml (Hutzler, 2014). Found in the following concentrations in SDSs: < 0.2%; 3.58%; 2.7%; < 1%; ≤ 2.5%. In 16 out of 28 liquids (Hutzler et al., 2014); In 28 out of 50 e-liquids (Kurcharska et al., 2016); In 7 out of 29 e-liquids (Nieuwesigaret, 2018).
Ethyl 2-methylbutyrate	62,160 (6.2%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; > 10%; 0.1 - 1.2%. In 4 out of 50 e-liquids (Kurcharska et al., 2016); In 6 out of 29 e-liquids (Nieuwesigaret, 2018).
Ethyl vanillin	42,000 (42 mg/ml or 4.2%)	Found in concentrations up to 8.4 mg/ml (Tierney, 2015). Found in the following concentrations in SDSs: < 1%; 4-4.5%; 0.07%; ≥ 1% and < 10%; ≤ 2.5%. In 14 out of 28 liquids (Hutzler et al., 2014); In 1 out of 50 e-liquids (Kurcharska et al., 2016); In 8 out of 29 e-liquids (Nieuwesigaret, 2018).
Geranyl acetate	73,920 (7.4%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 0.1-0.9%. In 2 out of 50 e-liquids (Kurcharska et al., 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Hexanal, aldehyde C6	4,320 (0.4%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; 1-5%. In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
Hexanoic acid (or caproic acid)	10,030 (1%)	Found in the following concentrations in SDSs: ≥ 0.05 ≤ 0.15%; ≥ 1% and < 10%.

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Substance	Limit value µg/mL (500 puffs)	Comparisons and remarks
		In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Cis-3-Hexen-1-yl acetate	13,920 (1.4%)	Found in the following concentrations in SDSs: < 5%; < 1.1%. In 1 out of 29 liquids (Nieuwesigaret, 2018).
Hexyl acetate	57,600 (5.8%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%; < 0.5%; 1-5%; < 0.6%, ≤ 2.5%. In 8 out of 50 e-liquids (Kurcharska et al., 2016); In 3 out of 29 e-liquids (Nieuwesigaret, 2018).
Isoamyl acetate	24,480 (2.5%)	Found in the following concentrations in SDSs: ≥ 0,05 ≤ 0,5%; ≥ 10%. In 6 out of 50 e-liquids (Kurcharska et al., 2016); In 9 out of 29 e-liquids (Nieuwesigaret, 2018).
Isoamyl alcohol	3,504 (0.4%)	Found in the following concentrations in SDSs: ≥ 10% In 5 out of 50 e-liquids (Kurcharska et al. , 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Isobutyl acetate	23,040 (2.3%)	Found in the following concentrations in SDSs: ≥ 0.05 ≤ 0.5%; 0.2-1.2%; ≥ 1% and < 10%; ≤ 2.5%. In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
Linalool	3,360 (~3.4 mg/mL or 0.34%)	Found in the following concentrations in SDSs: 0.1-0.9% and < 0.5%. In 6 out of 28 e-liquids (Hutzler et al., 2014); In 5 of 50 e-liquids (Kurcharska et al., 2016); In 5 of 29 e-liquids (Nieuwesigaret, 2018).
Mentha piperita oil (Peppermint essential oil)	41,760 (4.2%)	Found in the following concentrations in SDSs: ≥ 10%; ≤ 2.5%; 2-12% In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Menthol	78,240 (~78.2 mg/mL or 7.8%)	Found in 12 out of 28 e-liquids in concentrations up to 21,600 µg/mL (i.e. 2.2%) (Hutzler et al., 2014), up to 21.6 mg/mL (Tierney et al., 2015)
Methyl anthranilate	6,240 (0.6%)	Found in the following concentrations in SDSs: ≥ 1% and < 10%. In 2 out of 50 e-liquids (Kurcharska et al., 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Phenoethyl alcohol (phenethyl alcohol)	84,960 (8.5%)	Found in the following concentrations in SDSs: 0.2-1.2%; 0.31%; < 1%. In 3 out of 28 liquids (Hutzler et al., 2014); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
β-Pinene	6,720	Found in the following concentrations in SDSs: ≥ 1% and <

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Substance	Limit value µg/mL (500 puffs)	Comparisons and remarks
	(0.7%)	10%; 0.1-0.9%. In 1 out of 50 e-liquids (Kurcharska et al., 2016); In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
Propionic acid (or propanoic acid)	7,164 (0.7%)	Found in the following concentrations in SDSs: $> 1 \leq 5\%$.
α -Terpineol	10,800 (1.1%)	Found in the following concentrations in SDSs: $\geq 1\%$ and $< 10\%$; 0.2-1.2% In 3 out of 50 e-liquids (Kurcharska et al., 2016); In 1 out of 29 e-liquids (Nieuwesigaret, 2018).
Triethyl citrate	138,240 (13.8%)	Found in the following concentrations in SDSs: $\geq 1\%$ and $< 10\%$; 2-12% In 2 out of 50 e-liquids (Kurcharska et al., 2016); In 2 out of 29 e-liquids (Nieuwesigaret, 2018).
γ -Undecalactone (or aldehyde C-14 or undecan-4-olide)	22,464 (2.2%)	Found in the following concentrations in SDSs: 0.26%; $\geq 1\%$ and $< 10\%$; $< 0.5\%$; $\leq 2.5\%$; 2-12%. In 7 out of 50 e-liquids (Kurcharska et al., 2016); In 4 out of 29 e-liquids (Nieuwesigaret, 2018).
Vanillin (4-hydroxy-3- methoxybenzaldehyd)	180,000 (180 mg/ml or 18%)	Found in concentrations up to 33 mg/ml (Tierney, 2015). Found in the following concentrations in SDSs: $< 1\%$; 0.2-1.2%; 2-12%; 5-6%; 0.13%; 8.48%; $< 0.5\%$. In 22 out of 28 liquids (Hutzler et al., 2014); In 17 out of 30 samples (Tierney et al., 2015); In 11 out of 50 e-liquids (Kurcharska et al., 2016).

4.3 Conclusions and proposal

A comparison between the calculated limit values (for 500 puffs) and the concentrations identified in literature or in Safety Data Sheets shows that the reported maximum values are often of the order of magnitude of the limits or above. However, in some cases they are below. This holds true for some fragrances such as vanillin.

On the other hand, the measured minimum concentrations (or limits of quantitation) are often below the calculated limits. In such cases the limits can be met, e.g. by avoiding contamination (metals) or by reducing/avoiding certain fragrances.

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Solvents

The concentrations of the solvents **glycerine, propylene glycol and ethylene glycol** in e-liquids exceed the calculated limits considerably. As an example, the calculated limit for **propylene glycol** based on 500 puffs/day is 1% whilst the solvent has been found in liquids at levels of up to 79%. Conversely, one might argue that in this particular case the chosen threshold (EU-LCI) is based on (reversible) local irritation rather than severe toxic effects and thus might be of limited concern. In case of **glycerine** (OECD SIDS) and **ethylene glycol** (EU-LCI) similar considerations apply.

On the other hand, an RIVM (Dutch National Institute for Public Health and the Environment) Report (Visser et al., 2015) considers that exposure to the polyols in question not only involves a risk of damage to the respiratory tract (particularly in heavy vapers) but may also result in systemic effects (reduced lymphocyte count) for certain polyols. In addition, RIVM points out that the mode of action of the damage of the respiratory epithelium by various polyols may be the same. Thus, cumulative effects may be expected. Further, it must be borne in mind that also flavours and substances formed during vaping (such as formaldehyde) may exhibit irritant effects. Data on (combined) long-term effects of irritating substances are missing. It should be noted that PAS 54115 sets a (recommended) threshold of 0.1% for ethylene glycol (as for diethylene glycol) and AFNOR XP D 90-300-2 does not allow its use.

ANEC considers that this issue requires further clarification and debate before establishing a limit for the main solvents as apparently strict requirements in line with the calculated limits would essentially lead to non-compliance of all e-liquids (i.e. a ban) unless a suitable less toxic substitute could be identified.

Metals

Calculated limits (basis 500 puffs) for **cadmium** and **lead** are lower than limits in AFNOR XP D 90-300-2 even when using the same number of puffs (200). Nonetheless most of the liquids on the market are expected to comply with these limits as well as with the calculated limit for **nickel**.

ANEC considers the establishment of limits for these metals desirable and feasible. They may be complemented with limits for further metals in line with provisions in existing national standards.

Flavours

In case of flavours the maximum identified concentrations are mostly above the proposed limits. On the other hand, the limits can be met by eliminating the substances concerned or reducing their concentrations. Of course, not all flavours

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mixes would then be available any longer. The suggested limit for diacetyl is similar to the one included in the standard AFNOR XP D 90-300-2 (calculated for 200 puffs).

ANEC suggests using the calculated limits for the selected flavours as a starting point. Where measured concentrations are clearly above the calculated limits it is not necessary to establish limits. In the longer term a positive list similar to the one in the field of food (Regulation (EC) No 1334/2008) may be preferable in view of the huge number of flavours which may be potentially used.

Other substances in e-liquids

The EU Tobacco Directive contains some provisions for substances in nicotine-containing e-liquids. The following additives are not allowed:

- 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 (carcinogenic, mutagenic or toxic to reproduction) properties in unburnt form

ANEC considers that these provisions should apply equally to products which do not contain nicotine. The CMR ban needs further clarification. In ANEC's view this includes all categories of CMRs (1A, 1B and 2) and does not only cover substances with harmonised classification but also self-classified by industry. It may be useful to set a practical enforcement limit for such substances, e.g. 0.001% or 0.0001%.

Finally, ANEC also recommends reviewing existing further provisions for substances in available national standards to identify potential additional requirements.

5. Substances released or formed during vaping

5.1 Substances and their inhalation thresholds

Below is a table containing the selected released or formed substances, their type and the relevant inhalation thresholds (RfC) including references.

Substance	CAS no.	RfC (mg/m ³)	Comments	Reference
Acetaldehyde (ethanal)	75-07-0	0.160	For long-term exposure	ANSES, 2018
Acrolein (propenal)	107-02-8	0.0008	For long-term exposure	ANSES, 2018
Cadmium	7440-43-9	0.00001	MRL for inhalation	ATSDR, 2012
Formaldehyde	50-00-0	0.1	For long-term exposure	ANSES, 2018
Glyoxal	107-22-2	0.006	For local effects for short-time exposure	WHO, 2004
Lead	7439-92-1	0.0005	Air quality guideline for general population	WHO, 2000
Nickel	7440-02-0	0.0000025	Based on cancer risk of 1/1,000,000 of by inhalation	WHO, 2000

5.2 Calculated limits for formed or released substances

Substance	Limit value µg/500 puffs	Limit value µg/m ³ (based on 500 puffs)	Comparisons and remarks
Acetaldehyde (ethanal)	2,560	93,091	Found in concentrations up to 8 µg/puff (Hutzler et al., 2014) and in concentrations up to 120 µg/10 puffs (Bekki, 2014) or 210 mg/m ³ (Uchiyama et al., 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. AFNOR XP D 90-300-3: 3200 µg per 200 puffs
Acrolein (propenal)	12.8	465.5	Found in concentrations up to 3 µg/puff (Hutzler et al., 2014) and in concentrations up to 40 µg/10 puffs (Bekki, 2014) or 33 µg/10 puffs (73 mg/m ³) according to Uchiyama et al. (2014). This corresponds to a total of

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Substance	Limit value µg/500 puffs	Limit value µg/m ³ (based on 500 puffs)	Comparisons and remarks
			<p>1,650 to 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 (or 1,3 mg/m³). No LOD or LOQ is listed.</p> <p>BfR (2012) found acrolein in concentrations up to 9.3 mg/m³.</p> <p>AFNOR XP D 90-300-3: 16 µg per 200 puffs</p>
Cadmium	0.16	6	<p>Farsalinos (2015b) detected cadmium from 8 of 12 e-cigarettes. Concentrations were between 0.08 and 1.6 µg/1200 puffs, corresponding to between 0.03 and up to 0.67 µg per 500 puffs. No LOD or LOQ is listed, nor in the quoted original article (Goniewicz et al. (2014)).</p> <p>Half (6 of 12) measurements are found to be below the calculated limit value, and the rest above the calculated limit value.</p> <p>AFNOR XP D 90-300-3: 2 µg per 200 puffs</p>
Formaldehyde	1600	58,182	<p>Found in concentrations up to 5 µg/puff (Hutzler et al., 2014) and up to 140 µg/10 puffs (Bekki, 2014) or 260 mg/m³ (Uchiyama et al., 2014) corresponding to a total maximum amount of 7,150 µg for 500 puffs. In Bekki (2014), a total of 363 e-cigarettes from 13 different brands of e-cigarettes were analysed, where formaldehyde was detected in 9 of 13 brands (or in 226 of 363 e-cigarettes). Lowest concentration measured (if detected) was 1.3 mg/m³, i.e. 35.8 µg/500 puffs. No LOD or LOQ is listed.</p> <p>BfR (2012) found formaldehyde in</p>

Substance	Limit value µg/500 puffs	Limit value µg/m ³ (based on 500 puffs)	Comparisons and remarks
			concentrations up to 8.3 mg/m ³ (8,300 µg/m ³). AFNOR XP D 90-300-3: 200 µg per 200 puffs
Glyoxal	96	3,491	Found in concentrations up to 23 µg/10 puffs or 42 mg/m ³ (Uchiyama et al., 2014) corresponding to a total amount of 1,150 µg for 500 puffs (Bekki, 2014). In Bekki (2014), a total of 363 e-cigarettes from 13 different brands of e-cigarettes were analysed, where glyoxal was detected in 9 of 13 brands (or in 86 of 363 e-cigarettes). In 12 out of 13 brands glyoxal was not detected for some of the tests performed for the specific e-cigarettes within each brand. Lowest concentration measured (if detected) was 1.3 mg/m ³ , i.e. 35 µg/500 puffs. No LOD or LOQ is listed.
Lead	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, 2015b). These values correspond to between 0.33 to 1.8 µg/500 puffs with an average of 0.3 µg/500 puffs. AFNOR XP D 90-300-3: 5 µg per 200 puffs
Nickel	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. AFNOR XP D 90-300-3: 5 µg per 200 puffs

Remark: the limit value µg/500 puffs is calculated by the formula: $V_{air_daily} \times RfC_{substance}$ (and converted from mg into µg).

5.3 Conclusions and proposal

Published literature data suggest that measured maximum values often exceed the calculated limits but, conversely, many samples would comply with them.

Limits given in AFNOR XP D 90-300-3 are – with the exception of formaldehyde – moderately to significantly higher. Even when based on the same number of puffs the AFNOR limits are a factor of around 1,5 (lead), 3 (acetaldehyde, acrolein), 30 (cadmium) to 300 (nickel) higher.

ANEC considers the establishment of limits for the listed substances desirable and feasible. They may be complemented with limits for further substances in line with provisions in existing national standards.

6. Concluding remarks

The suggestions in the present paper are intended to stimulate a debate on the need to establish clear-cut substance specific rules for e-cigarettes and e-liquids (with or without containing nicotine). It is acknowledged that some of the proposed limits may need to be reconsidered and possibly may have to be modified.

Finally, it goes without saying that the proposals cannot be anything else than a departure point for restricting problematic substances in the products concerned. In the long run it may be preferable to adopt a positive list of allowed flavours (rather than setting thresholds for hundreds or even thousands of substances).

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