Study on the identification of potential risks to public health associated with the use of refillable electronic cigarettes and development of technical specifications for refill mechanisms

Final Report

Potential Risks from Electronic Cigarettes & their technical Specifications in Europe (PRECISE)

EUREST Consortium
Biomedical Research Foundation of the Academy of Athens (BRFAA)
European Network for Smoking and Tobacco Prevention (ENSP)

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Study on the identification of potential risks to public health associated with the use of refillable electronic cigarettes and development of technical specifications for refill mechanisms

European Regulatory Science on Tobacco (EUREST) Consortium

Led by the Biomedical Research Foundation of the Academy of Athens (BRFAA) in partnership with the European Network on Smoking and Tobacco Prevention (ENSP)

On the PRECISE project

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1. ABSTRACT

The report was prepared by the EUREST Consortium (European Regulatory Science on Tobacco) as part of the request for specific services No Chafea/2014/Health/17. The objective of the PRECISE project (Potential Risks from Electronic Cigarettes & their technical Specifications in Europe) was to provide the Commission with an overview of potential risks to public health associated with the use of refillable electronic cigarettes and information on technical specifications for refill mechanisms. To address this objective, four work packages (WPs) were designed. The first WP aimed at providing an overview of the EU e-cigarette market with a particular emphasis on refillable e-cigarettes, based on a sample of EU Member States (MS). For each sampled MS market, a comprehensive evaluation of popular products was performed, and a number of samples were purchased for further evaluation. Within WP2 and WP3, the objective was to identify and assess risks to public health associated with the use of e-cigarettes (WP2), and refillable e-cigarettes in particular (WP3). To address this objective, we performed an evidence collection from three sources: a) an overview and assessment of incidents and/or adverse events related to e-cigarettes for human health for the period 2009 - 2014, in the EU, b) a quantitative and qualitative chemical assessment of selected product samples and c) a systematic review of the published literature. Through the triangulation of these three sources, a list of potential risks was created and the scientific justification for each risk was presented. Finally in WP4, the objective was to identify technical specifications for refill mechanisms, based on the aforementioned risks, stakeholder feedback, European standards already in place and the evaluation of the purchased samples. Design features were identified that may limit the risks associated with the refilling processes, and may also address requirements that e-cigarettes do not leak and are child- and tamper-proof, thereby protecting both users and non-users, especially children.
2. EXECUTIVE SUMMARY

Article 20 of the Tobacco Products Directive includes provisions aiming to harmonise the safety and quality specifications for electronic cigarettes (e-cigarettes), requiring amongst other regulatory actions to develop technical standards for the refill mechanism of e-cigarettes and prepare a report to the European Parliament and the Council on the “potential risks to public health associated with the use of refillable e-cigarettes”. The aim of the PRECISE project was, therefore, to provide input for the Commission on their work in these two areas through four interrelated work packages.

The e-cigarette market in Europe has experienced a continuous expansion since 2008. Its estimated worth in 2014 was approximately 2.16 Billion Euro. Four European Member States (UK, Italy, Poland and France) were the largest EU markets, although there have been significant market fluctuations. According to our research in nine EU Member States, the two most popular types of e-cigarettes on the EU market were either rechargeable with disposable cartridges or refillable e-cigarettes. In all EU Member States studied (except for the UK) refillable e-cigarettes were the most prominent on the market. It was also noted that hundreds of brands and sub brands are available on the EU market, at different nicotine concentrations.

As regards the information provided on industry websites, almost all had a reference to the risk of accidental exposure to e-liquid via the skin and/or eyes and warnings to keep the product out of reach of minors. However, very few websites provided information on quality control and chemical testing. It is also important to note that a little under half of the industry websites had an age verification request. We concluded that continuous monitoring of both market and technological developments is needed due to the fluctuation in the market and as we anticipate that the area of product quality assurance will witness significant development.

As regards risks to public health associated with the use of e-cigarettes, and refillable e-cigarettes (including refill containers) three different approaches were employed to assess the potential risks, in particular:

✓ A systematic review of published peer reviewed literature.
✓ Incidents and/or adverse events related to e-cigarettes from EU Poison Centres.
✓ A qualitative and quantitative chemical assessment of the products purchased

Through the triangulation of these three data sources we were able to conclude that e-cigarettes may pose a threat to European public health. While further research is needed to determine the magnitude and gravity of each risk identified, this report provides a picture of the current status quo of the evidence. Key points of our report include:

✓ There are risks due to design and production flaws of refillable e-cigarettes, such as leakage and spillage.
✓ There is ample evidence that link e-cigarettes, and refillable e-cigarettes in particular, with accidental exposure to refill liquid- especially among children. Vomiting, dizziness and nausea were the most commonly reported symptoms.
✓ There are risks associated with inadequate or misleading information with regards to either product constituents or unwarranted claims on smoking cessation and health benefits.
✓ Refillable e-cigarettes in particular may be associated with risks due to the possibility to modify and/or blend refill liquids which may result in the production of
harmful compounds or allow for the consumption of illegal substances.

- E-cigarettes produce emissions that contain a number of hazardous substances that may be related to their design parameters and constituents.
- There is still uncertainty on the long-term public health effects of e-cigarettes but there is some evidence that e-cigarettes may be associated with reduced quit attempts, dual product use or retained nicotine addiction. Experimentation by non-smokers is also a potential risk, as it is possible that e-cigarettes may act as gateway products.
- Another potential health risk is the use of e-cigarettes where smoking is not allowed. The risks of passive vaping need to be studied further.

The final objective was to identify technical specifications for refill mechanisms, based on the aforementioned risks, stakeholder feedback, European standards already in place and the evaluation of purchased samples. Certain design features were identified that may limit the risks associated with the refilling processes and leakage during handling. Such parameters included the adoption of international standards on child resistant and tamper resistant packaging; an appropriate design and flow rate of the refill vial nozzle; use of a removable plastic seal; the existence of a silicon ring at sealing positions; a reduction in the steps needed to perform the refill and the use of warnings/leaflets to increase consumer caution during refilling.

It is important to outline that, to the best of our knowledge, there is no way to a priori eliminate the risks related to the refill process as this is inherent to the function of refillable e-cigarettes. However, design features may limit the risks associated with the refilling processes and may also address requirements that e-cigarettes do not leak and are child- and tamper-proof, thereby protecting both users and non-users, especially children.
Résumé du rapport

L’article 20 de la Directive sur le produits du tabac comporte des clauses, visant à harmoniser les spécificités en matière de sécurité et de qualité pour les cigarettes électroniques (e-cigarettes), et parmi d’autres mesures réglementaires exige le développement de normes techniques pour les mécanismes de recharge d’e-cigarettes et la préparation d’un rapport sur les « risques potentiels associés à l’utilisation des e-cigarettes rechargeables pour la santé publique » destiné au Parlement européen et au Conseil. Ainsi, l’objectif du projet PRECISE était de contribuer au travail de la Commission dans ces deux domaines au travers de quatre modules de travail.


En ce qui concerne les informations fournies par les sites de l’industrie, presque tous évoquent le risque d’exposition accidentelle aux e-liquides par la peau et/ou les yeux et contiennent des avertissements afin de garder le produit hors de la portée des mineurs. Cependant, très peu de sites fournissent des informations sur le contrôle de la qualité et les essais chimiques. Il est aussi important de noter qu’un peu moins de la moitié des sites de l’industrie exigent une vérification de l’âge. Nous avons conclu qu’une surveillance permanente du marché ainsi que des développements technologiques sont nécessaires dûs aux fluctuations du marché et au fait que nous prévoyons l’arrivée d’importants développements dans le domaine de l’assurance qualité.

En ce qui concerne le risque pour la santé publique associé à l’utilisation des e-cigarettes et des e-cigarettes rechargeables (y compris les flacons de recharge), trois approches différentes ont été employées afin de mesurer le risque potentiel, et plus précisément :

- Une analyse systématique des publications approuvées par des comités de lecture.
- Les incidents et/ou événements indésirables liés aux e-cigarettes et enregistrés par les centres antipoison européens.
- Une évaluation qualitative et quantitave des substances chimiques dans les produits achetés.

Grâce à la triangulation des ces trois sources de données, nous avons pu conclure que les e-cigarettes comportent un risque pour la santé publique européenne. Bien que d’autres recherches sont nécessaires afin de déterminer l’ampleur et la gravité de chaque risque identifié, ce rapport offre une image sur l’état actuel des preuves. Les points clés de notre rapport sont:
Des risques existent dus à des défauts dans la conception et la production des e-cigarettes rechargeables, tels que des fuites et des écoulements.


Des risques associés aux informations inappropriées et trompeuses existent en ce qui concerne aussi bien les composants des produits que des prétentions non fondées pour le sevrage tabagique ou des bienfaits médicaux.

Les e-cigarettes rechargeables peuvent plus particulièrement être associées aux risques dus à la possibilité de modifier et/ou mélanger les liquides, ce qui peut donner lieu à la production de composants dangereux ou la possibilité de consommer des substances illégales.

Les e-cigarettes produisent des émissions contenant de nombreuses substances dangereuses, qui peuvent être liées à leurs paramètres de conception et à leurs composants.

L’incertitude subsiste en ce qui concerne les effets des e-cigarettes sur la santé publique à long terme mais des éléments indiquent que les e-cigarettes peuvent être associées à la diminution du nombre de personnes essayant d’arrêter de fumer, à l’utilisation simultanée de produits ou bien au maintien des fumeurs dans leur dépendance à la nicotine. L’expérimentation des non-fumeurs représente aussi un risque potentiel puisque les e-cigarettes peuvent être utilisées comme des produits d’entrée (à la consommation du tabac).

L’utilisation des e-cigarettes dans les espaces non-fumeurs représente aussi un risque potentiel pour la santé. Les risques du vapotage passif doivent faire l’objet d’études plus poussées.

L’ultime objectif était d’identifier les caractéristiques techniques pour les mécanismes de recharge, en se basant sur les risques susmentionnés, les commentaires des parties prenantes, des normes européennes déjà mises en place et de l’évaluation des échantillons achetés. Certaines caractéristiques de conception ont été identifiées afin de limiter les risques associés au processus de recharge et aux fuites lors de la manipulation. Ces paramètres comprennent entre autres l’adoption de normes internationales pour la « sécurité enfant » et les emballages inviolables ; un design et un débit adéquats du bec verseur de remplissage; l’utilisation d’emballages étanches en plastique ; la présence d’une bague d’étanchéité en silicone aux endroits de fermeture ; une réduction du nombre d’étapes nécessaires pour effectuer le remplissage et l’utilisation de notices de mise en garde/mode d’emploi afin d’augmenter la vigilance de l’utilisateur pendant le remplissage.

Il est important de souligner qu’à notre connaissance, il n’existe aucun moyen d’éliminer les risques liés au processus de remplissage vu que c’est une fonction intrinsèque aux e-cigarettes rechargeables. Cependant, les caractéristiques du design peuvent limiter les risques associés au processus de remplissage et aussi répondre aux exigences d’anti-fuite, sécurité-enfant et anti-falsification, et ainsi protéger les utilisateurs et non-utilisateurs, et plus particulièrement les enfants.
3. INTRODUCTION

E-cigarettes have been regulated for the first time at EU level by the recently revised Tobacco Products Directive (TPD) 2014/40/EU. Article 20 of the TPD focuses on the regulation of e-cigarettes and includes provisions aiming to harmonise the safety and quality specifications for e-cigarettes, including but not limited to the volume of the refill container, the nicotine content and the existence of child-resistant refill containers. Article 20(13) TPD requires the Commission to “lay down (...) technical standards for the refill mechanism provided for in paragraph 3(g) of Art. 20.” Furthermore, according to Article 20(10) TPD, the Commission shall submit a report to the European Parliament and the Council on the “potential risks to public health associated with the use of refillable electronic cigarettes”.

The main purpose of the PRECISE project is, therefore, to (1) provide the Commission with a comprehensive overview and assessment of the risks associated with e-cigarettes and (2) to identify technical specifications that may potentially mitigate risks related to refill mechanisms.

To address these objectives, the PRECISE project was split into four inter-related work packages (WPs). The scope of WP1 was to provide an overview of the EU e-cigarette market with a particular emphasis on refillable e-cigarettes. Within WP2 and WP3, the objective was to identify and assess risks to public health associated with the use of e-cigarettes (WP2), and refillable e-cigarettes in particular (WP3). The scope of WP4 was to use the information from the three previous WPs so as to identify potential technical specifications for refill mechanisms, based on the aforementioned risks, stakeholder feedback, agreed European and International standards and the evaluation of the samples purchased in WP1.

An overview of the methodological approach, findings and conclusions per WP is presented below. Additional detail and scientific documentation is presented in the Annexes to this report.

4. METHODOLOGY AND FINDINGS PER WORK-PACKAGE

4.1 Summary of assessment of e-cigarettes on the EU market (WP1)

This work package primarily supports the work performed under WP2 and WP3, as it provides a factual overview of the EU market for e-cigarettes (in late 2014/early 2015). This overview provides a basis for the assessment of risks determined in WP2 and WP3 and in the assessment of potential design parameters for refill mechanisms identified in WP4.

Within WP1, three tasks were performed:
- An overview of the EU market of e-cigarettes;
- An evaluation of a selected sample of e-cigarettes in the EU market; and
- An exploratory overview of investor report analyses related to e-cigarette use.

### 4.1.1. Assessing the EU Market

The first task of WP1 was to provide an evidence-based overview of the EU market of e-cigarettes at the time (late 2014/early 2015) with a particular emphasis on refillable e-cigarettes. In this respect, we collected the requested information from two sources: purchased Nielsen data (where available) and in-house data from ECigIntelligence (obtained from DG SANTE).

Our hypothesis was that through the cross-checking of the above data sources, we would be able to identify the most popular brands of e-cigarettes and refillable e-cigarettes in selected EU MS markets (or most viewed online brands, where applicable - as a proxy of popularity). Based on the combination of geography, available market data and 2012 Eurobarometer e-cigarette prevalence data, we selected the following European Union Member States (EU MS) as example markets:

- Western Europe: Germany, France, Netherlands
- Northern Europe: Denmark, Latvia, United Kingdom
- Eastern Europe: Poland
- Southern Europe: Italy, Spain

More detailed results and the methodology for this choice is presented in Annex A.

### 4.1.2 Product Purchase

Based on the aforementioned selection of EU MS markets, we proceeded to identify the 2-3 main companies that do business in each, and for each of these companies a complete list of all their products, and the characteristics of each of these products was compiled including product types, safety features, design parameters, ingredients, humectant ratios, website statements and other information that was deemed important. From the list of most popular brands, a convenience sample of products (n=12) and refill liquids (n=38) was purchased for subsequent physical and design structure evaluation (WP1), chemical analysis (WP2/WP3) and to aid the identification of potential high and low risk product design features in WP4 through the assessment of their design and safety parameters.

### 4.1.3 Investor report analyses

As an exploratory assessment of grey literature, PRECISE experts also evaluated investor reports available to EUREST consortium researchers, as they were deemed to possibly contain information relevant for the EU e-cigarette market.
4.1.4. Synopsis of findings

An overview of key findings and conclusions is provided below.

- Systematic monitoring of e-cigarette sales across the EU within physical point of sale premises (by the market monitoring firm, Nielsen) is currently unavailable and, to date, information is fragmented. However, through cross referencing of two data sources, potential online sales (via Alexa.com) and, for some Member States, point of sale purchases (via Nielsen), we identified examples of the most popular websites and their marketed brands, in nine EU MS.

- The e-cigarette market in Europe has experienced a continuous expansion since 2008, and, in 2014, was estimated to be worth approximately 2.16 Billion Euro. The UK, Italy, Poland and France are the largest EU markets. The biggest increase (+100%) in market value was noted in the UK, from 2013-2014.

- The brand share within the e-cigarette market in the EU fluctuates significantly between years with regards to the type of products or companies that have the largest market share.

- Most of the industry sites with the highest visibility at the time of study marketed refillable e-cigarettes and/or refill liquids that can be modified. There seemed to be a range of “generic” tank systems marketed across sites that are modifiable (MODs) and that can be used with different types of e-liquid (taking into account VG/PG ratio compatibility).

- The two most popular types of e-cigarettes were either rechargeable with disposable refill cartridges or refillable e-cigarettes. In the UK, where Nielsen data from physical points of sale was available, rechargeable e-cigarettes had the largest market share. In other countries where data on online visibility was used, refillable e-cigarettes were the most popular.

- This difference could potentially be attributed to the route of sale of each type, however complete and comprehensive market data of both online and point-of-sale avenues would be needed to confirm this. The investor reports also support our finding that there is a transition and expected trend towards refillable e-cigarettes at the expense of disposable and rechargeable products.

- The most visited websites for e-cigarettes were not always brand specific but sometimes marketed multiple brands of devices and refill liquids. To a limited extent a few brand specific websites marketed hardware (of another brand) that could be used compatibly with their liquids.

- An overview of the most popular industry websites indicated that hundreds of brands and sub brands are available on the EU market, with e-liquid available at different nicotine concentrations. It is also noteworthy that a few websites allowed for the purchase of base liquids in very high volumes (up to 25 litres) and/or refill mixing bowls, nicotine concentrates and syringes/pipettes for home mixing. It is also important to note that websites that marketed modifiable e-cigarettes (MODs) also marketed their components, i.e. wicks, coils, batteries etc.

- Almost all the industry websites visited as part of WP1 had warnings related to the risk of accidental exposure to e-liquid via the skin and/or eyes, and also warnings to keep the product out of reach of minors. Precautionary measures, such as the use of gloves and the washing of hands, were often also indicated.

- Very few e-liquid companies provided information on quality control and chemical testing. A few company websites noted the existence of child proof caps, the vast majority did not.
Some company specific websites made health claims, regarding, for example, their products’ impact on quitting smoking or health outcomes. Other company specific websites made statements related to their products, but were cautious in the wording of claims made (i.e. no reference to quitting or health claims).

A little under half of the industry websites had an age verification request. Sponsorship activities were also observed (namely for sports) but on a limited scale.

The brands that were purchased in WP1 included 12 devices (MODs, disposable, rechargeable) and 38 refill liquids.

The investor reports evaluated had limited information relating to e-cigarettes and the EU market. The few articles of relevance did corroborate our finding that the e-cigarette market in general is witnessing a substantial expansion and there is a transition and expected trend towards refillable e-cigarettes (vs. disposable, rechargeable). Investor reports agreed with our finding that the e-cigarette market is constantly and rapidly evolving which does not allow for the easy monitoring of market shares.

Based on investor reports, our research on industry websites and the requirements laid down by the Tobacco Products Directive, we anticipate that the area of quality assurance of e-liquids and its constituents is going to be an area of significant development.

Continuous monitoring of both market and technological developments is needed due to the rapid market fluctuation, which may be very different within and across member states in the coming year(s).

4.2 Summary of the report on the risks of e-cigarettes and refillable e-cigarettes in particular (WP2-3)

The aim of WP2 and WP3 was to identify the potential risks to public health associated with the use of e-cigarettes, including refillable e-cigarettes (including refill containers).

Three different approaches were employed to assess the potential risks associated with the use of e-cigarettes, and refillable e-cigarettes in particular, within WP2 and WP3. Each approach is substantially different and together they provide a stronger evidence base for the extraction of solid conclusions. The three approaches used were:

a) A systematic review of published literature: the aim of this section was to perform an evaluation of the potential risks attributable to e-cigarettes, in particular refillable e-cigarettes, as identified through the published, peer reviewed literature.

b) An assessment of incidents and/or adverse events related to e-cigarettes, including refillables, based on reports from EU Poison Centres.

c) A qualitative and quantitative chemical assessment of the e-cigarette refills purchased in WP1

Based on the triangulation of the results from these three approaches, we proceeded to categorise the potential risks associated with the use of e-cigarettes, in particular refillable e-cigarettes, where possible. More detailed results of this analysis are presented in Annex B.
4.2.1 Poison data collection

The aim of this task was to collect and analyse data on e-cigarette-related cases of poisoning in Europe. Our research questions for this action were the following:

a) What are the demographics of e-cigarette poisonings in EU MS?
b) What is the main product type reported and what are the main routes of exposure, as well as the clinical outcomes of exposures in the EU?
c) How do European findings compare with findings from other jurisdictions?

Data collection: A request for data was sent to a list of poison centres within the European Union. Centres from ten EU Member States agreed to provide data: Sweden, The Netherlands, Ireland, Portugal, Austria, Slovakia, Lithuania, Hungary, Croatia and Estonia. Reports covering the time period from 2012 to March 2015 were requested and collected. Data for a total of 343 cases was reported. All information was de-identified and anonymised.

Detailed information was available for 277 cases, of which 92 (33.2%) were in children 5 years old or younger, 27 (9.7%) were among children between 6 and 18 years old and 158 (57.0%) were among adults. Detailed information on this task, including comparisons with other studies and other jurisdictions, is presented in Annex B.

The main findings were:

✓ One in four exposures (27.4%) among adults were reported as intentional, whereas only 6 out of 119 paediatric cases (5.1%) were reported as intentional.
✓ Regarding the type of product involved, refill liquids were responsible for the overwhelming majority of the reported cases in both children and adults. Only two paediatric cases were related to non-refillable e-cigarettes, while 19 cases were of unknown source.
✓ The majority of the recorded exposure cases did not result in serious effects. In 39.4% (n=82) no effect was reported and a further 53.8% of the cases (n=112) resulted in only minor effects, 6.3% of cases (n=13) reported moderate effects and 1 case (0.5%) reported a major effect.
✓ Age was associated with the noted medical outcome, as 68.3% of adult cases (62.5% minor – 5.8% moderate/major) vs. 49.4% of child cases (41.4% minor – 8.0% moderate/major) reported the existence of an outcome (p<0.05)
✓ Among cases that recorded a medical outcome (minor-moderate or major), 54.8% of cases were associated with ingestion, 28.6% with inhalation, 9.5% of ocular and 7.5% with dermal exposure.
✓ Ingestion was noted to be more frequent among children (81.4% vs. 57.6%, p<0.001). Adult cases were reported more frequently for exposure via the respiratory (22.2% vs. 8.5%, p<0.001) and ocular routes (11.4% vs. 2.5%, p=0.006).
✓ A wide range of symptoms were reported, of which vomiting (20.3%), dizziness (14.5%), nausea (13.8%) and throat conditions (9.1%) were the most common in both children and adults. Abdominal conditions, eye conditions, headache, diarrhoea, breathing conditions and tremor were also reported in a smaller numbers of cases.
4.2.2. Chemical analyses

Within WP2/3, the products containing e-cigarette liquid that were purchased in WP1 were sent for a chemical analysis of qualitative and quantitative character. Samples were appropriately prepared and assessed for the following compounds:

1. Nicotine
2. Propylene glycol, Glycerol, Linalool, Diethylene glycol
3. Five common flavours: methyl cyclopentanolone, acetyl pyrazine, ethyl maltol, 2,5 dimethylpyrazine, ethyl vanillin, 3,4 dimethoxy benzaldehyde
4. The existence of thirteen PAHs was investigated in each sample: acenaphthylene (PAH1), fluorene (PAH2), phenanthrene (PAH3), anthracene (PAH4), pyrene (PAH5), benzo-(a)-anthracene (PAH6), chrysene (PAH7), benzo-(k)-fluoranthene (PAH8), benzo-(a)-fluoranthen (PAH9), benzo-(a)-pyrene (PAH10), benzo-(g,h,i)-perylene (PAH11), dibenzo-(a,h)-anthracene (PAH12), indeno-(1,2,3-cd)-pyrene (PAH13)
5. Four tobacco specific nitrosamines were also evaluated:
   - NNAL 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol;
   - NNK 4’-(nitrosomethylamino)-1-(3-pyridyl)-1-butanol;
   - NAT N-nitrosoanatabine;
   - NAB N-nitrosoanabasine

In addition to the above quantitative analyses, each sample was evaluated from a qualitative perspective for the existence of other compounds and flavors, the results of which are presented in detail in Annex B.

To summarise, our laboratory analyses noted the following results:

- Three out of the 8 packages (37.5%) of refills arrived at our offices with evident leakage that took place during shipping and handling.
- Nitrosamines, PAHs, and diethylene glycol were not identified in the samples.
- No discrepancies in the reported vs. measured nicotine concentrations.
- A wide range of PG/VG ratios across products were identified.
- The qualitative assessment identified a range of flavours, a number of which were identified to have CLP classifications that warrant further investigation.

4.2.3 Systematic review

Within WP2/WP3, the third and most comprehensive task was a systematic review of publications relevant to electronic cigarettes and their potential risks through three separate databases: PubMed (Medline), Scopus and Web of Science. The search strategy was intentionally broad in scope, so as to ensure that all relevant studies were captured. No language, publication year or other limits were imposed. Opinion pieces, reviews, editorials and letters were not included within the review but evaluated for their references. Studies identified through the literature search were imported in an EndNote library and duplicate entries were removed. Two researchers independently assessed the titles and excluded publications that were clearly ineligible. In the following stage, two researchers independently read the abstracts of the remaining publications and excluded those that did not contain original data or did not fulfil the inclusion criteria. Publications that were deemed relevant were included in the review. Two experts independently extracted data from all included studies. Discrepancies in the potential classification were resolved through discussion with a third expert reviewer.
The systematic review was performed three times during the duration of this report, once in April 2015, once in October 2015 and a third time in January 2016, the results of which are included within the context of this report. Overall, a total of 319 publications meet all the criteria and were included in the systematic review (Figure 1 to the right).

4.2.4. Synopsis of findings

To summarise, while further research is needed, based on WP2 and WP3 it seems there is evidence to suggest that e-cigarettes are not risk-free for public health. It should be noted that the detailed report presented in Annex 2 covers only the possible risks attributed to e-cigarettes and refillable e-cigarettes. No grading of the available evidence was performed and no parallel comparison with tobacco products was performed, as this was out of the scope of the review. Furthermore, we must note that the articles included in the review were those that referred to the existence of a risk, as our aim was to compile a comprehensive list of potential risks and thus articles that identified no association were excluded.

The key findings were:

- E-cigarette liquids contain a wide variety of chemical components: humectants, nicotine, flavours, impurities and other substances. While our chemical analyses did not identify impurities, we identified a plethora of flavour additives, some of which have CLP classifications that warrant further investigation.
- There is growing evidence of potential risks from adverse effects in published cellular, animal and human studies. These include: evidence of cytotoxic effects of some refill liquids, especially when nicotine and flavour substances are present; oxidative stress, inflammation of the respiratory system and effects on blood glucose in animal or tissue models; and reports of adverse effects in e-cigarette users, such as pneumonia, chest pain, hypotension, dizziness, and nausea.
- There are risks due to design and production flaws of refillable e-cigarettes, such as leakage and spillage, a fact verified by our active data collection during which 3/8 samples arrived with evident leakage.
- There is ample evidence that link e-cigarettes, and refillable e-cigarettes in particular, with accidental exposure to refill liquid especially among children. Our active data collection corroborated the evidence within the published literature. Almost all unintentional exposures had no or a minor effect. Vomiting, dizziness and nausea were the most commonly reported symptoms.
- There are risks associated with inadequate or misleading information with regards to either product constituents or industry claims. We did not identify discrepancies...
in nicotine content but we did identify a broad list of unwarranted claims on smoking cessation and health benefits.

✓ Refillable e-cigarettes in particular may be associated with a number of risks due to the possibility to modify and/or blend refill liquids and to use incompatible devices, which may result in the production of harmful compounds. The ability to use refillable e-cigarettes for the consumption of illegal substances was also noted.

✓ E-cigarettes produce emissions that contain a number of hazardous substances that may be related to the design parameters and constituents (especially flavourings).

✓ There is still uncertainty on the long-term public health effects of e-cigarettes but there is some evidence that e-cigarettes may be associated with reduced quit attempts, dual product use or retained nicotine addiction which may be associated with sustained nicotine addiction at a population level. Further long-term research in these areas is needed.

✓ Experimentation by non-smokers is a potential risk as it is possible that e-cigarettes may act as a gateway product, influenced, amongst other aspects, by marketing, flavourings and perceptions of reduced risk.

✓ Another potential health risk is the use of e-cigarettes where smoking is not allowed. The risks of passive vaping need to be studied further.

✓ While further research is needed to determine the magnitude and gravity of each risk identified, this report provides a picture of the current status quo of the evidence.

4.3. Summary of the characteristics of technical specifications for refill mechanisms (WP4)

Article 20 of the TPD requires that “electronic cigarettes and refill containers are child- and tamper-proof, are protected against breakage and leakage and have a mechanism that ensures refilling without leakage.” These are the two core aspects of WP4, the results of which are presented in detail in Annex C.

Three tasks were performed under WP4:

a) An evaluation of the products identified under WP1 so as to identify brands with a high and low risk profile including a description of the refill mechanism used for the respective brands and with a particular emphasis on whether or not children/minors are protected.

b) An active data collection from i) a questionnaire to industry stakeholders, ii) available European and International standards and iii) published and grey literature.

c) Finally the third task was to merge the available evidence collected in a and b above, in light of the risks identified in WP2 and WP3 and identify potential technical specifications for e-cigarette refill mechanisms.

4.3.1 High and low risk product profile parameters

From our analysis of 33 refill liquids and 4 disposable e-cigarette products, we noted:

✓ Almost all products evaluated (n=34) had some form of child resistant cap. Notably, only those three products that did not have a nozzle but used another format (i.e. pipette etc.) were found not to have a child proof cap. While we were not able to formally evaluate compliance with ISO standards, it appears that most products are already child resistant.
Leakage during transfer was noted for a number of products, an issue which would lead to a classification as a “high risk brand” from the point of design specifications. As noted in WP2 and WP3, three of eight shipments received had evident leakage.

The existence of a mechanism to identify tampering (plastic ring or plastic sheath) was common among the products purchased.

Almost all vials had warnings. Only 8 out of 37 samples (6 of which were from the same company) did not have a hazard warning on the package. Different types of hazard pictograms warnings were noted, and included in some cases CLP warnings such as a skull and cross bones, an X and/or environmental risk warnings. In some cases the hazard pictogram was on the packaging and not on the actual vial itself.

Other “homemade” hazard pictograms also existed, such as warnings for pregnant women or for children under 3 years old due to risk of choking.

Text only warnings existed on most products, either on the refill vial or on the external packaging. Examples included:

- This product is not intended for persons with respiratory or cardiovascular diseases
- Nicotine is an addictive substance. Not suitable for pregnant women, nursing mothers, persons with respiratory or cardiovascular diseases, no smokers and persons under the age of 18. Keep away from children
- Danger toxic in contact to the skin. Contains Nicotine
- Please consult your doctor before using our products if any of the following apply: If you are unsure of the effects of nicotine; pregnant, planning to become pregnant or breast-feeding; in ill health.

Tactile warnings were present on most of the refill vials and on some of the external packages. The tactile warning in all cases was an elevated triangle.

Leaflets were available for 13 of the purchased products. Of the 13 products, 7 had a leaflet that was within the external package of the product, while 6 had a leaflet that was glued to the actual refill vial.

All products that had a nozzle and were not of “pipette or eye drop design” had elongated and thin nozzles. There were internal differences between the samples with regard to the length of the nozzle and the width of the nozzle spout, but in all cases they could be described as long and thin. This design would potentially allow for easier introduction of the refill liquid in the tank.

Instructions for use were only provided for 5 products (four of which were the same brand, while the fifth was within ampules and not vials). Our study of disposable or refillable e-cigarette devices (not in the list above) indicate that user instructions are frequent among hardware products, but not for refill liquid products.

Instructions to use gloves during the refill process were noted in products from three companies. “Wear protective gloves” was the phrase used commonly.

Ingredients were listed in almost all cases. The majority were however reported as “PG, VG, nicotine, flavours”. Few products provided a more detailed analysis of what the flavours were composed of and even fewer provided a detailed quantitative analysis of these flavours.

Instructions on what to do in case of an emergency were noted in 24 of the products. Examples of such instructions included:

- In case of accident with the eyes, wash with plenty of water. Poison call center +49 (0) 89- 19240
- In case of accident, or if you feel unwell seek medical advice immediately. Irritating to eyes and skin.
4.3.2. Synopsis of industry feedback & standards evaluation

The rationale behind this task was a) to obtain information from a sample of industry stakeholders, b) understand the European and International standards already in place and c) evaluate grey literature that would aid in the identification, assessment and proposal of existing and/or potential safety feature solutions to limit the risks associated with refillable e-cigarettes or refill containers.

For this task, a questionnaire was drafted and sent to 22 industry stakeholders, of which 12 responded. The questionnaire included questions on standards that may reduce the risks associated with refilling, designs and possible adjustments that protect against breakage and leakage in order to reduce adverse health effects and other related issues. All communications with stakeholders were undertaken in writing via an email account and fully documented for reasons of transparency. No communication through any other channel was facilitated. An overview of the answers provided was also sent to DG SANTE.

With respect to the available European and International standards that may apply to the opening and refill mechanisms of refillable electronic cigarettes or refill containers, a number of industry stakeholders referred to the following standards:

- AFNOR standards XP D90-300-1 and XP D90-300-2.
- BSI PAS 54115.
- ISO 8317,1 which provides for the testing of re-closable child-resistant packaging.
- EN 862,2 which provides for the testing of non-reclosable packages for non-pharmaceutical products.
- One stakeholder reported that REACH (EC No 1907/2006) and CLP Chemicals Legislation (EC No 1272/2008) may define labelling and packaging requirements.
- One stakeholder reported that they have patented a design that eliminates leakage/spillage.

According to the cross evaluation of information and standards, we note that:

- PAS 54115:2015 does not require a specific technology to ensure leakage free refilling but rather states that manufacturers/importers should include instructions to users on safe refilling (section 6.2) and ensure that bottles are designed with a delivery spout capable of delivering refill liquid without spillage (section 6.4).
- AFNOR XP-D-90-300 suggests that the outside diameter of the nozzle of a refill container should be smaller than the diameter of the tank and that refill containers should have a flow-control mechanism. It also states that e-cigarettes should be refilled according to the instructions in the product information manual and should not leak or come into contact with users. This should be tested through manual inspection of absorbent paper (section 5.1 of part 1).
- As regards labelling of e-cigarettes, AFNOR XP-D-90-300-1 (part 1) states that the unit packet should include a pictogram indicating the diameter of the tank filling hole (section 8.2). A product information leaflet should include information on the size of the tank refilling hole and the refilling mechanism of the e-cigarette (section 8.3.2).
As regards labelling of e-cigarette refill bottles, AFNOR XP-D-90-300-2 (part 2) states that for refill bottles a product information leaflet should include information on the diameter of the refill nozzle and refilling mechanism of the e-cigarette (sections 5.4.3 and 6.3.2).

ISO 8317 and EN862 standards may be used to make refill vials child resistant. ISO 8317 specifies the requirements and test methods for reclosable packages designated as resistant to opening by children. When applied, these standards should provide a satisfactory degree of resistance to opening by children while maintaining accessibility to its contents by adults. On the other hand, EN862 outlines the requirements and testing procedures for non-reclosable packages for non-pharmaceutical products.

In addition, CLP classifications and warnings may increase user caution during the refill process.

4.3.3. Synopsis of findings

Through the research performed in WP4, specific design parameters or user actions that could mitigate some of the risks identified in WP2 and WP3 were identified. We present below some general conclusions followed by suggestions for both refill vials and the actual e-cigarette itself. It is important to outline that, to the best of our knowledge, there is no way to a priori eliminate the risk related to the refill process as this is inherent to the function of refillable e-cigarettes.

Overall, design parameters or user actions that could mitigate overall risk during refilling include:

- Refill vials with an elongated and thin nozzle that fits seamlessly within the opening of the tank of the e-cigarettes.
- E-liquid should not flow freely from the refill vial when tipped on its side or when placed upside down (i.e. there should be a flow-control mechanism in the refill bottle).
- Refilling should not involve an additional transfer step with syringes or pipettes.
- E-cigarettes and refill containers could have a docking system which ensures that liquid only flows when they are connected.
- Plastic gloves could be used during the refill process to further mitigate the risks.
- Leaflets could instruct users how to safely refill e-cigarettes and include diagrams where necessary. These leaflets could be glued to the refill vial.
- Warnings could inform the consumer and increase user caution during refilling.

Refill vials: The below parameters were identified as those that would mitigate the risk of exposure from refill vials:

- The refill liquid vial must as a minimum conform to ISO 8317:2004 for a re-closable pack and EN 862:2005 for a non-reclosable pack to mitigate the potential risk of ingestion, especially among children – a risk which was evidently clear through WP2 and WP3.
- The addition of a removable plastic seal that would surround the cap and ensure that it would be transferred to the consumer in a tamper proof package. This seal would also add an additional safety layer for the protection from both unintentional ingestion by children and accidental leakage during shipping, by securing the cap on the vial.
Refill vials should be of suitable composition to be protected against corrosion/damage.

The addition of a silicon or equivalent ring between the nozzle and the cap of the vial of the refill liquid to further reduce leakage and potential dermal exposure.

An information sheet or leaflet with warnings and instructions for use and for refilling. These leaflets could be glued to the vial itself so as to ensure they stay with the refill vial.

Visual, text and tactile warnings on the refill vial itself would increase consumer caution both among users and non-users.

Moreover, the refill liquid vial should also adhere to three standards:

- Effectiveness standard. The child resistant packaging, tested by the protocol specified in 16 CFR 1700.20 and 16 CFR 1700.15(b).
- Compatibility standard. The packaging must continue to meet the effectiveness specifications when in actual use as an e-cigarette refill container. This requirement may be satisfied by appropriate scientific evaluation of the compatibility of the substance with the packaging to determine that the chemical and physical characteristics of the e-liquid will not compromise or interfere with the proper functioning of the child-resistant packaging and that the packaging will not be detrimental to the integrity of the product during storage and use.
- Durability standard. The child-resistant packaging must continue to meet the effectiveness and compatibility standards for the reasonably expected lifetime of the package, taking into account the number of times the package is customarily opened and closed.

**E-cigarette tank:** The following were identified as characteristics that may mitigate risks of leakage from the e-cigarette tank:

- The existence of a silicon or equivalent ring on the e-cigarette itself, at the area of connection between the seam of the tank and the tank cap.

**Anticipated consequences for Industry:**

Two main types of costs for the industry were identified. One relates to the one-off costs of redesigning the refill vials and one relates to recurring costs which would stem from the implementation of technical standards that would mitigate risk into routine production. The product redesigning that we suggest would consist of four main aspects a) making caps ISO compliant for child resistance, b) adding a plastic sheath that would hold the cap securely on the vial c) ensuring that the refill nozzle is long and elongated and ensure a steady drop rate d) adding appropriate instructions and warning on the refill vial. Based on our sample of products purchased and stakeholder feedback we do not anticipate that manufacturers would need to drastically redesign their products to comply with the technical design characteristics identified.
6. ANNEXES

Annex A. Assessment of e-cigarettes on the EU market
Annex B. Report on the risks of e-cigarettes and refillable e-cigarettes in particular
Annex C. Characteristics of technical specifications for refill mechanisms
ANNEX A. An overview of the EU Market of E-cigarettes

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Introduction

The first part of WP1 is to provide an evidence-based overview of the current EU market of e-cigarettes in late 2014/early 2015, with a particular emphasis on refillable e-cigarettes. In this respect, we collected the requested information from two sources: purchased Nielsen data (where available) and data available to DG SANTE (ECigIntelligence).

✓ ECigIntelligence data – of which their online ranking of e-cigarette retailers is based on internet site visits of Alexa.com, was used as a proxy of the brands visibility and popularity, taking into account that within a number of EU Member States (MS) consumers may also purchase their products online. We must acknowledge that this approach is not without limitations, as a) visibility does not necessarily mean purchases, and b) in some EU MS a percentage of purchases may be performed directly from stores (such as in the UK). However despite this limitation, it provides an indication of the market.

✓ Nielsen data was available for a few EU MS, with the drawback that Nielsen data covers points-of-sale, which include for the UK, “grocery, impulse, chemist” purchases and hence do not cover specialised stores (e-cigarette stores) or internet sales –that may sell other types of e-cigarettes. Hence the products identified in Nielsen are the most popular only through those avenues of sale.

Our hypothesis was that despite the limitations of each of the two sources, through their cross-checking we would be able to create a list of the potentially most popular brands (or most viewed online where applicable) of e-cigarettes and refillable e-cigarettes in selected EU MS markets as at the end of 2014, while recognising that these markets have significantly changed since this date.
EU MS were selected based on the following hierarchy: Existence of available market data > geographical position of the EU MS > prevalence of e-cig experimentation based on the 2012 Eurobarometer data (in order to have MS with low, mid and high prevalence’s)

- Western Europe: Germany, France, Netherlands
- Northern Europe: Denmark, Latvia, United Kingdom
- Eastern Europe: Poland
- Southern Europe: Italy, Spain

Within this WP we proceeded to identify the 2-3 main companies (based on their online popularity or Nielsen market share numbers where available) that do business in each of the 9 EU MS, and for each of these companies evaluate information on their products and websites. We provide a detailed presentation of the e-cigarette market in the selected EU MS, including an overview of:

- Description of the marketed products
- Design features and technical specifications if available and described
- Safety features related to the refill bottles
- Company Statements/warnings on the site
- The existence of an age verification system or otherwise
- Ingredients in the e-liquid
- Nicotine content marketed

**Overall EU Market**

Data on the overall EU Market as identified through a Euromonitor international report indicate the increasing market value of e-cigarette sales in the EU, with the current market worth approximately 2.16 Billion Euro (Figure 1).

![Figure 1. Value of the e-cigarette market in the EU 2009-2014](chart_image)

Among the EU MS, 6 account for the largest share of e-cigarette sales, as identified in Figure 2 below. The largest e-cigarette market (in value in 2014), is located within the UK with an estimated value of 569€mn, followed by Italy (346.5 €mn), Poland (330 € mn) and France (315 €mn). It is interesting to note that in 2013, the largest e-cigarette market was in Italy at 566 €mn, which subsequently lost half of its market value and is now surpassed by the UK in 2014, which doubled its market value.
Market in Germany

According to available ECigIntelligence data as at the end of 2014, the largest channel of purchase of e-cigarettes in Germany was via online purchases (45-55%), followed by purchases in vape stores (20-30%) and tobacco stores (15-25%). In the absence of Nielsen Market data, and acknowledging that approximately half of the sales are online purchases we used information on internet site traffic as a proxy of consumer interest in specific e-cigarette retailers or brands. The most visited sites were obtained through the Alexa.com website ranking provided by ECigIntelligence reports. The sites are a mixture of resellers that simply buy the main brands from China, and companies that have their own-brand products. According to this ranking\(^1\), the top 5 online retailers of e-cigarettes in January 2015 in Germany are detailed below:

<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 German Flavours</td>
<td><a href="http://www.germanflavours.de">http://www.germanflavours.de</a></td>
</tr>
<tr>
<td>2 XEO</td>
<td><a href="https://www.xeocigs.com">https://www.xeocigs.com</a></td>
</tr>
<tr>
<td>3 Pipeline</td>
<td><a href="http://pipeline-store.de">http://pipeline-store.de</a></td>
</tr>
<tr>
<td>4 Totally Wicked</td>
<td><a href="http://www.totallywicked-elixir.de">http://www.totallywicked-elixir.de</a></td>
</tr>
<tr>
<td>5 FreeSmoke</td>
<td><a href="http://www.freesmoke.eu">http://www.freesmoke.eu</a></td>
</tr>
</tbody>
</table>

**Company Name:** German Flavours

**Website:** [www.germanflavours.de](http://www.germanflavours.de)

**Product Description:** There are approximately 260 e-liquids with different flavors and 16 different e-liquid bases to choose from that are either pure, nicotine or caffeine based with various proportions.

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\(^1\)ECig Intelligence: Germany online Pricing analysis, January 2015. Excel sheet.
of PG/VG ratios. This company also markets empty containers, needles and syringes for home mixing of e-liquids.

**Design feature and Technical specifications:** The material of the bottles is soft plastic. They are provided in 2ml/ 10ml/ 30ml/ 50ml/ 100ml/250ml/ 500ml/ 1lt/ 5lt/ 25lt bottles. Needles are sold for the refilling of liquids.

**Safety feature:** Liquid bottles have a child safety cap.

**Statements/Warnings on the site include:**

- "Not recommended for: Pregnant and / or lactating mothers, people with heart diseases, blood pressure or lung disease (e.g. asthma, COPD, bronchitis, pneumonia).”
- "Keep away from children, Avoid skin and eye contact, Harmful if swallowed, Not suitable for pregnant women, Only to be used in e-cigarettes”
- "Our Liquids represent a stimulant. Merely intended solely for use in e-cigarettes.”
- "In an incompatibility of propylene glycol, glycerin or flavored or an allergic reaction, do not use e-cigarettes and associated liquids. If in doubt, consult your doctor or pharmacist for advice.”
- "It is strictly forbidden to make our liquids available to children and adolescents under 18 years.”
- "Flavors with known harmfulness / inhalation toxicity are not applicable. We expressly waive diacetyl. A research about diacetyl has shown that diacetyl promotes various aspects of amyloid-beta aggregation. Such beta aggregations are associated with alzheimer’s disease. Therefore we don’t use flavorings with diacetyl or related diketones in our products.”
- "No youth release according to § 14 Youth Protection Act”

**Age verification:** There is no age verification to access the website.

**Ingredients:** There are different proportions of PG/VG for purchase such as 50PG/50VG, 55PG/35VG, 86, 5PG/13,5VG, >99% VG, >95% PG, 100%PG.

- The company states that its "liquids are made of propylene glycol (PG), Glycerin (VG), nicotine and flavorings”. The purity of VG, PG and nicotine are provided in pdf form on the web.
- Nicotine is noted to be of USP grade.
- The manufacturer declares that the flavors they use are certified and comply with the German registration Regulation (EC) no. 1334/2008 of 16.12.2008 on flavorings and certain food ingredients with flavoring properties for use in and on foods.

**Nicotine content:** There are products without nicotine and others with 3 mg/ 6mg/ 9mg/ 12mg/ 15mg/ 18mg/ 24mg.

**Company Name:** XEO

**Website:** www.xeocigs.com

**Product Description:** The XEO markets starter kits, e-liquids and cartridges, disposables and e-shisha devices (disposable and rechargeable). For each of the disposable and refillable products, different flavors are available.

**Design feature and technical specifications:** Products are marketed to have a "No leakage through X-Vapor™ technology, Advanced Dual Air Flow Sensor and easy to change prefilled cap”. Refill bottles are marketed in 0,8ml, 1,6ml, 1,5ml, 2ml, 6,5ml, 10ml bottles. With regards to the refill process, the use of both cartridges (no handling of the liquid itself), and refill liquids for their refillable
products (or “e-juice from other brands”) is noted. This refill process and the proprietary design is not further described.

**Safety feature:** The manufacturer noted that a silicone ring is used to eliminate leakage.

**Statements/Warnings on the site include:**
- "No tar, no tobacco, no ash, no smell”
- "No Tobacco, no chemicals, no tar, no ash, no secondhand smoke, No pollution”
- "Smoke wherever you want: in the office, at the airport, or during a meeting”
- "Up to 70% cheaper than traditional cigarettes”
- "More social acceptance than traditional cigarettes”
- "Please dispose of the battery according to your legal regulations”

**Age verification:** The website has an age verification request.

**Ingredients:** The website does not specify the concentrations of the ingredients. The manufacturer refers that the ingredients can be found in the specific product details, with the product.

**Nicotine content:** The products are marketed in 0mg/8mg/16mg/20mg nicotine concentrations.

**Company name:** PIPELINE

**Website:** [http://www. pipeline-store.de](http://www. pipeline-store.de)

**Products Description:** The company provides cartomizers, clearomizers, drip-tips, tanks, modifiable e-cigarettes (MODs) and DIY material (wicks, coils, wires, cases, batteries etc.). All products are refillable. Multiple types of e-liquids are also sold as compatible with their products. Also marketed in the UK.

**Design feature and technical specifications:** e-Liquids are made and designed in Germany, produced and bottled under sterile laboratory conditions. There are glass bottles with a pipette that they are provided with in 1,5ml/ 10ml/ 30ml/ 50ml bottles. The refill mechanism is not described.

**Safety feature:** The manufacturer noted that the packaging is child-resistant according to ISO 8317.

**Statements/Warnings on the site include:**
- "FUEL e-Liquids are not suitable for children under the age of 18, non-smokers, people with allergies to nicotine or propylene glycol, pregnant or breastfeeding women and people with cardiovascular disease.”
- "The use of e-Liquid FUEL is solely at your own risk.”
- "Products are not for sale to, or use by, anyone under the age of eighteen”.
- "Electronic cigarettes are not "healthy" but they are less harmful than tobacco cigarettes”
- Battery Recycling information is also provided at the footnote of the site
- "Electronic cigarettes are not designed to treat nicotine addiction and are not suitable for smoking cessation”

**Age verification:** There is no age verification to access the website.

**Ingredients:**
- “PIPELINE FUEL e-liquid contains nicotine, propylene glycol, glycerin, distilled water and flavourings” notes the manufacturer. The liquid base is made of 55% PG (propylene glycol),
35% VG (Vegetable Glycerine) and 10% distilled water, but, also, there is a proportion of 50PG/50VG and 80PG/20VG for purchase.

- The company states that PG (propylene glycol) and VG (vegetable glycerine) have a purity of 99.5% which is the highest purity”.
- They also note that their liquids do not contain Diacetyl or added oil”, while the ingredients are either of food (for flavors) or pharmaceutical grade (nicotine). Flavors with known inhalation risks are also not used.
- Their e-liquid pamphlet is available for direct download from here: http://www.pipeline-store.co.uk/img/cms/Fuel_Leaflet_UK_Online.pdf (also available in German and French for the respective markets)
- Hazard and product data sheets are provided (page 9 of the pdf): Labelling and risk phrases for PG, G and Nicotine are provided.

**Nicotine content:** Pharmaceutical grade at 0mg/ml, 6mg/ml, 12mg/ml, /18mg/ml).

**Company name:** Totally Wicked

**Website:** http://www.totallywicked-liquid.de/

**Products Description:** There are e-liquids in various nicotine strengths, 100 plus flavors and capacities. There are starter kits, electronic cigarettes, pre-filled cartridges, disposable e-cigarettes, e-pipes, e-cigarettes tanks, atomizers, rechargeable batteries, filling bottles, fluid flasks, syringes, measuring cylinders, other accessories etc. They note that they have products that regulate either airflow, voltage or temperature. Also marketed in the UK

**Design feature and Technical specifications:**
- USA and UK made e-liquids, sold in 10ml, 20ml, 30ml, 50ml, 100ml bottles. The latter two volumes are for nicotine solutions, to be used during mixing.
- Refill Mechanism technology: Measuring cylinders, syringes and needles are for sale. Notably the “deluxe refilling kit“ comes with a 1ml syringe, 5 needles and a 50ml needle tip squeeze bottle.

**Safety feature:** The products are noted that they should be stored in a “childproof container”. The design is not provided.

**Statements/Warnings on the site include:**
- “Totally Wicked makes no claims that the electronic cigarette will cure a smoker’s addiction to nicotine. Specifically, the company claims that "the electronic cigarettes we sell serve the same purpose as a tobacco cigarette - they deliver its user nicotine". "If you do suffer from the disease of Tobacco/Nicotine Dependence Syndrome and want to take steps to give up smoking or cut down the quantity of cigarettes you currently smoke, we recommend you visit your health care provider to discuss NRT (Nicotine Replacement Therapy) or a nicotine harm reduction program. Please Note: TW is not a pharmaceutical company and we do not produce medical products.”
- "Keep cartridges and fluid out of reach from children. Nicotine in its pure form is a poison, and can cause harm. All nicotine cartridges and fluid must be kept in a safe place and away from children, as the amount of nicotine in a cartridge, if ingested by a small child could cause serious harm and medical assistance should be sought. Avoid contact with eyes and skin, if this occurs wash immediately with plenty of water. Do not ingest, if swallowed seek medical attention immediately".
• “In case of accident with e-liquid, or if you feel unwell seek medical advice immediately, and take the e-liquid bottle and box with you for information.” “Vapours may cause drowsiness or dizziness.” “E-liquid material and its container must be disposed of in a safe way. Use appropriate containment to avoid environmental contamination.”

• “Keep e-liquid out of the reach of children. Users should store and handle these items with special care as they may contain small parts and represent a choking hazard.”

• “E-liquid should not be used by any persons under the age of 18 years or who have demonstrated sensitivity to nicotine, or are pregnant, breastfeeding or have an unstable heart condition.”

• “ALWAYS keep cartridges and e-liquid out of the reach of children and pets.”

• “ALWAYS keep cartridges and e-liquid in a childproof container with the lid firmly on.”

• “E-liquid is toxic if swallowed and in contact with skin, may cause sensitisation, wash immediately with plenty of water.” “In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.”

• “Should a child or pet swallow a cartridge or ANY amount of e-liquid seek medical advice immediately, taking the bottle or similar cartridge with you, enabling the Doctor or Vet to identify the e-liquid ingredients.”

• “Should an adult swallow any amount of e-liquid seek medical advice immediately, again taking the bottle or similar cartridges with you.”

**Age verification:** There is no age verification to access this website.

**Ingredients:** The manufacturer provides a variety of flavours i.e. tobacco and menthols, fruity blends and. There are various proportions of PG/VG for purchase such as 70PG/30VG, 50PG/50VG and 80PG/20VG. Emphasis of the site is placed on home mixing.

**Nicotine content:** 0mg/ml, 6mg/ml, 8mg/ml, 10mg/ml, 11mg/ml, 14mg/ml, 18mg/ml, 24mg/ml, 30mg/ml, 35mg/ml. Also nicotine bases are available at 54mg/ml and 72mg/ml concentrations for self-mixing (these are notably high and would not be TPD compliant). These self-mixing products can be seen at: http://www.totallywicked-liquid.com/products/e-liquid/mix-your-own-products.html

**Market in France**

Estimates of the number of consumers that buy e-cigarettes online in France vary from around 10-25%. For example, the Observatoire Français des Drogues et des Toxicomanies survey estimates that 9% of e-cig users reported buying online, while other industry studies indicate that this proportion could be as high as 25% (ECigIntelligence data from 2014). Another study from 2014, with a smaller sample size than the OFDT’s, indicates vapers switching to the Internet (24%) from vape stores (49%). Vape stores however are not covered under Nielsen data and such information was not available to us, hence while information on internet site traffic was used as a proxy of consumer behaviour these results should be interpreted with caution. According to this ranking², the top 5 online retailers of e-cigarettes, in August 2014, in France are detailed below, the first four of which do not market only one brand but market multiple types of brands and liquids:

²ECig Intelligence: France online Pricing analysis, August 2014. Excel sheet.
<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Le petit fumeur</td>
<td><a href="http://www.lepetitfumer.fr">www.lepetitfumer.fr</a></td>
</tr>
<tr>
<td>2 Smok-it</td>
<td><a href="http://www.smok-it.com/en/">www.smok-it.com/en/</a></td>
</tr>
<tr>
<td>3 Vapotstyle</td>
<td><a href="http://www.vapotstyle.fr">www.vapotstyle.fr</a></td>
</tr>
<tr>
<td>4 Cigatec</td>
<td><a href="http://www.cigatec.net">www.cigatec.net</a></td>
</tr>
<tr>
<td>5 Pipeline-store</td>
<td><a href="http://www.pipeline-store.com">www.pipeline-store.com</a></td>
</tr>
</tbody>
</table>

**Company name:** Le petit fumeur

**Website:** [http://www.lepetitfumeur.fr](http://www.lepetitfumeur.fr)

**Product Description:** Not identifiable to one specific brand, this website markets numerous e-liquid brands and flavors (>120), and multiple e-cigarette “hardwares” (i.e. eGo one Joytech, Kangertech, Aspire, Innokin, Eleaf etc.), that are compatible with these liquids. MOD parts such as coiled, clearomisers, drip tips, resistances etc. are also sold.

**Design feature and technical specifications:** Some products made in US and other made in France. E-liquids are in bottles of PET (polyethylene terephthalate plastic). There are bottles with pipette and glass bottle with dropper. There are 5ml/6ml/10ml/ 15ml/30ml bottles.

**Safety feature:** Equipped with a tamper evident, a drop-account and an ISO 8317 compliant cap). The top caps also have a Braille triangle "Danger" for the visually impaired.

**Warnings on the site include:**
- "The top caps of our bottles also have a Braille triangle "Danger" for the visually impaired."

**Age verification:** The website does not request age verification to access the site.

**Ingredients:** There are different proportions of PG/VG such as 60PG/40VG, 80PG/20VG, 70PG/30VG, 50PG/50VG, 100% VG. Additional flavorings are noted.

**Nicotine content:** There are products in various nicotine strengths. For instance, the company markets products at nicotine levels of 0mg/ml, 3mg/ml, 5mg/ml, 6mg/ml, 8mg/ml, 10mg/ml, 11mg/ml, 12mg/ml, 15mg/ml, 16mg/ml, 18mg/ml, 24mg/ml.

**Company name:** SMOK-IT


**Product Description:** The site is a reseller of multiple products such as e-shisha, clearomizers, cartomizers and MODs. There are refillable products, rechargeable and disposable e-cigarettes as also e-liquids with 35 different flavors.

**Design feature and technical specifications:** There is no information for material of the bottles. There are clearomizers provided in 1,6ml/ 2,5ml/ 3,5ml, 10ml volumes and e-liquid bottles provided in 10 ml volumes.

**Safety feature:** The bottles that the company markets are stated to have child resistant closures. (the design is not provided). The company states “Our proven Liquid bottle with child safety and pointed filling needle for practical filling of liquids”. No refill mechanism is noted or discussed.
**Statements/Warnings on the site**: Some warnings accompany the age verification to access the site, these include:

- "Selling electronic cigarettes to minors is forbidden"
- "Are not advised for pregnant or breastfeeding women, people with cardiovascular disease or asthma, keep out of reach and sight of children"
- "Nicotine is addictive, do not start."
- The site has a dedicated “Health” tab with results from selected studies and media reports.

**Age verification**: The website has an age verification process to access this website.

**Ingredients**: The proportional of PG/VG within the e-liquids is noted. Some of the ingredients are also noted: i.e. Glycerol 70%, Damascenone 0,5%, Lialool 6%, 2-Acetylpyrazine 1,5%, Artificial Flavour 8%, Methylcyclopentenolone 2,5%, 2.5-Dimethylpyrazine 1%, Alpha-Inone 5%.

The site also notes that they sell products that are of pharmaceutical grade quality (PG, G and nicotine) and of food quality for flavorings.

**Nicotine content**: 0mg/ml, 5mg/ml, 6mg/ml, 9mg/ml, 10mg/ml, 12mg/ml, 15mg/ml, 16mg/ml concentrations.

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**Market in the Netherlands**

According to ECigIntelligence, as at the start of 2015, online sales comprise the largest part of the market in the Netherlands. Estimates vary, but about 60-90% of e-cig sales appear to go through this channel. Hence, in the absence of Neilsen data, internet site traffic is a good proxy of consumer interest in e-cigarettes retailers and brands. All of the most commonly visited websites market refillable e-cigarettes/MODs that belong to many different companies. Below are the top-ranking e-cigarette websites in the Netherlands in February 2015, all 4 of which market multiple starter kits, MODs, liquids and do-it-yourself material:

<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ZWOOFs</td>
<td><a href="https://www.zwoofs.nl">https://www.zwoofs.nl</a></td>
</tr>
<tr>
<td>2. ESigaretonline</td>
<td><a href="https://esigaretonline.nl/">https://esigaretonline.nl/</a></td>
</tr>
</tbody>
</table>

**Company name**: ZWOOFs

**Website**: [https://www.zwoofs.nl](https://www.zwoofs.nl)

**Products Description**: This site markets various brands of hardware components and brands of e-liquids. Multiple DIY components are sold. E-liquid flavors are also marketed.

**Design feature and technical specifications**: As the site markets multiple brands and types, there are many different design features and technical specifications. Some e-liquids come in obvious drip caps.

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Annex A-9
**Safety feature:** As the site markets multiple brands, the refill processes are different for their products. Sealant rings within the hardware to avoid leaking are also mentioned within upper range hardware systems.

**Warnings on the site include:**
- "Products are not suitable for people under 18, pregnant or lactating women, people with heart and / or vascular disease and people who are allergic and / or sensitive to nicotine-containing products”.
- "E-cigarettes are an alternative to smoking.”
- "Keep away from children and pets.”

**Age verification:** There is no age verification to access the website.

**Ingredients:** The various e-liquids have multiple PG/VG ratios, multiple ingredients.

**Nicotine content:** There are products in various nicotine strengths such as 0mg/ 6mg/ 12mg/ 18mg.

---

**Company name:** eSigaretonline

**Website:** [https://esigaretonline.nl/](https://esigaretonline.nl/)

**Products Description:** In this site there are various brands and e-liquids with different flavors to choose from. These include hardware and liquids as also DIY material for MODs. All are refillable.

**Design feature and technical specifications:** As a site with multiple products, both drip cap and eye-drop caps are used. Three main e-liquid companies are marketed through this portal. Syringes, mixing bottles, pipette vials and needles are sold to facilitate the filling process.

**Safety feature:** None identified.

**Statements/Warnings on the site include:**
- The site has a dedicated section on how e-cigarettes can be used to quit tobacco use.
- The website stresses to read the individual labelling of each product correctly.
- "Electric smoking is less harmful to health than smoking normal cigarettes. Cigarette smoke contains more than 600 hazardous substances that are very bad for you. The drink on Saturday night is worse for health than vapors with an electric cigarette.”
- "You can almost smoke everywhere. Although it is often kept by house rules, you can basically electrical smoke in a restaurant. Bystanders do not suffer from second-hand smoke”

**Age verification:** There is no age verification to access the website.

**Ingredients:** The various e-liquids have multiple PG/VG ratios, multiple ingredients.

**Nicotine content:** There are products without nicotine and with nicotine concentration of 6mg/ml, 9mg/ml, 11mg/ml, 12mg/ml, 16mg/ml, 18mg/ml, 24mg/ml.
Market in United Kingdom

Data for the UK market were available from two sources, ECigIntelligence and Nielsen. ECigIntelligence, corroborates the result that for the UK, convenience stores, supermarkets and gas station sales predominate as retail outlets for e-cigarettes (which is represented by the Nielsen data), although online sales still maintain a large presence, particularly for experienced users and the refillable e-liquids market. The market is dominated by larger players, with more than 80% market share held by the biggest ten. Hence we present both data sources. According to the ECigIntelligence ranking\(^4\), the top 5 online retailers of e-cigarettes, in October 2014, in UK are detailed below:

<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Truvape</td>
<td><a href="http://truvape.co.uk/">http://truvape.co.uk/</a></td>
</tr>
<tr>
<td>2 Nicolites</td>
<td><a href="http://www.nicolites.com/">http://www.nicolites.com/</a></td>
</tr>
<tr>
<td>3 Smoke Shop</td>
<td><a href="http://www.smokshop.com/">http://www.smokshop.com/</a></td>
</tr>
<tr>
<td>4 Freshcig</td>
<td><a href="http://www.freshcig.co.uk/">http://www.freshcig.co.uk/</a></td>
</tr>
<tr>
<td>5 FlavourVapour</td>
<td><a href="http://www.flavourvapour.co.uk/">http://www.flavourvapour.co.uk/</a></td>
</tr>
</tbody>
</table>

According to the Nielsen report\(^5\), the bestselling products in the retail e-cigarette market in March 2015, in UK were:

- 10 motives
- E-lites
- Blu

**Company name: 10 Motives**

**Website:** http://www.10motives.com/

**Products Description:** This company markets e-liquids with 30 liquids flavours, rechargeables and disposables e-cigarettes and cartomiser nicotine refills. On the website of 10 Motives there are also EVOD, Aspire and Innokin products as hardware products.

**Design feature and technical specifications:**

- "Ten Motives have all relevant Safety Certificates (CE & RoHS) making them legal to sell & use in the UK, USA & EU”.
- Also, the company states that "e-liquid bottles are completely childproof” and notes that "electronic cigarettes and nicotine cartridges have been fully tested by an independent laboratory.
- Our products comply with all relevant trading and medical standards”.
- **Refill process:** “To fill the clearomiser simply remove the black mouthpiece, insert the nozzle of the bottle at a 45 degree angle and squeeze the E-liquid into the tank. Take care to avoid the small air outlet tube which is located centrally underneath the black mouthpiece.”
- For the rechargeable non modifiable e-cigarettes, closed refills are available.

**Statements/Warnings on the site include:**

- "Not to be used by children”.

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\(^4\)Ecig Intelligence: UK online Pricing analysis, October 2014. Excel sheet.

• "Please consult your doctor before using Ten Motives products if any of the following apply to you: If you are pregnant, planning to become pregnant or breast feeding; If you have a medical condition, unstable heart condition, severe hypertension or diabetes; If you are allergic/sensitive to nicotine of any of the ingredients; If you are unsure of use/suitability. Do not use if you are allergic to any of the ingredients". (Emphasis with caps)

• "Keep Ten Motives products out of reach of Children (Emphasis with caps)

• “This website is for customers 18 years of age and above only.”

• “Electronic cigarettes do not contain tobacco or any other harmful substances which means by default they are not subject to any current laws on smoking and can be used indoors. However there are some establishments which ban the use of e-cigarettes, generally because it looks too similar to normal smoking. If you are unsure whether the establishment will allow you to use the e-cigarette then always please ask the proprietor for their permission prior to using it. If you are using an e-cigarette and are asked to stop then this is the right of the establishment to decide. Please check with airlines before flying if you intend to use an e-cigarette on board as rules vary.”

**Age verification:** The website does not have an age verification request.

**Ingredients:** The company’s liquids are made of propylene glycol, glycerine and vegetable glycerin. The website also states that liquids may contain nut traces.

**Nicotine content:** E-Liquids come in four nicotine strengths: 6mg/ml, 11mg/ml, 18mg/ml, 24mg/ml.

**Company name:** E-lites

**Website:** [http://www.e-lites.co.uk/](http://www.e-lites.co.uk/)

**Products Description:** This company markets electronic cigarette cartridges available in various nicotine strengths. There are regular strength (Reds), light nicotine strength (Golds) and menthol (Greens). These fit with two types of products, which are not modifiable. On the website, there are e-cigarettes starter kits and a wide range of e-cig accessories for purchase. The manufacturer notes that “the different strength and flavour electronic cigarette refills are fully interchangeable”.

**Design feature and technical specifications:** On the website, there is no information either about technical specifications. They do note though that they participate “in various standardization initiatives and were part of the AFNOR working group (April 2015; [http://www.afnor.org/en](http://www.afnor.org/en)). This has resulted in the first voluntary product standards to which E-Lites already complies and which cover both e-liquid ingredients and device safety.”

- E-liquid is Swiss-made according to CE standards.
- This company states that “E-Lites products are Trade Marked, rigorously tested and subjected to both Quality Control & CE Assessment”.

**Warnings on the site include:**

- "We do NOT recommend smoking E-Lites or ANY products containing nicotine whilst pregnant”.
- "E-Lites are designed as SMOKING ALTERNATIVES rather than a NRT (Nicotine Replacement Therapy). We are merely offering a tobacco free and tar free, better value alternative to
traditional cigarettes. E-Lites are not intended as nicotine replacement therapy nor are they a smoking cessation device”.

- “E-lites contain nicotine and are intended for use by existing smokers aged 18 or over as a smoking alternative”.
- The company declares about propylene glycol that "Propylene glycol (PG) is a colourless, odourless chemical that is used as a food additive, in cosmetics and in pharmaceuticals as an inert solvent or carrier. The ATSDR (Agency for Toxic Substances & Disease) states on its website, propylene glycol is a 'Generally Recognized as Safe' (GRAS) additive for foods and medications. PG has been used as the aqueous-based chemical additive in asthma inhalers and nebulizers since the 1950s, with no serious side effects known”. Also, the manufacturer notes that E-Tip does not contain Tobacco and does not produce Tar.

**Age verification:** The website has an age verification request to access it (date of birth).

**Ingredients:** The cartridge is made of a solution of propylene glycol, glycerol, flavourings and nicotine.

**Nicotine content:** There are a range of nicotine strengths available with pharmaceutical grade nicotine. E-Tips are available in regular (24mg/ml) nicotine strength (Reds), light (16mg/ml) nicotine strength (Golds), menthol with 16mg/ml (Greens) and nicotine free.

**Company name:** blu: ([http://www.blucigs.com/](http://www.blucigs.com/))

**Products Description:** This company markets a selection of rechargeable kits, flavor cartridges, disposables and accessories. These are not modifiable.

**Design feature and technical specifications:** No refilling process, the products have cartridges that contain the e-liquid. The company’s flavors are made in the USA, hardware is made in China. The manufacturer states about the refill mechanism that "the company’s tank is prefilled, and if you attempt to take the tank apart, it will not function correctly. Blu Tanks are intended for one-time use only”.

**Safety feature:** None identified.

**Warnings on the site include:** The manufacturer declares that:

- "Electronic cigarettes contain nicotine derived from tobacco. Nicotine is an addictive chemical. Therefore, our position is that electronic cigarettes are addicting”.
- "The materials have been approved to hold consumables and are safe for human contact”.
- Not for sale to Minors/ California proposition 65 – Warning: This product contains nicotine, a chemical known to the state of California to cause birth defects or other reproductive harm.
- WARNING: This product contains nicotine derived from tobacco. Nicotine is an addictive chemical.
- They should not be used by children, pregnant or breastfeeding women, people with heart disease, high blood pressure, diabetes or people taking medicines for asthma or depression. Consult your physician before using any electronic cigarette product.

**Age verification:** The website has an age verification request to access.

**Ingredients:** The ingredients that the manufacturer uses are the following: Nicotine (when applicable), PG, VG, Natural and Artificial Flavors and Distilled Water.
**Nicotine content:** There are products without nicotine and others with high nicotine concentration, which is 2.4% nicotine and medium nicotine concentration, which is 1.2 % nicotine.

**Retailers as identified via ECigIntelligence**

**Company name:** TRUVAPE

**Website:** [http://truvape.co.uk/](http://truvape.co.uk/)

**Products Description:** There are approximately 50 e-liquids with different flavors. This company also markets tanks. This is a brand specific website. Significant sponsorship activities are promoted on the landing page.

**Design feature:** Markets refillable and rechargeable e-cigarettes. The website provides detailed instructions of use of both their product types (rechargeable with cartridge) and refillable (for the tank models)

**Safety feature:** none described or depicted on the website

**Statements/Warnings on the site include:**

- You must be 18+ to be able to purchase any product from us. We have the right to cancel an order at anytime, should we feel the buyer is a minor or if someone is buying on behalf of a minor. (with an 18plus sign)
- Nicotine is a poison. Nicotine is an addictive substance and can be fatal if consumed incorrectly. We do not recommend our products to anyone who is not already a smoker. (with a skull and crossbones sign)
- "There is no smoke produced and the e-liquid contains no tobacco, tar or carbon monoxide”.
- "All of TRUVAPE’s products adhere to the strictest safety standards and our use of natural extract flavourings, combined with medical grade nicotine and the finest US Pharmaceutical grade PG and VG in their liquids”.
- "Our electronic cigarette devices are certified to CE, RoHS, WEEE and SGS standards”.
- "Our electronic cigarette is designed as a healthier smoking alternative rather than a smoking cessation device.”
- "One of the favorable benefits of electronic cigarette is that you can use e-cigs freely in public places like restaurants, pubs, and workplace etc., where regular smoking is banned. While there remains some debates on whether to allow it in certain areas, the best way to get over this is to get others to know more about it.”
- "TRUVAPE e-cig is available for users of legal smoking age. It is not intended to be used by children, women who are pregnant or by those sensitive to nicotine.”
- "You must be 18+ to be able to purchase any product from TRUVAPE”.
- Sport sponsorship: “Proud sponsors of Jack Geoff racing, Chepstow racing, Hull football club and Warrington Wolves” [https://truvape.co.uk/](https://truvape.co.uk/)
- "Old school sweet flavors from your childhood. Perfect for those grown-ups with a sweet tooth”
- Detailed Waste electrical and electronic equipment (WEEE) webpage.

**Age verification:** There is an age verification point to access the website.
Ingredients: The manufacturer declares that "e-liquids contain only the finest USP grade PG/VG and medical grade nicotine. The regular e-liquid contains four main ingredients: Propylene glycol (PG) is colorless, odorless and slightly sweet and is proved to be safe widely used as food additives; Vegetable glycol (VG) also known as glycerol, is slightly thicker and sweeter than PG. It offers less throat hit but produces more vapour. VG is an ingredient base used to dilute nicotine liquids; Nicotine; Flavoring concentration; The proportion of PG/ VG for purchase is 80%PG/20%VG.

Nicotine content: 0mg/ml, 6mg/ml, 12mg/ml, 18mg/ml of medical grade nicotine.

Company name: Nicolites

Website: http://www.nicolites.com/

Products Description: This company markets 2 starter kits (rechargeable), 3 disposable e-cigarettes and 12 cartomizers (in menthol and non menthol flavor), and an e-cigar. It does not market refill liquids. It is a company specific website.

Design feature and technical specifications: The site contains detailed information on the instructions of use of their products (https://www.nicolites.com/what-ecig)

Warnings on the site include:

- "E-cigarettes contain no tobacco or tar and as a result produce no smoky odour. Nicolites are designed to look and feel like a real cigarette but contain only nicotine, propylene glycol, water and additional flavouring."
- "Nicolites has been a well established brand and trusted supplier of e-cigarettes since 2009 and is a favourite in pharmacies across the UK (Source: Nielsen January 2015)"
- "As there is little research on the safety of any nicotine products during pregnancy, we advise that you do not use Nicolites in specific medical conditions, including whilst pregnant or breastfeeding. Please ask your GP for further advice on the risk of nicotine during pregnancy"
- "As with any known illness" we advise that you consult with your GP before using any of our products” (EUREST: heart condition or high blood pressure noted above),
- "All products are not intended for use by those under 18 years old, pregnant or breastfeeding women or persons in ill health”.
- "E-cigarettes are not subject to the smoking ban but as a matter of courtesy it is usually a good idea to check with the owner of the premises before you use your e-cigarette to make sure that they are happy for you to do so”

Age verification: The website does have an age verification request.

Ingredients: The manufacturer declares that "the only ingredients are water, propylene glycol, Nicolites flavouring and nicotine (in all Nicolites e-cigarettes and cartomisers), No Tar. None of our products contain VG (Vegetable Glycerin) as liquids made with high percentages of VG are more viscous. When VG liquids are left unused for long periods of time we have found that the device can become clogged, therefore PG liquids are preferable”.

Nicotine content: There are products without nicotine and others with 6mg/ml, 11mg/ml, 16mg/ml.
Market in Denmark

According to ECigIntelligence data as at the end of 2014, because of the ban of sales of nicotine-containing e-cigarettes in Denmark (domestic sale, distribution or marketing was illegal at this time), the most important sales channel was the internet, which enables vapers to import these products for personal use, which is allowed, from elsewhere. Estimates put online sales at around 90% of the market at this point.6

According to the Nielsen report7 (based on Grocery Trade incl. Hard Discount + Convenience) the top sales companies of electronic cigarettes, in February 2014, in Denmark are:

1. Vrige brand
2. SKANDI
3. EC SMOKE

Company name: SKANDI

Website: http://www.skandilight.dk/shop/e-cig-skandi-e-liquid-32c1.html

Products Description: The website of this company is not e-cigarette specific but also markets numerous other products including bioethanol grills, fireplaces etc. With regards to e-cigarettes they market a MOD, rechargeable products with cartomisers and e-liquids with nicotine and 10 different flavors to choose from. The same website also markets bioethanol grills, fireplaces and non-related products. As depicted from the parameters below there was extremely limited information on the website available

Design feature and technical specifications: There is lack of information about design and technical specifications provided on the website.

Safety feature: No reference to the safety mechanisms for child proofing or a leak free refill process exist.

Warnings on the site include: There are no warnings on the website.

Age verification: There is no age verification to access the website.

Ingredients: There is no information provided in the website about the ingredients. The site does indicate (in jpg format) quality assessment of some of its ingredients, however not large enough to read or distinguish. The bottles of refill liquids, viewable on the website indicate a list of ingredients.

Nicotine content: There are products without nicotine.

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Market in Latvia

ECigIntelligence data was not available for Latvia, while according to the available Nielsen report\(^8\), these products are sold in specialized stores and via the Internet, and hence Nielsen covers only a very small part of sales. In any case, the top two companies that market electronic cigarettes (according to limited Nielsen data), in February 2015, in Latvia are:

**Company name:** Air Smoke

**Website:** [https://www.airsmokecig.com/lv/](https://www.airsmokecig.com/lv/)

**Products Description:** There are refillable products such as e-liquids with different flavors, clearomizers and coil heads. Also, the company markets disposable e-cigarettes and MODs. The site provides multiple e-liquid brands.

**Design feature and technical specifications:** E-liquids are provided in 10 ml bottles. Most seem to be with the eye-drop lid.

**Safety feature:** None described.

**Warnings on the site include:**

- "Air Smoke electronic cigarettes, e-liquids, cartomizers and accessories are sold to persons who are 18/21 years old".
- "The liquid in AirSmoke cartridges and bottles contains propylene glycol and may contain nicotine. Nicotine is a poisonous and addictive substance which can cause, among other things, irritated central nervous system and raised blood pressure”.
- "AirSmoke products and accessories are only intended for smokers aged at least 18 or any other legal age for smoking in your country."
- "AirSmoke electronic cigarettes, accessories, cartridges and other products are not intended for non-smokers, minors, women who are pregnant or may become pregnant, or any person with an elevated risk of, or pre-existing condition of, a medical condition including, but not limited to, heart disease, diabetes, high blood pressure or asthma. If you experience any side effects or possible side effects, stop using the product immediately and consult a physician”.  
- "AirSmoke liquids and products are not a means for giving up smoking and have not been tested as such. AirSmoke electronic cigarettes and varieties thereof cannot completely substitute tobacco and are not guaranteed as such”.
- "AirSmoke liquids have not been evaluated by the Food and Veterinary Service and the State Agency of Medicines, nor are they intended to treat, prevent or cure any disease or medical condition.” Please keep out of reach of children and pets.”
- "Electronic cigarette is tobacco-free and can be used anywhere where regular smoking is banned. You can use them in pubs, offices, on board planes and restaurants. Attention! Before using electronic cigarette, please, contact the staff and make sure that the company’s policy allows it.”

**Age verification:** There is no age verification to access the website.

**Ingredients:** E-liquids are noted on the site to contain 4 components: PG, VG, flavour and nicotine.

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Nicotine content: There are products without nicotine 0mg/ml and others with 5mg/ml, 6mg/ml, 10mg/ml, 15mg/ml, 16mg/ml, 18mg/ml, 20mg/ml.

Company name: Shark

Website: http://www.shark-ecigarette.at/en/

Products Description: There are refillable products, e-liquids with 17 different flavors, 2 starter kits, 11 shisha-sticks, clearomizers and batteries.

Design feature and technical specifications: The liquids are noted to be “Made in Germany”.

Safety feature: None identifiable on the site

Statements/Warnings: No warnings or statements on the site.

Age verification: The website does have an age verification request.

Ingredients: None noted.

Nicotine content: There are products without nicotine and others with 6mg/ml, 9mg/ml, 12mg/ml, 18mg/ml.

Market in Poland

ECigIntelligence notes that Poland’s ecigarette market at the end of 2014 was predominantly a refillable tank/e-liquid market (approx. 80-90% of total sales). Moreover, there was a lack of brand loyalty in Poland, with 72% of respondents to the Polish National Consumer Advocates Federation survey saying that they couldn’t remember what brand they last bought and 7% using different brands at the same time. According to the same source, e-cigarette stores and branded retail points (e.g. in shopping centres) account for most purchases (40% branded retail stores, 20% independent stores), but consumers use the Internet more than in other EU MS markets (30% of consumers). Poland’s top online e-cigarette retailers, in August 2014, are listed below, based on rankings\(^9\) from Alexa.com

<table>
<thead>
<tr>
<th>Company</th>
<th>WebSite</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 iSmook</td>
<td><a href="http://ismook.pl/">http://ismook.pl/</a></td>
</tr>
<tr>
<td>2 NiePalPapierosow</td>
<td>Could not identify a website</td>
</tr>
<tr>
<td>3 eCigar</td>
<td>Security of our computers barred access</td>
</tr>
<tr>
<td>4 CasablancaCig</td>
<td><a href="http://casablanca">http://casablanca</a> cig.pl/</td>
</tr>
<tr>
<td>5 DPV9</td>
<td><a href="http://www.dpv9.pl">http://www.dpv9.pl</a></td>
</tr>
<tr>
<td>6 eDym</td>
<td><a href="https://www.e-dym.pl/">https://www.e-dym.pl/</a></td>
</tr>
<tr>
<td>7 ePapierosy24</td>
<td><a href="http://www.epapierosy24.com/">http://www.epapierosy24.com/</a></td>
</tr>
</tbody>
</table>

\(^9\) Ecig Intelligence: Poland online pricing analysis, August 2014. Excel sheet.
Company name: iSmook

Website: [http://ismook.pl/](http://ismook.pl/)

Products Description: This website hosts various brands. There are refillable products for purchase such as e-liquids which have approximately 420 different flavours in various capacities and in various nicotine strengths.

Design feature and technical specifications: There is lack of information about the design feature and technical specifications on the website, due to the fact that they market multiple products.

Safety feature: There is no information on bottle safety features. The liquids provided in 10ml/15ml/30ml/60ml/100ml bottles.

Statements/Warnings on the site include: -
- Link to support the initiative to challenge the TPD.-linked to totally Wicked.
- “Products in our store are designed for adults (with signage)”

Age verification: There is an age verification to access the website.

Ingredients: The website provides no information about the ingredients within the liquids.

Nicotine content: There is a variety in nicotine strengths on each brand that the website hosts. In general, there are free of nicotine liquids and with 6mg/ml, 11mg/ml, 12mg/ml, 18mg/ml, 24mg/ml.

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Company name: CasablancaCig

Website: [http://casablanca cig.pl/](http://casablanca cig.pl/)

Products Description: This company markets 6 e-liquids (with different nicotine strengths), each with 41 flavors. It also markets multiple e-cigarettes that are refillable.

Design feature and Technical specifications: None noted on the website.

Safety feature: There is no information on safety features of the refill liquids.

Statements/Warnings on the site: None were noted. A FAQ section would not load.

Age verification: There is no age verification to access the website.

Ingredients: The website provides no information about the ingredients within the e-liquid.

Nicotine content: The nicotine strengths depend on each brand. There are liquids without nicotine and liquids in various nicotine strengths, such as 6mg/ml, 11mg/ml, 16mg/ml, 24mg/ml, 36mg/ml.
Market in Italy

According to ECigIntelligence in December 2014\(^{10}\), the e-cigarette market in Italy has shrunk substantially, a fact corroborated by the Euromonitor data noted earlier in the Annex. In Italy, the main channel for electronic cigarettes are online sales which account for at least 50% of the total, with some estimates putting this proportion as high as 90%. In late 2014, there were approximately 1500–1600 vape stores in Italy (although this total has changed since). The most popular form of product in Italy was the tank, while the most popular website marketed only e-liquids. According to the ECigIntelligence Alexa site ranking\(^{11}\), the top 5 online retailers of e-cigarettes, in January 2015, in Italy are detailed below:

<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DEA</td>
<td><a href="http://www.deaflavor.com/es">http://www.deaflavor.com/es</a></td>
</tr>
<tr>
<td>2 E-Smokers</td>
<td><a href="http://www.e-smokers.it/">http://www.e-smokers.it/</a></td>
</tr>
<tr>
<td>3 Las vapoteca</td>
<td><a href="http://www.lasvapoteca.net/">http://www.lasvapoteca.net/</a></td>
</tr>
<tr>
<td>4 Esmove</td>
<td><a href="http://esmove.mcwstore.com/">http://esmove.mcwstore.com/</a></td>
</tr>
<tr>
<td>5 Flavour Art</td>
<td><a href="http://www.flavourart.it/">http://www.flavourart.it/</a></td>
</tr>
</tbody>
</table>

**Company name: DEA**

**Website:** http://www.deaflavor.com/es

**Products Description:** This company markets 50 e-liquids, base liquids, flavor concentration liquids and provides extensive quality assurance, production and ingredient information and certifications.

**Design feature and technical specifications:** The manufacturer notes that all DEA products are completely produced in Italy. The e-liquids are provided in 10ml, 20ml and 50ml bottles. The manufacturer notes that "Each packaging contains information leaflet that specifies the nature and the use of product; on the outer box of liquids, which contain nicotine, there are indicated safety and hazard phrases in different European Union languages depending on a state in which the product is sold.”

**Safety information reported:** On the website the manufacturer declares that:

- "All analyses carried out on DEA Flavor products are certified by accredited laboratory in compliance with UNI CEI EN ISO/IEC 17025 standard as prescribed by the Ministry of Health”.
- "The values shown in the test report confirm the high quality and the purity of DEA Flavor liquids for electronic cigarettes, the values are below the threshold values used as a reference in the analysis.
- On the DEA’s website the certification DEA Flavor S.r.I, is provided. (pdf file)
- On the DEA’s website the material safety data sheet is provided (34MB ZIP file)
- On the DEA’s website the chemical analysis of heavy metals is provided. (pdf)
- Microbiological awareness files in the bottling line is provided (two pdf files)
- "Bottles that have a secure hermetic sealing, which breaks on the first use, and a certified ISO 8317 child-proof cap”.

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\(^{11}\) Ecig Intelligence: Italy online Pricing analysis, January 2015. Excel sheet.
Statements/Warnings on the site include:
EUREST evaluated this site as one of the most comprehensive sites of those screened for informing consumers. All of the above safety information is freely available on the site.

- **Contact with a skin must be avoided while using liquids containing nicotine; for this reason you have to wear protective clothing when handling such liquid.**
- **If it comes in contact with your skin, wash off abundantly, and when necessary contact immediately a doctor.**
- **Nicotine is a toxic but not carcinogenic substance that causes dependence.**

**Age verification:** There is no age verification to access the website.

**Ingredients:** The information on the ingredients that the website provides is that e-liquids contain solely water, food flavourings (in compliance with EC Regulation 1334/08), vegetable glycerine, propylene glycol and nicotine. PG, VG, nicotine are of pharmaceutical grade (EU Pharmacopeia)

**Nicotine content:** 0mg/ml, 4mg/ml, 9mg/ml, 14mg/ml, 18mg/ml.

**Company name:** E-smokers

**Website:** [http://www.e-smokers.it/](http://www.e-smokers.it/)

**Products Description:** There are refillable products for purchase such as e-liquids with 40 flavours to choose from, 6 liquid bases and approximately 70 concentrated flavours. Also, this company markets starter kits, vaporizers, cartomizers, DIY liquids and components too.

**Design feature and technical specifications:** The liquid bottles are provided in 10ml, 12ml, 20ml, 100ml and 250ml volumes. Additionally, there are bottles with pipettes for purchase for home mixing.

**Safety feature:** The manufacturer declares that "the liquids comply with standards and made with ingredients and raw materials permitted by the Community 'European Union and the European Agency for Food Safety". On the website, there is the note that "the liquid base is sold in bottles with child-resistant cap and label on the back". A safety sheet for PG is noted on the site.

**Statements/Warnings on the site include:**
- "No smoke, No yellowing teeth, Nothing unpleasant odors, Nothing risk of burning or fires"
- "e-cigarettes are a great help for those who want to quit smoking"
- "...can be used everywhere, also in all the places where smoking is expressly prohibited by law (including the plane). Obviously a good "vaper" will use its e-cig to the extent that the good manners and common sense imposes."
- "It is forbidden to use children under 18 years old e-smokers. The company cancels order placed by minors".
- "...sells flavored liquid, comply with standards and made with ingredients and raw materials permitted by the Community 'European Union and the European Agency for Food Safety. Normally the spices are consumed combined with food, then swallowed. The intake of food involves the digestion of the same, resulting in certain biological processes and assimilation. On this point it should be noted that inhalation or steaming aromas, although it is a practice similar to the sense of smell in an open environment, and not 'been specifically tested, therefore cannot be excluded any unexpected effects. E-smokers.it will not take responsibility
‘for the use of these food flavorings in preparations to be vaporized and inhaled by atomizers, electronic cigarettes and similar equipment.

- The liquid base for electronic cigarettes contain nicotine, and are NOT 'a food and CAN NOT' AND MUST NOT BE SWALLOWED. Nicotine and 'a toxic, addictive and if ingested or taken topically (SKIN), can' create discomfort, vomiting and nausea”
- "there are currently no long-term safety assessments for the use of liquid nicotine and / or flavor, so this type of products are made at the discretion and risk of the end user”.
- "The use of this product is not 'recommended to pregnant women and people suffering from asthma, hypertension, diabetes, heart problems. If while using the liquid base side effects occur, stop taking them immediately and seek medical advice”.
- "Nicotine is absorbed easily by the skin, so it is recommended to use protective gloves when handling the liquid base”.
- "Nicotine is a toxic, addictive and if ingested or taken topically (SKIN), can create discomfort, vomiting and nausea”.
- "It is strongly recommended to store the bottles of liquid base out of the reach of children and pets”.

Age verification: The website does have an age verification request.

Ingredients: There are different proportions of PG/VG for purchase, such as VG (100%) or PG (100%) or PG(40%)/VG(40%)/water(10%). PG is noted to be of pharmaceutical grade.

Nicotine content: 0mg/ml, 9mg/ml, 18mg/ml, 24mg/ml, 36mg/ml.

Market in Spain

According to ECigIntelligence, as at the end of 2014, 70% of sales in Spain were thought to be online while franchises remained relatively small in number and independents form the main body of shops with more than 50% of the market is estimated to be independent and tobacco stores. For offline sales, up to 90% of consumers were buying from vape stores. With regard to product type, the form factor most common in Spain was the refillable “tank” e-cigarette. The top 3 e-cigarette websites in Spain in February 2015,12 based on ranking from Alexa.com are the following:

<table>
<thead>
<tr>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CigarrosElectronics</td>
<td><a href="http://www.cigarroselectronicos.com/">http://www.cigarroselectronicos.com/</a></td>
</tr>
<tr>
<td>2 El CigarroElectronicco</td>
<td><a href="http://www.elcigarroelectronicco">http://www.elcigarroelectronicco</a></td>
</tr>
<tr>
<td>3 Ivapeo</td>
<td><a href="http://www.ivapeo.com">http://www.ivapeo.com</a></td>
</tr>
</tbody>
</table>

Company name: CigarrosElectronics

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Website: http://www.cigarroselectronicos.com

Products Description: The company markets refillable products. There are, also, starter kits, electronic cigarettes, vaporizers, clearomizers, batteries, chargers, atomizers, mods and other accessories for purchase.

Design feature and technical specifications: The manufacturer states that "The liquids are manufactured in Germany under German quality controls and exclusively European ingredients. They are not Chinese import fluids, liquids are manufactured in Germany by pharmaceutical laboratories".

Safety feature: There is no information on the safety feature of the bottles on the site.

Warnings on the site include:
- "No sales of liquid vapor under 18 years".
- "Prohibited use by pregnant or women who are breastfeeding".
- "It is not a toy. Keep away from children".
- "The product contains nicotine. Avoid use in the following cases: severe cardiovascular disease (e.g., heart failure, vascular disease), hypertension, liver or kidney failure, ulcers, diabetes is not a therapeutic product or medical purposes, it is not a drug nor is it intended to be".

Age verification: The website does request age verification to access.

Ingredients: There are different proportions of PG/ VG for purchase such as 45PG/55VG; 55PG/45VG ratios. Also, the products are noted to contain ethanol, flavors and nicotine.

Nicotine content: There are various nicotine levels, such as 0mg/ml, 6mg/ml, 12mg/ml, 18mg/ml.

Company name: El CigarroElectronicco

Website: http://www.elcigarroelectronico.com

Products Description: The website hosts more than 40 brands and the site provides different products for sale. For instance, there are various e-cigarettes models such as mini e-cigarettes, M-series. There are 184 e-liquids with different flavours to choose from.

Design feature and technical specifications: There is lack of information on the design feature and technical specifications because they depend on each brand. Generally, there are 10ml and 15 ml e-liquids bottles.

Safety feature: The manufacturer states that "the liquids have the CE mark, SGS, MSDS and TUV". Also, it is noted that “the bottles are closed, they contain dropper and have a protective cover to prevent accidental opening”. The standards to which they adhere to are not described on the website. Leak proofing is not addressed either.

Warnings on the site include:
- "The liquids have the CE mark, SGS, MSDS and TUV facts showing they do not contain harmful substances that can damage your health”.

Age verification: The website does not request age verification in order to access it.

Ingredients: The e-liquids contain propylene glycol, vegetable glycerin, “natural” extracts, aromas (enhancers), natural flavor, distilled water and nicotine.
Nicotine content: There are various nicotine strengths, but also depends on brand but the general levels that are stated on the website are the following: 4mg/ml, 6mg/ml, 11mg/ml, 14mg/ml, 16mg/ml, 18mg/ml, 36mg/ml.

Conclusions

✓ Systematic monitoring of e-cigarette sales across the EU within physical point of sale premises (by the market monitoring firm, Nielsen) is currently unavailable and, to date, information is fragmented. However, through cross referencing of two data sources, potential online sales (via Alexa.com) and, for some Member States, point of sale purchases (via Nielsen), we identified examples of the most popular websites and their marketed brands, in nine EU MS.

✓ The e-cigarette market in Europe has experienced a continuous expansion since 2008, and, in 2014, was estimated to be worth approximately 2.16 Billion Euro. The UK, Italy, Poland and France are the largest EU markets. The biggest increase (+100%) in market value was noted in the UK, from 2013-2014.

✓ The brand share within the e-cigarette market in the EU fluctuates significantly between years with regards to the type of products or companies that have the largest market share.

✓ Most of the industry sites with the highest visibility at the time of study marketed refillable e-cigarettes and/or refill liquids that can be modified. There seemed to be a range of “generic” tank systems marketed across sites that are modifiable (MODs) and that can be used with different types of e-liquid (taking into account VG/PG ratio compatibility).

✓ The two most popular types of e-cigarettes were either rechargeable with disposable refill cartridges or refillable e-cigarettes. In the UK, where Nielsen data from physical points of sale was available, rechargeable e-cigarettes had the largest market share. In other countries where data on online visibility was used, refillable e-cigarettes were the most popular.

✓ This difference could potentially be attributed to the route of sale of each type, however complete and comprehensive market data of both online and point-of-sale avenues would be needed to confirm this. The investor reports also support our finding that there is a transition and expected trend towards refillable e-cigarettes at the expense of disposable and rechargeable products.

✓ The most visited websites for e-cigarettes were not always brand specific but sometimes marketed multiple brands of devices and refill liquids. To a limited extent a few brand specific websites marketed hardware (of another brand) that could be used compatibly with their liquids.

✓ An overview of the most popular industry websites indicated that hundreds of brands and sub brands are available on the EU market, with e-liquid available at different nicotine concentrations. It is also noteworthy that a few websites allowed for the purchase of base liquids in very high volumes (up to 25 litres) and/or refill mixing bowls, nicotine concentrates and syringes/pipettes for home mixing. It is also important to note that websites that marketed modifiable e-cigarettes (MODs) also marketed their components, i.e. wicks, coils, batteries etc.

✓ Almost all the industry websites visited as part of WP1 had warnings related to the risk of accidental exposure to e-liquid via the skin and/or eyes, and also warnings to keep the product out of reach of minors. Precautionary measures, such as the use of gloves and the washing of hands, were often also indicated.
✓ Very few e-liquid companies provided information on quality control and chemical testing. A few company websites noted the existence of child proof caps, the vast majority did not.

✓ Some company specific websites made health claims, regarding, for example, their products' impact on quitting smoking or health outcomes. Other company specific websites made statements related to their products, but were cautious in the wording of claims made (i.e. no reference to quitting or health claims).

✓ A little under half of the industry websites had an age verification request. Sponsorship activities were also observed (namely for sports) but on a limited scale.

✓ The brands that were purchased in WP1 included 12 devices (MODs, disposable, rechargeable) and 38 refill liquids.

✓ The investor reports evaluated had limited information relating to e-cigarettes and the EU market. The few articles of relevance did corroborate our finding that the e-cigarette market in general is witnessing a substantial expansion and there is a transition and expected trend towards refillable e-cigarettes (vs. disposable and rechargeable). Investor reports agreed with our finding that the e-cigarette market is constantly and rapidly evolving which does not allow for the easy monitoring of market shares.

✓ Based on investor reports, our research on industry websites and the requirements laid down by the Tobacco Products Directive, we anticipate that the area of quality assurance of e-liquids and its constituents is going to be an area of significant development.

✓ Continuous monitoring of both market and technological developments is needed due to the rapid market fluctuation, which may be very different within and across member states in the coming year(s).
ANNEX B. Report on the risks of e-cigarettes and refillable e-cigarettes in particular

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1. Introduction

Three different approaches were employed to assess the potential risks associated with the use of e-cigarettes, and refillable e-cigarettes in particular, within WP2 and WP3. Each approach is substantially different from the others and together they provide a stronger evidence base for the extraction of solid conclusions. The three approaches used were:

   a) A systematic review of published literature. The aim of this section was to perform an evaluation of the potential risks attributable to e-cigarettes, and refillable e-cigarettes in particular, as identified through the published peer reviewed literature, within three databases. References included at the end of the report are those that were included within the systematic review, while those noted as footnotes throughout the document provide key evidence from grey literature that support the positions in the text.

   b) An assessment of incidents and/or adverse events related to e-cigarettes, including refillables, based on reports from Poison Centres of a sample of EU MS.

   c) A qualitative and quantitative chemical assessment of the e-cigarette refills purchased in WP1

Based on the triangulation of these three approaches we categorise the potential risks associated with the use of e-cigarettes, and refillable e-cigarettes in particular when possible, the results of which are presented within this Annex.

2. Methods

2.1 Systematic review methods

The aim of the systematic review was to identify the available information within the published scientific literature related to potential risks attributable to e-cigarettes and refillable e-cigarettes in general.
Search strategy and selection criteria

Three separate databases, PubMed (Medline), Scopus and Web of Science were systematically searched for publications relevant to electronic cigarettes and their potential risks. The search strategy was intentionally broad in scope, so as to ensure that all relevant studies were captured. No language, publication year or other limits were imposed. Opinion pieces, reviews, editorials and letters were not included within the review but evaluated for their references.

Search terms:
The following search terms were applied for each of the following databases

- **PubMed:**

- **Scopus:**
  - TITLE-ABS-KEY ( "e-cig" OR "e-cigs" OR "e-cigarette" OR "e-cigarettes" ) OR (( TITLE-ABS-KEY ( electric OR electrical OR electronic* OR refillable OR "electrically heated" ) ) AND ( ( TITLE-ABS-KEY ( cigarette* ) OR TITLE-ABS-KEY ( "nicotine delivery" AND ( system* OR device* ) ) ) ) ) OR ( ( TITLE-ABS-KEY ( personal OR nicotine ) ) AND ( TITLE-ABS-KEY ( vaporiser* OR vaporizer* OR vapouriser* OR vapourizer* ) ) ) OR ( TITLE-ABS-KEY ( "e-liquid" ) )

- **Web of Science:**
  - TITLE: (("e-cig" OR "e-cigs" OR "e-cigarette" OR "e-cigarettes" ) OR (( electric OR electrical OR electronic* OR refillable OR "electrically heated" ) ) AND ( ( cigarette* ) OR ( "nicotine delivery" AND ( system* OR device* ) ) ) ) OR ( ( personal OR nicotine ) AND ( vaporiser* OR vaporizer* OR vapouriser* OR vapourizer* ) ) OR ( ( "e-liquid" ) ) OR TOPIC: (("e-cig" OR "e-cigs" OR "e-cigarette" OR "e-cigarettes" ) OR (( electric OR electrical OR electronic* OR refillable OR "electrically heated" ) ) AND ( ( cigarette* ) OR ( "nicotine delivery" AND ( system* OR device* ) ) ) ) OR ( ( personal OR nicotine ) AND ( vaporiser* OR vaporizer* OR vapouriser* OR vapourizer* ) ) OR ( ( "e-liquid" ) )

Inclusion criteria

- Among search results, a series of selection criteria were applied, in order to select relevant studies. No population limits were posed. Among studies on humans, interventions including the use of any type of electronic cigarette, refillable or not, were considered.
- We adopted an inclusive definition of e-cigarettes, so as to cover a wide range of names and types, including electronic nicotine delivery systems or devices, vaporizers etc. (see search terms above).
- Multiple study designs were considered, including randomized control trials, cross-sectional, cohort and case-control studies with all their variations, as well as experimental studies, chemical analyses and cell studies.

Data extraction

Studies identified through the literature search were imported in a bespoke EndNote library and duplicate entries were removed. Two researchers independently assessed the titles and excluded publications that were clearly ineligible. In the following stage, the two researchers independently read the abstracts of the remaining publications and excluded those that did not contain original data or did not fulfill the inclusion criteria.

Publications that were deemed relevant were included in the review. Two experts independently extracted data from all included studies. Discrepancies in the potential classification were resolved through discussion with a third expert reviewer.

Annex B-2
The systematic review was performed three times during the duration of this report, once in April 2015, once in October 2015 and a third time in January 2016, the results of which are included within the context of this report.

Overall, a total of 319 publications meet all the criteria and were included in the systematic review.

2.2 Poison centre data collection methods
The aim of this subsection of the report was to collect and analyse data on e-cigarette related cases of poisoning in Europe. Our research questions for this task were the following:

a) What are the demographics of e-cigarette poisonings in EU MS?
b) What is the main product type reported and what are the main routes of exposure and clinical outcomes of exposures in the EU?
c) How do European findings compare with findings from other jurisdictions?

Data collection: A request for data was sent to a list of poison centres within the European Union, of which ten EU agreed to provide data: Sweden, The Netherlands, Ireland, Portugal, Austria, Slovakia, Lithuania, Hungary, Croatia and Estonia. Reports covering the time period from 2012 to March 2015, were requested and collected.

All information was de-identified and anonymous. Data on age (≤5 years, 6-18 years, ≥19 years), gender (male, female), reason of exposure (intentional, unintentional, abuse, misuse, suspected suicide or unknown reason); route of exposure (ingestion, respiratory, dermal and ocular); initial type of exposure (e-cigarette refill liquid, e-cigarette non refill, unknown type); management of incident (residence/on site, hospital, ambulance, other/unknown), medical outcome (minor effects, moderate effects, major effects, death based on the provided data) and adverse effects were collected.

Where possible data were analysed using the SPSS software (IBM SPSS Statistics for Windows, Version 21.0).

2.3 Chemical analysis methods
The aim of this subsection of the report was to perform a qualitative and quantitative chemical analysis of e-cigarette refills, the purpose of which was to respond to the following research questions.

a) Are impurities identified within e-cigarette refills in the EU?
b) Does the nicotine content reported agree with the nicotine content measured?
c) What are common flavours/additives in refill liquids?

Sample selection
Within WP1 we identified the 2-3 main companies, based on their online popularity or Nielsen market share numbers where available, that operate in each of the selected 9 EU MS, and for each of these companies we performed a purchase of a convenience sample of e-cigarettes (hardware) and e-liquids (refill liquids and cartridges) with different nicotine concentrations and flavours. Details on this sampling procedure is available in Annex 1. In short the following samples were purchased from each EU MS (coded):

- Germany (refill liquid samples G1, G2, G3, G4, G5, G6, G7, G8)
- Netherlands (refill liquid samples N1, N2, N3, N4, N5, N6, N7, N8)
- UK (disposable UN1, UN2, UN3, UN4 and refill liquids UN5, UN6)

Annex B-3
- France (refill liquid samples F1, F2, F3, F4, F5, F6, F7)
- Italy (refill samples D1, D2, D3, D4)
- Latvia (refill samples L1, L2, L3)
- Spain (refill samples ES1, ES2, ES3, ES4)

**Preparation of samples**

*For Propylene Glycol (PG), Glycerin (G), Linalool (L) and Diethylene Glycol (DG) analysis*

For the determination of the main humectants ingredients of e-liquids, PG and G, as well as for the detection of L and DG a derivatization process with MSTFA followed. In 5 mg of each sample, 0.1 ml MSTFA and 0.1 ml pyridine were added. Each solution was incubated in ambient temperature for 30 minutes with intermediate mechanical shaking (every 10 min). Then solutions were properly diluted in methanol (to provide a final concentration range from 0 to 500 ppm), 10 μg of ketamine was also added (as an external standard) and then Gas Chromatography-Mass spectrometry (GC-MS) analysis commenced.

*For Polycyclic aromatic hydrocarbons (PAH)s analysis*

For the detection of PAHs, 5 mg of each sample were diluted in acetonitrile and 10 μg ketamine were added as an external standard (final volume 1 ml per sample) and analysed by GC-MS. A total of thirteen PAHs was investigated in each sample: acenaphthylene (PAH1), fluorene (PAH2), phenanthrene (PAH3), anthracene (PAH4), pyrene (PAH5), benzo-(a)-anthracene (PAH6), chrysene (PAH7), benzo-(k)-fluoranthene (PAH8), benzo-(a)-fluoranthene (PAH9), benzo-(a)-pyrene (PAH10), benzo-(g,h,i)-perylene (PAH11), dibenzo-(a,h)-anthracene (PAH12), indeno-(1,2,3-cd)-pyrene (PAH13).

*For nicotine analysis*

For the determination of nicotine an amount of 100 mg of each sample was diluted in 5 ml ultrapure water. Further dilutions of the samples were done in order to achieve a sample content of 0.2 mg per one ml and 10 μg ketamine were added before analysing by Liquid Chromatography-Mass spectrometry (LC- MS). All dilutions were done using ultrapure water.

*For main flavour ingredients analysis*

Five flavour ingredients (FL1-FL5) were investigated and quantified in each sample. An amount of 100 mg of each e-liquid sample was added in 5 ml ultrapure water. Further dilutions were done in order to achieve a sample content of 2 mg per one ml and 10 μg ketamine were added before analysing by LC- MS. All necessary dilutions were done using ultrapure water.

*For nitrosamines analysis*

For the detection of four nitrosamine compounds (NNAL, NNK, NAT, NAB) 100 mg of each sample were diluted in 5 ml ultrapure water. Further dilutions were done in order to achieve a sample content of 2 mg per one ml and 10 μg ketamine were added before analysing by LC- MS. All necessary dilutions were done using ultrapure water.

**Instrumental conditions**

*Gas chromatography-mass spectrometry (GC-MS) system*

GC-MS technique was used for the determination and quantification of PG and G, as well as for the detection of L, DG and PAHs as aforementioned. Electron ionization mass spectrometric analysis was performed on a GC-MS QP-2010 Shimadzu system (Shimadzu, Japan) equipped with a DB-5 (30 m × 0.25 mm, 0.25 μm) capillary column (Agilent Technologies, USA) for PG, G, L and DG analysis and with a SLB-5ms (30 m × 0.25 mm, 0.25 μm) capillary column (Supelco, USA) for PAHs analysis. Pure helium (99.999%) with a column flow of 1 ml/min was used as a carrier gas. One μl of each solution was injected into the system in the splitless mode and analysed under the following conditions: the column temperature was initially held at 55°C for 2 min and...
raised to 320°C at 20°C/min (for PG, G, L and DG analysis), while the temperature was initially held at 120°C for 3 min, raised to 310°C at 5°C/min where held for 1 min and finally raised to 325°C at 10°C/min where held for 1 min (for PAHs analysis). The injector temperature was 230°C. The interface temperature was set at 310°C. The ion source temperature was 220°C. An auto-tune of the mass spectrometer using perfluorotributylamine (PFTBA, tuning standard) was performed before the analysis of every batch of samples. Quantitative analysis was achieved in selected ion monitoring (SIM) mode with a scan time of 0.2 s, using one target ion for quantification and two qualifier ions for the confirmation of each compound. Data acquisition and processing was performed by using the GC-MS Solution software (Shimadzu, version 3.40.307).

**Liquid chromatography-mass spectrometry system**

For the determination and quantification of NIC, flavours (FL1-FL5) and nitrosamine compounds an LC-MS technique was performed. Liquid chromatography was carried out using a Shimadzu Prominence LC system consisting of a binary LC pump, a vacuum degasser, an auto-sampler and a column oven (Shimadzu, Japan). A gradient program of two mobile phases was selected for the analysis of the aforementioned compounds. Total mobile phase pumped at 0.5 or 0.6 ml/min through a GraceSmart RP 18 5u (250 mm x 4.6 mm, 5 μm) column (Grace, Belgium) thermostated at 30-45°C. An aliquot of 10 μl of each sample was injected in the mobile phase flow for separation and analysis.

A mass spectrometer (LCMS-2010 EV Shimadzu), in conjunction with an atmospheric pressure chemical ionization (APCI) interface with a single quadrupole mass filter, was used to detect and quantify the analytes in column effluent. Interface, curved desolvation system (CDL) and heat block temperatures were 400°C, 200°C and 200°C, respectively. The detector voltage was 1.5 kV and the nebulizing gas flow 2.5 L/min. The mass spectrometry operating conditions were tuned according to the manufacturer procedure. Data acquisition and processing were performed using LC-MS Solution software (Shimadzu, version 3.40.307).

**Calibration and quantification**

Stock solutions of PG, G, L and DG at the concentration of 1 mg/ml were prepared in methanol. Working solutions of each analyte were prepared before each batch analysis of samples by dilutions in methanol and by following the same derivatization process as described before (section: preparation of samples). The concentrations of PG and G were 0, 31.25, 62.5, 125, 250 and 500 μg/ml, while for L and DG were 0, 2.5, 5, 10 and 20 μg/ml. Stock mix solution of thirteen PAHs described before at the concentration of 1 mg/ml was prepared in acetonitrile. Working solutions were prepared by dilutions in acetonitrile at the concentrations of 0, 0.5, 1, 2.5 and 5 μg/ml. Stock solution of NIC, flavour (FLs) and nitrosamines at the concentration of 1 mg/ml was prepared in methanol. Working solutions were prepared by dilutions in methanol at the concentrations of 0, 0.5, 1, 2.5, 5 and 10 μg/ml for NIC and FLs and of 0, 0.1, 0.25, 0.5 and 1 μg/ml for nitrosamines.

**Method validation**

*Optimization of PG, G, L and DG derivatization parameters*

For the optimization of derivatization parameters of PG, G, L and DG the proper aliquot of the derivatization reagent MSTFA was tested in two different levels (62.5 and 250 μg/ml). The examined aliquots were 50, 100 and 150 μl. After following the procedure described before for the derivatization of analytes, each sample was analysed by GC-MS (section preparation of samples). Results were compared and found that adding 100 μl of MSTFA for 30 min at room temperature provides the better results and so this was selected as the sufficient amount of derivatization reagent.
Linearity
Internal standard method was used for analytes quantification. The instrument response was linear in the concentrations range between 31.25 and 500 μg/ml for PG and G, from 2.5 to 20 μg/ml for L and DG, from 0.5 to 5 μg/ml for PAHs, from 0.5 to 10 μg for NIC and investigated flavour ingredients, and from 0.1 to 1 μg/ml for nitrosamines, with $r^2 > 0.99$ in all cases.

Limits of quantification
Limit of quantification (LOQ) of the method was determined as the concentration of analyte at which the signal-to-noise ratio of the quantification ion was at least 10. LOQ values ranged from 0.003 μg/ml (for three PAH compounds) to 1.187 μg/ml (for G).

Method precision and accuracy
The precision (inter-days) and the accuracy of the method were calculated for the most commonly detected compounds in replacement e-liquid samples. Inter-days precision was measured and expressed as % relative standard deviation (%RSD) of instrument response for replicate measurements ($n=6$) of calibration samples in concentrations of three different levels for each analyte (62.5, 125 and 250 μg/ml for PG and G, 2.5, 5 and 10 μg/ml for NIC and the main flavour ingredients). Precision was calculated below than 16% in all cases. Accuracy was also determined for the same concentration levels of each analyte ($n=6$) (>99.1% for all cases).

3. Results

3.1 Poison centre results
Data for a total of 343 cases was reported. However, three countries –Ireland (53 out of the 90 Irish cases), Croatia (3 cases) and Estonia (10 cases)- were only able to provide summary statistics for cases reported to their centres, due to lack of detailed data or confidentiality regulations. Thus, these 66 cases were excluded from the statistical analysis and we analysed 277 cases from a total of eight EU MS (Table 1).

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden (SE)</td>
<td>121</td>
<td>43.7</td>
</tr>
<tr>
<td>Nederland (NL)</td>
<td>78</td>
<td>28.2</td>
</tr>
<tr>
<td>Ireland (IE)</td>
<td>37</td>
<td>13.4</td>
</tr>
<tr>
<td>Portugal (PT)</td>
<td>25</td>
<td>9.0</td>
</tr>
<tr>
<td>Austria (AT)</td>
<td>8</td>
<td>2.9</td>
</tr>
<tr>
<td>Slovakia (SK)</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Lithuania (LT)</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Hungary (HU)</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Demographic characteristics: Among the 277 cases that we analysed, 92 (33.2%) were among children 5 years old or younger, 27 (9.7%) were among children between 6 and 18 years old and 158 (57.0%) were among adults. There was approximately an equal ration of male/female exposures, as 118 (50.6%) were male and 115 (49.4%) were female.
**Exposure Characteristics:** As noted in **Table 2**, unintentional exposure was the most frequently cited reason (71.3%), followed by intentional exposure (17.8%). Abuse, misuse and suspected suicide were less frequently reported. It is important to note that one in four exposures (27.4%) among adults were reported as intentional, whereas only 6 out of 119 paediatric cases (5.1%) were associated with intentional exposure.

**Table 2. Exposure Characteristics of reported cases**

<table>
<thead>
<tr>
<th>Exposure Reason</th>
<th>Paediatric (≤18 years)</th>
<th>Adults (≥19 years)</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td><strong>Exposure Reason</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintentional</td>
<td>104</td>
<td>88.1</td>
<td>92</td>
</tr>
<tr>
<td>Intentional</td>
<td>6</td>
<td>5.1</td>
<td>43</td>
</tr>
<tr>
<td>Abuse</td>
<td>4</td>
<td>3.4</td>
<td>11</td>
</tr>
<tr>
<td>Misuse</td>
<td>1</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>Suspected Suicide</td>
<td>1</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td><strong>Exposure route</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingestion</td>
<td>96</td>
<td>81.4</td>
<td>91</td>
</tr>
<tr>
<td>Respiratory</td>
<td>11</td>
<td>9.2</td>
<td>35</td>
</tr>
<tr>
<td>Dermal</td>
<td>8</td>
<td>6.7</td>
<td>17</td>
</tr>
<tr>
<td>Ocular</td>
<td>3</td>
<td>2.5</td>
<td>18</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>3.4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Initial type of exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-cigarette refill liquid</td>
<td>97</td>
<td>82.2</td>
<td>143</td>
</tr>
<tr>
<td>E-cigarette non refill</td>
<td>2</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Unknown type</td>
<td>19</td>
<td>16.1</td>
<td>14</td>
</tr>
</tbody>
</table>

Regarding the initial type of exposure, refill liquids were responsible for the overwhelming majority of the reported cases in both age categories. Only two paediatric cases out of the 277 reported cases were related to non-refillable e-cigarettes. We must state though that this may also be due to the fact that refillable e-cigarettes may account for a substantially larger market share a fact that may impact the frequency of exposure.

With regards to the route of exposure, two-thirds of all exposures (67.5%) occurred as ingestion of e-liquids, followed by exposure via the respiratory route (16.6%), dermal route (9.0%) and ocular (7.6%) route. Ingestion was noted to be more frequent among children (81.4% vs. 57.6%, \( p<0.001 \)). Adult cases were reported more frequently for exposure via the respiratory (22.2% vs. 8.5%, \( p<0.001 \)) and ocular routes (11.4% vs. 2.5%, \( p=0.006 \)) in comparison to children.

**Management and medical outcome:** The original classification of case management included both “residence”, if the incident took place and was managed at somebody’s home, and “on site”, if the incidence took place at any other location, but was managed in that location as well. The two categories were merged and are presented as one (**Table 3**). The majority of cases were managed on site (70.0%), but 56 cases (23.7%) were managed in a hospital and 4 cases (1.7%) in an ambulance.
Table 3. Management and medical outcome

<table>
<thead>
<tr>
<th>Management of incident</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence/ on site</td>
<td>166</td>
<td>70.0</td>
</tr>
<tr>
<td>Hospital</td>
<td>56</td>
<td>23.7</td>
</tr>
<tr>
<td>Ambulance</td>
<td>4</td>
<td>1.7</td>
</tr>
<tr>
<td>Other/ Unknown</td>
<td>11</td>
<td>4.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Outcome</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor effect</td>
<td>112</td>
<td>53.8</td>
</tr>
<tr>
<td>No effect</td>
<td>82</td>
<td>39.4</td>
</tr>
<tr>
<td>Moderate effect</td>
<td>13</td>
<td>6.3</td>
</tr>
<tr>
<td>Major effect</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The majority of the recorded exposure cases had a favourable outcome. In 39.4% of them, no effect was reported and a further 53.8% of the cases resulted in only minor effects, 6.3% reported moderate effects and 1 case reported a major effect. No deaths were recorded as a result of an e-cigarette exposure within the data collection period and within our data collected.

- Age was associated with the noted medical outcome, as 68.3% (62.5% minor – 5.8% moderate/ major) of adult cases vs. 49.4% (41.4% minor – 8.0% moderate/ major) of child cases reported an outcome ($p<0.05$)
- Among cases that recorded a medical outcome (minor-moderate or major), 54.8% of cases were associated with ingestion, 28.6% with inhalation, 9.5% of ocular and 7.5% with dermal exposure.

**Clinical Effects:** Clinical effects reported in e-cigarette exposure cases are reported in Table 4. A wide range of symptoms were reported, of which vomiting (20.3%), dizziness (14.5%), nausea (13.8%) and throat conditions (9.1%) were the most frequently reported in both children and adults. Abdominal conditions, eye conditions, headache, diarrhoea, breathing conditions and tremor were also reported in smaller numbers of cases.

Table 4. Most frequently identified clinical effects

<table>
<thead>
<tr>
<th>Clinical effects</th>
<th>Paediatric (≤18 years)</th>
<th>Adults (≥19 years)</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27</td>
<td>22.7</td>
<td>29</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>11.8</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11.8</td>
<td>24</td>
</tr>
<tr>
<td>Throat Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>9.2</td>
<td>14</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>5</td>
<td>4.2</td>
<td>4</td>
</tr>
<tr>
<td>Burning Throat</td>
<td>2</td>
<td>1.7</td>
<td>3</td>
</tr>
<tr>
<td>Oral Mucosal</td>
<td>3</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Salivation</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Conditions</td>
<td>7</td>
<td>5.9</td>
<td>10</td>
</tr>
<tr>
<td>Eye Conditions</td>
<td>1</td>
<td>0.8</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>2.5</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>1.7</td>
<td>6</td>
</tr>
<tr>
<td>Breathing Conditions</td>
<td>4</td>
<td>3.4</td>
<td>4</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>23.7</td>
<td>47</td>
</tr>
</tbody>
</table>
**Time trends:** The increase in the number of e-cigarette poisonings/incidents in the EU (Figure 1) indicate a sharp increase in the number of incidents between 2012-2013, a similar pattern was noted in the UK\(^1\) which indicated a jump in e-cigarette related incidents between 2012/2013 and 2013/2014 reporting years). Events related to e-cigarette product exposure reported to the American Association of Poison Control Centres increased 42% from 2011 (n=256) to 2012 (n=438), while after the beginning of 2013 a dramatic increase in the number of exposures to e-cigarettes and their refills was seen in the US, which peaked in April 2014 and comprised 35% of all nicotine-related single exposure calls [1-3].

![Figure 1. Trends in reports to EU poison centers regarding e-cigarettes](image)

**Comparison of our poison centre results with other studies:** This is the first study to report exposure cases recorded by poison centres in multiple EU MS. However, similar reports have been published in the United States, analysing data from all exposures involving e-cigarettes reported to the National Poison Data System by U.S. Poison Centres [4]. Our results are compared with the US data in **Table 5**. Among cases reported to U.S Poison Centres, there was a greater proportion of cases in children ≤5 years (42.2%) compared to the European data (33.2%). Overall, results are quite similar between the two studies. Unintentional exposures constitute the majority in both the EU (71.3%) and the US (80.0%), while about two thirds of the cases were exposed through ingestion (67.5% in Europe and 64.9% in the US- as also in the UK), followed by the respiratory, dermal and ocular routes.

Regarding management, 70.0% of the cases in Europe and 68.1% of cases in the US were managed on site, followed by the ones that were managed in a healthcare facility. The classification of management differed between Europe and the US, so comparisons may have limitations, however it is clear that the majority of cases did not involve utilisation of healthcare. Results on outcome are also similar between the two studies. More than 80% of the cases that were followed-up had no or only minor effects and a very small number of cases had major effects. One death was recorded in the US, while there were no deaths among the 277 European cases. Vomiting, nausea and dizziness were the most frequent symptoms reported in cases of e-cigarette exposure both in the US and Europe, followed by several other symptoms. Dizziness (14.5% vs. 5.4%) and throat conditions (9.1% vs. 2.3%) were more frequent in European cases compared to the US, but the overall profile of clinical effects were quite similar between the sites.

---

Table 5. Comparison between exposures related to e-cigarettes recorded in European and United States (US) poison centres.

<table>
<thead>
<tr>
<th></th>
<th>EUREST EU data</th>
<th>U.S Poison Centres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Total Sample</td>
<td>277</td>
<td>1,700</td>
</tr>
<tr>
<td>Duration</td>
<td>1/2012-3/2015</td>
<td>7/2010-9/2013</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>92</td>
<td>33.2</td>
</tr>
<tr>
<td>6-18</td>
<td>27</td>
<td>9.7</td>
</tr>
<tr>
<td>≥19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>158</td>
<td>57.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>115</td>
<td>49.4</td>
</tr>
<tr>
<td>Male</td>
<td>118</td>
<td>50.6</td>
</tr>
<tr>
<td>Exposure Reason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintentional</td>
<td>196</td>
<td>71.3</td>
</tr>
<tr>
<td>Intentional</td>
<td>49</td>
<td>17.8</td>
</tr>
<tr>
<td>Exposure Route</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingestion</td>
<td>187</td>
<td>67.5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>46</td>
<td>16.6</td>
</tr>
<tr>
<td>Dermal</td>
<td>25</td>
<td>9.0</td>
</tr>
<tr>
<td>Ocular</td>
<td>21</td>
<td>7.6</td>
</tr>
<tr>
<td>Management of incident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence/ on site</td>
<td>158</td>
<td>70.0</td>
</tr>
<tr>
<td>Hospital&lt;sup&gt;b&lt;/sup&gt;</td>
<td>56</td>
<td>23.7</td>
</tr>
<tr>
<td>Medical Outcome&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No effect</td>
<td>82</td>
<td>39.4</td>
</tr>
<tr>
<td>Minor effect</td>
<td>112</td>
<td>53.8</td>
</tr>
<tr>
<td>Moderate effect</td>
<td>13</td>
<td>6.3</td>
</tr>
<tr>
<td>Major effect</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Clinical effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>56</td>
<td>20.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>14.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>13.8</td>
</tr>
<tr>
<td>Throat Conditions</td>
<td>25</td>
<td>9.1</td>
</tr>
<tr>
<td>Abdominal Conditions</td>
<td>17</td>
<td>6.1</td>
</tr>
<tr>
<td>Eye conditions</td>
<td>14</td>
<td>5.0</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>4.0</td>
</tr>
<tr>
<td>Diarrheal</td>
<td>8</td>
<td>2.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> ≥20 years old in the US study; <sup>b</sup> Defined as “patient in/en route to healthcare facility” in the US study; <sup>c</sup> Among those followed
3.2 Chemical analyses results

Our laboratory analyses identified the following:

✓ Three out of the 8 shipments (37.5%) of refills arrived with evident leakage.
✓ No existence of nitrosamines, PAHs, Diethylene Glycol and a range of PG/VG ratios
✓ No discrepancies in the reported vs. measured nicotine concentrations
✓ Our qualitative assessment identified a wide range of flavours with CLP classifications.

Table 6. Qualitative assessment of e-cigarette refill liquids in the EU market

<table>
<thead>
<tr>
<th>Flavour Name</th>
<th>Flavour CAS</th>
<th>CLP classifications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4 cineole</td>
<td>470-67-7</td>
<td>H226</td>
</tr>
<tr>
<td>1,8 cineole</td>
<td>470-82-6</td>
<td>H226, H317, H225, H315, H318, H335, H304, H411, H412</td>
</tr>
<tr>
<td>2,3 dimethyl pyrazine</td>
<td>5910-89-4</td>
<td>H226, H302, H315, H318, H335, H319</td>
</tr>
<tr>
<td>2,3,5 - trimethyl pyrazine</td>
<td>14667-55-1</td>
<td>H226, H302, H315, H319, H335</td>
</tr>
<tr>
<td>3 - hexen-1-ol, acetate</td>
<td>928-96-1</td>
<td>H319, H226, H228, H315, H332, H335 H412</td>
</tr>
<tr>
<td>3,6, Dimethyl-2-ethyl pyrazine</td>
<td>27043-05-6</td>
<td>H319, H315, H302, H335</td>
</tr>
<tr>
<td>3-octanol</td>
<td>589-98-0</td>
<td>H319, H315, H335</td>
</tr>
<tr>
<td>4-ketosiphorone</td>
<td>1125-21-9</td>
<td>H226, H302, H317, H315, H319, H335</td>
</tr>
<tr>
<td>4-methyl-2 propyl 1,3,dioxolane</td>
<td>4352-99-2</td>
<td>H226, H319</td>
</tr>
<tr>
<td>5-hydroxy octanoic acid lactone</td>
<td>698-76-0</td>
<td>H319, H315</td>
</tr>
<tr>
<td>acetic acid, benzyl ester</td>
<td>64-19-7</td>
<td>H226, H314</td>
</tr>
<tr>
<td>acetic acid phenylmethyl ester</td>
<td>140-11-4</td>
<td>H319, H335, H411, H315, H370, H372, H302</td>
</tr>
<tr>
<td>alloocimene</td>
<td>673-84-7</td>
<td>H315, H319, H411, H226, H317, H302 H412</td>
</tr>
<tr>
<td>almond artificial essential oil</td>
<td>100-52-7</td>
<td>H302</td>
</tr>
<tr>
<td>alpha - cedrol</td>
<td>77-53-2</td>
<td>H411, H315, H319</td>
</tr>
<tr>
<td>alpha (+) pinene</td>
<td>7785-70-8</td>
<td>H335, H315, H319, H410, H411 H400, H302, H312, H226, H304, H317, H332</td>
</tr>
<tr>
<td>alpha-ionone</td>
<td>127-41-3</td>
<td>H334, H317, H411</td>
</tr>
<tr>
<td>amylacetate</td>
<td>628-63-7</td>
<td>H226</td>
</tr>
<tr>
<td>anethol</td>
<td>104-46-1</td>
<td>H411,H317</td>
</tr>
<tr>
<td>banana oil (isopentyl acetate)</td>
<td>123-92-2</td>
<td>H226, H412 H335, H411, H315 H317, H319, H336</td>
</tr>
<tr>
<td>benzyl benzoate</td>
<td>120-51-4</td>
<td>H410, H411, H400, H302, H332, H412</td>
</tr>
<tr>
<td>beta-caryophyllene</td>
<td>87-44-5</td>
<td>H304, H315, H319, H335</td>
</tr>
<tr>
<td>beta-pinene</td>
<td>127-91-3</td>
<td>H335,H315, H319, H410, H411, H400, H302, H312 H226, H304, H317 H413</td>
</tr>
<tr>
<td>carveol dihydro</td>
<td>619-01-2</td>
<td>H315, H319 H335</td>
</tr>
<tr>
<td>cyclohexanol</td>
<td>108-93-0</td>
<td>H335,H315, H319, H411, H302, H226 H332</td>
</tr>
<tr>
<td>diphenyl ketone</td>
<td>119-61-9</td>
<td>H335,H315, H319, H410, H411 H373 , H412 H400, H351 H302</td>
</tr>
<tr>
<td>Geraniol</td>
<td>106-24-1</td>
<td>H335 H315, H317, H319, H318 H410 H411</td>
</tr>
<tr>
<td>menthol</td>
<td>89-78-1</td>
<td>H335 H315 H319, H318, H302</td>
</tr>
<tr>
<td>menthol acetate</td>
<td>89-48-5</td>
<td>H411</td>
</tr>
</tbody>
</table>

* List of mentioned CLP Classifications: H226 flammable liquid and vapour; H302 harmful if swallowed; H304 may be fatal if swallowed and enters airways; H315 may cause skin irritation; H317 may cause allergic skin reaction; H319 causes serious eye irritation; H332 Harmful if inhaled; H334 May cause allergy and asthma symptoms or breathing difficulties if inhaled; H335 may cause respiratory irritation; H336 may cause drowsiness or dizziness; H373 May cause damage to organs through prolonged or repeated exposure; H400 very toxic to aquatic life; H410 very toxic to aquatic life with long lasting effects; 411 toxic to aquatic life with long lasting effects; H412 Harmful to aquatic life with long lasting effects.

Annex B-11
3.3. Systematic Review and triangulation of the evidence

It is important to note that the present chapter covers only the possible risks attributable to e-cigarettes, with a particular focus on refillable e-cigarettes. No grading of the available evidence was performed and no parallel comparisons with other tobacco products was performed, as this was out of the scope of the review. Furthermore we must note that the articles included in the review were those that referred to the existence of a risk, as our aim was to compile a complete list of potential risks and thus articles that identified no association were excluded.

Based on the triangulation of our methods we grouped the potential risks into the below categories and subsequently we present collectively the available evidence from the three aforementioned sources (literature review, chemical analyses, poison centre reporting).

**Overall the main categories of risk are:**

1. Risk from constituents/toxins/impurities/nicotine
2. Risk of adverse effects (cellular, animal and human)
3. Risk due to production design flaws (leakage/electric failures/inconsistent dosing)
4. Risk of toxicity from accidental/intentional exposure to refill liquids
5. Risks associated with inadequate/misleading information
6. Risks associated with the possibility to modify refillable e-cigarettes or associated with home/own blending of e-liquids (including narcotics)
7. Risk of encouraging dual tobacco product use
8. Risks of reduced quit attempts
9. Risk of the ex-smoker transitioning from abstinence to e-cig use and to relapse and conventional tobacco use
10. Risk as use as a gateway product to nicotine addiction and subsequent smoking initiation
11. Risk due to second hand exposure – emissions /clean indoor air
12. Risk of renormalizing nicotine addiction
13. Risk to the environment

**Risk from constituents/toxins/impurities/nicotine:**

E-cigarette liquids contain a wide variety in chemical components, the main groups of which are described below.

**Dilutents/humectants:** Propylene glycol and Vegetable glycerine are two commonly used humectants in e-cigarettes and measured in emissions [5, 6]. While studies have assessed that exposures to mixtures containing propylene glycol (i.e. artificial mist, solvents, etc.) may lead to respiratory symptoms [7] as it may also be rapidly absorbed during inhalation [8], while recent studies have indicated that humectants in e-cigarettes may induce the release of cytokines and pro-inflammatory mediators [9] and under certain conditions potentially cause irritation of the airways [10]. Furthermore, the Health Council of the Netherlands report on propylene glycol concluded that propylene glycol does have weak irritating effects to the skin and respiratory tract (predominantly in animal models), while industry funded research has noted that extensive e-cigarette use may lead to levels of exposure close to the calculated threshold limit values of occupational exposure limits [11]. Propylene glycol is not classified as hazardous under the EC Regulation 1272/2008. Further research on the long term effects with animal models is needed.

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3 Health Council of the Netherlands. Propylene glycol (1,2-Propanediol); Health based recommended occupational exposure limit. The Hague: Health Council of the Netherlands, 2007; publication no. 2007/02OSH.
to improve the current understanding of the potential effect of chronic humectant exposure on pulmonary/human health.

**Nicotine:** Nicotine is a toxic and potent substance\(^5\). Nicotine contained in e-cigarettes is sufficient to increase levels of plasma nicotine and elevate the heart rate [12-15], as well as systolic and diastolic blood pressure [14], with higher nicotine uptake related to experience, product evolution and nicotine content of the refill liquid [16-17]. Discrepancies in the reported vs. measured nicotine concentrations have been noted in the past [18-23], while nicotine degradation products (such as cotinine, myosmine, anatabine, anabasine, and b-nicotyrine) have also been noted [18]. Exposure to nicotine may pose an additional risk to vulnerable populations (i.e. children, adolescents, adults with certain comorbidities)

**Flavours:** Flavours are a primary component of e-cigarette liquids [24]. The plethora of flavours and additives may make e-cigarettes more attractive for certain population groups [25]. Interest of smokers for e-cigarettes may vary depending on the flavour [26-27], while flavours in e-cigarettes may play a role in increasing ease of use, reducing harshness (menthol), suppressing withdrawal and producing anticipatory reward perceptions [28], with preferences that potentially related to concurrent cigarette use [29, 30]. The impact of flavours on youth experimentation is an area relatively untouched that warrants further research, however preliminary findings have indicated that in the US the majority proportion of ever users and past 30 day users reported use of a flavoured e-cigarette [31].

The Flavour and Extract Manufacturers Association evaluates the safety of chemicals used in food flavourings, many of which also may be used in ENDS. Some flavours are characterized as “generally regarded as safe (GRAS)”, which however is related to the evaluation of the chemicals used in food flavours with regards to their ingestion, not their inhalation. Indeed, certain flavours have been recently noted to be potential respiratory health hazard [32]. To address this hypothesis in WP2-3 we performed a qualitative chemical assessment of the 38 refill liquids purchased within WP1 for which the flavours were identified and matched with their CLP classification.

Flavours may potentially also have an impact on indexes of cytotoxicity and oxidative stress [33]. For instance, cinnamon flavourings in refill fluids have been linked in one study to cytotoxicity [34], coffee-flavoured e-liquid produced a cytotoxic effect on cultured mammalian fibroblasts [35], menthol in e-liquid refills has been noted to be associated with a reduction in proliferation rates of human periodontal ligament fibroblasts [36], while a cytotoxic effect in human keratinocytes and epithelial lung cells attributable to flavouring components has also been noted [37].

Refillable e-cigarettes have a significantly larger number of flavours available for consumers in comparison to non-refillable e-cigarettes, due to the fact that they are created to address multiple niche preferences. Research on the US market identified over 7500 different flavours [38], many of them with potentially youth oriented flavours [39], while research among Polish youth indicated that the majority of e-cigarette only users preferred fruit flavoured products, followed by chocolate and vanilla flavours, with only a small percentage preferring tobacco flavoured products [40]. Furthermore, there is also a possibility that the aromas and flavours of e-liquids may make


Annex B-13
them more attractive to infants/young children who may be at a greater risk of accidental ingestion of e-liquid. Results of WP1 indicated flavours such as bubble-gum, apple pie, pina colada, stracciatella and many aromas that simulate sweets, alcoholic beverages and fruits.

**Carbonyl compounds:** Studies have shown that e-cigarettes may emit toxic carbonyl compounds, generated from thermal decomposition [22, 41-52]. For example, acetaldehyde and acrolein in e-cigarette emissions have been reported [53-54]. Formaldehyde or acetaldehyde in a number of refill fluids have been identified [55-56]. Overall, the risk of exposure to thermal breakdown products (i.e. carbonyls) may be possibly higher in refillable e-cigarettes that have the ability to modify the electrical output, and hence the temperature at which the e-liquid is vaporized.

**Heavy and trace metals:** Research has identified concentrations of Cd, Ni, Pb, Zn, Ag from components of the device, not the e-liquid itself [22, 57-60].

**Particle production:** Fine particles can be variable and chemically complex. Particle emissions have been measured following e-cigarette use [6, 8, 53, 61-67], and a human deposition model has indicated that a percentage of these particles would be deposited in alveoli (arterial delivery) and the head and neck (venous delivery) [68]. However it is not clear whether the particles delivered by e-cigarettes have health effects and toxicity, the possibility of health risks must be considered.

**TSNAs:** Previous research⁶ has identified that tobacco-specific nitrosamines TSNA may be present in certain e-liquids [42, 69, 70]. Our chemical assessment of the 38 samples from WP1 did not identify the existence of TSNAs.

**Volatile Organic compounds and Polycyclic aromatic hydrocarbons (PAHs):** Toluene and p,m xylene have been identified in the past in some e-cigarette refill liquids [22, 71]. Indications that PAH’s may be released in emissions also exist [8, 72]. Our chemical analysis did not identify such compounds in popular brands in the EU market.

**Impurities:** Diethylene glycol has previously been identified in e-cigarette refill liquids [49] however other reports do not note their existence [19]. Our chemical assessment of the 38 samples from WP1 did not identify the existence of diethylene glycol in refill liquids.

**Other substances:** Small amounts of two pharmaceutical substances, amino-tadalafil and rimonabant, have been identified in EC liquids [18,73], while minor tobacco alkaloids have been identified in another [74]. Recently, concentrations of diethyl phthalate, diethylhexyl phthalate, Triethylene glycol, tetraethylene glycol and pentaethylene glycol were quantified in a number of Chinese refill liquids on the Korean market [75], while other impurities have also been noted [49, 76] Other substances detected in refill liquids include glycerol [3], propylene glycol, ethylene glycol, acetamide, and the known skin allergens eugenol, linalool, benzyl alcohol, anis alcohol etc. [77]. The pH of the e-liquids have also been noted as an area of concern [78].

**Risk of adverse effects**

**Cellular studies**

A number of refill fluids used for refillable e-cigarettes have been found to have cytotoxic effects [79-81], especially when nicotine and flavour substances were present [9]. It is important to note however, the chemical composition of refill liquids may vary, even between different bottles of the same product; therefore it may be difficult to estimate the cytotoxicity associated with each product, or to attribute causality to a specific ingredient (i.e. nicotine or a flavour). Moreover results between studies, are often conflicting which could be attributable to different

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Annex B-14
methodologies, e-liquids used and different exposure protocols and cytotoxicity tests [82]. Examples of evidence indicating potential cytotoxicity include:

- E-liquid samples may have cytotoxic properties on cultured cardio-myoblasts, which the authors attribute to be associated with the production process and materials used in flavours [83].
- Cinnamon flavourings in refill fluids have been linked in one study to cytotoxicity [81].
- Coffee-flavoured e-liquid produced a cytotoxic effect on cultured mammalian fibroblasts [80].
- Menthol in e-liquid refills has been noted to be associated with a reduction in proliferation rates of human periodontal ligament fibroblasts [84].
- A cytotoxic effect in human keratinocytes and epithelial lung cells has also been noted [9].
- Humectants have been found to induce the release of cytokines and pro-inflammatory mediators [9].
- Human embryonic stem cells and mouse neural stem cells were identified as sensitive to cytotoxicity from chemicals contained in e-cigarette liquids [79].
- Human tracheobronchial epithelial cells exposed to e-liquid indicate an inflammatory response, while in mouse models e-liquid (both without nicotine and with nicotine) inhibit host defense against respiratory viral (i.e., human rhinovirus, HRV) infection [85].
- Soluble components of e-liquids, including nicotine, cause dose-dependent loss of lung endothelial barrier function within lung microvascular endothelial cells, which is associated with oxidative stress and inflammation [86].
- Exposure to e-cigarette emissions have been also identified to lead to autophagy impairment, oxidative stress, apoptosis in murine lung cells [87].
- Conference reports have indicated that e-cigarettes may alter gene expression in bronchial epithelial cells, leading to a higher malignant transformation, in a similar way to traditional cigarettes [88].
- E-cigarette refill liquid has been identified to be able to alter the metabolome of human bronchial epithelial cells [89].
- Exposure of human cells (epithelial cells, alveolar macrophages, and neutrophils) to e-cigarette emissions led to cytotoxicity in a dose dependent manner. Addiction of nicotine increased cytotoxicity while the addition of flavours to e-liquids did not influence cytotoxicity and a reduced antimicrobial activity against Staphylococcus aureus [90].
- A dose–response result of cell viability (MTS assay) and IL-8 and human beta defensin 2 (HBD2) mRNA expression from stimulated A549 cells was noted following exposure to e-cigarette emissions [91].
- Exposure of normal human bronchial epithelial cells to e-cigarette emissions led to lower cell viability and increased oxidative stress levels compared to clean air exposed cells. Cells exposed to glycerol show a significantly reduced viability compared to clean air as well as e-cigarette vapor exposed cells [92].
- Exposure of blood neutrophils to e-cigarette emissions extract increased MMP-9 and CXCL8 release, observed along with an increase in MMP-9 gelatinase activity and increased p38 MAPK activation. Furthermore, neutrophil shape change, and dual CD11b and CD66b expression increased in response to exposure compared to unexposed cells. The above findings indicate an inflammatory response. (Conference proceeding) [93].
- Exposure of human bronchial epithelial cells (on a background of silenced p53 and activated KRAS) to e-cigarette constituents led to differentially expressed genes following in vitro exposure (Conference proceeding) [94].
- Exposure of primary rat lung endothelial cell or primary human lung microvascular cells to e-cigarette solutions was found to disrupt endothelial barrier function in a dose dependent manner (Conference proceeding) [95].
• Exposure of Calu3 cells to certain e-liquid flavours decreased cell proliferation and evoked changes in calcium signalling (conference proceeding) [96].
• Exposure of blood neutrophils to e-cigarette emission extract led to an inflammatory response from neutrophils and macrophages including increased MMP-9 and CXCL8 release. (conference proceeding) [97].
• An experimental study exposing Calu3 airway epithelial cells to e-cigarette to e-liquid or emissions inhibited CFTR- ion transport (conference proceeding) [98].

Animal Studies

• A laboratory study on mice indicated that the inhalation of refill liquids may aggravate airway inflammation and hyper responsiveness and stimulate cytokine production (increasing synthesis of IL-4, IL-5, IL-13, and IgE) when it is delivered by intratracheal route in mice [99].
• Another study on mice indicated a significant increase in oxidative stress and moderate macrophage-mediated inflammation and increased pulmonary susceptibility to bacterial infections (due to impaired pulmonary bacterial clearance following an intranasal infection with Streptococcus pneumonia). Exposed mice also displayed enhanced virus-induced illness and mortality after exposure to Influenza A [100].
• Addition of e-liquids to cell culture media induces morphological changes in human lung fibroblasts, while e-cigarette aerosol exposure causes lung inflammation and pro-inflammatory response in mouse lungs [33].
• Exposure to e-cigarette emissions led to reduced cell proliferation in mice models [101].
• Exposure to e-cigarette emission extracts led to an inflammatory response, oxidative stress production and cytokine release in Kupffer macrophages [102].
• Exposure to e-cigarette emission extracts, both containing and not containing nicotine, was cytotoxic to epithelial cells and head and neck squamous cell carcinoma cells and identified to lead to DNA strand breaking through comet assay and γ-H2AX immunostaining [88].
• Exposure to e-cigarette emissions lead to increased levels of inflammatory cytokines in bronchoalveolar lavage among mice and increased bacterial (MRSA) biofilm formation in a dose-dependent manner [90].
• Intraperitoneal administration of e-liquid with and without nicotine in Wistar rats was performed. The administered dose of e-liquid or nicotine didn't show any short term mortality or sign of toxicity however the results indicated a disruption of glucose homeostasis in rats with a significant decrease in food and energy intake after exposure to e-liquid with nicotine. Blood glucose increases, hepatic glycogen rate was decreased as was total cholesterol. Liver transaminases significantly increased as did liver gene expression involved in glucose metabolism, in both nicotine and non-nicotine containing e-liquids [103].
• Exposure of c. elegans larval worms to nicotine, propylene glycol, e-liquid or distilled e-liquid emissions. The results indicated that PG treated worms and nicotine exposed worms were smaller than the negative controls and had smaller brood sizes, while PG was capable of inducing a mild oxidative stress response. Exposure to distilled e-liquid emissions provided similar results, albeit not statistically significant [104].
• Exposure of mice to e-cigarette emissions was associated with pulmonary and systemic oxidative stress as indicated by a rapid increase in neutrophils and increased 9-OHdG concentrations in the bronchoalveolar lavage fluid (conference proceeding) [95].
• Mice exposed in utero to e-cigarette emissions indicated gene alterations within frontal cortex samples. (conference proceeding) [105].
Human Studies
E-cigarette users have reported a variety of adverse events, ranging from very minor to more serious. The frequency of adverse events varies between studies and between products. The most frequent adverse events come from the mouth and throat, the neurological and respiratory systems [106, 107]. However, which constituent (i.e. nicotine or humectant or flavour) is responsible, how this may be related to e-cigarette user topography and how it may impact vulnerable populations (youth, pregnant women, adults with co-morbidities) is an area which warrants further research.

Possible adverse events, or user reported responses to e-cigarette use, that exist in the literature include:

a) Self-reported adverse events to the US Centre for Tobacco Products of the Food and Drug Administration (FDA):
   - Pneumonia [107]
   - Congestive heart failure [107]
   - Disorientation [107]
   - Seizure [107]
   - Hypotension [107]
   - Aspiration pneumonia [107]
   - Dizziness [107, 108]
   - Confusion/stupor [107]
   - Shortness of breath [107]
   - Abdominal pain [107]
   - Pleurisy [107]
   - Blurry vision [107]
   - Nausea and/or vomiting [107]
   - Chest pain [107]

Among non-users the US Centre for Tobacco Products of the FDA noted the following self-reported adverse events [109]:

- Respiratory symptoms (asthma exacerbations, bronchitis, cough, difficulty breathing and pneumonia)
- eye irritation
- headache, dizziness
- nausea
- sore throat/irritation
- racing/irregular heart rate (n=5)
- burns (due to contact with an overheated device and to device explosion)
- one report of lip cheilitis and
- one report of infant death after choking on an e-liquid cartridge

The only population based study to assess the impact of e-cigarette use among adolescents indicated that e-cigarette use was significantly associated with past respiratory symptoms (AOR, 1.28; 95% CI, 1.06-1.56), especially among never-smokers (AOR, 2.06; 95%CI, 1.24-3.42) [110].

Other potential interactions with human physiology (and potentially not all adverse effects) include:

- Chest pain and rapid heartbeat [107, 111]
- Dyspnoea [112]
- Small elevation of diastolic pressure [113]
- Deep vein thrombosis [114]
• A case report of Paroxysmal atrial fibrillation [115]
• Impact on respiratory flow resistance, impedance, [116-118]
• Changes in the Fraction of exhaled nitric oxide (FeNO) [116, 119]
• Headache [111, 120-122]
• Decrease in systolic blood pressure [123]
• A case report of subacute bronchial toxicity [124]
• Mouth and throat irritation [13, 15, 106, 107, 111, 125-130]
• Cough/sputum [107, 111, 112, 121, 122, 127, 128, 130]
• Sleepy/tired [107, 111]
• Gastrointestinal discomfort [111]
• inhibition of cough reflex sensitivity [131]
• A case report of Eosinophilic pneumonitis [132]
• Colonic necrotizing enterocolitits during pregnancy [133]
• A case report of ulcerative colitis [134]
• A case report of Nickel contact dermatitis [135]
• A case report of acute inhalational lung injury [136]
• A case report of lipoid pneumonia [137]
• Decrease in subcutaneous blood flow [138]

It is important to note that the existence of causality between exposure and outcome in a number of the above individual based effects has not been evaluated, and the actual clinical impact of the above potential effects have not been assessed, for which further research is needed.

Risk due to production design flaws (leakage/electric failures/inconsistent dosing)
Poor manufacturing quality and fluid leakage have been reported in the literature [126, 139-141], [142] which may result in accidental exposure to e-liquid. Filter malfunctions have also been recorded [140], as well as a case of second-degree burns to the face when the e-cigarette exploded in a user’s mouth [107]. The electronic equipment of e-cigarettes may be the cause of accidents, however reports are only noted in mainstream literature, or via the US FDA adverse events reporting system [143]. Quality control mechanisms incorporated within the production process may mitigate these risks, including those relating to battery use and charging.

Notably, the importance of the implementation of design standards was stressed by the fact that within our active product collections within WP1, 3 out of the 8 shipments of refills received (which corresponded to 37.5% of all shipments) were received with evident leakage of the e-liquid within the packaging that took place during shipping and handling. The implementation of standards that handle design aspects related to the leaking of e-cigarettes and their refill liquids would be able to substantially reduce risks attributable to design flaws, an area which we address in Annex C, and that have been recently outlined by one peer reviewed article [144].

The literature has indicated that there seems to be a lack of standardisation in many of the existing refillable products (primarily those belonging to earlier generations) and, as a result, existing studies have indicated that the composition of different batches of the same brand/product may differ significantly or differ from what is labelled [18, 24, 56, 79, 145-148]. Moreover, users who are concurrently using e-cigarettes and other tobacco products may falsely believe that they are not receiving sufficient nicotine through the e-cigarettes, when in fact they do [5, 46, 149]. As a result, they could potentially overdose on nicotine. However due to the effect of nicotine overdosing (i.e. nausea, dizziness) it is most likely that consumers would self-titrate their dosage. Recent research has also identified nicotine within e-liquid flavours [150]. Our independent analysis of common brands within the EU market did not identify such a discrepancy in the declared vs. measured nicotine content as those that were noted to not have a nicotine content were identified indeed as nicotine free. It is possible that the risks of overdosing/inconsistent dosing would be more likely among refillable e-cigarettes that are
modifiable as these allow for the user to choose a range of parameters that may influence e-liquid uptake [148].

**Risk of toxicity from accidental/intentional exposure to refill liquids**
The risk of poisoning from accidental exposure among non-users (including pets) has been substantially discussed in the scientific literature [1, 151-166]. It is these potential risks that warrant the development of child-resistant packaging, as children are noted as the population group at a higher risk for the occurrence of such incidents [4, 156, 158, 167]. Evidence that support the existence of this risk is available from the UK National Poisons Information Service, which received numerous calls regarding poisoning from ingestion of refill fluids, of which 36.4% (from 2007-2013) referred to children younger than 4 years old [164]. Moreover, according to a CDC report, exposure among young children amounted for slightly more than 50% of the calls relevant to e-cigarettes (51.1% from 2010-2014) [167]. In American and Italian poison centres, the most frequent route of exposure was ingestion, followed by inhalation, dermal and ocular routes [167-169]. Refillable e-cigarettes are a priori more likely to be related to accidental/intentional exposures in comparison to non-refillable e-cigarettes due to the need to refill the e-cigarette tank once it is empty (dermal, ocular exposure) and the existence of refill containers that may be opened and ingested (oral exposure). While research has indicated that transdermal absorption of nicotine following skin contamination by e-liquids is possible,[170] further research is needed to quantify this risk, which currently may be of concern predominantly within refillable e-cigarettes and mainly in home blending, where a base liquid may be spiked with a high concentration nicotine liquid that may contain nicotine in concentrations significantly higher than those outlined in the TPD. Dermal exposure can also pose a risk as due to high nicotine concentration in certain refill liquids, skin contact may lead to complications [171]. This would be especially the case for refillable e-cigarettes that are home blended (where the consumer purchases their own flavours, dilutents and nicotine liquids-the latter of a significantly elevated concentration). The above risks could be mitigated through the use of gloves during handling, a leak proof refill mechanism and the reduction in the concentration of the nicotine content of e-liquids.

It is noteworthy that ocular exposures were present in 7.6% of the cases, in some instances this was due to spillage during the refill process as also due to the consumers mistaking e-liquids for eye drops – an issue which may potentially be mitigated through more prominent warning labels.

Overall, the risks within this section are mainly attributable to refillable e-cigarettes as the majority of call to poison centres that have to do with e-cigarettes refer to unintentional exposure to refill fluids (87.3% vs. 0.7%) in both our study and others in the literature [154, 176].

Poisoning from ingestion of refill liquids may also be intentional, as suicide attempts have been reported [160, 161, 164, 168, 169, 172-175]. Suicides have also been recorded, by intravenous injection and ingestion of refill liquids [176, 177]. No deaths associated with e-cigarette exposures were reported to the European Poison Centres from which we collected data in the time period studied. One death was however noted in the US dataset (the aforementioned intravenous suicide), while the literature has identified one case of ingestion of an e-liquid reported to have resulted in the death of a 34-year-old [49].

**Risks associated with inadequate/misleading information**
Labels and content specifications have been identified in some circumstances to be misleading and do not always correspond to actual concentrations of substances like nicotine [18, 23]. Earlier studies have found poor concordance of labelled and actual nicotine content in commercially available refill liquids [20, 23, 178]. Other studies have detected nicotine in products that were advertised as nicotine-free [5, 46, 149]. Hence, it is possible that ex-smokers who currently use e-cigarettes may also be exposed to nicotine in reportedly nicotine free e-liquids [5, 46, 149].

Annex B-19
Similarly, it has been noted that flavour liquids may contain undisclosed nicotine [150]. While quality control issues would regulate the above, it may pose a risk to ex-smokers thus exposing ex-smokers to nicotine and posing a risk for nicotine addiction to users who thought they were not exposed to nicotine. According to the analysis performed on the 38 e-cigarette refill liquids purchased, we did not identify any discrepancy in the nicotine content disclosed on the package and the nicotine content we measured.

Online advertisements have also been found to make unsubstantiated claims regarding the potential effects of e-cigarettes, such as that they “emit only water vapour” or present the products as suggested by doctors [39, 179-182], while videos about e-cigarettes on YouTube make claims of safety, use, economic or social benefits [183-185]. Another evaluation of online and mass media messaging indicated messages related to health, price, smoking cessation and the circumvention of clean indoor air policies amongst others [39, 186, 187]. Our research performed in WP1 also identified a number of bold claims on industry websites. To date, no study has evaluated the potential impact of these positions, the extent to which they may or not be misleading and the effect they may have on consumer purchases or youth experimentation. Further research is needed on all of the above.

**Risks associated with the possibility to modify refillable e-cigarettes or associated with home/own blending of e-liquids**

There is a possibility that modifications of battery/voltage parameters of refillable e-cigarettes may lead to an increased risk of exposure to non-nicotine toxicants, such as carbonyls, especially among inexperienced users. Similarly modifiable, "direct drip atomizers" (DDAs) may also involve greater exposure to non-nicotine toxicants due to the potentially higher temperatures reached by the coil [188]. Moreover animal models have indicated that design of refillable e-cigarettes that can be used for "dripping" as an option for consumers may lead to increased oxidative stress at the cellular level, an area in which further research is needed [33]. Emission parameters may be directly related to the device and power applied [189].

Another identifiable risk that is associated with the common practice of home/own blending of e-liquids is that this may lead to the creation e-liquids with an unknown (and possibly lower or higher) nicotine content. Moreover, it is possible that the home blended e-liquid may not have the ideal, and quality control tested, PG/VG ratios compatible with the type of e-cigarette hardware used, which may result in the production of unwanted by-products. In addition to the above, home blended liquids that are not obtained from quality controlled manufactures may also be inappropriate for use [190, 191].

It is possible that refillable e-cigarettes can potentially be used with illegal substances [192-195]. A very recent study has added to these concerns, investigating for the first time the rates of high-school students in the US who use the e-cigarettes in order to vaporize cannabis. Among a sample of 3847 students, 18% of students vaporized cannabis and were e-cigarette users, while there was an ever higher rate (26.5%) of students with dual use of cannabis and e-cigarettes [196]. Furthermore, there is evidence that adolescents believe that e-cigarettes with an addition of other substances could have minor health effects in comparison to the conventional tobacco [197]. Taking this into consideration, adolescents might be in a greater risk of smoking e-cigarettes with narcotics [196, 198, 199, 200] While this risk is potentially present we are unable to classify the gravity of such a risk, nor its potential impact on consumer health. This risk predominantly is attributable to refillable e-cigarettes, as non-refillable e-cigarettes do not easily allow for the opening of the cartridges and the inclusion of homemade substances which may contain narcotics. Although not illegal, alcohol can also be added to the e-liquids a practice that has been noted in the literature [201].
Risk of encouraging dual use with tobacco products;
Dual use with cigarettes has been associated with a number of sociodemographic parameters [202] and indicated to result in delayed or deferred quitting. Indeed, among adults current e-cigarette users are most often current smokers [203], while high levels of dual use are also noted among adolescents, with 80.5% of current high school e-cigarette users concurrently smoking conventional cigarettes [204]. Adolescent e-cigarette users may also be more likely to concurrently use tobacco products such as water pipe [200]. Dual product use is also noted among smokers for example, with 6.2% of current smokers also e-cigarette users, a percentage noted to be similar among adults in the EU (4%) [203, 205]. Unfortunately we were not able to identify the number of e-cigarette users who also concurrently use tobacco products from the data.

Even though it is not clear whether e-cigarette use usually precedes or follows the regular use of cigarettes or other tobacco products, several surveys have found that dual use of e-cigarettes and another tobacco product is frequent. However, longitudinal studies are needed in order to explore whether e-cigarette use actually encourages dual use of tobacco products or whether this is a transitional stage between regular smoking and cessation or exclusive e-cigarette use.

Risks of reduced quit attempts
Based on the 2014 Eurobarometer7 data, information from 28 EU MS indicate that 49% of ever e-cigarette users reported that e-cigarettes had not helped them reduce or stop smoking tobacco, while 14% were able to quit completely, 13% succeeded initially but then relapsed and 21% were able to reduce their tobacco use but not quit. A number of population based studies have indicated that smokers who use e-cigarettes may be at an increased risk of not being able to quit smoking completely while using e-cigarettes [206].

A meta-analysis of five population studies examining the association between e-cigarette use and quitting cigarettes showed that e-cigarette use was associated with significantly lower odds of quitting cigarettes (pooled OR of 0.61 (95% CI, 0.50–0.75), hence the cumulative evidence may indicate at the population level that e-cigarettes may pose a threat to smoking cessation attempts—even though a number of parameters, such as the level of nicotine addiction, may have influenced this result [207].

Risk of the ex-smoker transitioning from abstinence to e-cig use and to relapse and conventional tobacco use;
It is not clear whether e-cigarettes can increase relapse among people who have achieved smoking cessation, as there is limited evidence from cohort studies on ex-smokers with research to date of cross sectional design which cannot attribute causality. However, there are indications that achieved abstinence among smokers who attempt to quit may be lower among those who are also using e-cigarettes [208]. In line with the hypothesis of this potential risk, population based studies in the US have indicated that ex-smokers were 3.24 times (95%C.I: 1.13-9.30, p<0.05).[209] or 4.33 times (95%C.I: 3.08-6.09) more likely than daily cigarette smokers to be established users of e-cigarettes [210]. Similarly in the EU, and although the cross sectional methodology of the 2014 Eurobarometer8, the odds of ever using an e-cigarette among ex-smokers were significantly higher among respondents aged 15–24 years (aOR 6.75, 95% CI 3.85 to 11.84), or 25–39 years (aOR 3.83, 95% CI 2.54 to 5.79), or 40–54 (aOR 2.42, 95% CI 1.56 to 3.73), when compared with respondents aged ≥55 years [203]. Recent data from Great Britain further support the above, as between 2014-2015 the proportion of ex-smokers using electronic cigarettes rose from 4.5% to 6.7% in 2015, more than half of which stated that the principal

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reason was to "help me stop smoking completely (61%). Furthermore, ex-smokers were more likely to report using e-cigarettes daily compared to smokers (84% vs. 45%)⁹. Recent data has indicated that 4% of ex-smokers in the US had used an e-cigarette, 5% among Canadian ex-smokers [211, 212]. The aforementioned sustained nicotine addiction may lead to an increased risk of relapse as research has also indicated that current e-cigarette use is negatively associated with past-month (aPOR=0.21, 95% CI: 0.11-0.38) and past-year cigarette abstinence (aPOR=0.14, 95% CI: 0.10-0.22).[213] In addition to the above, research among US youths has indicated that ex-smokers are more likely than never smokers to report to be open to using e-cigarettes in the future [214]. Further research on the temporal aspects of e-cigarette use is needed so as to identify when, e-cigarette use was initiated (before vs. after cigarette cessation).

It is possible that ex-smokers who are also e-cigarette users may maintain e-cigarette use, afraid that they will relapse and start smoking again [126, 215, 216]. Coupled by the fact that nicotine dosing in e-cigarettes may be inefficient when compared to cigarettes, especially among naïve users, it is possible that there is a risk that they may transition back to cigarette use. Further research is needed to quantify this risk.

Risk as use as a gateway product to nicotine addiction and subsequent smoking initiation;

E-cigarettes are typically viewed as less addictive and less harmful than cigarettes [31, 121, 217-231], which could encourage experimentation through lower perceived risk [232, 233] that may also be enhanced through visual cues in e-cigarette advertisements [234, 235] or the plethora of flavours provided [31]. This is particularly important as a proportion of adolescents seem to be open to trying e-cigarettes [236], may have experimented with e-cigarettes [237-240], have favourable views of the social acceptability of e-cigarettes [218, 241], or say they would experiment with an e-cigarette if offered by a friend (peer influence) [236, 242]. A recent study among US teens reported that 43% of teens using e-cigarettes had a positive intention to use traditional cigarettes in the future [243], while ever use of e-cigarettes and other tobacco products among young adults was also associated with being open to cigarette smoking in the future[244]. In Wales, non-smoking children aged 10-11 years who had used e-cigarettes reported weaker antismoking intentions and were more likely to say that they will be smoking in two years [245]. Three regional longitudinal studies in the US indicated that adolescents who had ever used e-cigarettes were more likely to report initiation of combustible tobacco use over the next year compared to those who had never used e-cigarettes [246-248]. Moreover, other studies have reported a proportion of current cigarette smokers who experimented with e-cigarettes before initiating regular cigarette smoking and may currently be dual users [121]. Tobacco advertising has also been associated with experimentation with e-cigarettes among US adolescents as students who were exposed most of the time/always to retail or Internet pro-tobacco advertisements were 1.7 and 1.6 times respectively more likely to experiment with e-cigarettes compared with those who were non-exposed [249], while within the context of a randomized control trial, exposure to e-cigarette ads were found to potentially enhance curiosity and trial with e-cigarettes in never users [250]. Moreover under experimental conditions, adolescents exposed to ads that depicted flavoured products did elicit greater appeal and interest in buying and trying e-cigarettes then those exposed to ads of non-flavoured products [251].

In addition to the above e-cigarettes may be seen as gadgets, especially by smokers, adolescents and young adults, and this is something that is being exploited by manufacturers, who consistently promote e-cigarettes as “technologically advanced” products [39, 252, 253].

Furthermore, the plethora of flavours and additives may make e-cigarettes, and especially refillable e-cigarettes, more attractive for certain population groups [25, 31]. A study has found

⁹ ASH Fact Sheet. May 2015. Use of electronic cigarettes (vapourisers) among adults in Great Britain
that the interest of smokers for e-cigarettes varied depending on the flavour [26], something that could potentially be a factor among non-smokers as well.

Moreover there is a small percentage of never smoker adults who experiment with e-cigarettes: 1-5% among US adults, [212, 254], 3-5% among Canadian adults and youth [255, 256], small percentages are also noted by other studies [257-261]. The extent to which these experimenters transition to cigarette use is an area imperatively need of further research.

**Risk due to second hand exposure - emissions**

E-cigarette emissions may be perceived as less harmful than cigarette smoke, however they produce similar mainstream aerosols [262] and have similar particle deposition patterns in the lungs [263], and a number of components therefore could both have local or/and systematic effects on humans.

Following exposure to e-cigarette vapour may negatively affect lung function. An experimental study found that FEV1/FVC ratio was reduced after exposure to second-hand smoke from e-cigarettes, indicating short-term lung obstruction, while cotinine levels also increased [264, 265]. To date an association between increased inflammatory markers and passive e-cigarette smoking has not been identified [266]. Beyond laboratory experiments, concentration of airborne nicotine was found to be higher in homes where someone was using an e-cigarette compared to smoke-free homes [267].

As mentioned earlier, analyses of e-cigarette emissions have detected substances such as ethylbenzene, benzene, benzaldehyde, toluene, m/p xylenes, acetone, formaldehyde, radon, acetaldehyde, acrolein, nicotine and nitrosamines [22, 42, 51, 53, 54, 72, 77, 268-272]. E-cigarettes have also been found to be sources of high particle dose in the respiratory system [22, 23, 6, 42, 53, 65, 71, 189, 273] while further research is needed to evaluate the parameters that are being measured as particulate matter (fine particles or diluents). Most environmental markers were at low levels even in second [274] and third generation e-cigarettes [275]. However, some authors had a conflict of interest as several of the above studies were funded by manufacturers or authors had affiliations with e-cigarette producing companies [50, 189, 274, 275]. Another study found that e-cigarette use was associated with increases in fine particles, ultrafine particles and volatile organic compounds such as 1,2-propanediol, 1,2,3-propanetriol, flavourings, and traces of nicotine [8]. Metal and silicate particles have also been detected in e-cigarette aerosols, with some of them (e.g. aluminium and nickel) in higher concentrations that those found in cigarette smoke. Such particles can cause adverse effects in the respiratory system, reproduction and development, while some of them are also carcinogenic [60, 63, 64].

Acetoin, 2,3-pentanedione and diacetyl have also been identified in emissions, the latter a flavouring compound that has been associated with the development of “Popcorn Lung” in workers after past inhalation exposure [276]. Other flavour compounds, such as acetylpyrazine [273], pyrazine-acetyl, pyrazine C4, isoamyl isovalerate and ethyl isovalerate have also been identified in e-cigarette emissions [277], as have limonene, followed by β-pinene, myrcene, menthol and 1-carophyllene [278]. It is further possible that certain flavours in e-cigarette liquids may results in emissions such as benzaldehyde, that are not identified in non-flavoured products [271], while the impact of the heating of other additives, such as sucrose –which may lead to the development of aldehydes, should be further investigated [279].

Moreover, there are indications that e-cigarette use might pose a threat to health through third-hand exposure to nicotine, as nicotine could be deposited on surfaces [280]. Further research on the potential impact of such exposure is warranted.

The implementation of smoke free environments from combustible tobacco products has significant impacts on population health indexes and hence there is a risk that e-cigarette use
may be used by smokers to circumvent clean indoor air legislations [281-285]. Indeed, research has indicated that a proportion of e-cigarette users (including youth) reported to use them in places where smoking is prohibited, a reason reported by 58.9% of youth respondents of the US PATH Survey [31] and the 2014 Eurobarometer in which 44% of e-cigarette users reported to have started using e-cigarettes so as to smoke where tobacco smoking is not allowed [222]. Moreover in a survey in the United States, 46.4% of flight attendants reported having witnessed use of e-cigarettes in airplanes or/and airports, indirectly undermining smoking bans [286]. The risk of impacting the success for smoke free environments is further augmented by e-cigarette manufacturers who make relevant claims on their websites (i.e. that e-cigarettes can be used in places where cigarette smoking is not allowed) [39, 182, 287].

Moreover, the risk of normalizing e-cigarette use within enclosed public places is closely linked to the risks to maintaining clean indoor air environments [288]. Smoke free environments not only increase smoking cessation attempts, increase awareness on the harm surrounding tobacco but also remove the social acceptability of smoking in public places. Research has indicated that exposure to visual depictions of e-cigarettes may increase smoking cues [289] and the desire both for e-cigarettes and conventional cigarettes [290, 291]. Furthermore, under controlled conditions within a pilot study, viewing a video of a participant using an e-cigarette did induce a neurocognitive response among long-term e-cigarette users [292]. In line with the above, with the use of e-cigarettes indoors there is a risk that they may weaken some of the aforementioned benefits of smoke free environments, including the existence of cues and the renormalization of tobacco use. This is further supported by the fact that policy support for banning use of e-cigarettes in public places was identified in a population based study to be lower among respondents who reported observing others use e-cigarettes in public places five or more times in the past 30 days than for those who never observed others using e-cigarettes in public places [293].

Furthermore, based on the quantitative assessment of e-cigarette emissions noted in the previous paragraph we conclude that e-cigarettes would also be a source of indoor air pollution, hence exposure to e-cigarette emissions in public places may potentially also pose a risk to population health.

**Risk of renormalizing nicotine addiction and youth experimentation**

Almost 40% of youth and adults in the EU report themselves as exposed to ads or promotions for e-cigarettes or similar devices in the last 12 months. Points of sale are the most mentioned location (36%), followed by advertising on television (35%). Such marketing of e-cigarettes may circumvent advertising bans and restrictions, and with the increasing availability of e-cigarettes, there is a risk that it may threaten to renormalize smoking-related behaviours [294-296].

Marketing activities of e-cigarette companies have exponentially increased over past years in both traditional [144, 297-299] and social media [300-304]. Research has indicated that exposure to e-cigarette advertising was associated with lower support for restrictions not only of e-cigarette use, but of cigarette smoking public places as well [305]. Furthermore, e-cigarette specific advertisements could also encourage thoughts of smoking cigarettes, thus indirectly promoting cigarette use [306], and children may misperceive e-cigarettes to be cigarettes [307]. In the US, youth who have never used e-cigarettes previously perceive e-cigarettes as cooler, more fun, healthier, and more enjoyable after the viewing of an e-cigarette advertisement [308]. Interestingly in the 2014 Eurobarometer, young respondents were more exposed than any other

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Annex B-24
age category to ads or promotions for e-cigarettes: 12% of them reported have seen them often vs. 5% of those aged 55+. Similarly, research using Nielsen household data in the US has indicated that youth exposure to television e-cigarette advertisements increased by 256% from 2011 to 2013 [309].

In addition to advertising via television, radio or at point-of-sale, e-cigarettes are broadly advertised and communicated through websites and social media portals [39] [181, 182, 306, 310-314]. As many advertisements focus on issues related with increased social acceptability [179], it is possible that the increasing popularity of e-cigarettes may be partially related to the social acceptability of e-cigarette use as portrayed by advertisements, the media and certain films, and as perceived in some instances by adolescents [241, 315]. E-cigarettes have been increasingly appearing in movies, television shows and even supported by celebrities on television appearances and promotional websites [39, 287, 316]. Indeed, research has indicated that smoking initiation is strongly associated with the portrayal of smoking in movies, a risk which may be similar with e-cigarettes [317]. Furthermore, sponsorship of sporting events and sport clubs has also been noted, as identified in the website content analysis of WP1. In line with the above it is important to stress that the e-cigarette industry also frequently use e-commerce platforms without any age verification mechanism [198], an aspect we also identified in WP1. While the above risks is foreseeable, the extent and impact of these on a population basis is an area in need of further research.

**Risk to the environment**

The potential impact of e-cigarettes on the environment have been studied and include emissions related to manufacturing, environmental harm caused by the disposal of packaging material, batteries, cartomisers etc., as well as the generation of aerosol with high concentration of metals or/and other particles that might pose a threat to the health of humans and the degradation of the environment [318]. Despite this, several e-cigarette producing companies claim to be environmentally friendly [39, 182]. Moreover, there was a lack of studies on the effect that the manufacturing and packaging of e-cigarettes have on the environment. We were, however, unable to identify any evidence to indicate that this would be significantly different from other consumer products. Differences may exist between the magnitude of risk to the environment between refillable and non-refillable (disposable) e-cigarettes with the latter potentially more likely to lead to a higher production of waste. Such an increased risk to the environment would also be expected for disposable cartomisers.

For example, a study explored the oxidant reactivity of disposable components of the e-cigarette, i.e. cartomisers and batteries, and has found that it is comparable to filters from manufactured cigarettes [60]. The same study reported that the concentration of copper particles in aerosol from e-cigarettes were about six times higher compared to conventional cigarette smoke [60]. Finally, it is interesting to note that our chemical assessment of the flavours noted within the sample of e-cigarette refill liquids do contain nicotine and did identify flavours that were “toxic to aquatic life with long lasting effects”.

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4. Conclusions

While further research is needed, e-cigarettes, as evaluated through the triangulation of a peer review of the international literature, chemical analyses and poison centre cases may pose a threat to European public health. It is noteworthy that the available evidence that was published during the time of writing of the current report more than doubled indicating the interest of both the public and the scientific community. Key points of our report are summarized as follows:

- E-cigarette liquids contain a wide variety in chemical components: humectants, nicotine, flavours, impurities and other substances. While our chemical analyses did not identify impurities, we identified a plethora of flavour additives, some of which have CLP classifications that warrant further investigation.
- There is growing evidence of potential risks from adverse effects in published cellular, animal and human studies. These include: evidence of cytotoxic and/or oxidative effects of some refill liquids, especially when nicotine and flavour substances are present; inflammation of the respiratory system and oxidative stress in animal models; and potential cardiopulmonary effects in human studies.
- There are risks due to design and production flaws of refillable e-cigarettes, such as leakage and spillage, a fact verified by our active data collection during which 3/8 samples arrived with evident leakage.
- There is ample evidence that link e-cigarettes, and refillable e-cigarettes in particular, with accidental exposure to refill liquid- especially among children. Our active data collection corroborated the evidence within the published literature. Almost all unintentional exposures had no or a minor effect. Vomiting, dizziness and nausea were the most commonly reported symptoms.
- There are risks associated with inadequate or misleading information with regards to either product constituents or industry claims. We did not identify discrepancies in nicotine content but we did identify a broad list of unwarranted claims on smoking cessation and health benefits.
- Refillable e-cigarettes in particular may be associated with a number of risks due to the possibility to modify and/or blend refill liquids and to use incompatible devices, which may result in the production of harmful compounds. The ability to use refillable e-cigarettes for the consumption of illegal substances was also noted.
- E-cigarettes produce emissions that contain a number of hazardous substances that may be related to the design parameters and constituents (especially flavourings).
- There is still uncertainty on the long-term public health effects of e-cigarettes but there is some evidence that e-cigarettes may be associated with reduced quit attempts, dual product use or retained nicotine addiction which may be associated with sustained nicotine addiction at a population level. Further long-term research in these areas is needed.
- Experimentation by non-smokers is a potential risk as it is possible that e-cigarettes may act as a gateway product, influenced, amongst other aspects, by marketing, flavourings and perceptions of reduced risk.
- Another potential health risk is the use of e-cigarettes where smoking is not allowed. The risks of passive vaping need to be studied further.
- E-cigarettes, and disposable e-cigarettes in particular, may pose an environmental burden.

While further research is needed to determine the magnitude and gravity of each risk identified, this report provides a picture of the current status quo of the evidence.
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ANNEX C. Characteristics of technical specifications for refill mechanisms

Contents

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Introduction

The aim of WP4 of PRECISE was to use the information from the three previous WPs to identify technical specifications for refill mechanisms, based on the identified risks, stakeholder feedback, European and International standards and the evaluation of the samples purchased in WP1.

Task 1: The first task was to perform an evaluation of the products identified under WP1 so as to identify brands with a high and low risk profile. This should include a description of the refill mechanism and an evaluation whether children are protected.

Task 2: The second aspect was to perform an active data collection from a) via questionnaire to a selected sample of industry stakeholders, b) available European and International standards and c) published and grey literature.

Task 3: Finally the third task was to merge the available evidence collected in the above tasks, in light of the risks identified in WP2 and WP3 and subsequently to identify potential technical specifications for e-cigarette refill mechanisms.

Task 1: High and Low Risk product profiles

Within PRECISE we evaluated 33 refill liquids and 4 disposable e-cigarette products. These were purchased and evaluated for criteria/parameters such as the existence of the following:

1. **A child proof cap**: For this criteria we evaluated if the vial was equipped with a type of child resistant cap. Direct compliance with ISO criteria was not evaluated.

2. **A tamper evident or prevention mechanism**: With this criteria researchers evaluated if the product had some form of mechanism to ensure that it was not tampered with from the point of production. This may include a plastic connector that has to be broken for the cap to be opened or a plastic cover that would enclose the product and/or the seal.

3. **Warnings on the refill vial, package or leaflet**: Researchers evaluated if there were warnings on either the vial and/or the package of the refill liquid. Three types of warnings were evaluated, these included either
   i. **Text warnings**: i.e. nicotine is toxic, keep out of reach of children etc.
ii. **Hazard signs**: i.e. skull and cross bones, toxic, environmental harm etc.

iii. **Tactile**: i.e. the existence of an elevated triangle on the product.

4. **A leaflet**: The existence of a leaflet was evaluated. The contents of the leaflet were not evaluated within the high vs. low risk profiling.

5. **A plastic cover**: The existence of a plastic cover over the product was evaluated that would ensure that the lid is safely secured on the vial and act as an additional tamper evident seal.

6. **Thin nozzle**: Nozzle diameter was evaluated on a quantitative basis (thin vs. thick), without measurement of the nozzle diameter, which in most cases would have been unnecessary due to the huge differences in design between products that have or do not have a thin nozzle. This was evaluated as a proxy of the ease of which it would be able to fit within e-cigarette tank easily during the refill process.

7. **User instructions**: These included the existence of step by step instructions on how to use the e-liquid refills.

8. **Note of the use of gloves**: Researchers evaluated the existence or not of a recommendation to use gloves during the refill process.

9. **Emergency actions**: Researchers evaluated if the product was accompanied by instructions to take in the case of accidental exposure which included i.e. reference to seek medical advice, reference to the need to wash hands or eyes, or remove clothes.

10. **Ingredients**: This was evaluated by PRECISE researchers using a three category approach. This included either no information on ingredient composition (no), limited information on ingredient composition (yes) or detailed composition including quantitative measures of composition (detailed) noted by the manufacturer on the product, leaflet or package.

An overview of the results of product characteristics can be found below in **Tables 1, 2 and 3**.
<table>
<thead>
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<th>Product</th>
<th>Warnings on the refill vial</th>
<th>Warnings on the external packaging</th>
</tr>
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<td>Hazard info</td>
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<tr>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
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<td>S8</td>
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</tr>
<tr>
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<td>toxic</td>
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<tr>
<td>S10</td>
<td>yes</td>
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</tr>
<tr>
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</tr>
<tr>
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Annex C-3
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<td>ESP</td>
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1: A few vials had the leaflet glued to the bottle
2: Detailed description of ingredients including percentage
3: Individual ampules,
4: Pipette dropper
### Table 2. Overview of product characteristics related to high and low risk brands

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<th>Thin Nozzle</th>
<th>Nozzle Diameter (Mm)</th>
<th>Nozzle Length (Mm)</th>
<th>Needs Pressure To Flow</th>
<th>Drop Rate/Min</th>
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1: A few vials had the leaflet glued to the bottle; 2: Detailed description of ingredients including percentage; 3: individual ampules, 4: Pipette dropper

Annex C-5
Table 3. Estimated compliance with CLP among the sample

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**Explanation of the respective numbers**

1. Name, address and telephone number of the supplier(s).
2. The nominal quantity of the substance or mixture in the package where this is being made available to the general public, unless this quantity is specified elsewhere on the package.
3. Product identifiers.
4. Hazard pictograms, where applicable.
5. The relevant signal word, where applicable.
6. Hazard statements, where applicable.
7. Appropriate precautionary statements, where applicable.
8. A section for supplemental information, where applicable.
9. Tactile warning of danger in accordance with EN ISO 11683 and a child-resistant fastening.
10. Extra non obligatory supplemental information

✓* only child resistant fastening
✓** only tactile
n/a not available

Annex C-6
Conclusions related to high and low risk brands

From our analysis of 33 refill liquids and 4 disposable e-cigarette products, we noted:

- Almost all products evaluated (n=34) had some form of child resistant cap. Notably, only those three products that did not have a nozzle but used another format (i.e. pipette etc.) were found not to have a child proof cap. While we were not able to formally evaluate compliance with ISO standards, it appears that most products are already child resistant.
- Leakage during transfer was noted for a number of products, an issue which would lead to a classification as a “high risk brand” from the point of design specifications. As noted in WP2 and WP3, three of eight shipments received had evident leakage.
- The existence of a mechanism to identify tampering (plastic ring or plastic sheath) was common among the products purchased.
- Almost all vials had warnings. Only 8 out of 37 samples (6 of which were from the same company) did not have a hazard warning on the package. Different types of hazard pictograms warnings were noted, and included in some cases CLP warnings such as a skull and cross bones, an X and/or environmental risk warnings. In some cases the hazard pictogram was on the packaging and not on the actual vial itself.
- Other “homemade” hazard pictograms also existed, such as warnings for pregnant women or for children under 3 years old due to risk of choking.
- Text only warnings existed on most products, either on the refill vial or on the external packaging. Examples included:
  - This product is not intended for persons with respiratory or cardiovascular diseases
  - Nicotine is an addictive substance. Not suitable for pregnant women, nursing mothers, persons with respiratory or cardiovascular diseases, no smokers and persons under the age of 18. Keep away from children”
  - Danger toxic in contact to the skin. Contains Nicotine
  - Please consult your doctor before using our products if any of the following apply: If you are unsure of the effects of nicotine; pregnant, planning to become pregnant or breast-feeding; in ill health.
- Tactile warnings were present on most of the refill vials and on some of the external packages. The tactile warning in all cases was an elevated triangle.
- Leaflets were available for 13 of the purchased products. Of the 13 products, 7 had a leaflet that was within the external package of the product, while 6 had a leaflet that was glued to the actual refill vial.
- All products that had a nozzle and were not of “pipette or eye drop design” had elongated and thin nozzles. There were internal differences between the samples with regard to the length of the nozzle and the width of the nozzle spout, but in all cases they could be described as long and thin. This design would potentially allow for easier introduction of the refill liquid in the tank.
- Instructions for use were only provided for 5 products (four of which were the same brand, while the fifth was within ampules and not vials). Our study of disposable or refillable e-cigarette devices (not in the list above) indicate that user instructions are frequent among hardware products, but not for refill liquid products
- Instructions to use gloves during the refill process were noted in products from three companies. “Wear protective gloves” was the phrase used commonly.
Ingredients were listed in almost all cases. The majority were however reported as “PG, VG, nicotine, flavours”. Few products provided a more detailed analysis of what the flavours were composed of and even fewer provided a detailed quantitative analysis of these flavours.

Instructions on what to do in case of an emergency were noted in 24 of the products. Examples of such instructions included:

- In case of accident with the eyes, wash with plenty of water. Poison call center +49 (0) 89- 19240
- In case of accident, or if you feel unwell seek medical advice immediately. Irritating to eyes and skin.
- Wash hands thoroughly after handling. Do not eat, drink or smoke when using this product. – IF SWALLOWED: immediately call a POISON CENTRE or doctor/physician. Rinse mouth. – IF ON SKIN: Gently wash with plenty of soap and water. Store locked up

Task 2a: Stakeholder data collection on design/safety characteristics

The rationale behind this activity was to obtain information from a representative sample of industry stakeholders on the main safety issues relating to e-cigarettes. For this purpose a questionnaire was created and sent to a sample of electronic cigarette industries the complete list of which is noted in the following lines. This questionnaire requested information on standards that reduce the risks associated with the refilling processes, designs and possible adjustments that protect against breakage and leakage in order to reduce adverse health effects and other related issues.

So as to reduce the likelihood of industry interference in this activity, and to protect EUREST researchers from personal ramifications, a project specific email account was created. Keeping in mind Article 5.3 of the FCTC and in light of full transparency in communications with the industry, all communications with stakeholders were performed only in writing via that email account and fully documented. No communication through any other venue was facilitated.

In total, 22 industry stakeholders were contacted of which 12 sent the questionnaire responses. An overview of the answers provided was also sent to DG SANTE.

Moreover three consumer organisations were contacted, however they responded that they were unable to provide information to the project at that current time.

Overall the points that were brought forward by industry stakeholders included:

1. With respect to the technical design standards or specifications that have been/are being developed within or outside the EU that would mitigate risks associated with the opening and refill mechanism of refillable electronic cigarettes or refill containers, a number of companies referred to existing product standards:
   - AFNOR standards XP D90-300-1 and XP D90-300-2.
   - BSI PAS 54115 which was published on the 25th of May 2015.
   - ISO 8317,1 which provides for the testing of re-closable child-resistant packaging.

Annex C-8
• BS EN 862,2 which provides for the testing of non-reclosable packages for non-pharmaceutical products.
• One company stated that there are REACH (EC No 1907/2006) and CLP Chemicals Legislation (EC No 1272/2008) which defines labelling and packaging requirements.

2. Regarding the development or the process of developing any standards, specifications or mechanisms that would make their own e-cigarettes or refill containers child- and tamper-proof and/or that would protect these products against leakage and breakage and ensuring refilling without leakage, the industry stakeholders responded that there are already existing global standards for child resistance and tamper evidence.
• One company noted that the bottle/container must as a minimum conform to ISO 8317:2004 for a re-closable pack and BS EN 862:2005 for a non-reclosable pack.
• Additionally, one e-cigarette industry stakeholder reported that they have made adequate provision for their refill containers to be child-resistant and tamper-evident, but it should be noted this does not mean they are child-proof and tamper-proof in absolute terms.
• One stakeholder suggested a proprietary technology and provided supplementary information on this design.
• One stakeholder noted that thin and long drip tips should be standardized so that it can easily be inserted in the e-liquid reservoir during filling. This was complemented by the fact that XP D90-300-1 and XP D90-300-2 have notably created 2 icons (for the refill bottle and the device), so the vaping industry can specify the diameter of the electronic cigarette’s filler hole and the diameter of the nozzle of the e-liquid dropper bottle.

3. With respect to technical requirements/mechanisms/standards that - in their view - be used to make e-cigarettes or refill containers child- and tamper proof, protect them against leakage and breakage and ensure refilling without leakage, two companies noted that there is a range of existing international standards
• In addition to the child safety cap, an additional removable plastic seal could reduce the occurrence of leakage.
• Furthermore, one company stated that e-liquid should be handled with the same considerations as chemical based household products and appropriate CLP guidelines and ISO testing standards (8317) should be followed to ensure protection.
• It is worth noting that one company argued that that the lack of studies regarding the toxicity of nicotine should be taken into consideration.

4. Regarding the risks that stakeholders have considered when developing the standards, specifications or mechanisms, one stated that their main considerations are focused around leak-free filling and ISO 8317 compliance. Two companies noted that the primary risks appear to be:
  o Accidental exposure while refilling
  o Leaking from the assembled device
  o Access to e-liquid by children.
One expressed their concern about the aromas/ flavours that are attractive to children but potentially fatal if ingested. Additionally, one company noted that there are currently several scientific analysis and expertise’s loopholes, which undermine the definition of the risks that should be covered through the development of refill mechanisms, regarding the dermal toxicity and oral toxicity of nicotine used in e-liquids partly.

5. With regards to the potential upcoming market evolutions and product families:
   a) One stated that there are two main categories/formats:
      i. “‘portable’ systems i.e. direct link between refill unit - device (an evolution of current bottles & open tanks)
      ii. ‘Refill stations’, i.e. e-cigarette interfaces to a standalone unit (desktop, vending, etc.) which dispenses E-liquid.”
   b) Another referred that there are: "the 1st generation products, also named "cigalikes”, the 2nd generation products with refillable cartridges or tanks and the 3rd generation products, also named "MODs”.
   c) One noted the following: "Refillable cartomizer”; “Tankomizer”; "Top coil” tank; "Bottom coil” tank.

**Task 2b: Evaluation of existing standards and costs**

According to the cross evaluation of information and standards, we note that:

- PAS 54115:2015 does not require a specific technology to ensure leakage free refilling but rather states that manufacturers/importers should include instructions to users on safe refilling (section 6.2) and ensure that bottles are designed with a delivery spout capable of delivering refill liquid without spillage (section 6.4).
- AFNOR XP-D-90-300 suggests that the outside diameter of the nozzle of a refill container should be smaller than the diameter of the tank and that refill containers should have a flow-control mechanism. It also states that e-cigarettes should be refilled according to the instructions in the product information manual and should not leak or come into contact with users. This should be tested through manual inspection of absorbent paper (section 5.1 of part 1).
- As regards labelling of e-cigarettes, AFNOR XP-D-90-300-1 (part 1) states that the unit packet should include a pictogram indicating the diameter of the tank filling hole (section 8.2). A product information leaflet should include information on the size of the tank refilling hole and the refilling mechanism of the e-cigarette (section 8.3.2).
- As regards labelling of e-cigarettes refill bottles, AFNOR XP-D-90-300-2 (part 2) states that for refill bottles a product information leaflet should include information on the diameter of the refill nozzle and refilling mechanism of the e-cigarette (sections 5.4.3 and 6.3.2).
- CLP classifications and warnings may increase user caution during the refill process.
- ISO 8317 and EN862 standards may be used to make refill vials child resistant. ISO 8317 specifies the requirements and test methods for re-closable packages designated as resistant to opening by children. When applied, these standards should provide a satisfactory degree of resistance to opening by children while maintaining accessibility to
its contents by adults. On the other hand, EN862 outlines the requirements and testing procedures for non-reclosable packages for non-pharmaceutical products.

**Anticipated consequences for Industry:**

Two main types of costs for the industry were identified. One relates to the one-off costs of redesigning the refill vials and one relates to recurring costs which would stem from the implementation of technical standards that would mitigate risk into routine production. The product redesigning that we suggest would consist of four main aspects a) making caps ISO compliant for child resistance, b) adding a plastic sheath that would hold the cap securely on the vial c) ensuring that the refill nozzle is long and elongated and ensure a steady drop rate d) adding appropriate instructions and warning on the refill vial. Based on our sample of products purchased and stakeholder feedback we do not anticipate that manufacturers would need to drastically redesign their products to comply with the technical design characteristics identified.

**Task 3: Synopsis of WP4 findings**

Through the research performed in WP4, specific design parameters or user actions that could mitigate some of the risks identified in WP2 and WP3 were identified. We present below some general conclusions followed by suggestions for both refill vials and the actual e-cigarette itself. It is important to outline that, to the best of our knowledge, there is no way to a priori eliminate the risk related to the refill process as this is inherent to the function of refillable e-cigarettes.

Overall, design parameters or user actions that could mitigate overall risk during refilling include:

- Refill vials with an elongated and thin nozzle that fits seamlessly within the opening of the tank of the e-cigarettes.
- E-liquid should not flow freely from the refill vial when tipped on its side or when placed upside down (i.e. there should be a flow-control mechanism in the refill bottle).
- Refilling should not involve an additional transfer step with syringes or pipettes.
- E-cigarettes and refill containers could have a docking system which ensures that liquid only flows when they are connected.
- Plastic gloves could be used during the refill process to further mitigate the risks.
- Leaflets could instruct users how to safely refill e-cigarettes and include diagrams where necessary. These leaflets could be glued to the refill vial.
- Warnings could inform the consumer and increase user caution during refilling.

**Refill vials:** The below parameters were identified as those that would mitigate the risk of exposure to liquid from refill vials:

- The refill liquid vial must as a minimum conform to ISO 8317:2004 for a re-closable pack and EN 862:2005 for a non-reclosable pack to mitigate the potential risk of ingestion, especially among children – a risk which was evidently clear through WP2 and WP3.
- The addition of a removable plastic seal that would surround the cap and ensure that it would be transferred to the consumer in a tamper proof package. This seal would also add

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an additional safety layer for the protection from both unintentional ingestion by children and accidental leakage during shipping, by securing the cap on the vial.

✓ Refill vials should be of suitable composition to be protected against corrosion/damage.
✓ The addition of a silicon or equivalent ring between the nozzle and the cap of the vial of the refill liquid to further reduce leakage and potential dermal exposure.
✓ An information sheet or leaflet with warnings and instructions for use and for refilling. These leaflets could be glued to the vial itself so as to ensure they stay with the refill vial.
✓ Visual, text and tactile warnings on the refill vial itself would increase consumer caution both among users and non-users.

Moreover, the refill liquid vial should also adhere to three standards:

✓ Effectiveness standard. The child resistant packaging, tested by the protocol specified in 16 CFR 1700.20 and 16 CFR 1700.15(b).
✓ Compatibility standard. The packaging must continue to meet the effectiveness specifications when in actual use as an e-cigarette refill container. This requirement may be satisfied by appropriate scientific evaluation of the compatibility of the substance with the packaging to determine that the chemical and physical characteristics of the e-liquid will not compromise or interfere with the proper functioning of the child-resistant packaging and that the packaging will not be detrimental to the integrity of the product during storage and use.
✓ Durability standard. The child-resistant packaging must continue to meet the effectiveness and compatibility standards for the reasonably expected lifetime of the package, taking into account the number of times the package is customarily opened and closed.

**E-cigarette tank:** The following were identified as characteristics that may mitigate risks of leakage from the e-cigarette tank:

✓ The existence of a silicon or equivalent ring on the e-cigarette itself, at the area of connection between the seam of the tank and the tank cap.
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