



RECOMMENDATIONS OF THE SUPERIOR HEALTH COUNCIL no. 9265

State of affairs: the electronic cigarette

In this scientific advisory report on public health policy, the Superior Health Council of Belgium provides an updated risk assessment for electronic cigarettes (with or without nicotine) for smokers, non-smokers and vapers.

This report aims at providing politicians, public health authorities, healthcare providers, teachers, youngsters, smokers and vapers with specific recommendations on the toxicity and safety of electronic cigarettes (vs. traditional tobacco cigarettes).

Version validated at the Council Meeting of
October 2015

I INTRODUCTION AND ISSUE

In January 2015, the Superior Health Council (SHC) was asked by the Ministerial Policy Unit led by Maggie De Block MP to review its recommendations of December 2013 (SHC 8941, 2013) on electronic cigarettes (e-cigarettes).

There are several types of e-cigarettes. Each type contains three main components: a battery, a tank holding e-liquid (also called a cartridge) and an atomiser. In some models the cartridge and atomiser are combined to form a single component. When air is drawn through the mouthpiece or when a button is pressed, the battery heats the resistor in the atomiser. The e-liquid in the wick atomises and is inhaled by the user.

The basic ingredient of the e-liquid is formed by a propylene glycol and/or vegetable glycerine solution, which atomises to produce a visible aerosol.

E-liquid also contains water and flavourings and may contain nicotine. The range of flavourings is huge: mint, chocolate, coffee, vanilla, etc. (Tierny et al., 2015).

More particularly, the Minister has asked that clear and precise answers be given to the following questions:

- What are the quality requirements that e-cigarettes (with or without nicotine) should comply with?
- What are the harmful effects of e-cigarettes and can they be weighed against the harmful effects of tobacco cigarettes?
- In the case of tobacco smokers who use e-cigarettes with nicotine there are the obvious questions of:
 - o Do they help reduce or even stop smoking?
 - o Does use of both cause any additional harm?
 - o Can an e-cigarette without nicotine help tobacco smokers through the final stage of “stopping smoking”?
- In the case of non-smokers,
 - o Do non-smokers run the risk of being encouraged to use E-cigarettes with nicotine?
 - o Is there also a risk of non-smokers more readily using e-cigarettes without nicotine and then moving on to e-cigarettes with nicotine or tobacco products?

The core of this question is two-fold: the potential health hazard associated with the use of e-cigarettes, and the potential role of the e-cigarette in tobacco control policy.

However, the SHC was of the opinion that the role of the e-cigarette should be reviewed from the broader perspective of tobacco control policy and for this reason decided to broaden the scope of its recommendations.

The SHC was asked to give its recommendations within 6 months.

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II SCIENTIFIC CONCLUSIONS, OTHER CONSIDERATIONS AND RECOMMENDATIONS

1 Preliminary comments

Before presenting its main conclusions and recommendations, the SHC sets out several key concepts and basic points relating to the effect of tobacco products and e-cigarettes on public health.

Smoking: The SHC defines smoking as the practice of burning tobacco cigarettes and other tobacco products and inhaling the smoke produced.

Vaping: The SHC defines vaping as the use of e-cigarettes. An e-cigarette contains a liquid which is electrically heated to create an aerosol (usually called a vapour) which is then inhaled by the user. The SHC uses the term “vaping” with no further explanation to mean the use of e-cigarettes with nicotine. Where e-cigarettes without nicotine are meant, this will be specified explicitly.

The SHC’s conclusions and recommendations in response to the Policy Unit’s request rest on the following considerations:

- Smoking is extremely harmful to human health. The health hazard is caused chiefly by the inhalation of combustion products in tobacco smoke and repeated exposure to these products through addiction to nicotine, further reinforced by psychological habituation to the routines of smoking. It should be noted that the harmful effect of nicotine *in itself* is relatively limited, and clearly much less than tobacco smoke.
- There are considerable public health benefits to be gained from reducing and ultimately eliminating smoking and nicotine dependence. From a health perspective, reducing nicotine dependency is secondary to the primary goal of eliminating smoking.

The SHC notes that according to figures for 2013 (SIPH, 2013) an estimated 23% of the Belgian population smokes, with 19% (the overwhelming majority) smoking daily and 4% occasionally. In the 15-24 age group the figure is 21.8 percent and in the 25-34 age group 26.2 percent. Even this snapshot reveals that current Belgian tobacco control policy has not had sufficient effect among one of the most relevant groups, i.e. the young population. In addition, it seems that there are more smokers among people of lower income and education: 18% of managers, 23% of non-manual workers, 41% of manual workers and up to 46% of unemployed people smoke. Though it is beyond the scope of this request for recommendations, the SHC calls for an intensification of the tobacco control policy in Belgium. This policy intensification would support the role assigned to vaping by the SHC, which we explain below.

The considerations also imply that the SHC evaluates vaping in these recommendations as a component of tobacco control policy and not as a modern stimulant in itself.

2 Answers to the requests for recommendation

2.1 What are the quality requirements that e-cigarettes (with or without nicotine) should comply with?

The quality requirements applicable to e-cigarettes with nicotine (to be complied with from May 2016) are set out in article 20 of European Directive 2014/40/EU (EU, 2014). The SHC endorses these requirements but points out that the toxicity of the scents, colourings and flavourings added to e-cigarettes (with and without nicotine) has not been adequately assessed, because the effect of inhalation of the heated substances may be entirely different from their ingestion in foods.

The SHC recommends that the quality standards applied to e-cigarettes with nicotine be the same as those for e-cigarettes without nicotine (except where the nicotine is concerned).

The technology used in e-cigarettes, with or without nicotine, is constantly evolving. Besides, on the subject of quality requirements for e-cigarettes, further progress is expected from the work currently being done at the ECS (*European Committee for Standardization*), which aims to further clarify the quality requirements for e-liquids as well as their electronic vaporisers.

2.2 What are the harmful effects of e-cigarettes and can they be weighed against the harmful effects of tobacco cigarettes?

Nicotine aside, user exposure to toxic substances is considerably reduced through vaping when compared to smoking. This is because vaping releases none of the products of tobacco combustion, and instead releases just a small number of toxic products. This conclusion assumes that all e-cigarettes meet the set of strict conditions set out in the EC Directive (in relation to additives, flavourings, etc.).

In this context, the SHC observes that the health effects associated with long term use of e-cigarettes (over many months or years) are still uncertain. But this is hardly surprising given that in the past ten years the number of users has risen from zero to a significant percentage (at least in countries like the United States, the United Kingdom and France (but much less so in Belgium)), meaning there are few long term users and there are not enough long-term studies from which to draw convincing conclusions. Given that nicotine and other substances inhaled through vaping are certainly not harmless, or could be harmful, the SHC takes the view that the electronic cigarette, with or without nicotine, should be introduced with the necessary caution and vigilance. Vaping is not recommended for pregnant women due to the lack of knowledge about the potential harm for the unborn child.

It is also the case that cartridges of nicotine-containing liquids (can) produce acute toxic effects in the case of accident or incorrect use.

2.3 In the case of tobacco smokers who use e-cigarettes with nicotine, there is the obvious question of: do they help reduce or even stop smoking?

As indicated above, e-cigarettes containing nicotine are not yet well enough established and there are insufficient study results available to make appropriate statements about the effectiveness of vaping in smoking reduction or cessation. The experiences reported in the scientific literature to date are, however, encouraging . It seems that vaping may play a positive role in smoking cessation. It seems that adolescents do not use the electronic cigarette as a means of stopping smoking (Wang et al, 2015). The SHC sees no reason to refuse market access to e-cigarettes containing nicotine, provided they are used with the primary goal of preventing tobacco smoking within a smoking control policy.

2.4 In the case of tobacco smokers who use e-cigarettes with nicotine, there is the obvious question of: does the use of both cause any additional danger?

The SHC is unable to provide an answer to this question based on information published to date. It is, however, clear that smokers must stop smoking in order reduce the risks posed to their health by smoking. If they do not, the risks associated with smoking remain dominant.

There are no strong indications in the literature to suggest that this combination would be beneficial in the long term through a reduction of the risks. To have a positive effect on health and alleviate chronic bronchitis, for example, use of tobacco must be reduced by more than 85%. A beneficial effect on the heart can only be achieved by stopping smoking altogether (Rigotti & Clair, 2013 ; Lee et al., 2013).

However, this question is less relevant in the framework envisaged by the SHC: in the first place, vaping must be part of a smoking control policy. In addition, the SHC points out that simultaneous use of tobacco cigarettes and e-cigarettes can give people the illusion of having made a healthier choice while still experiencing the harmful effects of smoking.

2.5 Can an e-cigarette without nicotine help tobacco smokers through the final stage of “stopping smoking”?

If we understand this question in the sense of “stopping tobacco smoking”, the answer is already included in section 2.3 above. If we understand it in the sense of “after stopping tobacco smoking, (then) stopping vaping”, the SHC cannot yet give an answer due a lack of appropriate data from user surveys. However, the SHC considers this a relevant subject for further study.

2.6 Do non-smokers run the risk of starting to use e-cigarettes with nicotine?

Is there also a risk of non-smokers more readily using e-cigarettes without nicotine and then moving on to e-cigarettes with nicotine or tobacco products?

There is certainly a chance of non-smokers becoming habitual users of nicotine-containing e-cigarettes, but as yet there is little to suggest this. Experimenting seldom leads to habitual use and the overwhelming majority of habitual vapers are (former) smokers.

Based on the current publications, the SHC can neither rule out nor confirm the assumption that increasing use of e-cigarettes (with or without nicotine) would be a gateway to tobacco smoking, known as the gateway hypothesis.

The SHC sees this uncertainty as a reason to advocate caution and vigilance in the further introduction of e-cigarettes with or without nicotine, both in general and among children under the age of 18.

Summary

In summary, the SHC is of the opinion that the use of electronic cigarettes with nicotine can become part of tobacco control policy. In this context, the primary focus is the reduction of tobacco smoking. Secondly, the SHC views unlimited (continued) use of the electronic cigarette as undesirable from a public health viewpoint. It advocates including the reduction of vaping and nicotine use within that policy. It also calls for vigilance to ensure that the secondary goal does not get in the way of the primary goal (reducing the prevalence of smoking): this is because continuing to use a means of nicotine replacement (*Nicotine replacement therapy* (NRT) / electronic cigarette) in the long term is to be preferred above running the risk of returning to tobacco smoking.

3 Other considerations

3.1 Equal treatment

It certainly cannot be the intention to take a stricter approach to e-cigarettes compared to tobacco cigarettes, given that the former are less harmful than the latter. Equal treatment of the two products is required at the very least, if not stricter treatment of tobacco (cigarettes) compared to e-cigarettes.

On the other hand, measures to regulate e-cigarettes must not result in weakening of the regulations on tobacco cigarettes (on advertising or smoking in public places, for example).

3.2 Non-smokers

Given that nicotine is a product which may also be harmful to health, the use of e-cigarettes with nicotine is not recommended for non-smokers because not enough is known about the long-term toxicity and the effects of scents and flavourings; however, this principle may be difficult to apply in practice. The same applies to e-cigarettes without nicotine.

3.3 Special presentations, names, likenesses to tobacco cigarettes, disposable cigarettes

E-cigarettes, with or without nicotine, are placed on the market with certain designs, tastes, scents, names, gadgetry, prices, ... with a view to encouraging people to vape. This is diametrically opposed to tobacco control policy. These practices must be regulated, controlled or banned, as is the case with tobacco cigarettes.

3.4 Scents, flavourings, colourings

We are aware of very little toxicological data relating to the properties of the scents, flavourings, etc., added to e-cigarettes, and especially the inhalation of these substances after heating (this is also the case for tobacco cigarettes). The European Directive states that it is up to the manufacturers or importers to provide the necessary toxicological data when submitting notification about the placement of e-cigarettes on the market, but it is ultimately up to the government to assess and demonstrate any serious risks to public health. Practical experience of the requirement to prove the effects of some substances shows that this is extremely difficult and can also be highly time, labour and cost intensive.

The SHC is not against the addition of flavourings as part of a tobacco treatment policy, provided these products are guaranteed to be harmless. However, the flavourings must not include types such as alcohol, cannabis, etc.

3.5 Substantial modification

The European Directive leaves it up to the party who places the e-cigarettes on the market to assess whether “substantial” modifications, which are notifiable to the government, have been made to the product. However there is no definition of the term “substantial”.

3.6 Place of sale

Neither tobacco nor e-cigarettes should be freely and easily obtainable, e.g. at supermarket checkouts or other places to which the public and, more particularly, non-smokers have easy access. It would be better to restrict the sale of e-cigarettes to specialist points of sale for e-cigarettes, where the necessary information is present and, better still, where trained personnel offer guidance, although specific training does not yet exist.

Where tobacco is concerned the SHC is of the opinion that these points of sale should be restricted to tobacconists’ and newsagents’, at which there should be no advertising, and with a display ban.

3.7 Market surveillance authority, scientific support

The European Directive imposes a number of obligations on the Member States relating to market surveillance and monitoring as well as inspection of documents submitted by manufacturers and importers, toxicity assessment of the ingredients, sampling, analysis, etc. Funding and manpower must be made available; the Directive also mentions the possibility of enforcing proportionate penalties.

3.8 Sale of e-cigarettes and use in public places; current legal status

Current Belgian law equates nicotine containing e-cigarettes to medicinal products and states that they may only be sold in a pharmacy. In May 2016 article 20 of European Directive 2014/40/EU will come into effect, meaning that sales will be allowable outside the pharmacy provided the product satisfies certain conditions. E-cigarettes without nicotine may be freely sold.

The law of 22 December 2009 states that the use of an e-cigarette (with or without nicotine) is forbidden in any place covered by a smoking ban.

3.9 Ecological impact

Although beyond the scope of these recommendations, the SHC would like to draw attention to the possible ecological impact of disposable e-cigarettes, batteries, empty cartridges, etc.

4 Recommendations

4.1 Measures on smoking and vaping

It follows from the conclusions and other considerations above that restrictions on smoking and vaping should not differ and that restrictions on e-cigarettes should not be stricter than those on tobacco cigarettes, nor should they lead to a relaxation of the regulations on smoking. For this reason the SHC supports a general vaping ban in enclosed public spaces, as is the case with tobacco cigarettes, another reason being the difficulty of telling electronic cigarettes and tobacco cigarettes apart when applying the ban.

One member is of the opinion that “A general ban on the use of the e-cigarette in enclosed public spaces seems disproportionate to the minimal third party health risk, and if anything it appears to him counterproductive in pursuing the primary goal of reducing the prevalence of tobacco smoking. For that reason the member does not support the general vaping ban in enclosed public areas, but selective restrictions (exhaustive list of places with a smoking ban (for example: schools, public transport, shared workplace)).”

This approach means that the desired (stricter) restrictions on purchases of cigarettes and other tobacco products must also apply to e-cigarettes (and therefore the sale of cigarettes and e-cigarettes in supermarkets, superstores, petrol stations, etc.). The SHC views special points of sale as a good alternative for e-cigarette sales.

In addition, the SHC repeats its previous observation that there is good reason to intensify tobacco treatment policy with a view to improving both individual and collective health. For this reason the SHC advocates extension and stricter supervision of current restrictions on the sale of tobacco products and on smoking. This involves, inter alia, a ban on advertising, a ban on the display of tobacco products, the introduction of plain packaging, restriction of points of sale for tobacco cigarettes to newsagents' and tobacconists', enforcement and better implementation of the legislation on non-smoking environments, etc.

The SHC recommends that the age limit on the purchase of cigarettes be raised from 16 to 18.

The SHC also recommends measures which have already been adopted in other countries, such as total prohibition of tobacco advertising or the introduction of plain packaging for cigarettes. For instance, due to the current system of prices and duties, tobacco products, including roll your-own tobacco, are still much cheaper in Belgium compared to neighbouring countries; cigarettes and roll-your-own tobacco are readily available for sale and displayed attractively in the stores, often beside the confectionery and magazines; tobacco advertising is still permitted in strategic locations.

Another tobacco control measure, i.e. the introduction of plain packaging, has already proven its effectiveness in studies and in practice in Australia; countries such as Ireland, the United Kingdom and France have announced this measure for 2016.

The SHC's recommendations on e-cigarettes are linked to this policy (the e-cigarette is not a magic wand that can tackle the tobacco problem in our country, but it does offer not-to-be-missed opportunities as part of a powerful and revitalised anti-smoking policy).

4.2 Health education

Information and education are key aspects of the tobacco control policy. The SHC recommends that any work done in this area also be extended to vaping and e-cigarettes. Apart from non-smokers and non-vapers more generally, young people are a prominent target group for educators (schools, parents, etc.) and care providers. The aim of education is to advise against smoking and vaping, and in the latter case to advise against e-cigarettes with as well as without nicotine.

The SHC envisages an educational role for vendors of e-cigarettes. They must be aware of the role that vaping can play in tobacco control policy and must be able to give users adequate information about this.

This is an argument for sales via special points of sale.

4.3 Use of e-cigarettes with nicotine

The SHC places vaping firmly within the framework of a tobacco control policy. The use of e-cigarettes for other purposes cannot be recommended. This applies in particular to non-smokers and non-vapers.

Where tobacco smokers are concerned, the aim is to stop smoking, through a (possibly temporary) switch to vaping. If giving up cigarettes (tobacco or e-cigarettes) is not possible in an individual case, or not preferred/desired, then the use of the electronic cigarette is preferable to tobacco smoking.

4.4 Use of e-cigarettes without nicotine

As indicated, it is not clear whether, and if so, how the use of e-cigarettes without nicotine fits into the framework of tobacco control. In line with its earlier recommendations (SHC 8941, 2013), the SHC advises caution in the introduction of these products. The main arguments for this are the unknown long-term effects of some of the ingredients in the aerosol produced by the e-cigarette and possible repercussions for tobacco control policy.

4.5 The role of business and industry

The SHC notes that the production and placing of e-cigarettes on the market is controlled for the most part by tobacco multinationals. We should seek to avoid any repetition of the history of tobacco cigarettes, in which, despite knowledge of the health hazards, tobacco sales were promoted in every possible way by making cigarettes more attractive, also to

young people. It has proven difficult for governments to stem the tide. At the present time we are seeing tobacco industry campaigns which present e-cigarettes as harmless. The SHC is of the opinion that health is better served by nipping campaigns like these in the bud. This means, inter alia, a ban on the promotion of e-cigarettes among young people, avoiding similarities between electronic cigarettes and tobacco cigarettes and not permitting the placement of disposable electronic cigarettes on the market.

4.6 Advertising

Advertising and labelling are means of both conveying information and promoting sales and use.

With regard to public information (radio, TV, newspapers and magazines, billboards, etc.) the SHC is of the opinion that the current ban on tobacco cigarettes should extend (or continue to extend) extend to electronic cigarettes.

As regards the authorities' choice of phrasing on packaging units and the outer packaging of e-cigarettes with nicotine and refill containers (art. 20, 4, b, iii) of the Directive), the SHC prefers the phrasing: *"This product contains nicotine, which is a highly addictive substance. It is not recommended for use by non-smokers."*

4.7 The European Directive

The EU Directive of 2014 (EU, 2014) sets out a legal framework which Belgium, as a Member State of the EU, must respect. The SHC is of the opinion that there are points on which the Directive can be improved and advocates that Belgium raise these at the European level.

These relate in the first place to the assessment of the aromas, scents and flavourings added to e-cigarettes. The SHC is of the opinion that the manufacturers should bear greater responsibility, as is currently the case in for example the pharmaceutical and food industries.

The second point is the requirement of the manufacturers to give notification of any substantial modification of an electronic cigarette on the market. The SHC signals that the term "substantial modification" has not been defined, either rendering the present Directive useless or otherwise making it a source of conflict.

4.8 Surveillance authority

The SHC points out the need for adequate surveillance and enforcement. This need arises from our advocated intensification of tobacco control policy, but applies equally to any action needed to implement the European Directive in Belgian national law.

The government must put in place a control mechanism to verify and guarantee the safety and quality of e-cigarettes and e-liquids for consumers.

The governments must closely supervise any possible toxicity and addictiveness of the ingredients, provide the resources needed and cooperate with European scientific bodies in order to ensure this. For this reason the SHC recommends the establishment at Belgian level of an effective and permanent supervisory organ which will be in a position to assess notifications (cf. medicine registration files, food supplement notification files, etc.), to take samples, conduct analyses, etc. and which has, or is able to draw on, sufficient scientific expertise and research funding. This supervisory organ could be funded by means of taxes and penalties paid by those who place tobacco and e-cigarettes on the market.

Analogous with other systems (pharmacovigilance, materiovigilance, etc.) the government must set up systems of tabaccovigilance and e-cigvigilance.

4.9 Ecological viewpoint

The SHC recommends that limitations be placed on the ecological impact of such products, from production to disposal; this would involve, inter alia, the promotion of recycling materials and prohibition of disposable e-cigarettes.

The SHC also recommends that preference be given to materials which involve minimum exposure to metals and that particular attention be paid to the generation of nanoparticles through heating.

5 Recommendations for study

The SHC is of the opinion that further study is recommendable into the role of e-cigarettes in the context of tobacco control policy and into their potential harm to public health.

For this reason the SHC recommends the following:

- Funding independent research on the long-term health effects associated with use of e-cigarettes (among former smokers, *dual-users* and possibly among non-smokers), and on the impact of e-cigarettes on smoking prevalence and nicotine use among the Belgian population.
- Research on the toxicity and addictiveness of the ingredients.
- Further study is shown to be needed with regard to the metals in the heating system, in order to enable a more accurate assessment of the risks, particularly with regard to the possible presence of metal nanoparticles.
- Long term studies on the effects on smoking cessation of vaping with e-cigarettes containing nicotine.
- Long term studies on the potential risk of e-cigarettes as a step up to tobacco smoking, among adolescents in particular.
- Long term studies on the potential role of the e-cigarette without nicotine in smoking cessation.
- Study of the tobacco industry's role in e-cigarette promotions that seek to establish a link with the smoking of tobacco cigarettes and cigarette brand names.

6 Points of difference with SHC 8941 - 9106 recommendations of December 2013

In late 2013, the SHC made its recommendations on the “Place of the electronic cigarette as a quit-smoking aid and the toxicity and addiction risk associated with its use and use of the shisha pen”. The current recommendations differ from the position taken by the SHC in 2013 on several points:

- Although no long term studies are as yet available, a number of quality requirements have now been set out in a European Directive. If followed correctly, these requirements should resolve a number of problems relating to labelling, dosage, batteries, cartridges, flavourings, etc.
- The SHC no longer advocates that electronic cigarettes be sold exclusively through the pharmacy; it does not make sense to take a more restrictive approach to a product (e-cigarette) which is considered less toxic than a product recognised as extremely toxic (tobacco cigarettes and other tobacco products).
- By the same logic, the SHC is no longer of the opinion that e-cigarette advertising must be subject to the requirements for medicinal products, but it must be subject to the requirements for tobacco cigarettes.

7 6th state reform in Belgium

In view of the 6th state reform and the scope of the recommendations in this paper, the SHC further recommends coordination of the policies of the ministers of the federal and federated bodies competent in matters of public health, prevention, education, social promotion, professional training, and the ministers competent for consumer protection and wholesale/retail regulation, advertising regulation, media and films, youth protection and science policy.

Mots clés et MeSH *descriptor terms*¹

MeSH terms	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Electronic cigarettes	Electronic cigarette	Electronisch sigaret	Cigarette électronique	
Tobacco	Tobacco	Tabak	Tabac	
Behavior, addictive	Addiction	Verslaving	Assuétude	
Smoke	Smoke	Roken	Fumer	
Nicotine	Nicotine	Nicotine	Nicotine	
Cessation, smokeless tobacco	Smoking cessation	Stoppen met roken	Arrêt tabagisme	
Cigarettes	Cigarette	Sigaret	Cigarette	
	Vaper	Dampen	Vapoter	

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed <http://www.ncbi.nlm.nih.gov/mesh>.

III METHODOLOGY

Having assessed the request, the Board and the chairman of the study group identified the expertise needed. An *ad-hoc* study group was set up accordingly, containing experts from the following fields of expertise: tobaccology, toxicology, addiction psychology, chemical contaminants, pneumology, tobacco control, environmental health. The group experts submitted a general declaration of interests and an *ad-hoc* statement and the potential for a conflict of interests has been assessed by the Committee for Deontology and Ethics.

As part of its work, the study group took statements from representatives of associations in the field and the various administrations involved in this issue.

The recommendations are based on an overview of the scientific literature, both from scientific journals and reports by national and international organisations with expertise in this matter (*peer-reviewed*), as well as the opinions of the experts.

Once approved by the study group, the recommendations were validated by the Board.

¹ Le Conseil tient à préciser que les termes MeSH et mots-clés sont utilisés à des fins de référencement et de définition aisés du scope de l'avis. Pour de plus amples informations, voir le chapitre « méthodologie ».

IV OBJECTIVES AND RATIONALE

List of abbreviations

ADHD	<i>Attention deficit hyperactivity disorder</i>
ASH	<i>Action Smoking and health</i>
ATS	<i>American Thoracic Society</i>
CAR	<i>Continuous abstinence rate</i>
COPD	<i>Chronic obstructive pulmonary disease</i>
CVA	<i>Cerebrovasculaire accident</i>
e-cigarette	<i>Electronic Cigarette</i>
e-liquid	<i>Liquid which turns into aerosol when heated</i>
ECHA	<i>The European Chemicals Agency</i>
ECLAT	<i>EffiCiency and Safety of an electronic cigarette</i>
ETP	<i>Emerging tobacco products</i>
SHC	<i>Superior Health Council</i>
IARC	<i>International Agency for Research on Cancer</i>
INPES	<i>Institut national de prévention et d'éducation pour la santé</i>
MAOIs	<i>Monoamine oxidase inhibitors</i>
NAB	<i>N'-nitroso anasabine</i>
NAT	<i>N'-nitroso anatabine</i>
NHS	<i>National Health Service</i>
NICE	<i>National Institute for Health and Care Excellence</i>
NNK	<i>4(-methylnitroamino)1-(3-pyridyl)-1-butanone</i>
NNN	<i>N'-nitrosonornicotine</i>
NRT	<i>Nicotine replacement therapy</i>
OFT	<i>Office Français de prévention du Tabagisme</i>
RCT	<i>Randomized Controlled Trial</i>
NIPHE	<i>The National Institute for Public Health and the Environment (Netherlands)</i>
ROS	<i>Reactive oxygen species</i>
SLT	<i>Smokeless tobacco</i>
THR	<i>Tobacco Harm Reduction</i>
TSNA	<i>Tobacco-specific nitrosamines</i>
UCSF	<i>University of California, San Francisco</i>
AADP	<i>Association for Alcohol and other Drug Problems</i>
SIPH	<i>Scientific Institute of Public Health</i>

1 Toxicity of tobacco, nicotine and other substances

1.1 Tobacco smoking

1.1.1 Active smoking

Smoking leads to premature death in one half of smokers, or 6 million deaths per annum around the globe. More than 5 million of these are smokers or former smokers and more than 600,000 are non-smokers who were involuntarily exposed to smoke (WHO, 2015).

Active smoking is directly attributable to the development of chronic pulmonary diseases (*Chronic obstructive pulmonary disease* (COPD) and emphysema) and lung cancer (Forey et al., 2011). Smoking is a risk factor in cancers (of the lung, larynx, oesophagus, stomach, liver, mouth, pancreas, colon/rectum, kidney, breast, prostate) (Torre et al., 2015). Smoking increases the risk of inflammation of the gastrointestinal tract (Crohn) (Coward et al., 2015).

Smoking is linked with an increased risk of developing cardiovascular diseases (cardiac arrest, cerebrovascular accident (CVA), high blood pressure, peripheral artery disease) (Ambrose & Barua, 2004; Barnoya & Glantz, 2005; Tunstall-Pedoe, 2003). Smokers have a higher risk of diabetes type 2 (Willi et al., 2007), of kidney diseases (Speeckaert, 2013) and of other complications arising from these diseases. Smoking increases the risk of osteoporosis. Smoking is linked to an increased risk of infectious diseases (Leung et al., 2015; Nuorti et al., 2000). It aggravates some neurological diseases (multiple sclerosis) (Ragamopalan et al., 2013). Smoking is linked to an increased risk of dental and periodontal disease (Ojima & Hanioka, 2010). Smoking increases the risk of complications during surgery under general anaesthetic (Rodrigo, 2000).

Smoking during pregnancy presents a significant inequality in terms of the health of the unborn child (WHO, 2014). Smoking during pregnancy increases the risk of perinatal mortality, prematurity and cot death (Blair et al., 2006 ; Gray et al., 2009 ; Jaddoe et al., 2008). Smoking during prenatal life damages the health of the foetus, the infant, the child and the adult in the making, in particular because it increases respiratory (Haberg et al., 2007 ; Jones et al., 2011 ; Morre et al., 2010 ; Skorge et al., 2005), cardiovascular (Blake et al., 2000 ; Brion et al., 2008), metabolic (Durmus et al., 2011, Pryor et al., 2011, Montgomery & Ekblom, 2002), neurological (Lindblad & Hjern, 2010 ; O’Callaghan et al., 2011; Stroud et al., 2009) and dental (Julihn et al., 2009) morbidity, and later affects adult fertility (Jensen et al., 2004). Smoking during pregnancy is linked with an increased risk of nicotine deprivation in the newborn child (Godding et al., 2004) and increases the risk of the child becoming a dependent smoker (Buka et al., 2003).

The annual report of the “Perinatal Epidemiology Study Centre” looks at the biggest trends in childbirth and delivery. One of the ten biggest is the high and rising number of pregnant smokers in Flanders. In 2013, 10% of women smoked through pregnancy (in 2012 this figure was 9%). On this subject the “Agency for Care and Health” website says: *“Aware as we are, from the medical literature, that the actual number of smokers is underreported through fear of admission, it is fair to assume that at least 7,000 Flemish mothers smoke during*

pregnancy. This presents another enormous task for prenatal care providers. Smoking during pregnancy is a complex problem linked to low socioeconomic status and social deprivation”.

Smoking and socioeconomic factors

Smoking is clearly linked with health inequalities. There are major social differences in relation to health in our country. Several welfare indicators reveal inequalities between different socioeconomic groups: life expectancy, number of years spent in good health, child mortality, health status, medical consumption and health-related behaviour: diet, (lack of) exercise and use of tobacco. Smoking has played a major role in creating and further widening the health gap and continues to do so today. It is one of the main causes of health inequality.

Smoking behaviour is largely determined by socioeconomic status. By a young age it is already clear that smoking in adulthood goes hand in hand with lower status: smoking is more prevalent in vocational education than in general secondary education. The percentage of smokers, daily smokers and heavy smokers is higher among people with lower qualifications. People with a low-skilled educational background start smoking (daily) at a younger age, smoke more cigarettes a day on average and are more often dependent on tobacco than people with a high-skilled educational background. The difference in tobacco use between low and high-skilled people has increased in recent decades because a relatively higher number of high-skilled people has stopped smoking. Smoking behaviour is often linked to social vulnerability. Health inequalities related to tobacco use and harm begin before birth and play a role throughout the life cycle: during childhood, when starting smoking, when stopping smoking and when tackling the health problems caused by smoking. Experience of various aspects of socioeconomic deprivation only amplifies the inequalities in tobacco related harm.

Health inequalities and tobacco use exist at several levels:

- In the broad social context: poverty, unemployment, social exclusion, cultural norms in relation to tobacco, availability of and access to tobacco, etc.
- In exposure to other smokers in the environment (growing up in a smoking environment doubles a person's chances of becoming a smoker) and to other factors relating to tobacco use (chronic stress, lower impact of anti-smoking campaigns in some groups of smokers, etc.).
- In the greater vulnerability associated with tobacco use (e.g. some groups of smokers show a higher co-morbidity)
- In access to healthcare and quit-smoking aids.

It is alarming to note that the inequalities in tobacco consumption and tobacco-related harm to health continue to grow in Europe.

Recently published figures from the Heath Survey² show that almost one in four Belgians still smoke: 23% smoke, 19% smoke daily, 4% occasionally. The number of smokers has fallen by just 2% since 2008. Smoking prevalence is at its highest in the working age population (25 to 64 years of age): between 26% and 29% smoke. There is also a worrying rise in

² [https://his.wiv-isp.be/nl/Gedeelde %20%20documenten/TA_NL_2013.pdf](https://his.wiv-isp.be/nl/Gedeelde%20documenten/TA_NL_2013.pdf)

smoking and daily smoking among young women. And smoking is, as the Health Survey tells us, “*mostly a habit among people and social milieus that have not experienced higher education*”.

The number of cigarettes consumed daily (16 on average) has remained unchanged in the past ten years. One in six of daily smokers shows signs of heavy tobacco dependence. The number of smokers and daily smokers is highest in the 35-44 age group (29% and 24% respectively).

Another source of information is the annual smoking survey conducted by the Cancer Foundation³. The figures (2014) show that the smoking population in Flanders is 25%, Wallonia 26% and Brussels 30%. This survey also shows the strong connection between smoking and social class: the higher the social class, the lower the number of smokers. In the lowest social classes we see 36% smokers, in the highest 18% (in 2013 this was 34% opposed to 19%). 18% of managers smoke, 23% of non-manual workers, 41% of manual workers, and 46% of unemployed.

In Flanders and Belgium the number of young smokers also remains high. One new trend is that young adults are still taking up smoking, as shown by both the Health Survey and the Pupils' Survey⁴ conducted by the Association for Alcohol and other Drug Problems (AADP). The latter also shows the continuing gap between the general secondary, technical secondary and vocational secondary education systems. Smoking is increasingly a problem among pupils in vocational secondary education, where almost 1 in 3 continue to smoke today. In general there is a considerable difference in smoking behaviour between pupils in the A stream and pupils in the B stream. In the A stream 8.2% has smoked at some point, in the B stream this is 23.1%. In addition, the vast majority in general secondary education indicated that they had never smoked (68.2%), as opposed to 51.3% in technical secondary education and 43.2% in vocational secondary education. Among last year's users, pupils in vocational secondary education more often indicated that they smoked regularly than in the other forms of education, i.e. 28.7%, as opposed to 14.6% in technical secondary education and 6.1% in general secondary education. 23.9% of pupils in vocational secondary education are daily smokers. It is also alarming to note that tobacco use among young people has strongly increased in the past year, across all forms of education, in all age groups and among boys and girls alike. These increases are between 4% and 8%.

Despite assumed general knowledge about the harmfulness of smoking, the ban on advertising, the distinct progress made in helping people quit smoking and existing medicinal aids, there has been no decline in tobacco use. The seriousness of nicotine addiction is seen as a reason why people fail to stop smoking.

1.1.2 *Bystanders/environment*

Passive smoking is the inhalation of environmental tobacco smoke present in the ambient air, in enclosed spaces or covered areas. Environmental smoke is a group 1 human carcinogen (IARC, 2004) and differs in composition from mainstream smoke. Environmental

³ http://www.kanker.be/sites/default/files/Stichting_tegen_kanker_enquete_Rookgedrag.pdf

⁴ <http://www.vad.be/alcohol-en-andere-drugs/onderzoek/leerlingenbevraging.aspx>

tobacco smoke is the leading source of air pollution in buildings (Eisner, 2007). Passive smoking can be measured using markers in the ambient air (CO; nicotine; particles (PM 2.5)) or using biomarkers in the exposed subject (cotinine).

Short-term exposure to environmental tobacco smoke has an immediate effect on the airways and causes irritation of the ocular, nasopharyngeal and bronchial mucous membranes (Flouris et al., 2009). At cardiovascular level, short-term exposure also increases blood pressure and causes platelet activation (Davis et al., 1989).

Chronic exposure to environmental tobacco smoke is harmful to children's health, because it increases the risk of bronchitis, bronchiolitis, pneumonia in children under the age of 2 (Jones et al., 2011), cot death (Golding, 1997), lower respiratory infections (Burke et al., 2012), asthma (Vork et al., 2007), and ear infections in children under the age of 2 (Jones et al., 2012). In addition, exposed children have a much higher risk of respiratory complications under general anaesthetic (Seyidov et al., 2011 ; von Ungern-Sternberg et al., 2010) and lower resistance to serious infections (den Boon et al., 2007 ; Murray et al., 2012). Passive smoking aggravates the development of chronic diseases in children, and is proven to effect asthma, cystic fibrosis (Collaco et al., 2008) and diabetes type 1.

Chronic exposure to environmental tobacco smoke is harmful to adult health, because it increases the risk of cardiovascular disease (Barnoya et al., 2005) which can cause premature death (Gallo et al., 2010 ; Pell et al., 2009) and coronary artery disease (increased risk of cardiac arrest, recurrent cardiac arrest) (Hamer et al., 2010), stroke (Lee et al., 2006), peripheral vascular disease (He et al., 2008), arterial hypertension (Vozoris et al., 2008); the risk of bronchial diseases (COPD, emphysema, asthma and chronic cough) (Ebbert et al., 2007 ; Hooper et al., 2012 ; Jaakola et al., 2003). Finally, passive smoking increases the risk of cancer among adults, in particular lung cancer (Taylor et al., 2007), breast cancer (Johnson et al., 2008), cervical cancer (Tsai et al., 2007), pancreatic cancer (Vrieling et al., 2010) and laryngeal cancer (Lee et al., 2008).

The introduction of the smoking ban in public places has had an important effect in the area of public health, with regard to both the cardiovascular health of adults (17% reduction in hospitalisations due to cardiac arrest) (Cox et al., 2013 ; Meyers et al., 2009), and the health of children (reduction in number of hospitalisations due to asthma, premature birth) (Cox et al., 2014 ; Mackay et al., 2010). A study by the University of Hasselt for the Flemish League against Cancer (Come out against Cancer) shows that *“there are over 425 fewer cardiac arrest fatalities a year as a result of the smoking ban in the workplace”*.⁵

1.2 Nicotine

Little is known about the harmfulness of pure nicotine in the long term. The toxicological profile of nicotine-containing products which are licensed as a form of NRT is, however, reassuring, although there is uncertainty as to whether nicotine is carcinogenic (*International*

⁵ <http://www.uhasselt.be/UH/Nieuws/Actueel-Nieuws-2014/Rookverbod-op-werk-zorgt-in-Vlaanderen-jaarlijks-voor-ruim-425-dodelijke-hartinfarcten-minder.html>

Programme on Chemical Safety) and there are indications, from animal testing, that nicotine may have a teratogenic effect ⁶.

Many animal studies relating to nicotine toxicity conclude the existence of vascular, liver and lung toxicity (Fahim et al., 2014 ; Wang et al., 2012 ; Yokohira et al., 2012); kidney toxicity (Arany et al., 2011); neurological toxicity (Gould et al., 2014). Additionally, a recent animal study has shown that administering nicotine could promote tumour growth and metastasis formation (Davis et al., 2009). Exposure to nicotine *in utero* has neurological effects (Schneider et al., 2010 ; Gould et al., 2014). Perinatal exposure may promote asthma in successive generations of rats (transgenerational transfer) (Bruin et al., 2010 ; Dwyer et al., 2009).

From the information currently available in the literature it cannot be shown with certainty that regular use of pure nicotine is associated with long term toxicity.

Where chronic exposure to nicotine is concerned:

- Although there are no studies to demonstrate the danger of chronic nicotine use in large populations there are many studies relating to the **impact on human health of tobacco in non-combusted form (snus⁷)**. Snus gives the user a serum nicotine value twice as high as that of patches, contains substantial doses of tobacco-specific nitrosamines (TSNAs: 4-(methylnitroamino)1-(3-pyridyl)-1-butanone (NNK) & N'-nitrosonornicotine (NNN)) and polycyclic aromatic hydrocarbons (PAHs), but does not give the user any of the toxic substances produced through the burning of tobacco. 60% of smokers who use snus to stop smoking remain dependent on the product (Macara, 2008). The use of snus appears to be linked to an increased risk of cardiac weakness (Arefalk et al., 2012), death through cardiac arrest (Hansson et al., 2012) and a higher systolic blood pressure (Overland et al., 2013). Other studies however show no link between snus and other cardiovascular or cerebrovascular risks, or cardiac arrhythmia (Hansson et al., 2009; Hansson et al., 2012; Hansson et al., 2014; Hergens et al., 2014). A meta-analysis in 2014 shows an absence of serious cardiovascular side effects for NRT, but an increase in less serious cardiovascular events (mostly tachycardia) (Mills et al., 2014).
- A 10-year prospective study in Sweden links long-term and intensive use of snus with an increased risk of diabetes type 2 (Ostenson et al., 2012). Other studies report no clear link (e.g. Wändell et al., 2008).
- Human and animal data give us some understanding of the impact of exposure to nicotine during certain vulnerable developmental periods (from foetus to adolescence). These conditions relate to brain and lung development during intrauterine life and maturing of the cerebral cortex and hippocampus in adolescents (England et al., 2015).

⁶ <http://www.inchem.org/documents/pims/chemical/nicotine.htm>

⁷ Snus is a moist powder tobacco product which is mostly consumed in Sweden and Norway. The product is normally consumed by placing it between the gum and the upper lip and keeping it there for anything from a few minutes to a few hours (<https://nl.wikipedia.org/wiki/Snus>).

- Information is also available on the development of behavioural disorders among children: *Attention deficit hyperactivity disorder (ADHD)* (Tiesler & Heinrich, 2014).
- There is plenty of well validated information on the impact of nicotine on sensitisation of the reward system. Nicotine operates on the cellular mechanisms of synaptic plasticity (Gould et al., 2014). Nicotine is a highly addictive alkaloid which can sensitise the reward system to disrupt reasoned behaviour and sensitise for other psychotropic substances. On the other hand there are indications that the addictiveness of nicotine is significantly dependent on (a) interaction with other substances (such as MAOIs present in tobacco cigarettes) (Brennan et al., 2013); and (b) Pavlovian learning processes relating to the non-pharmacological cues (flavour, visual cues, “throat hit”, hand-mouth-movement) associated with nicotine administration (or smoking behaviour). In test animals, behaviour which led to the self-administration of nicotine was controlled not only by the primary reward effects of nicotine, but the secondary (learned) reward effect of non-nicotine cues (e.g. visual or auditory stimuli) associated with the nicotine-administration (Markou & Paterson, 2009 ; Caggiula et al., 2009). Studies on nicotine craving reduction and smoking satisfaction among humans also indicate the how crucial both facilitating factors are (Rose et al., 2000; Rose et al., 2003; Rose et al., 2010; Rose et al., 2006).
- Nicotine cannot be delivered as fast and effectively from e-cigarettes as it can from tobacco cigarettes. Therefore, there could well be addiction stimulation differences between these two means of self-administration (Etter & Eisenberg, 2014; Farsalinos et al., 2014).
- Nicotine also has an effect on appetite and there are strong indications of a bidirectional relationship between smoking and depression, which tends to be attenuated by nicotine (Picciotto & Mineur, 2014)).
- The effects of nicotine intake via e-cigarettes on a young, healthy population are unknown and even less known in a population with underlying chronic illness.
- No dose of nicotine is proven to be harmless during pregnancy (Suter et al., 2015).

Therefore, nicotine is certainly not a product without consequences for human health, but the risk of nicotine is limited compared to the risks of tobacco smoke. The misconception that nicotine is in itself one of the most harmful components of tobacco smoke is widespread and in some ways obstructs the successful implementation of smoking cessation through NRT and e-cigarettes. Very recently (August 2015) the British *Royal Society for Public Health* set up a publication and media campaign in an effort to dispel this harmful misconception⁸.

In tobacco addiction treatment it has traditionally been advocated that nicotine replacement should be used over a short period of time. But more recently it has been the view that

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http://www.rsph.org.uk/filemanager/root/site_assets/our_work/position_statements/rsph_smoking_positional_final.pdf, accessed 17-09-2015.

continuation of NRT (the electronic cigarette) over a longer period of time is to be preferred above running the risk of returning to tobacco smoking. Similar advice is currently being given by the American Food and Drug Administration (April 2013) (*“Users of NRT products should still use the product for the length of time indicated in the label— for example, 8, 10 or 12 weeks. However, if they feel they need to continue using the product for longer in order to quit, it is safe to do so in most cases. Consumers are advised to consult their health care professional if they feel the need to use an OTC NRT for longer than the time period recommended in the label.”*)

1.2.1 Vapers

On the subject of acute toxicity (ingestion of a large quantity of e-liquid)

Acute nicotine toxicity shows high interspecies variability. The only studies available are often old and the methods used are debatable. A great many *case reports* and the clinical experience of tobaccologists tend to query the current toxicity limit and intuitively place it at a higher level. For example, Mayer (2014) recently called for a review of the toxicity limit *“in light of overwhelming data indicating that more than 0.5 g of oral nicotine is required to kill an adult.”*

But *“[t]he data on humans are reported to help decide the ultimate LD₅₀⁹ values. They are difficult to interpret due to a lack of information about the reported cases and the very great differences between cases. This is because there are huge interindividual differences in the speed at which the nicotine is absorbed and the speed at which it is eliminated”* (ANSES Report 2014).

“As a consequence, the specialist committee of experts is of the opinion, where oral ingestion is concerned, and account taken of:

- *the fact that the information in the literature is old and sparse,*
- *the interspecies and interindividual differences in terms of sensitivity,*
- *data on people who show signs of intoxication which can occur at 0.3 mg/kg in adults and 0.2 mg/kg in children,*

that it is impossible to rule out the possibility of small doses having an effect, especially among people who have not developed an addiction. As a consequence and by way of precaution, we adopt the weakest LD₅₀ obtained for the mouse, i.e. 3.34 mg/kg (Lazutka et al., 1969), despite the limitations of this study.” (ANSES Report 2014)

E-liquids containing nicotine can, however, if ingested, have serious, even fatal effects on children and probably anyone who has not developed a tolerance (England et al., 2015).

It should be noted that the Netherlands has submitted to the European Chemicals Agency (ECHA) a proposal for a harmonised nicotine classification. The proposal relates to acute nicotine toxicity, mainly by oral exposure. The Dutch report assesses that the nicotine hazard level should be raised to category 1 acute toxicity by the oral exposure route (the

⁹ "Lethal Dose, 50%" or median lethal dose

most serious) and category 2 for inhalation. The proposal and accompanying literature have been submitted for public consultation in line with procedure. The proposal is listed on the September agenda of the ECHA's scientific Risk Assessment Committee (RAC). This committee, which is made up of independent experts, will issue a statement on the acute toxicity of nicotine. Once the RAC's position is known there will be an official European vote on the matter for inclusion in annex VI of (EC) Regulation 1272/2008 (CLP regulation). The European vote on this classification will become mandatory across the territory of the European Union. The current documents (Dutch report and comments at the public consultation) are available via the following link: <http://echa.europa.eu/fr/harmonised-classification-and-labelling-previous-consultations/-/substance-rev/8708/term>. We do not yet know the exact date on which the RAC will state its position. Several meetings may have to be held in order to reach consensus.

1.2.2 Bystanders/environment (“passive vapers”: pregnant women, children, etc.)

Although no studies are available to demonstrate the danger of chronic nicotine use in large populations, there are plenty of human and animal data referring to the impact of exposure to nicotine during vulnerable periods of development (from foetus to adolescence). These conditions relate to the development of the foetus, as well as that of the lungs, cerebral cortex and hippocampus in adolescents (England et al., 2015).

In utero exposure to tobacco products in unburned form

Nicotine is a toxin which affects development and whose properties are well demonstrated *in vitro* and *in vivo* (Dwyer et al., 2009). The effects of conventional smoking by the mother on the development of the foetus, neonatal morbidity and the health of the child and adult are well known (Mund et al., 2013).

The absorption of nicotine in unburned form also has toxic effects on the foetus and the pregnancy. Studies conducted in India, Sweden and the United States link use of tobacco products in unburned form (snus, betel¹⁰) during pregnancy with an increased risk of dysmaturity (OR¹¹ 25% increase), prematurity, perinatal mortality and neonatal apnoea, comparable with the effects of the traditional cigarette (Baba et al., 2012; Baba et al., 2013; Gupta & Subramoney, 2004; Gupta & Subramoney, 2006; Steyn et al., 2006; Wikström et al., 2010; Günnerbeck et al., 2011). It is therefore probable that the e-cigarette, another form of nicotine uptake in unburned form, will have comparable effects (England et al., 2015).

Exposure of children to environmental nicotine released by the e-cigarette

Unlike a cigarette (which produces not just the exhaled “mainstream” smoke, but passive “sidestream” smoke), an e-cigarette only generates aerosol when the user inhales and then exhales the aerosol (exhaled “mainstream” aerosol only). The inhalation of this secondary vapour in adult non-smokers with 1 hour exposure causes serum cotinine concentrations comparable to those measured in exposure to conventional cigarettes (Flouris et al., 2009), and about 20 times lower than the serum cotinine concentrations obtained by active smoking or vaping.

¹⁰ Betel: is a stimulant containing aceroline. Chewing preparation which can contain tobacco

¹¹ Odds ratio

A Spanish study established airborne nicotine concentrations in the homes of e-cigarette users which were between the nicotine concentrations observed in the homes of smokers and non-smokers, as well as saliva cotinine concentrations that were much higher among test subjects exposed to e-cigarettes at home than among non-exposed test subjects, but were very low in absolute terms (600 times lower than among active cigarette smokers) (Ballbe et al., 2014).

A recent study by Czogala et al. (2014) measured nicotine concentrations in the ambient air after volunteers smoked tobacco cigarettes in the study room, and then after using e-cigarettes. The average nicotine concentration was 10 times higher after tobacco smoking than after the e-cigarette. In a recent study by O'Conelle et al. (2015) finally, in which airborne chemical concentrations in a study room were measured before, during and after the use of e-cigarettes, no increased nicotine concentrations were found in the ambient air compared with control sessions in which no e-cigarettes were used and compared to baseline "background" measurements.

Other studies show that the nicotine vaporised by e-cigarettes is deposited on surfaces in the indoor environment where it can be absorbed by non-users through tertiary flow (Goniewicz et al., 2013). This tertiary flow presents a particular risk to young children who put objects to their mouth and move around the room by crawling (Goniewicz & Lee, 2015; Matt et al., 2011). On the other hand it is the case that, although measureable, the levels of nicotine deposits in the homes of e-cigarette users are very low in absolute terms, and practically insignificant when compared to levels measured in the homes of cigarette smokers (Bush & Goniewicz, 2015).

1.3 Other substances (solvents, scents, flavourings, metals, etc.)

A distinction must be made between substances which are added to e-liquids deliberately (such as solvents, flavourings, additives, etc.) and those which tend to be generated during vaporisation (metals, short-chain aldehydes, etc.). A distinction can also be made between the toxic or harmful effects of the individual substances identified and those resulting from exposure to the vapour itself or vapour condensates, including cocktails of unidentified substances.

If e-liquids do indeed contain countless substances which could present a hazard, or if potentially harmful substances are emitted during heating, then it is necessary that an assessment of the real risk be made. When doing this, account should be taken of the expected level of exposure, and the risks run by vapers must be weighed against those run by smokers of conventional cigarettes.

Effects observed following exposure to individually identified substances

The NIPHE (report National Institute for Public Health and the Environment (Netherlands) 2014-0143 - Visser et al. 2015) has produced a comprehensive risk assessment for vapers (daily, occasional, average or heavy) based on the chemical analysis results for 183 e-liquids. The main analysis results for substances other than nicotine can be summarised as follows:

- In the case of solvents (polyol carriers) the main substances found are **glycerol** and **propylene glycol**. The glycerol and propylene glycol levels are higher than in tobacco smoke. The main effects associated with these two substances are (reversible) damage to the airway epithelium (increase in goblet cells and/or increased mucin production by existing goblet cells in the nasal cavity) and, in the case of propylene glycol, a drop in the number of lymphocytes. The NIPHE risk assessment shows that heavy vapers risk harmful effects and in some cases (according to the e-liquid analyses); this also applies to average or occasional vapers.
- In the case of **aldehydes (formaldehyde, acetaldehyde, acrolein)** it should be noted that these are generally produced when the vapour is produced. Formaldehyde, which the IARC (*International Agency for Research on Cancer*, 2004) categorises as a Group 1 carcinogen, was detected regularly in the NIPHE study, whereas acrolein and acetaldehyde were incidental. Concentrations of these substances in the vapour vary considerably (difference in formaldehyde level of up to factor 25 for two devices from the same manufacturer using the same e-liquid). Formaldehyde and acrolein were present in concentrations that could be harmful to the airways. In some cases formaldehyde concentrations were so high that an increased risk of respiratory cancers was determined. If acetaldehyde, acrolein and diacetyl (see below) occur in the vapour alongside formaldehyde in concentrations which are harmful to the airways, this can lead to an increased risk of tumour due to formaldehyde.

According to the *American Thoracic Society* (ATS, 2015) the formation of acrolein, acetaldehyde and formaldehyde by such a device depends on the power of the heating element. Under certain circumstances (at times not representative of reality) the level of substances produced was comparable with that in the smoke of conventional cigarettes. The production of combustion products is also demonstrably linked to the glycerol:propylene glycol ratio (Sullivan et al., 2015). A recent study by Farsalinos et al. (2015) has experimentally revealed that high concentrations of aldehydes are indeed obtained through improper use of the e-cigarette, under conditions described as “dry puff” (insufficient supply of liquid and heating element set too high, so that the liquid overheats, through which an unpleasant taste ensues, which is rapidly detected by the user).

The NIPHE report states that volatile organic compounds (benzene, toluene, diacetyl) can be found in e-liquids and the vapour they produce, but that the levels are generally lower than in tobacco smoke (in the case of benzene), and concludes that these low concentrations do not present a health risk. Additionally, the variety and quantity of volatile organic compounds is much greater in the case of tobacco smoke (examples: butadiene and polycyclic aromatic hydrocarbons). As regards diacetyl, which is detected in some e-liquids and the vapour they produce (see the section on additives and flavourings), the NIPHE risk assessment points out that when detected in the vapour, diacetyl concentrations are high enough to have a significant effect on the airways of the heavy vaper (high daily use). Similar effects cannot be ruled out for moderate users.

- As regards **tobacco specific nitrosamines**, the NIPHE study states that there is a higher general risk of tumour formation in the airways of heavy vapers, even though levels vary considerably according to the type of e-liquid tested. Of the 4 nitrosamines analysed (NNN, N'-nitrosoanatabine (NAT), N'-nitrosoanasabine (NAB), NNK), NNK is the most powerful carcinogen and is also the one encountered most frequently. However, nitrosamine levels detected in tobacco smoke are 400 times higher compared to e-liquid vapours.
- The **metals** (13 elements) found in vapour from e-cigarettes do not originate from the e-liquid, but from the heating element used to create the aerosol. The risk due to exposure to cadmium, lead, nickel and arsenic is lower for the e-cigarette user than the tobacco cigarette smoker (cadmium and lead levels are 155 to 3.5 times lower respectively in e-cigarette vapours). On the other hand, chrome values can be 1.7 times higher than in cigarette smoke, meaning that where this element is concerned, the vaper's risk is comparable to that of the tobacco smoker.

Another study (Lerner et al., 2015) suggests that copper can be found in e-cigarette vapour in concentrations 6.1 times higher than those reported for cigarette smoke. The authors are of the opinion that some of the levels observed could be nanometric and that further study is needed on the toxicity of metals in nanoparticle form.

Another study published by Saffari et al. (2014) confirms that many toxic elements and organic substances are present in lower quantities in e-cigarette vapour compared to the smoke from conventional cigarettes, but this is not the case for chrome (absent from cigarette smoke) and nickel (4 times higher in e-cigarette vapour). Similar findings were reported in the study by Farsalinos et al. (2015) which concludes that, based on the data available, exposure to metals as a result of e-cigarette use should not be a cause for concern for tobacco smokers who switch to the e-cigarette. However, e-cigarettes are an unnecessary source of exposure for anyone who has never smoked. The analysis of metals should therefore be extended to more products. In addition, the choice of materials used in the manufacture of the e-cigarette should rest on a preference for materials that pose the minimum level of exposure risk.

Extensive studies of metals are shown to be needed to assess the potential risks, particularly those associated with the presence of metallic nanoparticles.

- As regards **flavourings and additives**, a study by Tierney et al. (2015) shows that the flavourings certified as safe for oral ingestion by the *Flavor Extracts Manufacturers Association* may not offer an acceptable level of safety when present in e-cigarettes. The study identifies and measures the chemical flavourings used in 30 e-cigarette liquids. A significant number of chemical flavourings were aldehydes, a class of compound known as *primary irritants* of the mucous membranes of the respiratory tract. Many of the products contained the same chemical flavourings: vanillin and/or ethyl vanillin, one of the top three chemical flavourings, was found in 17 of the liquids in quantities ≥ 0.5 mg/ml. The levels of some chemical flavourings in some e-cigarette liquids are high enough to cause concern over vaping inhalation

exposure from a toxicological viewpoint. For example, there are workplace exposure limit values for benzaldehyde and vanillin, which are known as an irritant to the airways. Daily consumption of about 5ml of e-cigarette liquid exposes the user to values twice as high as the recommended workplace limit values in 2 of the 30 liquids tested. Therefore, concentrations of some chemical flavourings in e-cigarette liquids are high enough to cause concern over vaping inhalation exposure from a toxicological viewpoint. It is necessary to set limit values on some of the most worrying chemicals and on the total level of chemical flavouring content.

Effects observed as a result of exposure to non-identified substances (raw vapours, condensates)¹²

There are several studies of cell cultures and animals (rat), but few of humans, which sometimes do, sometimes do not, demonstrate harmful health effects. Further toxicological study is therefore required.

By way of illustration, we discuss 2 studies whose results provide the greatest cause for concern.

According to Lerner et al. (2015) the oxidants/ reactive oxygen species (ROS) related to e-cigarette vapours may present a hazard of oxidant/ROS induced toxicity when inhaling e-cigarette vapours. The materials and liquids used in the electrical devices may contain heavy metals, aldehydes, plastic and other chemicals that also act as oxidants. When heated, these substances produce ROS or accumulate semiquinones and carbonyls/aldehydes which can cause harmful health effects comparable to those caused by conventional cigarettes. These e-cigarette-related oxidants may present unforeseen risks to public health and the environment in the future. Further study is therefore necessary. This also applies to tobacco products.

In another study, reported by ATS (2015), reduced cough reflex sensitivity was observed after one-time exposure to e-cigarette vapours among 30 healthy non-smokers who participated in the study. The cough reflex stimulates a cough to clear and protect the upper respiratory tract against incoming foreign material. In a previous study, the researchers showed that chronic tobacco cigarette smokers presented reduced sensitivity to the cough reflex. The researchers suggested that the cause of this reduced sensitivity was desensitisation of the cough receptors in the airways due to chronic cigarette smoking.

1.4 User behaviour

The behaviour of the user can influence the absorption of nicotine. The factors that can make a difference are length of draw, depth of inhalation and frequency of use. In the conventional cigarette, nicotine delivery increases with quicker, deeper puffs, but in the case of ENDS (electronic nicotine delivery systems) it may decrease due to cooling of the heating element (WHO, 2014).

¹² Scientific Committee on Emerging and Newly Identified Health Risks- Preliminary Opinion on 10 Additives used in tobacco products. 2015

The information currently available appears to suggest that users of e-cigarettes containing nicotine tend to use these devices longer than traditional NRT (Bullen et al., 2013). Nonetheless, the smoker/vaper population is far from homogenous in the period of stopping smoking and no comparisons can be made between the use by different individuals.

The fact that the behaviour continues based on inhalation of a substance with slower psychotropic effect, raises a question mark over the vaper's *coping* strategy.

For some, vaping can be a useful *coping* strategy to modify behaviour, whereas for others it can be an avoidance strategy (at behavioural, not biological level) which keeps the memory of smoking behaviour alive.

Pharmacokinetic studies show that nicotine is not absorbed as quickly through the e-cigarette as it is through tobacco cigarette smoking, certainly

(a) when using first generation e-cigarettes (Eisenberg, 2010 ; Farsalinos et al., 2014),
and

(b) when the user is still inexperienced in the use of e-cigarettes.

Use of 2nd (and 3rd) generation e-cigarettes (Farsalinos et al., 2014 ; Lechner et al. 2015), and experience gained with the e-cigarette enable the user to absorb more nicotine (Hajek et al, 2014). Experienced e-cigarette users can present plasma nicotine levels comparable with those measured in tobacco smokers (Vansickel & Eissenberg, 2013).

There are indications that e-cigarette users go through a learning curve when discovering the topography of inhalation, and linked to this, the quantity of nicotine they obtain when using the e-cigarette. In a recent study by Lee et al (2015), smokers with no experience using e-cigarettes were asked to switch to the e-cigarette. Baseline measurements were taken of their inhalation topography (number of inhalations, volume per inhalation, interval between inhalations, duration of inhalations, and inhalation "flow rate"), after one and again after two weeks. The main finding was that the participants learned spontaneously to puff longer (2.2 s → 3 s) and slower (30.6 ml/s → 25.1 ml/s), which probably delivered more nicotine per inhalation (higher "nicotine flux" (microgram/s) (Shihadeh & Eissenberg, 2015 ; Talih et al, 2014). Finally, Farsalinos et al. (2015) compared smokers who were using the e-cigarette for the first time against experienced vapers and observed that both after the first 10 inhalations (within 5 minutes) and during a subsequent 60 minutes of use *at libitum*, the blood nicotine level was about 50% lower (46% after 5 minutes, 43-54% in the next 60 minutes) in the inexperienced smokers compared to the experienced smokers. Both groups took the same number of puffs, but the vapers' puffs were longer than the smokers' (3.5 s as opposed to 2.3 s).

1.5 Harmfulness of e-cigarettes compared to conventional cigarettes

There is undoubtedly a lack of certainty as to whether the electronic cigarette is harmful or not. The literature provides no examples of harmful effects in the short term (Mc Robbie et al., 2014), but not enough is known about e-cigarette use in the long term.

The e-cigarette does appear to be much less harmful than the conventional cigarette (Hajek et al., 2014; Konstantinos et al., 2014; Laugesen et al., 2015; Misra et al., 2014).

Whatever the toxin found in the aerosol/vapour of e-cigarettes with or without nicotine, it is present in lower numbers and volumes compared to those present in the smoke of conventional cigarettes. *Current state of knowledge about chemistry of liquids and aerosols associated with e-cigarettes indicates that there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces.*

Even when compared to workplace standards for involuntary exposures, and using several conservative (erring on the side of caution) assumptions, the exposures from using e-cigarettes fall well below the threshold for concern for compounds with known toxicity. That is, even ignoring the benefits of e-cigarette use and the fact that the exposure is actively chosen, and even comparing to the levels that are considered unacceptable to people who are not benefiting from the exposure and do not want it, the exposures would not generate concern or call for remedial action (Burstyn, I., 2014).

According to the OFT (*Office Français de prévention du Tabagisme*, 2013) “the aerosol from e-cigarettes which are properly manufactured and used in accordance with the information available contain far fewer substances harmful to health than tobacco smoke, in other words neither solid particles, nor tar, nor other carcinogens, nor carbon monoxide (CO)”.

However, a recent publication has created a stir by suggesting that the e-cigarette is more carcinogenic than the conventional cigarette; this is because the e-cigarette is said to release high concentrations of formaldehyde, a known carcinogen.

The experts (Nitzkin et al., 2015; Sodhi & Khanna, 2015; Thomson & Lewis, 2015) cast doubt on the results of this study because it was not conducted under the usual operating conditions for the electronic cigarette (heat in excess of 400 °C, excessive voltage/wattage). As stated before, Farsalinos et al. (2015) later showed that these results were only obtained through improper use of the e-cigarette, i.e. under “*dry puff*” conditions (overheating and insufficient liquid supply). Moreover, the study was confined to two less significant carcinogens, whereas cigarettes contains dozens of carcinogens, some of which are significant.

1.6 Use of the e-cigarette with the conventional cigarette

There are no strong indications in the literature to show that this combination might be beneficial in the long term through risk reduction where other tobacco-related pathologies are concerned.

To have a positive effect on health and for example alleviate chronic bronchitis, users must reduce their tobacco consumption by more than 85%. A beneficial effect on the heart can only be obtained by stopping smoking altogether (Rigotti & Clair, 2013 ; Lee et al., 2013).

2 Qualitative aspects of the e-cigarette

Products which can be lawfully traded must satisfy certain quality and safety requirements. This is also in the interest of public health. For this reason the SHC dedicates this section to present and future quality requirements in relation to e-cigarettes and to the health hazards associated with their use.

Numerous components and factors play a role in the overall health risk posed by electronic cigarettes. Some of these factors are set out in the European Directive of 3 April 2014, but there are no stipulations regarding their implementation. Other factors are in need of attention too, such as batteries and temperature, and have been added to the list for this reason.

2.1 Nicotine content

The Directive of 3 April 2014 states that Member States must ensure that:

- a) *“nicotine-containing liquid is only placed on the market in dedicated refill containers not exceeding a volume of 10 ml, in disposable electronic cigarettes or in single use cartridges and that the cartridges or tanks do not exceed a volume of 2 ml;*
- b) *the nicotine-containing liquid does not contain nicotine in excess of 20 mg/ml”.*

The most common e-liquids on the market contain 6, 12 and 18 mg/ml.

The e-cigarettes in the study by Bullen et al. (2013) contain nicotine cartridges of 16 mg.

2.2 Purity of the nicotine

“only ingredients of high purity are used in the manufacture of nicotine-containing liquid. Substances other than the ingredients referred to in point b) of the second subparagraph of paragraph 2 of this Article are only present in the nicotine-containing liquid in trace levels, if such traces are technically unavoidable during manufacture”;

The impurities in the vapour originate from nicotine extracted from tobacco, such as anatabine, nicotinine, anabasine, nitrosamines.

2.3 Consistent release of nicotine

The Directive of 3 April 2014 states that Member States must ensure that:

“electronic cigarettes deliver the nicotine doses at consistent levels under normal conditions of use”;

2.4 Composition of the mixture

The Directive also states that:

- *“except for nicotine, only ingredients are used in the nicotine-containing liquid that do not pose a risk to human health in heated or unheated form;*

- *the nicotine-containing liquid does not contain additives listed in Article 7 (6);”*

This means no:

- *vitamins or other additives that create the impression that a tobacco product has a health benefit or presents reduced health risks;*
- *caffeine or taurine or other additives and stimulant chemical compounds that are associated with energy and vitality;*
- *additives having colouring properties for emissions;*
- *for tobacco products for smoking, additives that facilitate inhalation or nicotine uptake, and*
- *additives that have CMR properties in unburnt form (CMR: **carcinogenic, mutagenic, reprotoxic**).*

Inappropriate ingredients have been found in electronic cigarettes in the past. For example, diethylene glycol¹³, found at level of 1% in earlier e-cigarettes (Burstyn, 2014; FDA, 2009), medicines such as sildenafil and even alcohol (percentage seldom in excess of 4%). These additives are banned outright in Europe (OFT, 2013). (See point 1.3. and 6.5.)

2.5 Reliability and safety of batteries and cartridges

Battery voltage and unit circuitry differences can result in considerable variability in the products’ ability to heat the solution to an aerosol and, consequently, may affect delivery of nicotine and other constituents, and may contribute to the formation of toxicants in the emissions (WHO, 2014).

2.6 Temperature

The mix is heated by means of a battery in the disposable e-cigarettes and rechargeable batteries. A pressure sensitive micro-switch supplies heat to the mix when the user inhales (automatic e-cigarettes) or presses a button (manual e-cigarettes). The current batteries often have a means by which the voltage (and therefore the wattage) can be regulated. From this we can conclude that the temperature of the filament will depend on the user’s desire to quickly obtain the desired effect, which is now adjustable by means of settings.

Lack of a clear-cut temperature control could, therefore, lead to synthesis of various toxic substances such as acrolein, as well as formaldehyde hemiacetals, as has been recently proven (Jensen et al., 2015). The IARC lists formaldehyde as a group 1 carcinogen. Some new “high-end” batteries allow the filament temperature to be set directly within certain limits (“*temperature-controlled mods*”), thereby ruling out toxic emissions through overheating.

¹³ *The frequently stated concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains based on a single sample of an early- technology product (and even this did not rise to the level of health concern) and has not been replicated (Burstyn, 2014)*

The German report (Cancer Research Center Heidelberg, 2013) quotes 50° C to 120° C, but in addition points out that when glycerine is used as an additive, traces of acrolein can be found, which are not formed with glycerine below 275°C.

The height of the temperature is also linked to the filament activation time. In the case of activation in excess of 5 seconds in laboratory conditions, the temperature in some cases (insufficient supply of liquid to the wick - “dry hit” phenomenon) reaches 300° C, which causes toxic degradation products to form (such as acroleine from glycerine, as well as formaldehyde hemiacetals from propylene glycol) (Jensen et al., 2015). However, manufacturers automatically restrict operation of the e-cigarette to 5 seconds.

3 Do e-cigarettes containing nicotine help reduce or even stop smoking?

3.1 General principles of smoking reduction and smoking cessation

To help users of traditional cigarettes to reduce and even stop smoking, a number of recommendations covering several forms of *harm reduction* are described in the guidelines of the British *National Institute for Health and Care Excellence* (NICE, 2013):

- Stop smoking but keep using one or more licensed NRT products as long as necessary to prevent relapse
- Cut down before stopping smoking, with or without help of a licensed nicotine-containing product (“*cutting down to quit*”)
- Reduce smoking, with or without help from a licensed nicotine-containing product
- Temporarily abstain from smoking, with or without help from a licensed NRT product.

These options are justified by the fact that:

- a) (long-term) use of NRT has little or no harmful effects on health, certainly several orders of magnitude less than smoking tobacco (Nutt et al., 2014);
- b) although the relationship between the number of cigarettes smoked daily and the risk of serious cardiovascular pathology, lung pathology and cancer are certainly not linear, cutting down is less harmful than smoking more;
- c) smoking reduction is a good predictor of possible later smoking cessation (Klemperer & Hughes, 2015).

The information above reinforces the position of tobaccologists who recommend smoking cessation with help of a variety of licensed medicinal treatments, such as nicotine replacement (including e-cigarettes containing nicotine). The initial goal of treatment is to stop using the treatments and stop using nicotine for good. Use of the e-cigarette with nicotine could be a means of nicotine replacement, but its use must be limited and appropriate to the needs of the person stopping smoking, and must not lead to reduced use of other, i.e. psychological, quitting aids.

In the case of some smokers or risk populations (psychiatric risk, for example) it may be necessary to extend the use of nicotine replacers (NRT or e-cigarette). In such cases, the advice is that it is preferable to continue using nicotine replacement (NRT/e-cigarette) in the long term, rather than running the risk of smoking tobacco again (NICE, 2013). Ideally, this situation should only be proposed when a smoking cessation treatment applied in accordance with the prevailing recommendations fails.

It can be said that today's smokers would generally like to give up. The latest Health Survey shows that the desire to stop smoking is gaining ground. According to the Health Survey 2013, 71% of daily smokers have already refrained from smoking for at least 24 hours in an effort to quit smoking (compared with 68% in the period 2004-2008). One quarter of this group is a potential candidate for quitting entirely.

The percentage that has smoked some time but stopped has risen to 48%. But smoking is highly addictive: the majority of smokers smoke daily (82%). About one third of daily smokers are heavy smokers. Socioeconomic background plays a role when quitting (as it does in all behaviour connected to smoking): attempts to quit smoking, recent attempts and successful attempts are more prevalent among people with a certificate of higher education than among people with lower qualifications.

It is therefore important that we (also) see smoking as a chronic addiction which is strongly linked to low socioeconomic status and health inequalities, but at the same time linked to a desire to stop among the vast majority of smokers.

The present discourse on tobacco addiction, promulgated, inter alia, by the Flemish Platform against Tobacco, which is coordinated by VIGeZ and FARES, stresses that smokers do not find it easy to quit (several attempts are generally needed and are quite normal), but that this is their goal and they need help (to find their way to the best help available, because this help considerably increases their chances of success).

3.2 Benefit of the e-cigarette with nicotine to smoking reduction or smoking cessation

The first harm reduction option, "stop smoking but keep using NRT", ties in seamlessly with the philosophy behind the *Tobacco Harm Reduction* (THR) approach (Rodu & Godshall, 2006; Sweanor et al., 2007; Polosa et al., 2013; Nitzkin, 2014). Advocates of THR view the tobacco smoker as a patient in need of a cure, rather than as a "consumer" whose choices and preferences (i.e. smoking and nicotine use) not only lead to personal benefits, but also have very harmful health effects. Working on the assumption that not every smoker can, wants or would like to stop every form of nicotine and/or tobacco use, it attempts to provide the smoker with alternatives, besides the classic quitting scenario, which are designed to reduce the (social and health) harm caused by this preference as much as possible. These include forms of nicotine use which present a low (or at least lower) risk compared to tobacco cigarettes: snus, NRT (nicotine spray, nicotine gum), or electronic cigarettes (Nutt et al., 2014). One possible hypothesis is that smokers who would like to reduce or prevent the harmful effects of tobacco smoking on their health, but do not want to give up the routine and psychological "*benefits*" of the smoking ritual and nicotine use, will benefit greatly from a (full) switch to the electronic cigarette (Britton & Bogdanovica, 2014; Hasting et al., 2012).

As regards health risk changes in the long term for smokers who only partially replace the tobacco cigarette with the electronic cigarette, it should be said that at present there are no long term studies on which to base an expert statement about dual use of the electronic and tobacco cigarette.

3.3 Benefit of the e-cigarette with nicotine as a means to stop smoking

Randomised and prospective studies

Few **randomised trials** (RCT) have been conducted to investigate the effectiveness of the e-cigarette as a means of stopping smoking.

The first randomised controlled trial (Bullen et al., 2013) compares e-cigarettes (16 mg nicotine), nicotine patches (21 mg) and placebo e-cigarettes (e-cigarettes without nicotine). Only very limited behaviour therapy was offered in support. Between 9/2011 and 7/2013, 657 smokers were randomised at a ratio of 4:4:1. After six months the *continuous abstinence rate* (CAR) was 7.3% (21/289), 5.8% (17/395) and 4.1% (3/73) respectively. One third of the e-cigarette users continued to use e-cigarettes after six months.

The results showed no significant difference in results between the three treatment groups. The e-cigarette with nicotine was at least as effective as the NRT patches and there were no differences in side effects. This incomplete observation was due to the study's lack of statistical strength. In other words, the trial merely revealed a "trend" in relation to the e-cigarette containing 16 mg nicotine.

The second **prospective and randomised trial**, named ECLAT (*EffiCiency and Safety of an eLectronic cigAreTte*) was conducted by Caponetto et al. (2013). A total of 300 smokers was divided into three groups:

- group 1: using e-cigarette with a nicotine content of 7.2 mg for 12 weeks
- group 2: using e-cigarette with 7.2 mg for 6 weeks and with 5.4 mg for 6 weeks
- group 3: placebo e-cigarette for 12 weeks.

There was no significant difference in *quit rates* after 52 weeks: 13%, 9% and 4% respectively or a global *quit rate* of 8.5%. In addition, smoking reduction of at least 50% was observed in 15% (groups 1 and 2) and in 12% (group 3) of the participants. At the end of the trial about 26.9% of the *quitters* continued to use the e-cigarette. As was the case with the RCT above, one major limitation of this trial was its use of a fairly inefficient e-cigarette ("*obsolete and underperforming compared with current models*" in the words of the authors).

A few **prospective interventional cohort studies** have been conducted to monitor changes in smoking behaviour (and undesirable side effects) with use of (nicotine-containing first generation) electronic cigarettes over 6 to 24 months.

Polosa et al. (2011; 2014) reported (CO verified) *quit rates* of 22.5% after 6 months and 12.5% after 24 months among smokers who had had no intention of stopping. Additionally, one third (32.5%) reduced smoking after 6 months by a minimum of 50% (27.5% after 18 and after 24 months).

In a comparable prospective interventional cohort study among schizophrenic smokers (n= 14), Caponetto et al. (2013) observed 14% total abstinence after 12 months; an additional 50% cut down their tobacco cigarette smoking by at least 50%. Finally, Ely (2013) studied the smoking behaviour of 48 smokers who wanted to stop smoking and/or switch to e-cigarette over 6 months, and reported a (biologically unverified) *quit rate* of 44%.

The results of these RCTs, prospective studies, and four other, non-interventional longitudinal studies (Etter & Bullen, 2014; Grana & Popova, 2014; Choi & Forster, 2014; Polosa et al., 2014) were recently evaluated and summarised in a **Cochrane Review** (McRobbie et al. ; 2014). The “*plain language summary*” of this review reads:

“Key results *Combined results from two studies, involving over 600 people, showed that using an e-cigarette containing nicotine increased the chances of stopping smoking long-term compared to using an e-cigarette without nicotine. Using an e-cigarette with nicotine also helped more smokers reduce the amount they smoked by at least half compared to using an e-cigarette without nicotine. We could not determine if e-cigarette was better than a nicotine patch in helping people stop smoking because the number of participants in the study was low. More studies are needed to evaluate this effect. This study showed that people who used e-cigarette were more likely to cut down the amount they smoked by at least half than people using a patch.*

There was no evidence that using e-cigarette at the same time as using regular cigarettes made people less likely to quit smoking.

None of the studies found that smokers who used e-cigarette short-term (for 2 years or less) had an increased health risk compared to smokers who did not use e-cigarette.

More studies of e-cigarette are needed.”

The Cochrane Review also urged future study to focus on

- (1) a comparison of e-cigarettes against “usual care” or minimal treatment, existing pharmacotherapy and behavioural treatment;
- (2) studies using *state-of-the-art* e-cigarettes (“*good nicotine delivery and representative of the best current standards in terms of reliability and user satisfaction*”);
- (3) studies of adequate ecological validity (allowing for individual preferences for nicotine strength, flavours and e-cigarette type)

A more recently dated meta-analysis (Rahman et al., 2015) published in PLOS One, *reaches similar conclusions.*

Two recent studies looked into the effectiveness of **2nd generation cigarettes**. In a small-scale RCT, Adriaens et al. (2014) **randomised** 48 smokers with no intention of quitting according to three conditions:

- group 1: 8 weeks of e-cigarette type 1 (“Joyetech eGo-C”, 18mg/ml nicotine) v
- group 2: 8 weeks e-cigarette type 2 (“Kanger T2-CC”, 18 mg/ml nicotine) v
- group 3: 8 weeks self-monitoring (control group).

At the end of the 8 weeks the participants in the control group were offered an e-cigarette, after which the 3 groups were monitored to a point 8 months after the trial’s commencement. After 2 months 34% of the group 1 and 2 participants were smoke-free (CO verified), as opposed to 0% in the control group. After 5 months 37% of the group 1 and 2 participants were smoke free; 3 months after being offered an e-cigarette 38% of the control group participants were observed to be abstinent. After 8 months the quit rates for groups 1-2 and

group 3 were 19% and 25% respectively; after 8 months, an additional 25% and 19% of participants respectively showed a reduction of at least 50% in tobacco cigarettes smoked.

Polosa et al. (2014) conducted a **prospective cohort** study of 50 smokers (with no intention of stopping), who were monitored for 6 months after receiving a **2nd generation e-cigarette** (“EGO/CE4”, 9mg/ml nicotine). At the end of the study, 36% of the participants were smoke free (CO verified) and 83% of the quitters were still using the e-cigarette. In addition, 30% reduced their smoking by at least 50%.

In a **longitudinal, non-interventional** study (**Biener & Hargraves, 2015**) based on two representative samples from large urban areas in the United States (Texas and Indiana; N=5155) smokers (N=1374) were surveyed first in 2011/2012 and for a second time in 2014 (N=695) on their smoking behaviour, attempts to quit and use of e-cigarettes. It was observed that “intensive users” of the e-cigarette (daily for least a month, 23% of the sample) - but not occasional users (29%), reported 6 times more (OR: 6.07, 95% CI¹⁴ = 1.11; 33.2) smoking cessation (at least 1 month smoke free on 2nd contact; *quit rate* 20.4%) than non-users of the e-cigarette.

In a cross-sectional, retrospective study of smokers (n = 5.863) who had attempted to quit at least once in the past 12 months with the help of either an e-cigarette or classic NRT (without additional support), or without quitting aid, it was noted that the quit rate among e-cigarette users was 1.63 times higher (20% quitters) than among NRT users, and 1.61 times higher than among people who used no quitting aid (**Brown et al., 2014**)

Finally, we report a prospective study which monitored the smoking behaviour of smokers (n=71) who purchased their first e-cigarette in a specialist “*vapeshop*” over a 12-month period (Polosa et al, 2015). In this aselect sample, the quit rate after 12 months was 40.8%; in addition, 15.5% reduced their cigarette consumption by more than 80%, and 9.9% by more than 50%; only 33.8% of the customers failed to reduce their cigarette consumption by at least 50% (or could no longer be reached after 12 months, i.e. 31% of the 33.8%). This study shows that personalised professional advice combined with use of a high quality e-cigarette can lead to very high success rates among smokers who are sufficiently motivated to stop smoking and to visit a *vapeshop*. Obviously these findings cannot be extrapolated to the full population of smokers.

When assessing all of the above, we should also consider the fact that the ultimate public health effect of e-cigarettes in terms of smoking reduction and smoking cessation is not merely a matter of the product’s effectiveness, but a matter of its acceptance and degree of penetration among the smoking population. The most recent information from ASH in relation to the United Kingdom (*Action on Smoking and Health 2014*) shows that use of e-cigarettes among smokers and former smokers is high; the number is estimated at 2.1 million (700,000 former smokers and 1.3 million smokers (“*dual users*”). About 50% of all smokers have at some point tried the e-cigarette and about 18% of smokers are currently using one. The “*Smoking Toolkit*” (ASH, *Smoking in England, 2015*) also shows that use of the e-cigarette in an attempt to quit smoking has risen to about 30%, as opposed to 10-15% for classic NRT, or prescribed medicinal aids, and 5% application of the NHS (*National*

¹⁴ confidence interval

Health Service) guidelines for stopping smoking. Figures published by *Baromètre Santé* INPES (*Institut national de prévention et d'éducation pour la santé*, 2014) show that about 3 million French people (6% of the population between 15 and 75 years of age) use the e-cigarette regularly, and half of this figure (3% - 1.5 million) daily; the share of former smokers is estimated at 15% of e-cigarette users (about 400,000 former smokers). In the Netherlands, finally, the share of smokers (figures for 2014) who ever tried an e-cigarette is estimated at 40%, whereas current use is about 16% (about 1/3 of which daily) (Hummel et. al., 2015)

The e-cigarette's "acceptance" and degree of penetration among smokers would appear to be high (at least in those countries where e-cigarettes containing nicotine are freely available), ultimately increasing its impact on a population level (i.e. smokers).

A survey conducted by the Cancer Foundation in 2014 shows that the e-cigarette is yet to make a breakthrough in Belgium. Only 0.5% of the population use the e-cigarette daily and 1% use it weekly or less frequently. By way of comparison: in November 2013 daily use of the e-cigarette in France was about six times higher compared to Belgium.

The limited success is due to the stricter regulation of the e-cigarette in Belgium compared to neighbouring countries. In Belgium, e-cigarettes with nicotine can only be placed on the market if they are registered as a medicinal product, with corresponding strict requirements on quality, safety and effectiveness.

Summary

From the results available to us from RCTs, prospective interventional cohort studies and non-interventional longitudinal studies we conclude that the e-cigarette may be effective as an aid for smoking reduction and/or smoking cessation. It is not possible, however, to assess the e-cigarette's relative effectiveness compared to traditional smoking cessation treatments based on the available study data, and this relative effectiveness will be partly determined by aspects such as the quality of e-cigarettes available and under study.

If the position and effectiveness of e-cigarettes were to be confirmed by more thorough studies, the directions for use would have to state, as is the case with other nicotine replacement products, that their use be restricted in time, and recommendations would have to be given with regard to users who may require a longer time (i.e. that continuing nicotine replacement (NRT/e-cigarette) in the long term is to be preferred above risking return to tobacco smoking (NICE, 2013)).

At the present time, however, it is not possible to confirm the absence of risk for long-term e-cigarette users by means of epidemiological data, because the control period is not of sufficient length.

Clinically speaking it can, however, be reasonably assumed that long term use of the e-cigarette with nicotine is very clearly less harmful than continuing to smoke tobacco cigarettes. This statement does not apply to dual use of electronic cigarettes and tobacco cigarettes. The assumption rests on analogous studies on the long-term use of nicotine replacement products and on many epidemiological studies confirming the exceptionally low level of respiratory cancers, etc., in Sweden, where many tobacco users use snus as an alternative to tobacco smoking.

4 Can an e-cigarette without nicotine help tobacco smokers through the final stage of quitting smoking?

Strictly speaking, a smoker who has made the “switch” from smoking tobacco to using the (nicotine free) e-cigarette, has already “stopped smoking”. The question might be better rephrased as two questions

- a) whether use of the e-cigarette can be of assistance in reducing nicotine use; and
- b) whether switching to sole use of the e-cigarette (becoming a “vaper” rather than a smoker) can in time lead to quitting the e-cigarette (without starting smoking again).

Findings of relevance to both questions are largely limited to the results of questionnaires completed by (long-term) e-cigarette users.

Etter and Bullen (2014) studied a group (n = 477) consisting mostly of daily e-cigarette users (76% daily users; 72% former smokers) to observe the trend in use over a 12-month period. When the baseline measure was set, the overwhelming majority of daily cigarette users (95%) were using nicotine-containing liquid (average 16mg/mL); after 12 months, 89% were still using the e-cigarette, and the overwhelming majority (96%) were still using nicotine-containing liquid (average 16mg/mL). Of the former smokers who used the e-cigarette when the baseline measure was set, only 6% reported a return to (daily or occasional) smoking after 12 months.

A worldwide survey of 19,000 e-cigarette users by **Farsalinos et al. (2014)**, in which 81% of the respondents reported smoking cessation (full substitution of smoking by e-cigarette use) and had used the e-cigarette for 10 months beforehand (median), reported that the nicotine concentration of the e-liquid was 18 mg/mL (median) at the outset, whereas the concentration at the time of the survey had fallen to 12 mg/mL (median). Only 3.5% of the participants were currently using nicotine free (0 mg/mL) e-liquid.

A survey of 215 “vapor store” customers (specialist e-cigarette store) by **Tackett et al. (2015)**, in which 66% of the participants were smoke free (CO verified) and had used the e-cigarette for 7.4 months on average (78% 2nd or 3rd generation e-cigarette), reported an average nicotine concentration of 18 mg/mL. Only 3.6% of the participants were using nicotine free (0 mg/mL) e-liquid.

A similar survey of 159 “vapor store” customers by **Lechner et al. (2015)**, in which the participants had used an e-cigarette for an average of 6.8 months (and the average number of tobacco cigarettes smoked had fallen from 19.8/day to 2.9/day), observed a significant drop in reported nicotine concentration from the start to the time of current use.

In a survey of Dutch youths (N = 990, 12-21 years of age, average age 16.5) conducted by the **Trimbos Institute** (Buisman et al., 2014), it was observed among 423 young people who reported having used an e-cigarette at some point, that both e-cigarettes with nicotine and e-cigarettes without nicotine were used (“39% of the youngsters always used e-cigarettes

without nicotine and 31% always with nicotine. A number of youngsters sometimes used e-cigarettes with nicotine (17%) and a number (13%) usually used e-cigarettes with nicotine. A look at specific age categories shows that older adolescents (17-21) more often have experience of e-cigarettes with nicotine (76%) than adolescents in the 12-16 group (61%).

In a Dutch survey by **Hummel et. al., 2015**, 84.9% of e-cigarette users reported using nicotine-containing liquid as opposed to 11.7% using nicotine-free liquid (3.4% did not know) (2014 data).

In a questionnaire by **Etter and Eissenberg (2015)**, which measured user dependence on e-cigarettes, nicotine gum and tobacco cigarettes, it was observed among a group of former smokers currently using e-cigarettes daily and exclusively (N = 796, average about 5 months' use) that 766/796 (96.2%) of respondents used e-cigarettes with nicotine (average 12 mg/mL) whereas just 30/796 (3.8%) used e-cigarettes without nicotine.

When smoking cessation strategies are designed to cut out tobacco and nicotine altogether, the chances of relapse are high. Because many adopt the e-cigarette as a “lasting” substitute for the tobacco cigarette (“*switchers*”), it seems that there is a smaller chance of going back to tobacco cigarettes *a priori* compared to when conventional quitting aids are used (which leaves the user “empty handed” over time, and/or do not give the smoking-related cues needed to reduce cravings). This is confirmed by the available study results. In a longitudinal survey (2011-2013; n=367), Etter and Bullen (2014) observed that of those who used the e-cigarette daily when the baseline measure was set, 89% were still using it daily a year later; at the same time it was shown that of the former smokers (complete *quitters*) who used the e-cigarette daily when the baseline measure was set, only 6% had relapsed into tobacco smoking a year later. It also appears that the e-cigarette itself is perceived as much less “addictive” than tobacco cigarettes: a recent study by Etter and Eissenberg (2015) on user dependence on e-cigarettes compared to dependence on nicotine gum and tobacco cigarettes, concluded that “some e-cigarette users were dependent on nicotine-containing e-cigarettes, but that these products were less addictive than tobacco cigarettes. e-cigarettes are probably as addictive or a little less addictive as nicotine gum, which is not in itself that addictive”.

In psychological terms

Thinking and saying you have stopped smoking by using a device called a “cigarette” (even if it is electronic, the term is ubiquitous), does not allow the brain to easily and comfortably accommodate a change which is all about undoing the act of smoking. The semantic power of the device produces a daily physical and overall presence in the mind of the smoker, who actually wants to be rid of the cigarette and to quit smoking.

Stopping smoking, and therefore dispersing smoke (for this is its primary function), while still performing a hand-to-mouth action combined with the inhalation and exhalation of a vapour which looks like the “real” smoke, does not allow one to unlearn a habit once practised intensively, sometimes for decades. Smoking a pack of cigarettes every day for 25 years means repeating the same action 182,000 times on average, the most frequent conscious action a smoker makes.

Relapses during the process of stopping are very common. Relapse after several months, even after many years, is largely due to the fact that the former smoker (and not the non-smoker) has not entirely dismissed the magical powers he attributed to smoking and his omnipotent cigarette. The same magical powers can be attributed to the e-cigarette and it is exactly for this reason that it appears unsuitable for anyone who wishes to stop all nicotine inhalation (smoking/vaping), because its use maintains the behaviour and allows no new ways of behaving or thinking and prevents other cognitive strategies and responses from developing. In addition, there is also the risk that the would-be former smoker might, if unable to use the e-cigarette in a given context (broken, forgotten), draw on the conventional cigarette, because he will not have developed new responses. In short, there is a certain risk that the would-be former smoker will start smoking again in the fairly near future, because he smokes e-cigarettes and has not chosen to learn new strategies, whereas the risk may be smaller if he stops smoking (no joint, cigar, water pipe, pipe, cigarillo and/or e-cigarette) and makes use of other cessation aids.

Motivation and commitment to stopping smoking are still the main prerequisites for success. The processes used to train motivation in patients who do not wish to stop reveal the partial efficacy of this, even if a large percentage of “hardened” smokers remain.

This efficacy can be optimised and increased with specialist care from a tobaccologist, who can provide general information, advice and guidance to his smoker patient: in other words physically, behaviourally and psychologically.

Summary

The large majority of successful “switchers” use an e-cigarette with nicotine-containing liquid and continue to use it. It is observed with some regularity that long-term users choose to lower the nicotine concentration. Actual (arriving at the) use of e-cigarettes without nicotine tends to be marginal. In the case of continued daily use of the e-cigarette, it seems that the chance of relapse (starting to smoke tobacco again) is small but nonetheless does occur. The addictiveness of the nicotine-containing electronic cigarette is of the same order of magnitude or slightly less than the addictiveness of nicotine gum.

5 Do non-smokers run the risk of starting to use e-cigarettes with nicotine?

When analysing the epidemiological data available to us on e-cigarette use among smokers and non-smokers we must differentiate between *experimentation* (e.g. “*ever used*”/“*tried out*”) and occasional/sporadic use (e.g. “*ever used in the previous month*”) on the one hand and regular use of the e-cigarette (e.g. “*daily use*”) on the other. Finally we must also keep in mind that a correlation (between for example “*smoking*” and “*e-cigarette use*”) does not necessarily imply a causality (either may be caused by a common third factor (*confounding*), e.g. an environmentally and/or genetically determined “*propensity*” for nicotine/tobacco/drug use, “*thrill-seeking*” and risk behaviour), and that the “*direction*” of any causal relationship need not be immediately transparent (smoking can go hand-in-hand with use of the e-cigarette, both if e-cigarette use leads to smoking and when smokers use the e-cigarette in an effort to stop or reduce smoking).

These important issues have been broached in two recent, authoritative and exhaustive reviews of the research findings on electronic smoking prevalence. Hajek et al. (2014) state in *Addiction* (see Farsalinos & Polosa, 2014; West & Brown, 2014, for very similar conclusions): “*E-cigarettes would generate negative outcomes if (...) young people who would not try cigarettes otherwise start using e-cigarette and then move on to become smokers. Evidence: although there have been claims that e-cigarette is acting as a ‘gateway’ to smoking in young people, the evidence does not support this assertion. Regular use of e-cigarette by non-smokers is rare and no migration from e-cigarette to smoking has been documented (let alone whether this occurred in individuals not predisposed to smoking in the first place). The advent of e-cigarette has been accompanied by a decrease rather than increase in smoking uptake by children. Ongoing surveillance is needed to address this important point.*”

In the most recent report on this theme (West & Brown, 2014) Smoking in England state the following (see also Britton & Bogdanovica, 2014 in the report for Public Health England¹⁵: “*US surveys suggest there has been an increase in experimentation and recent (past 30-day) use by never smokers in recent years (King et al., 2015; McMillen et al., 2014; Johnston et al., 2015). However, there is no evidence of regular use by never smokers (King et al., 2015). Surveys of 11-14 year olds in Britain have shown 1-2% of never smokers have tried e-cigarettes in 2013, with almost no never smokers reporting current use (ASH 891, 2014; ASH 715, 2014). In England, prevalence of e-cigarette current use among never smokers aged 16+ is currently 0.2% which is similar to use of licensed nicotine products (West & Brown, 2015). In the UK and US, the proportion of adolescents who smoke traditional cigarettes has continued to decline at least as fast as previously making it unlikely that e-cigarettes are acting as a gateway into smoking at a population level (Fuller & Hawkins, 2014; CDC, 2014).*”

Cancer Research UK concluded in a recent study (presented June 2015, survey of 1205 children) that e-cigarette is not currently a gateway to regular nicotine use. Children between

¹⁵ report by Public Health England of 19 August 2015 <https://www.gov.uk/government/news/e-cigarettes-around-95-less-harmful-than-tobacco-estimates-landmark-review>

10 and 16 who never smoked are not/do not become regular e-cigarette users. 12% of children say they have tried an e-cigarette, 2% say they use e-cigarette more than monthly and 1% more than weekly but these children also smoked tobacco. Non-smoker experimentation with e-cigarettes is infrequent (3% of children). Prof. Linda Bauld of the University of Stirling says: "There's a common perception that the rise we've seen in the use of electronic cigarettes will lead to a new generation of adults who have never smoked but are dependent on nicotine. This fear is based on the expectation that due to the appeal of the products, children who have never used tobacco will be attracted to e-cigarettes and start to use them regularly. Our survey is in line with others in the different parts of the UK that show this is not happening. Young people are certainly experimenting with e-cigarettes, some of which do contain nicotine. However, our data show that at the moment this experimentation is not translating into regular use."

Several other studies published in 2015 have qualified these conclusions to some extent.

A **prospective** American study followed a cohort of more 2500 youngsters in their third year of secondary school (average age 14) for 12 months starting from the autumn of 2013. Youngsters who have at some point used an e-cigarette showed an increased risk of reporting tobacco smoking 6 or 12 months later (tobacco smoking is defined here as "any frequency of use, including no more than a few puffs") (OR, 2.73 [95% CI, 2,00-3.73]) (Leventhal et al., 2015).

Another study looked at a population of 4,300 young adult non-smokers, 7.9% of whom had at some point tried an electronic cigarette or were still using one. Earlier use of the e-cigarette was associated with a less assertive rejection of the "possibility of ever smoking a tobacco cigarette next year" (OR 2,4; 95% CI= 1,7-3,3) (Coleman et al., 2015).

A third study looked at data from 2011, 2012 and 2013 from the US *National Youth Tobacco Surveys* of secondary school pupils. The number of non-smoking pupils who had at some point used an e-cigarette tripled between 2011 and 2013, from 79,000 to over 263,000. Among those who had at some point used an e-cigarette, 43.9% were not absolutely sure that they would not smoke a tobacco cigarette in the next year, compared to 21.5% of those who had never used an e-cigarette. Those who had at some point used an e-cigarette had a smaller chance of being "absolutely certain" that they would not smoke a tobacco cigarette next year (OR=1,70; 95% CI1,24-2,32) (Bunnell et al., 2015).

In Poland there was a comparison of two transversal studies conducted among 15-19 year-old pupils in the periods 2010-2011 and 2013-2014. This revealed a considerable increase in 2013-2014 (compared to 2010-2011) in the use of: e-cigarettes (29.9% v. 5.5%; $p < 0.05$); e-cigarettes and cigarettes together (respectively 21.8% v. 3.6%; $p < 0.05$) and cigarettes (38.0% v. 23.9%; $p < 0.05$) (Goniewicz et al., 2014).

A survey by the Cancer Foundation in 2014 shows that young Belgians aged between 15 and 24 experiment more with e-cigarettes than do other age groups, but that there is no difference between the age categories when use is regular (daily to weekly). In 2014, 1.5% of the Belgian population used e-cigarettes: one half of a percent (about 45,000 people) used the electronic cigarette daily and one percent (about 90,000 people) used the e-cigarette weekly or less frequently.

There are also findings available from two recent studies which looked explicitly at the transition between different nicotine-containing products (tobacco cigarettes, water pipe tobacco, “smokeless tobacco (SLT)”, NRT, “dissolvable tobacco”, snus and e-cigarettes). Meier et al. (2015) studied a sample of 1304 students (average age of 19.5) to see which nicotine-containing product was used first and which nicotine-containing product was used next (“never used”, “tried at some point”, “occasional use” and “daily use”). Tobacco cigarettes were the most common first-used nicotine-containing product (50.6%), followed by water pipe tobacco (24.2%); SLT (15,1%); and emerging tobacco products (ETPs, (dissolvables, snus, and e-cigarettes) (9.2%). They concluded that although water pipe tobacco and ETPs are increasingly the first nicotine-containing product tried, it is rare for the use of ETPs to continue, and, moreover, this does not appear to lead to daily or occasional use of tobacco cigarettes and SLT. On the basis of results obtained in the *Total Tobacco Migration Tracker* (n= 11.173) and *National Tobacco Behavior Monitor* (n = 30.136) (both in the USA) Curtin et al. (2015) report that “the overwhelming majority of e-cigarette users (97%) were regular users of tobacco cigarettes before starting regular use of e-cigarettes; and, that regular use of the e-cigarette is not a significant gateway to regular use of tobacco cigarettes (transition below 2%)”.

A study by the University of San Francisco (UCSF - Dutra & Glantz, 2014)¹⁶ on the relationship between e-cigarette use and smoking among youngsters in the United States shows that in the recent past youngsters who used e-cigarettes were more inclined to smoke tobacco cigarettes and less inclined to stop smoking. *“Use of e-cigarettes was associated with higher odds of ever or current cigarette smoking, higher odds of established smoking, higher odds of planning to quit smoking among current smokers, and, among experimenters, lower odds of abstinence from conventional cigarettes. Use of e-cigarettes does not discourage, and may encourage, conventional cigarette use among US adolescents.”* E-cigarettes, promoted as a means of stopping tobacco smoking, *“may actually be a new route to conventional smoking and nicotine addiction for teenagers”*, in the opinion of these researchers. They also point out that e-cigarettes are marketed to young people aggressively (in the United States, and generally on the Internet): *“Electronic cigarettes are devices that deliver a heated aerosol of nicotine in a fashion that mimics conventional cigarettes while delivering lower levels of toxins than a conventional combusted cigarette. They are being aggressively marketed using the same messages and media channels (plus the Internet) that cigarette companies used to market conventional cigarettes in the 1950s and 1960s, including on television and radio where cigarette advertising has been prohibited for more than 40 years. In addition to these traditional media, e-cigarettes have established a strong advertising presence on the Internet, and e-cigarette companies heavily advertise their products through electronic communication. Studies have demonstrated for decades that youth exposure to cigarette advertising causes youth smoking. Electronic cigarettes are also sold using characterizing flavors (e.g., strawberry, liquorice, chocolate) that are banned in cigarettes in the United States because they appeal to youths.”* Prof. Glantz, director of the “Center of Tobacco Control Research and Education” said in response to this study¹⁷: *“It looks to me like the wild west marketing of e-cigarettes is not only encouraging youth to*

¹⁶ <http://archpedi.jamanetwork.com/article.aspx?articleid=1840772>

¹⁷ <https://www.ucsf.edu/news/2014/03/112316/e-cigarettes-gateway-nicotine-addiction-us-teens-says-ucsf-study>

smoke them, but also it is promoting regular cigarette smoking among youth". This study also showed that e-cigarette use among secondary school pupils and higher education students doubled between 2011 and 2012, from 3.1% to 6.5% and dual use of e-cigarettes and conventional cigarettes is also high among youngsters (76.3% of e-cigarette users also smoke tobacco cigarettes).

The UCSF says that these study results are consistent with a similar study of 75,000 Korean students. Other researchers have disagreed with the UCSF's conclusions on the basis that the relation observed does not necessarily imply causality¹⁸.

Nonetheless, the SHC stresses the need for caution here. A correlation between smoking and e-cigarette use among young people does not necessarily imply causality (other factors may be involved such as "thrill-seeking" and risk behaviour, in themselves, of course, a cause for concern) and/or the direction of any causal relationship may not be immediately transparent. This means that the link between e-cigarette and tobacco use among young people is in need of further study, in this country too, and should be monitored critically.

At the present time our conclusions can only be provisional. The (initiating) role of the e-cigarette among young people in the future is not clear. Finally, electronic cigarettes are relatively new products. At the present time we know too little about the effects of e-cigarettes and about how they are used, more particularly by young people, here in our own country (we have very little information on the subject here). We can only assume that they will grow in popularity, particularly among young people, as they have done for adolescents and adults in other countries (the switch from normal to electronic smoking, or should we say the switch to dual use, is yet to happen in our country, whereas the trend has already started in neighbouring France and countries like the United Kingdom).

Among young people, risk behaviour is also linked with educational level: young people with lower qualifications exhibit risk behaviour more often and at a younger age than young people with a higher level of education, they smoke more, for example (Schrijvers & Schuit, 2010)¹⁹, the AADP's recent Pupils' Survey reiterates the strong link between smoking and education type - many more pupils smoke in vocational education compared to technical secondary and general secondary education, and more in technical secondary education compared to general secondary education. Does this mean that these young people are particularly vulnerable to electronic cigarette smoking and the risks associated with this? These groups are probably more likely to experiment; a study has shown that "*little is currently known about the characteristics of those young people that are accessing e-cigarettes*" (Hughes et al., 2015). The study does, however, show that 15.8% of the young people who accessed e-cigarettes had never smoked tobacco cigarettes and that there is a link between the risk behaviour of young people (smoking tobacco, drinking alcohol weekly and binge drinking) and access to e-cigarettes.

The study concludes that: "*There is an urgent need for controls on the promotion and sale of e-cigarettes to children. Findings suggest that e-cigarettes are being accessed by teenagers more for experimentation than smoking cessation. Those most likely to access e-cigarettes may already be familiar with illicit methods of accessing age-restricted substances.*" Will e-

¹⁸ <http://archpedi.jamanetwork.com/article.aspx?articleid=1890731>

¹⁹ <http://www.rivm.nl/bibliotheek/rapporten/270372001.pdf>

cigarettes become another recreational drug for some groups alongside existing forms of addictive risk behaviour?

In response to this study, Dr. Compton of the *US National Institute of Drug Abuse*²⁰ listed the risks posed by e-cigarettes to the next generation, his greatest concern being for the young people group. In this group, the popularity of e-cigarettes is rising (both in the United States and in the United Kingdom; in the United States in 2014 e-cigarette use (“used at some point during the past 30 days”) was reported by 17.1% of 17-18 year-olds and by 16.2% of 15-16 year-olds; one fifth of the first group and almost one third of the second “*had no lifetime cigarette or smokeless tobacco use, thus indicating that these devices are not solely being used by current cigarette smokers as quit aids*”). M. Bellis, one of the study’s authors on risk behaviour and the e-cigarette, said of the increasing use of e-cigarettes among young people in the United Kingdom that “*such rapid penetration into teenage culture of what is essentially a new drug use option is without precedent*”²¹.

The publication makes reference again to associations with other risk behaviours in the area (of addictive substances): drinking in order to get drunk, binge drinking, getting around age restrictions to gain access to alcohol. A warning is also issued in relation to the lack of strict regulation and controls of e-cigarettes (“*The authors underscore the urgency in this situation: The longer we wait for stricter controls on these products, the more young people will be exposed to them and want to access them illicitly if and when they are banned for underage use.*”). The dangers of nicotine to the young person’s brain are also pointed out (the reward effect is stronger at that age, nicotine has the ability “*to ‘change the brain’ at this age*”). On the subject of the e-cigarette as a ‘*gateway drug*’ the study says: “*A 2011 mouse study by Eric R. Kandel and colleagues at Columbia University identified an epigenetic pathway that increases sensitivity to cocaine’s rewarding effects following nicotine exposure; if such a mechanism for priming the brain to other drugs’ rewarding effects is also present in humans, then e-cigarettes could indeed be a gateway drug.*”

The following conclusions and concerns were expressed, with which the SHC is in agreement: “*One of the biggest questions, which only further research will be able to answer, is whether the 15.8 percent of North West English teens—or the comparable number of American youth—who accessed e-cigarettes but who had never (yet) used conventional cigarettes will go on to try—and enjoy—conventional tobacco products. The last thing we want to see is for these sleek, shiny, and safe-seeming new devices to re-glamorize smoking behavior and reopen the door to conventional cigarette use in a population that has been consistently using less and less tobacco since the 1990s. That would undo decades of successful prevention efforts and put the health of yet another generation of kids at risk.*”

Whether non-smokers could be induced to start using e-cigarettes with nicotine in the future (and perhaps tobacco cigarettes too) probably depends on the image surrounding the e-cigarette (or the image that could be created by interested parties with purely financial intentions). If the e-cigarette makes smoking the most normal thing in the world again, if the e-cigarette becomes much more popular (among non-smokers) and/or very easily available

²⁰ <http://blogs.biomedcentral.com/bmcseriesblog/2015/03/31/e-cigarettes-teens>

²¹ <http://www.cnn.com/2015/03/31/e-cigarettes-the-new-gateway-drug-for-teens.html>

to the wrong groups of consumers, and/or people get the idea that the e-cigarette is harmless, assisted by manufacturers who manipulate this with trendy products in cool colours and tastes, it may well lower the threshold to start smoking (conventional or electronic) even further (because the threshold for tobacco smoking is already very low for some of groups of young people (especially those with a low level educational background) in our country).

For this reason the e-cigarette must be a product which is aimed at current smokers (rather than at non-smokers or young people), and in this sense it must be regulated. It is not a toy, nor is it an item of confectionery for minors. It is important that e-cigarettes do not become a trend among young people and young adults and that they do not introduce non-smokers to nicotine addiction and/or tobacco use (Newsmax, 2015).

Another development of major concern is that the established tobacco industry is acquiring more of the e-cigarette industry and beginning to manufacture its own e-cigarettes. Indeed this development is also a factor in answering this question. Again, it is impossible to make a final judgement: the answer is partly dependent on how the electronic cigarette is further developed and commercially placed on the youth (and young adult) market. It is still unclear whether and by what marketing strategies tobacco manufacturers seek to get young non-smokers (e-)smoking in the future. If the market for the conventional cigarette disappears and that for the e-cigarette takes its place, commercial strategies will be developed to move young people towards electronic smoking and (as long as conventional smoking and e-smoking exist side by side and as long as this form of combined smoking remains lucrative for the industry) conventional smoking (via the e-cigarette if possible).²²

The shisha-pen (without nicotine), which some school children “smoke” on the playground these days, but which is also aimed at a hip and older audience, appears to be the perfect vehicle for the tobacco industry to lower the threshold to (e-cigarette) smoking, to entice young people to (electronic) smoking and then (later) introduce them to the (e-)smoker culture. A small step up perhaps, because in the end the story involves nicotine, the substance which binds the new smoker to the product in the first place, and marks the start of years and often decades of smoking. Not enough is known about the marketing strategies of tomorrow, but after a decade in which tobacco advertising has been increasingly restricted, items like the shisha-pen would seem to be a dream-tool to make (the step up to) smoking acceptable again to young minors.

Summary

The risk of non-smokers (especially non-smoking youths) using electronic cigarettes, and, coupled with this, the risk of said use leading non-smokers to nicotine addiction or to start smoking tobacco cigarettes (the “gateway” hypothesis), are difficulties which must be taken seriously. The fear expressed by some, partly through the (correctly) perceived lower risk of

²² A new American study was recently published, for example, on the subject of how youth come into contact with tobacco advertising and offerings via the social media. The researchers call for clear regulations because social media have broken down the walls of the school playground. This enables the industry to advertise and market e-cigarettes (possibly with tobacco cigarettes too)? *"Our findings underscore the need for policy strategies to more effectively monitor and regulate tobacco advertising via new media outlets."*, Cavazos-Rehg, e.a. *Hazards of new media: youth's exposure to tobacco ads/promotions*, <http://www.ncbi.nlm.nih.gov/pubmed/24163285>

the e-cigarette, that substantial numbers of non-smokers could become regular e-cigarette users, is currently not evidenced by the facts. Especially, whereas experimentation (“ever used/tried out”) with the e-cigarette, chiefly among smokers but some non-smokers, does appear to be on the increase, the data available do not for the time being show that non-smokers are becoming regular e-cigarette users. Nor do the data available at this time confirm the e-cigarette as a cause or gateway to becoming a tobacco smoker. It would seem obvious that constant monitoring of the prevalence of e-cigarette use and tobacco smoking is necessary in the future, in order to quickly trace any (unwelcome) changes to the trends described above. On this subject, the SHC would like to point out the shortage of research data in this country (how do young people view the e-cigarette (while the figures for youth tobacco smoking in Flanders continue to rise)?), the further need to study the correlations between tobacco smoking and e-cigarette smoking (vaping) in general, the need to critically monitor the marketing strategies of the tobacco manufacturers who still see young non-smokers as new target groups (in the tobacco and e-cigarette markets) and the need to regulate e-cigarette use to prevent minors and young adults (who do not (or do not yet) smoke) from being targeted by e-cigarette manufacturers.

6 Other considerations

6.1 Equal treatment

During discussions about the place of e-cigarettes containing nicotine, opinions were voiced in favour of including them under medicinal products and restricting their sale to pharmacies. The SHC does not agree with this, unless tobacco and tobacco products were also restricted to the pharmacy. This is because the e-cigarette containing nicotine is less toxic than the tobacco cigarette and is probably not carcinogenic. It makes little sense to impose stricter access rules on a product which is less toxic, and to allow the real perpetrator, the tobacco cigarette, with thousands of deaths to its name, to remain freely available for sale. At the very least equal treatment of the two products is needed, if not stricter treatment of tobacco (cigarettes) compared to e-cigarettes. Measures to regulate e-cigarettes must not result in weakening the regulations on tobacco cigarettes (on advertising or smoking in public places, for example).

6.2 Non-smokers

Given that nicotine is a toxic substance, the use of e-cigarettes with nicotine is not recommended for non-smokers. The same applies to e-cigarettes without nicotine, because not enough is known about the toxicity and effects of the scents and flavourings they use.

6.3 Special presentations, names, likeness to tobacco cigarettes, disposable cigarettes

E-cigarettes are available on the market, with and without nicotine, with attractive colours, glow in the dark, bearing names like “bio” or “light”, referring to established brands such as “Red Bull”, “Mojito”, shaped to closely resemble a tobacco cigarette, featuring a light that glows like the tip of a “cigarette” when you inhale, etc. Clearly this is all designed to entice people, and young people in particular, into buying them.

The same is true for very cheap disposable e-cigarettes which are clearly placed on the market to enable people with less spending power to make their first purchase, as was formerly the case when cigarettes were packaged in 10s. The clear aim here is to keep the vaping threshold as low as possible and promote the step up to greater consumption, and possibly the step up to tobacco smoking.

6.4 Scents, flavourings, colourings

There is a risk, as is the case with tobacco cigarettes, of all kinds of substances being added to affect the smell, taste and colour of the smoke, etc. (Tierney et al., 2015). Given that little or nothing is known about their toxicity when heated and inhaled, our approach to these products should be one of caution; some form of surveillance should operate when insufficient data are available (OFT, 2013). For example, although acceptable for use in

foodstuffs, diacetyl propionyl and acetyl propionyl have been prohibited because of their link to bronchiolitis obliterans when inhaled (Farsalinos et al., 2014).

There is a risk, as is the case with tobacco²³, of a number of scents, flavourings and/or colourings being employed to encourage people to start vaping, especially young people; there are e-cigarettes on the market already which taste of mint, peach, vanilla, cocoa, etc., containing alcohol, which give a blueish vapour, etc. This also applies to e-cigarettes without nicotine.

In this context, the SHC draws attention to §52 of the preamble of the aforementioned Directive, which states that the European Commission should draw up a positive list of the ingredients that can be used, may be present in or may be added to tobacco products. The Commission should also evaluate the available scientific evidence on the toxic and addictive effects of ingredients. It must be stated clearly that it is the responsibility of the industry to conduct the necessary studies to demonstrate that their products are safe and carry no risk of addiction, and that it is the responsibility of the government to evaluate these studies. To avoid all possible risk, the principle of a positive list of additives and flavourings must apply in line with the example of the foodstuff and tobacco product requirements set out in the EU regulations. We note here, however, that since these products are inhaled and not administered orally, the industry is required to conduct studies specific to exposure by inhalation. It will also be necessary, given that little is known about what happens to these substances through pyrolysis (converted products, new products), to conduct studies that account for every possible substance present in the vapour of an electronic cigarette as the result of actual heating of additives and flavourings prior to inhalation, including improper use and malfunction.

6.5 Substantial modification

Besides notification of every new e-cigarette that is placed on the market, Article 20 of the Directive provides for a new notification of every “substantial modification”; the Directive does not however give a definition of this term, so that it is up to the manufacturer / party placing the e-cigarette on the market to decide what constitutes a substantial modification. This brings with it the risk that some modifications, which may actually be “substantial”, will not be reported, with the result that a product on the market no longer matches its file or, worse still, modifications are made with potential toxic effects.

6.6 Place of sale

At the present time, tobacco is freely available for sale; cigarettes are usually positioned near the till, especially in supermarkets, where they draw people’s attention at checkout and most certainly won’t slip the shopper’s mind. It cannot be the aim to adopt a stricter approach to e-cigarettes, because they have been proven to be less harmful. The two products should be treated equally and should not, in the opinion of the SHC, be placed near the checkout, beside the chewing gum, the mints, etc. It would be better if smokers were

²³ For a recent article on this subject in the "New England Journal of Medicine": <http://www.nejm.org/doi/full/10.1056/NEJMc1403015>. Tobacco contains the same flavourings as popular sweets and soft drinks

dissuaded at the point of sale, given the necessary information, and, even better, under the guidance of trained personnel.

6.7 Surveillance authority, scientific support

It is clear that the Directive imposes obligations on the government (see above). It is necessary, therefore, that any structure set up by the government be invested the competence to fulfil these obligations in the realm of inspection and surveillance, as well as control of submitted dossiers, assessment of the toxicity of ingredients, taking of samples, analyses, etc. The necessary funding and manpower must be provided; the Directive also mentions the possibility of imposing penalties.

6.8 Smoking in public places, legal status

Article 3, paragraph 3 of the law of 22 December 2009, which introduces general regulations to keep enclosed public areas free of smoke and protect employees against tobacco smoke in the workplace, states: “Any element likely to encourage smoking or to give the impression that smoking is permitted is prohibited in the areas referred to in paragraphs 1 and 2.” It is thus forbidden to use any electronic cigarette (all three types, without exception) in enclosed public spaces, including bars and restaurants, in Belgium.

It is recommended that this legislation be left as it is, since otherwise there is a danger of the smoke free legislation being relaxed for tobacco products, or disrespected if e-cigarette smoking is permitted in enclosed public spaces. Another reason is the difficulty of telling electronic cigarettes and tobacco cigarettes apart when applying the ban.

One member of the SHC study group is of the opinion that: “*A general ban on the use of the e-cigarette in enclosed public spaces seems disproportionate to the minimal third party health risk, and if anything it appears to him counterproductive in pursuing the primary goal of reducing the prevalence of tobacco smoking. For that reason the member does not support the general vaping ban in enclosed public areas, but selective restrictions (exhaustive list of places with a smoking ban (for example: schools, public transport, shared workplace).*”

6.9 The increasing role of the tobacco industry

Whereas electronic cigarette manufacturers used to be small entrepreneurs, independent from the tobacco industry, the tobacco industry is gradually taking over the electronic business. All of the major cigarette companies now offer electronic cigarettes (WHO, 2014).

There is a fear that the attraction of the e-cigarette will grow among young people, through advertising, trendy products and tobacco industry-inspired flavourings. In addition, large international cigarette manufacturers are placing “heat not burn” cigarettes on the market, made from tobacco and carrying cigarette brand names, which could solidify the relationship between smoking and the e-cigarette. The above products are not covered by these

recommendations. Philip Morris International, for example, is investing 2 billion USD in “vape products” with (and without) tobacco, with the aim of placing Marlboro heat sticks on the market and achieving sales of 30 billion units by the end of 2016.^{24,25}

For this reason the SHC recommends that the current regulations governing tobacco product advertising also be applied to e-cigarettes.

6.10 Tobacco policy

There is a need to raise awareness about the various forms of electronic smoking in schools (teachers, etc.) and among care providers. Objective information must be available on the subject of electronic smoking, in the health and education sectors in particular. Current communication on the e-cigarette is often confusing and incomplete.

There is also a need to conduct more studies on the e-cigarette in this country. The Health Survey conducted by the Scientific Institute for Public Health (SIPH) has missed the introduction of the e-cigarette completely (the survey yields 5-yearly figures only); and the Pupils’ Survey run by the AADP tells us nothing about how young people use/see the e-cigarette today.

What our country lacks is a coherent and energetic approach based on a set of efficient, mutually-reinforcing measures. Belgium is behind on the positive developments taking place in neighbouring countries (such as the United Kingdom). The government is currently also failing in its efforts to protect young people against tobacco smoking and tobacco addiction.

According to the latest Health Survey²⁶ almost 1 in 4 Belgians still smoke. The drop in the number of smokers has not been significant for a long time. The number has reduced by barely 2% since 2008. This reduction is, according to the Health Survey, “smaller than expected and calls for greater efforts in the fight against tobacco use”. Smoking is actually on the increase among young women, “a hitherto unknown phenomenon”. Smoking is also strongly linked to socioeconomic background. Smoking is, the Health Survey tells us, “mostly a habit among people and social milieus that have not experienced higher education.” Tobacco creates and reinforces major health inequalities between the different social groups in our society.

Young people who wish to resist the temptation have to stand strong. According to the AADP’s most recent Pupils’ Survey²⁷ smoking among young people in Flanders has increased sharply in the past year across all age groups and education forms (general secondary education, technical secondary education, vocational secondary education), and among boys and girls alike. These figures, depending on the group, show rises of between 4% and 8%. Does this mean that there is a new generation of smokers on the way? Does it mean that smoking has become “more ordinary” again for the younger generation?

²⁴ <http://www.cbc.ca/news/business/marlboro-heatsticks-heat-tobacco-instead-of-burning-it-1.2689213>

²⁵ PMI, **Investor Day -Reduced-Risk Products, Lausanne, June 26, 2014**

²⁶ https://his.wiv-isp.be/nl/Gedeelde%20%20documenten/TA_NL_2013.pdf

²⁷ <http://www.vad.be/alcohol-en-andere-drugs/onderzoek/leerlingenbevraging.aspx>

The difference in smoking behaviour between education types is reconfirmed by the recent Pupils' Survey. Far fewer young people in general secondary education smoke compared to technical secondary education, and in technical secondary education far fewer compared to vocational secondary education. In secondary vocational education almost 1 in 3 youngsters smoke regularly (regular smokers: in general secondary education 6.1%, in technical secondary education 14.6% and in vocational education 28.7%). In the past year, 25.6% smoked in general secondary education, 38.2% in technical secondary education and 45.5% in vocational secondary education. They may not all have been regular smokers, but the figures are still striking. Tobacco products are not at all expensive in Belgium. Roll-your-own tobacco is cheap. Cigarettes and roll-your-own tobacco are widely available for sale and are displayed attractively in the stores, often beside the confectionery and magazines. In addition, tobacco advertising is still permitted at strategic points in our country: the tobacco industry extols its wares in the newsagents', inside and out. Many European countries have already introduced a total ban on tobacco advertising and tobacco can no longer be visibly displayed at the point of sale.

Another tobacco control measure, i.e. the introduction of plain packaging, has already proven its effectiveness in studies and in practice in Australia; countries such as Ireland, the United Kingdom and France have announced the measure for 2016.

The SHC's recommendations on the e-cigarette are linked to this policy (the e-cigarette is not a magic wand that can tackle the tobacco problem in our country, but does offer not-to-be-missed opportunities as part of a powerful and revitalised anti-smoking policy).

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VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: [composition and mode of operation](#).

All experts joined the working group *in a private capacity*. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: [conflicts of interest](#)).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Jean NEVE**; the scientific secretary was Muriel BALTES.

BAEYENS Frank	Psychology	KULeuven
BODO Martial	Psychology, tobaccology	Bordet
BOUDREZ Hedwig	Psychology, tobaccology	UZGent
JOOSSENS Luk	Tobacco prevention	Foundation against Cancer
NEMERY DE BELLEVAUX Benoît	Toxicology, Occupational Medicine	KULeuven
NEVE Jean	Pharmacology, Pharmacotherapy	ULB
PASSCHIER Wim	Risk analysis for health	Maastricht University
PUSSEMIER Luc	Chemical additives, contaminants	CODA-CERVA
ROCOUR Muriel	Pharmacist, tobaccology	Independent
TYTGAT Jan	Toxicology, pharmacology	KULeuven
VAN LAREBEKE Nick	Toxicology	UZGent

The following experts were heard but did not take part in endorsing the advisory report:

BARTSCH Pierre	Pneumology	ULB
GALANTI Laurence	Tobaccology	UCL
GODDING Véronique	Pediatric pneumology, tobaccology	UCL
LUSTYGIER Vincent	Psychiatry, tobaccology	CHU Brugmann
NACKAERTS Kristiaan	Pneumology	KULeuven

The following administrations and/or ministerial cabinets were heard:

CAPOUET Mathieu	Tobacco legislation	FPS HFCSE, DG4
DE BUCK Philippe	Authorization / inspection	FAMHP
DUSSART Aurélie	Risk control chemicals	FPS HFCSE, DG5
JACQUES Sarah	Safety of products and services	FPS Economy
MAES Gwennaëlle	Risk control chemicals	FPS HFCSE, DG5
PAUWELS André	General counsel , coordinator	SHC
VAN DEN MEERSSCHE Paul	General counsel, inspection of consumer products	FPS HFCSE, DG4

The following firms/associations/etc. were heard:

HENDRICKX Stefaan	Tobacco prevention	VIGEZ
SAEVELS Jan	Pharmacist	APB

This advisory report was translated by an external translation agency.

VII APPENDICES

APPENDIX 1: LEGISLATIVE FRAMEWORK

The prevailing legislation allows the competent Belgian authorities to consider e-cigarettes and similar products in three categories.

1 Electronic cigarettes containing nicotine

E-cigarettes containing nicotine, an active pharmacological substance, are seen as medicinal products under the law of 25 March 1964 because of their function. These products can only be sold once a licence has been obtained to place them on the market. To be registered as a medicinal product, data must be provided on their quality, safety and efficacy. Electronic cigarettes which do not contain nicotine but are described as a stop smoking aid are considered medicinal due to their presentation and must satisfy the same requirements. In practice, not one e-cigarette of this type is licensed for sale in Belgium; since not one licence application has been made to date, no licence has been granted.

In this case there is still a need to distinguish between the inhalation liquid and the electronic component. According to the definition in the Royal Decree on Medical Devices of 18 March 1999, the electronic component is a medical device. The medical device is designed to deliver the medicine, in other words the inhalation liquid.

2 Electronic cigarettes without nicotine, tobacco extracts or description as a stop smoking aid

Electronic cigarettes which do not contain nicotine and are not described as a stop smoking aid are subject, as are their nicotine-free refill containers, to the obligation to register the chemical products they contain if listed by the REACH regulation (EC) no. 1907/2006 of the European Parliament and of the Council.

The REACH regulation makes it compulsory to register every substance or mixture (hazardous or otherwise) used in Europe or placed on the European market. The registration obligation rests on the manufacturer or importer of the liquid, or on the manufacturers (if the liquid is made from substances or mixtures purchased from a European supplier subject to the registration obligation) or importers (if the liquid is manufactured from imported substances or mixtures) of the substances present in the liquid. Registration applies to each substance separately and is required if the quantities of the manufactured or imported substance amount to one tonne or more a year. The substance is registered with the European Chemicals Agency and registration includes information on the identity of the substance and its toxicity if any, dependent on designated use. In this case the manufacturer and distributor of the liquid contained in the e-cigarette (or refill container) must ensure that when registering the substance, they state use for the manufacture of e-cigarettes as one of the substance's uses.

If the liquid in an e-cigarette without nicotine or its refill container contains hazardous substances or mixtures (explosives, corrosives, carcinogens ...), it is in addition also subject to the obligations imposed by regulation no. 1272/2008 on classification, labelling and packaging of substances and mixtures. Under this regulation, the label on e-cigarettes and refill containers must state the category of hazard presented by these mixtures or substances (i.e. the hazard pictograms). Notification of these cigarettes and refill containers must be made to the anti-poison centre to enable fast and efficient response in case of poisoning (regulation no. 1272/2008 of the European Parliament and of the Council and Article 13 of the Royal Decree of 11 January 1993 regulating the classification, packaging and labelling of hazardous mixtures with a view to their use or placement on the market).

3 Electronic cigarettes with tobacco extracts

Besides nicotine, these e-cigarettes can contain tobacco extracts, for example to provide flavour. In the eyes of the law they are tobacco products. In other words, these products must satisfy the requirements set out in the law of 24 January 1977 concerning consumer health with regard to foodstuffs and other products, as well as the Royal Decree of 13 August 1990 concerning the manufacture and placement on the market of tobacco-based and similar products. In practice this means that all of the legislation governing conventional tobacco products applies to electronic cigarettes of this type: notification, regulation of sale, health warnings on the packaging, advertising ban, etc. The FPS Public Health has not yet received notification of a single product of this type.

4 Regulations common to all types of electronic cigarette

Generally speaking, these three classes of product must satisfy the general requirements of the law of 21 December 1998 concerning product standards to promote sustainable patterns of production and consumption and to protect the environment and public health²⁸. The law provides that products placed on the market must be designed so that their manufacture, intended use and disposal are not harmful to public health. There is no penalty for an infringement of this obligation, but if a product presents a serious and acute danger to public health, the minister may take provisional measures to forbid the product's use, placement and retention on the market.

In addition, e-cigarettes fall under the Code of economic law, volume IX on the safety of products and services. This regulation states that products and services may only be placed on the market if they are safe. This means that a product or service placed on the market must not involve risk under the normal and foreseeable conditions of use. The producer and/or distributor are responsible for effects caused by any defect in their product or service. In the present case, the electronic safety aspect is covered by the Royal Decree of 28 February 2007 concerning electromagnetic compatibility, as well as the Royal Decree of 17 March 2013 restricting the use

²⁸ This law applies to products which fall under the scope of the legislation on medicines provided that the provisions are not inconsistent with or contrary to the objectives of this legislation (Article 3, § 2 of the law of 21 December 1998).

of some hazardous substances in electric and electronic devices and the Royal Decree of 27 March 2009 on the placement on the market and provision of end user information on batteries and rechargeable batteries and forbidding or only partly allowing the use of certain chemical substances, such as mercury and cadmium, in e-cigarettes, the batteries they contain and/or refill containers. A first sample study shows that some manufacturers are not observing this legislation.

Finally, in Belgium e-cigarettes are believed to encourage smoking. Article 3, paragraph 3 of the law of 22 December 2009, which introduces general regulations to keep enclosed public areas free of smoke and protect employees against tobacco smoke in the workplace, states: “Any element likely to encourage smoking or to give the impression that smoking is permitted is prohibited in the areas referred to in paragraphs 1 and 2.” It is thus forbidden to use any electronic cigarette (all three types, without exception) in enclosed public spaces, including bars and restaurants, in Belgium.

5 Legislative framework: future situation

Article 20 of European Tobacco Products Directive, 2014/40/EU, which was approved in May 2014, relates specifically to e-cigarettes containing nicotine. It allows Member States to choose between application of the legislation on medicinal products (Directive 2001/83/EC and Directive 93/42/EEC) or application of the new provisions of Directive 2014/40/EU and considers the e-cigarette as an ordinary consumer item, but imposes certain restrictions with a view to safety and consumer protection. The Directive must be transposed by 20 May 2016 at the latest.

Minister De Block is in favour of the second option and, therefore, application of Article 20, which specifies:

- Notification by the manufacturers of information on ingredients, toxicological information, parts of the electronic component, etc.
- A maximum nicotine content and maximum quantity of nicotine in each e-cigarette
- A mechanism to prevent leaks of nicotine-containing liquid
- Specific health warnings on the packaging
- A ban on certain types of advertising for these products.

Given that this article only applies to e-cigarettes containing nicotine, the legislation should also be adapted to e-cigarettes without nicotine if additional measures are to be taken in relation to all e-cigarettes, including those without nicotine. This may relate, for example, to advertising, use in public places, sale to minors, labelling, etc.

APPENDIX 2: SUMMARY

Key Messages

This document contains a summary of the scientific recommendations issued by the Superior Health Council under no. 9265 (80 pages). These recommendations rest on a meticulous analysis of more than 200 scientific studies and international reports on the subject (see point V of these recommendations) by a group of independent Belgian experts (see point VI of the recommendations). These experts submitted a general declaration of interests and the potential for a conflict of interests was assessed by the Committee for Deontology and Ethics. Finally, the recommendations were approved by the Board of the SHC, which is made up of 40 Belgian experts in the field of public health and environment.

1. Tobacco in Belgium

a. The many health hazards of tobacco

The World Health Organisation (2015) tells us that half of all smokers die prematurely. Every year, smoking claims the lives of about 6 million people around the world, more than 5 million of whom are smokers or former smokers and over 600,000 of whom are non-smokers who were exposed to smoke involuntarily.

“Smoking kills” because smokers have a higher chance of contracting a number of diseases, or run a higher risk of aggravation of the same: various types of cancer, chronic bronchitis (COPD), cardiac arrest, high blood pressure, CVA, diabetes, Crohn’s disease, osteoporosis, infections, multiple sclerosis, gum and tooth diseases, complications following surgery under general anaesthetic, etc.

Smoking makes people addicted to nicotine, costs money, reduces athleticism and stamina and accelerates ageing of the skin.

In addition, regular smoking in the presence of non-smokers makes smoking appear normal and increases the risk of non smokers developing cancer, respiratory diseases and heart disease.

Smoking during pregnancy harms the health of unborn children, who will have to suffer the harmful effects for the rest of their lives.

b. Risk groups in Belgium

Given the opinion of the study group experts and the most recent figures available for Belgium^{29,30}, the SHC believes that greater effort is needed in the fight against smoking. Because,

- Almost 1 in 4 Belgians still smoke: 23% smoke, 19% smoke daily, 4% smoke occasionally.
- The number of smokers has fallen by barely 2% since 2008.

²⁹ https://his.wiv-isp.be/nl/Gedeelde%20%20documenten/TA_NL_2013.pdf

³⁰ <http://www.vad.be/alcohol-en-andere-drugs/onderzoek/leerlingenbevraging.aspx>

- The number of cigarettes consumed daily (16 on average) has remained unchanged during the past ten years.
- There is also a worrying rise in smoking and daily smoking among young women and therefore possibly among pregnant women or women who want to have children.
- There are more smokers in the lowest social classes: 18% of managers smoke, 23% of non-manual workers, 41% of manual workers and 46% of unemployed people.
- The number of young smokers is still high. One new trend is that young adults are still taking up smoking.
- Smoking is a growing problem among vocational secondary school pupils; almost 33% smoke daily. The higher the level of education, the fewer the pupils who smoke.

2. The e-cigarette

There are two parts to the problem:

- How harmful can use of the e-cigarette be, and how harmful compared to tobacco smoking?
- What is the role of the e-cigarette (with or without nicotine) in tobacco control policy and the fight against nicotine addiction? For smokers, as an effective aid to quit tobacco and nicotine; for non-smokers, as a potential gateway to nicotine and tobacco addiction or as a means of normalising smoking again in a social context?

-

a. Harmfulness of e-cigarettes versus tobacco

- The recent European standards ensure that e-cigarettes placed on the market are safer and of better quality. However, we should remain cautious of products which are not registered in Europe (Directive) or are sold on the internet or whose origin has not been verified. EC marking offers a guarantee that the manufacturer has satisfied these standards.
- Nicotine aside, e-cigarettes are significantly less toxic than tobacco. Vaping releases none of the products of tobacco combustion, just a relatively low quantity of a small number of toxins. This conclusion assumes that all e-cigarettes meet the strict set of conditions set out in the EC Directive.

Nonetheless,

- The toxicity of the scents, colourings and flavourings currently used and permitted in e-cigarettes has not been adequately tested in the context of e-cigarette use. The substances can be safely used in foods, but in the case of the e-cigarette they are heated and inhaled, which is very different to ingestion by eating.
- Not enough is known about the long-term health effects of chronic e-cigarette use at present.
- Liquid refill containers containing nicotine could lead to acute and even fatal poisoning in case of accidental or improper use (if a child drinks the liquid, for example). This is much less common in the case of tobacco products. It is a new risk which manufacturers and users must take into account.

b. E-cigarettes containing nicotine for smokers who wish to stop smoking

- The e-cigarette containing nicotine appears to be an effective quitting aid for smokers. Although the control period is still too short, initial results are positive and encouraging; however, confirmation through further study is recommended. The SHC sees no reason, therefore, to refuse market access to e-cigarettes containing nicotine provided they are used as part of a smoking control policy.
- This makes little sense if the smoker continues to smoke tobacco while using the e-cigarette. He must cut down his tobacco smoking by 85% to have a positive effect on chronic bronchitis (COPD) and stop smoking altogether to have a positive effect on cardiovascular disease. The e-cigarette, therefore, along with the many other available treatments, must be seen as a potential aid to stop smoking *altogether*, after which the e-cigarette should in time be given up.
- However, if stopping the e-cigarette is not possible, or desirable, it is better to keep using the e-cigarette in the long term than to risk returning to tobacco smoking. In the process, an attempt can be made to gradually reduce the nicotine dose in the e-cigarette.

c. E-cigarettes without nicotine for smokers who wish to stop

- At the present time we do not know whether an e-cigarette without nicotine can help a smoker to stop, or whether an e-cigarette without nicotine can help reduce e-cigarette use. Further study is needed and caution is advised.

d. E-cigarettes with and without nicotine for non-smokers

- Initial studies show that more and more people are trying the e-cigarette, but do not become regular users in the long term.
 - Very few new users of the e-cigarette switch over to the tobacco cigarette.
 - Young e-cigarette users, like adult users, are often tobacco smokers already.
- The control period is too short and vaping is not yet sufficiently established to allow a definitive statement on this subject. The SHC views this uncertainty as a reason for advising caution and vigilance in the introduction of e-cigarettes. Because,
- The hypothesis that e-cigarettes are a gateway to tobacco use is still acceptable and deserving of further attention.
 - The tobacco industry has become involved in the manufacture of e-cigarettes and will probably intensify and diversify e-cigarette advertising (young audience, female audience, internet and social networks, etc.), as it did for tobacco cigarettes.
 - The e-cigarette must not give smoking the “positive”, “fun” and “healthy” image it once had in the early days of tobacco advertising. Disposable, flavoured and novelty (lights, coloured vapour, etc.) e-cigarettes carry the risk of making smoking appear normal again and attracting non-smokers to the product.

3. Recommendations to intensify current tobacco control policy and frame the introduction of the e-cigarette

The SHC recommends:

- More controls and surveillance to ensure strict implementation of the current legislation on tobacco products.
- Raising the minimum legal age to purchase e-cigarettes, tobacco cigarettes and tobacco products from 16 to 18.
- Increasing the prices of tobacco products and putting the new revenue towards controls and smoking prevention.
- A total ban on tobacco advertising together with special surveillance of the internet and social networking sites widely used by a young audience.
- Introducing plain packaging in Belgium (an effective smoking prevention measure which was developed in Australia), as will be done in Ireland, the United Kingdom and France in 2016.
- Promoting health education among the general population, focusing on schools, pregnant women, the lowest social classes and smokers.
- Incorporating e-cigarettes in a general smoking prevention policy. Not viewing the e-cigarette as a modern stimulant in itself to be assessed alongside other tobacco products.

Cigarettes and roll-your-own tobacco are readily available for sale and displayed attractively in the stores, often beside the confectionery and magazines. Neither tobacco nor e-cigarettes should be freely and easily obtainable, e.g. at supermarket checkouts or other places to which the public and non-smokers have easy access.

- o It would be better to restrict the sale of e-cigarettes in Belgium to specialist points of sale, where the necessary information is provided and, better still, where trained personnel offers guidance, although specific training does not yet exist.
- o Where tobacco is concerned, the SHC is of the opinion that the points of sale should be restricted to tobacconists' and newsagents', and that an advertising and display ban should be introduced.

As a framework for the arrival of e-cigarettes on the Belgian market, the SHC also recommends that:

- Tobacco products and e-cigarettes be treated equally or that tobacco products (tobacco cigarettes) be given even stricter treatment than e-cigarettes. The use of e-cigarettes with or without nicotine is to be advised against and access is to be restricted for people who do not smoke.
- That vaping in the workplace and in enclosed public spaces be restricted.
- E-cigarette advertising be banned, together with special surveillance of the internet, apps and social networking sites.
- Disposable e-cigarettes, with or without nicotine, are being placed on the market with certain designs, tastes, scents, names, gadgetry, prices, ... with a view to getting people vaping. This is diametrically opposed to tobacco control policy. These practices must be regulated, controlled or banned at the points of sale and on the internet.

- The SHC is not against the addition of flavourings (in e-cigarettes only) provided these products are guaranteed to be harmless. However, these flavourings must not be alcohol or cannabis.
- As regards the heating element, preference must be given to materials which involve minimum exposure to metals and particular attention must be paid to the potential hazard of nanoparticles released when the e-cigarette is heated.
- It is the responsibility of the manufacturer to demonstrate that the products are not harmful to health when placed on the market, when technical modifications are made or when a change is made to the composition. This is the philosophy applied in the medicinal product and foodstuffs sectors, but not to e-cigarettes. In this case it is up to the Member States to establish and demonstrate that these products do not pose a serious risk to public health. For this reason SHC advises that the current European Directive be applied in this area and that the general principle and responsibilities be reversed.
- A tobaccovigilance and e-cigvigilance system be set up in Belgium.
- A system of funding be put in place to cover a number of independent studies on subjects in which uncertainty or lack of knowledge still prevails.

Finally, in view of the 6th state reform and the scope of the recommendations in this paper, the SHC recommends intensive coordination of the policies of the ministers of the competent federal and federated bodies. Public health, prevention, education, consumer protection, wholesale and retail, advertising regulation, media and films, youth protection and scientific research are all competencies to which, in the view of the Board, recommendations no. 9265 of the Superior Health Council relate.

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 40 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.