



Nicotine use among children and young people

Consequences and prevention

Report by

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Colophon

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This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable.

The report is available for download free of charge at www.vidensraad.dk

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Preface

The market for nicotine products has become more fragmented. For more than half a century, cigarettes and other types of tobacco almost completely dominated the consumption of nicotine in Denmark, but over the past 10-15 years a wide range of nicotine products have appeared in the market. These new products are very diverse and are used in different ways but have in common that they contain nicotine and that they are widely used by children and young people, including young people who are not smokers - or who have not previously smoked tobacco.

Therefore, it is relevant to explore the health-related consequences nicotine as a constituent has on young users, regardless of how it is consumed. The Council on Health and Disease Prevention therefore established a working group tasked with gathering current and updated knowledge about the consequences of nicotine use on the brain and somatic health of young people in this report. Additionally, The Working Group has assessed which preventive measures would be effective in the field of nicotine. The group made this assessment based on a previous thematic report from the Council on Health and Disease Prevention on smoking among children and young people.

The overall objective of the Council on Health and Disease Prevention is to ensure that decisions on the population's health and wellbeing are rooted firmly in research-based knowledge. We therefore hope that the present report may serve as a professional basis for the debate on nicotine use among children and young people and ensure that decisions made in this field are based on research.



Morten Grønbæk
Head of the Council on Health and Disease Prevention

“An ever-increasing share of children and young people use one or more of the many nicotine products available on the market. Therefore, it is important to collect the knowledge we have about any consequences of nicotine use on their health.”

Jørgen Vestbo
Head of the Working Group

Report summary

The number of children and young people who consume smokeless nicotine products has increased considerably in the past 5-10 years. Today, children and young people are exposed to a growing selection of nicotine products, including e-cigarettes, pouches, Swedish snus and chewing tobacco among others. The ample selection of available nicotine products in conjunction with their low price compared with cigarettes, the taste additives used and a packing that appeals to children and young people may be attractive to these groups and contribute to their rising popularity.

In view of the increasing consumption of this addictive drug among children and young people, the National Centre for Health Promotion and Prevention perceives that with this report we meet a need to present current research-based knowledge about the consequences of nicotine consumption for the health and wellbeing of children and young people. Additionally, the report summarises knowledge about tobacco prevention with the aim of strengthening the decision basis for preventive measures targeting nicotine consumption.

Prevalence of nicotine products

In Denmark, around one in every three (31%) children and young people aged 15-29 years consume some type of nicotine products daily or occasionally. Excluding consumption of cigarettes from the figures, 14.7% of children and young people consume nicotine products. In other words, around half of the children and young people who consume nicotine products only use other nicotine products than cigarettes. Among the smoke-free nicotine products, the more prevalent ones are Swedish snus and nicotine pouches.

Health risks

Among the harmful effects of nicotine for children and young people's health, the effect on the development of the brain is particularly worrying. The human brain is not fully developed until around 25-30 years of age, and use of nicotine at a young age has various negative effects on the development of the brain.

Dependence and addiction: Nicotine is an appealing substance because it has an energizing effect and elevates mood. Furthermore, it is one of the most addictive drugs known.

Gateway effect: Based on current research originating from human and animal studies, The Working Group assesses that moderate to strong evidence supports that nicotine increases the likelihood of becoming addicted to cigarettes and drugs in general. Thus, nicotine seems to have a so-called 'gateway' effect.

Cognitive functions: Moderate evidence indicates that early-onset nicotine consumption has a detrimental effect on cognitive function, among others on attention and motivation.

Self-control: Additionally, nicotine consumption in childhood and up to the age of 25 years may affect the person's self-control, e.g., the ability to control emotions and impulsivity.

Mental illness: Moderate evidence indicates that nicotine has a detrimental effect on mental health and may contribute to producing symptoms of anxiety and depression.

Stress: Stress and nicotine interact and mutually aggravate each other. Being affected by stress increases the risk of initiating nicotine consumption and, conversely, nicotine use in children and young people increases the risk of subsequently developing an increased sensitivity to stress.

Inflammation of the brain: Nicotine consumption at a young age may lead to the development of an inflammatory condition in the brain, and it seems that this inflammation is involved in disturbances of the maturation of the brain that increases the risk of depression, anxiety, and dependence.

In addition to affecting the brain, nicotine is associated with a range of other harmful effects: **Congenital malformation:** Moderate to strong evidence shows that nicotine exposure during pregnancy is associated with an increased risk of reduced foetal growth, poorer pulmonary function in the child, premature birth, and stillbirth.

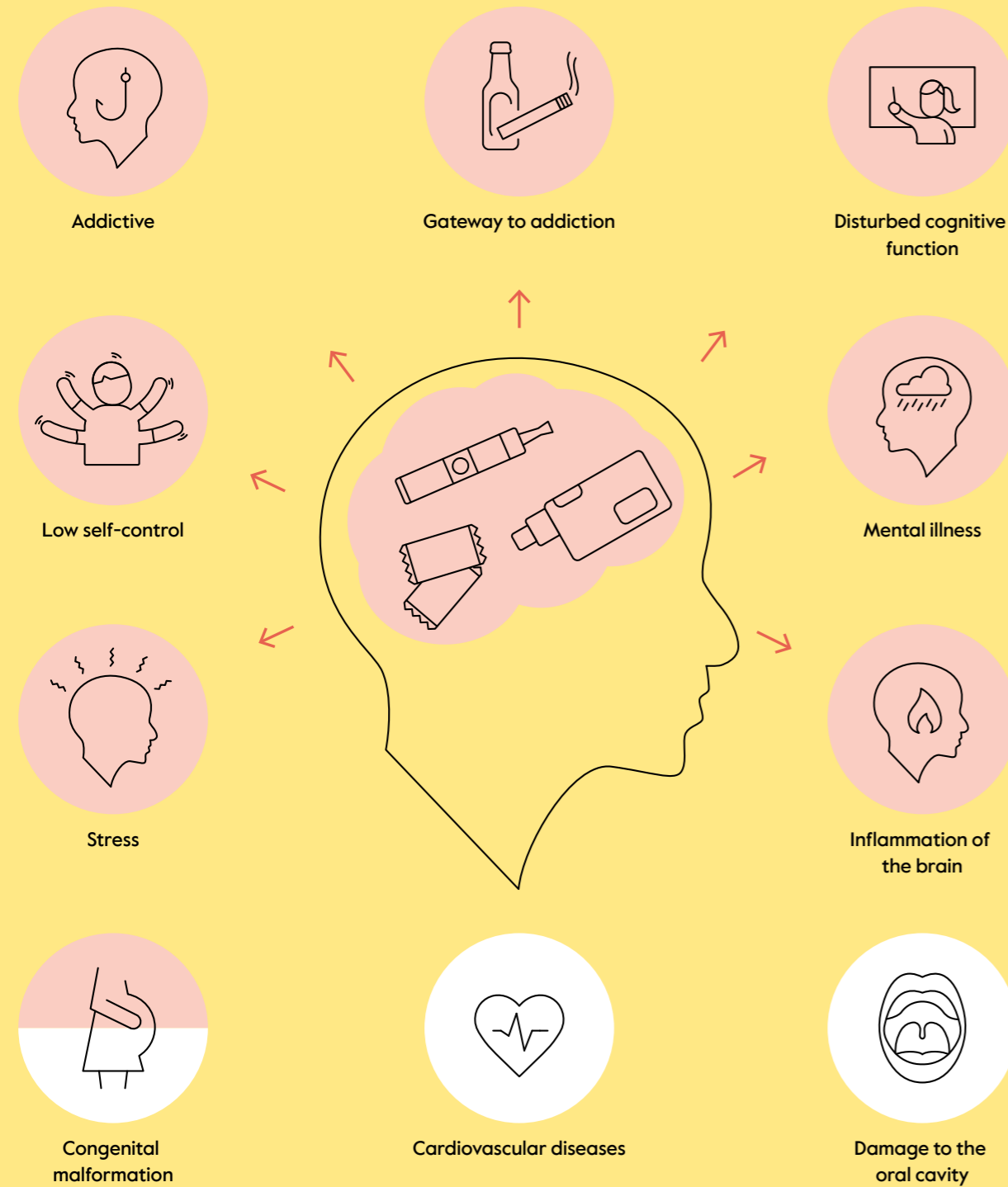
Cardiovascular diseases: The Working Group has found strong evidence that nicotine has harmful effects on the heart and vascular system, which in the longer term increases the risk of high blood pressure, cardiac disease, and blood clots.

Damage to the oral cavity: Studies indicate that nicotine may damage the gums, the mucosa of the mouth and the teeth, but this field has been studied only sparsely.

Cancer, immunocompromising or performance-enhancing effect and fertility: No evidence was found that exposure to nicotine among children and young people has a carcinogenic, immunocompromising or performance-enhancing effect. Current evidence is insufficient to draw any conclusions as to the possible links between nicotine and fertility. However, these fields are so poorly studied that any associations also cannot be excluded.

Health risks associated with nicotine use among children and young people

■ CONSEQUENCES FOR THE BRAIN
■ CONSEQUENCES FOR OTHER PARTS OF THE BODY



Prevention

The assessment of The Working Group is that strong parallels may be drawn between traditional tobacco prevention and prevention of the use of nicotine products. Therefore, The Working Group recommends employing the structural measures that we know have a strong preventive effect from measures to prevent tobacco consumption in the prevention of the use of other nicotine products among children and young people. The most effective form of prevention is achieved through multi-tiered measures that combine state-level structural measures with local measures and by including as many stakeholders as possible.

Courses of action

The state may, among others, ensure that the statutory instruments in place in the tobacco area are extended to comprise all nicotine-containing products rather than only some individual products as is now the case. As part of this measure, the state may introduce neutral packaging for all nicotine products along with a ban on taste additives. The state may also raise the age limit for nicotine product sales. Additionally, municipalities, schools, retail outlets and social media owners may collaborate to ensure that the current legislative measures are observed, e.g., the presentation ban, the no-smoking and no nicotine at school provision, the age limit on nicotine product sales and the advertising ban.

Conclusion

Childhood and young age stretching into the mid-twenties are periods of life that carry an increased risk of becoming addicted to nicotine and they are particularly sensitive periods for developing permanent harmful effects of nicotine, particularly effects affecting the brain. Additionally, nicotine increases the risk of starting to smoke cigarettes and consuming other drugs. Based on current evidence for the harmful effects on the health of children and young people, there is ample basis for concern because a growing number of children and young people start using nicotine, which is very addictive. Therefore, an urgent need exists to initiate measures that may rapidly prevent the development of additional addiction and harmful effects.

1 Introduction

This chapter initially provides a description of the backdrop of the present report. Next, the aim of the report is presented. Furthermore, the chapter lists the target group and defines central concepts used in the report.

Subsequently, we share how the report was delimited and describe the methodology employed.

This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

1.1 Background

Children and young people are currently exposed to an ever-increasing range of nicotine products, including e-cigarettes, heated tobacco, Swedish snus, chewing tobacco, nicotine pouches, tobacco powder and tobacco pods, and the share of young people who use smoke-free nicotine products has increased considerably in the past 5-10 years. In Denmark, the past few years have seen a decline in the share of children and young people who smoke cigarettes (1-5). Currently (May 2022), the price of most nicotine products is substantially lower than the price of cigarettes, and until recently several of the new nicotine products had taste additives, often sweet tastes like fruit or sweets, that make the products attractive to children and young people (6,7). Furthermore, the packaging used, e.g., the package design, use of colours and fonts, seems to have been chosen to ensure an appeal within a broad target group of children and young people (7). The extensive selection of available nicotine products, the low price, and the taste additives and packaging designs used may contribute to the increasing popularity of the products and to attracting the attention of children and young people.

Table I below gives a broad outline of the most frequent product types on the Danish market. Due to the increasing use of these new nicotine products, a need exists to describe any harmful effects of the drug nicotine from other sources than cigarettes, particularly among children and young people. We chose to focus on children and young people, as consumption has mainly increased in this group, and as the potential risk of impacting behaviour, causing addiction and health damage is presumably greatest in this group based on experiences from cigarettes and other tobacco products for smoking. On this basis, the Council on Health and Disease Prevention has established a working group to collect a new and updated knowledge basis that may allow us to make informed decisions on any preventive measures.

The knowledge basis is rooted in a joint overall assessment of the results of current literature on the health-related consequences of the drug nicotine and knowledge accumulated from prevention of tobacco smoking.

1.2 Objectives

The report aims to summarise the research literature to make visible the consequences of nicotine use on the health and wellbeing of children and young people. Additionally, the report summarises knowledge about tobacco prevention to strengthen the decision basis for preventive measures targeting nicotine consumption.

Table I

Frequently occurring nicotine products

	Contains tobacco [A]	Is heated [B]	Nicotine is absorbed through	Available in several different nicotine concentrations
Heated tobacco [D]	Yes	Yes	The lungs	No
E-cigarettes [D]	No	Yes	The lungs	Yes
Swedish snus [C] and chewing tobacco [D]	Yes	No	The mouth	Yes
Nicotine pouches [D]	No	No	The mouth	Yes

[A] Tobacco contains a range of toxic substances, e.g., carcinogenic tobacco-specific nitrosamines. In Danish legal provisions, products that do not contain tobacco are coined "tobacco surrogates".

[B] Is not combusted but heated electronically. When heated, new, often harmful, chemical compounds are formed.

[C] It is not illegal to sell Swedish snus in Denmark. Selling chewing tobacco is legal.

[D] Selling to young people below 18 years of age is illegal in Denmark.

1.3 Target group

The main target group of this report is decision makers responsible for national-level preventive measures in the field of tobacco and nicotine. Additionally, the report will also inform stakeholders at regional and municipal levels about the consequences and prevention of use of nicotine products among children and young people. Other stakeholders who want access to the latest knowledge about the effects of nicotine among children and young people and preventive measures may also benefit from reading the report.

1.4 Concepts

Nicotine

Nicotine is a toxic substance that occurs naturally in tobacco. Nicotine binds to receptors in the brain, among others, and is extremely addictive (see Chapter 3). Nicotine also affects the rest of the body, among others by increasing the production of various hormones and making the heart beat stronger and faster and by increasing blood pressure.

Nicotine products

A wide range of nicotine products is available in the Danish market. In this report, we primarily include the more recent nicotine products: e-cigarettes, heated tobacco, Swedish snus, chewing tobacco, nicotine pouches, tobacco powder and tobacco pods. Nicotine is also found in waterpipe tobacco and in other tobacco products, e.g., cigarettes, cheroots, pipe tobacco and medicinal nicotine products, but these products were not included in this report.

Smoke-free nicotine products

In this report, the term smoke-free nicotine products is an umbrella term denoting the products of Swedish snus, chewing tobacco and nicotine pods. These products look similar, and children and young people often themselves use the term "snus" when referring to any of these products (4). It is often discussed if e-cigarettes and heated tobacco are smoke-free or not as these products do not actually cause combustion but produce steam. We adopt the definition of nicotine products proposed by the Danish Health Authority, according to which "smoke-free" nicotine products are products in which the nicotine is not inhaled, i.e. neither e-cigarettes nor heated tobacco.

Children and young people

When this report refers to children and young people, we refer to the age group up to 30 years of age. You may argue that the threshold could be lower (e.g., 25 years). Even so, we have maintained the 30-year limit as several of the referred studies have used this limit.

1.5 Nicotine products

Below, we provide a short description of the included nicotine products.

E-cigarettes

Many different types and brands of e-cigarettes exist, but they all consist of a small container for the e-liquid, a burner, and a battery. The burner heats the e-liquid forming an aerosol of particles and gasses, which is then inhaled (see Table I). E-cigarettes do not contain tobacco and are available with as well as without nicotine.

Heated tobacco

Heated tobacco is also called heat sticks. The product consists of an electronic hardware part into which tobacco sticks are inserted and heated, after which the nicotine-containing aerosol is inhaled (see Table I).

Swedish snus and chewing tobacco

Swedish snus and chewing tobacco are smoke-free nicotine products. The small sachets are placed inside the oral cavity after which the nicotine is absorbed through

the mucosa. Swedish snus and chewing tobacco contain tobacco and nicotine, among others. It is illegal to sell Swedish snus in Denmark, but the product may be bought legally and brought home from Sweden and Norway. Chewing tobacco, in which the tobacco is cut slightly more coarsely, may be sold legally in Denmark (see **Table I**).

Nicotine pouches

Nicotine pouches are smoke-free nicotine products that do not contain tobacco. The pouches are used in the same way as Swedish snus and chewing tobacco. It is legal to sell nicotine pouches and they may currently contain taste additives such as cola, melon, etc. (see **Table I**) (8).

Tobacco powder

Tobacco powder is pulverised tobacco, sniffed into the nasal cavity. This product is occasionally also called Swedish snus. It is sold in cans similar to Swedish snus cans, but in contrast to Swedish snus, it is a loose powder, i.e. not packed in bags.

Tobacco pods

Tobacco pods are made from tobacco leaves and contain nicotine. Tobacco pods are designed for chewing.

1.6 Delimitations

This report does not focus on literature on cigarette smoking as the harmful effects hereof are well known (9). However, to some extent, results concerning cigarette smoking will be referred to as a considerable share of our knowledge about the long-term effects of nicotine in children and young people stems from studies on the effects of cigarette smoking. Literature on waterpipes is not included as this is a limited and specialised problem, which is not considered to be very extensive among Danish children and young people.

The report may not fully cover all existing nicotine products, as the market evolves quickly and new nicotine products are constantly being introduced, or marginal products gain popularity. We have chosen not to include medicinal nicotine products approved for smoking cessation as these are rarely used by children and young people (the age limit when buying is 18 years) and because these are not stimulants, but typically used only briefly. In this report, we focus on Danish children and young people, and therefore do not include data on, e.g., the use of nicotine products in other countries. In this report, we have not included the possible different effects of nicotine salts, with respect to their meaning for nicotine uptake. Finally, in this report, we did not include the effect of additives that may promote nicotine uptake and possibly the direct harmful health effects that these or other additives may have.

1.7 Methodology

The knowledge base is established by presenting important current knowledge about how nicotine affects children and young people, and how nicotine use among children and young people may be prevented. The report gathers and presents research-based knowledge that leading Danish researchers assess represents the current professional consensus on the questions posed. The presented knowledge is based on peer-reviewed overview articles (systematically collected knowledge, critically appraised by several experts in the field), meta-analyses and main reports from renowned journals, research institutions and organisations or authorities aiming to control disease. Where relevant, the report also includes original literature, e.g., when an overview article is not available, to represent the latest knowledge or to describe the findings of a specific study. To ensure that the report is rooted in a national setting, Danish and Nordic population-based observational studies and intervention studies will be included when possible, even though they may be based on more modest empirical data than similar international studies. With respect to prevention, the available knowledge remains limited. In preparing this report, we have therefore drawn on knowledge about prevention of smoking.

Generally, when aiming to establish a direct causal relationship between two factors, the study design will typically be that of a randomised trial where randomly selected participants are exposed to the intervention or serve as controls. Naturally, it would be unethical to conduct randomised trials in which children and young people use either a nicotine product or a placebo product with no nicotine for a longer period of time. Therefore, such studies do not exist. However, causal relationships may also be established in other ways.

In cross-sectional studies of a population group, it is possible to observe what the group exposed to an exposure (in this case use of nicotine products) in forms of, e.g. symptoms, and this information may then be compared with that of those not exposed. Naturally, to do so, researchers need to take into account any differences between the participants caused by other factors than nicotine consumption. Furthermore, other sources of error may exist; e.g., selection for participation. Therefore, the studies should be interpreted with caution and serve mainly to generate hypotheses. Even so, they may be useful in identifying possible problem clusters (in this case use of nicotine products) in different population or age groups. A stronger method is the so-called cohort studies where a group that has been exposed to a given exposure (in this case use of nicotine products) is compared with a group that was not exposed. The included groups are typically compared through one or more follow-up studies. One example may be a study aiming to determine if persons who have used nicotine products during their teenage years carry an increased risk of developing anxiety later in life than do persons who have not used nicotine. Such studies also need to consider other factors that may contribute to the differences between the groups, including social, financial and educational factors, alcohol

consumption or significant life events. This is important to consider before stating that a difference observed between the two groups was, in fact, caused by the exposure. It is also important to consider if reverse causality may be in play. If, e.g., you want to determine whether persons with anxiety use more nicotine, relying only on observational studies would make it difficult to calculate the exact risk that nicotine produces anxiety. In such a case, various types of study will typically be combined. Findings from observational studies in humans are combined with findings from genetic studies, clinical human studies (e.g., brain scans), animal experiments (that may be conducted as randomised trials) and cell studies. These experimental studies may provide more precise knowledge about causal relations and a deeper understanding of specific exposure effects while unearthing possible mechanisms of action.

Even though results from rat or mice studies cannot always be transferred directly to humans, many reactions apply to all mammals. Decades of animal experiments have shown that disease conditions found in mice and rats that have been exposed to tobacco smoke are very much in line with the smoking-related damage found in humans. We have a strong presumption that good agreement also exists between animal trials focusing on exposure to nicotine and the effects of nicotine in humans.

Additionally, researchers may study dose-response relations (i.e. if a higher dose is associated with more severe symptoms) and reversibility (if symptoms recede once the exposure ceases). In conjunction, all this knowledge allows researchers to describe causal relations. If findings from animal, cell and human studies point in the same direction, this indicates that a causal relation likely exists.

In this report, we have included literature ranging across a combination of the below research methods to assess if a causal relation exists between nicotine and various sequelae.

1.7.1 Evidence assessment

The four evidence levels used in this report are: strong evidence, moderate evidence, weak evidence, and very weak evidence. Each level is defined as follows:

- Strong evidence: It is very unlikely that further research will change our confidence in the described effect.
- Moderate evidence: It is likely that further research will considerably affect our confidence in the estimated effect and possibly change the estimate.
- Weak evidence: It is very likely that further research will considerably affect our confidence in the estimated effect and research will likely also change the estimate.
- Very weak evidence: All estimates of any effect are very uncertain.

When assessing the total evidence for a causal relation between two factors as, e.g., weak or very weak, this does not necessarily mean that no causal relation exists. It may mean that only few studies have been conducted and that more research is needed before a well-founded conclusion can be made. For instance, research is too limited (weak evidence) to conclude if nicotine affects fertility negatively (causal relation). When the evidence is strong, this may be proof that a causal relation exists or that no causal relation exists between nicotine and health. To take an example, a sufficient amount of good-quality research has been conducted (strong evidence) to conclude that nicotine is harmful to the heart and blood vessels (causal relation).

1.8 The Working Group and other contributors

The Head of the Working Group is appointed by the Executive Committee of the Council on Health and Disease Prevention, whereas the members of the Working Group are appointed jointly by the Head of the Working Group and the Executive Committee of the Council on Health and Disease Prevention. The members of the Working Group are selected based on their professional competences and to ensure sufficient professional breadth in relation to the described topics.

Below, we list the Working Group members. Initially the head and then each of the members in alphabetical order by surname:

- **Jørgen Vestbo** (Head of the Working Group), professor of respiratory medicine, DMSc, University of Manchester, United Kingdom and member of the Council on Health and Disease Prevention.
- **Jesper Tobias Andreasen**, assistant professor of psychopharmacology, PhD, University of Copenhagen.
- **Lotus Sofie Bast**, senior researcher of tobacco prevention, PhD, National Institute of Public Health, University of Southern Denmark.
- **Lisbeth Lund**, PhD student, National Institute of Public Health, University of Southern Denmark.
- **Charlotta Pisinger**, professor in tobacco prevention, PhD, University of Copenhagen.

From the Secretariat of the Council on Health and Disease Prevention, the following persons have assisted the Working Group:

- **Diana Reerman**, special consultant, Secretariat of the Council on Disease and Health Prevention, project lead and professional editor.
- **Emilie Jensen**, student worker (stud.scient.san.publ.), intern and project employee.

The Working Group extends its gratitude to the following subject matter experts for professional commenting on selected parts of the report:

- **Rune Becher**, senior researcher, Folkehelseinstituttet, Norway.
- **Linnéa Hedman**, reader, Institutionen för folkhälsa och klinisk medicin, Avdelningen för Hållbar hälsa, OLIN-studierna, Umeå universitet, Sverige.
- **Troels W. Kjær**, professor, University of Copenhagen, Consultant at Department of Neurology, Zealand University Hospital.
- **Mads Uffe Pedersen**, professor, Center for Alcohol and Drug Research, Department of Psychology, Aarhus University.
- **Henrik Rindom**, psychiatrist, consultant, Stofrådgivningen.
- **Håkon Valen**, senior researcher, Folkehelseinstituttet, Norway.

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2

Prevalence of nicotine products

In the next chapter, we provide an overview of the prevalence of nicotine products among Danish children and young people. We include heated tobacco, e-cigarettes and smoke-free nicotine products, Swedish snus, chewing tobacco, nicotine pouches, tobacco pods, and tobacco powder. Next, we describe how the prevalence varies by product type, age, gender and education.

This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

2.1 Background

A wide range of nicotine products is currently available. This report comprises the following nicotine-containing products: heated tobacco, e-cigarettes, and smoke-free nicotine products. A short description of the most frequently used products is presented in Table I of the previous chapter. The data presented in this chapter are based mainly on the study §SMOKE - A study of tobacco, behaviour and regulations'.

2.2 Prevalence of nicotine products among children and young people

The new nicotine products have proven to appeal to children and young people. With respect to the total consumption of nicotine products (here including heated tobacco, e-cigarettes, Swedish snus, nicotine pouches, tobacco pods, and tobacco powder) among children and young people in Denmark not including cigarettes, figures from the autumn of 2021 show that 14.7% of the 15-29-year-olds use at least one

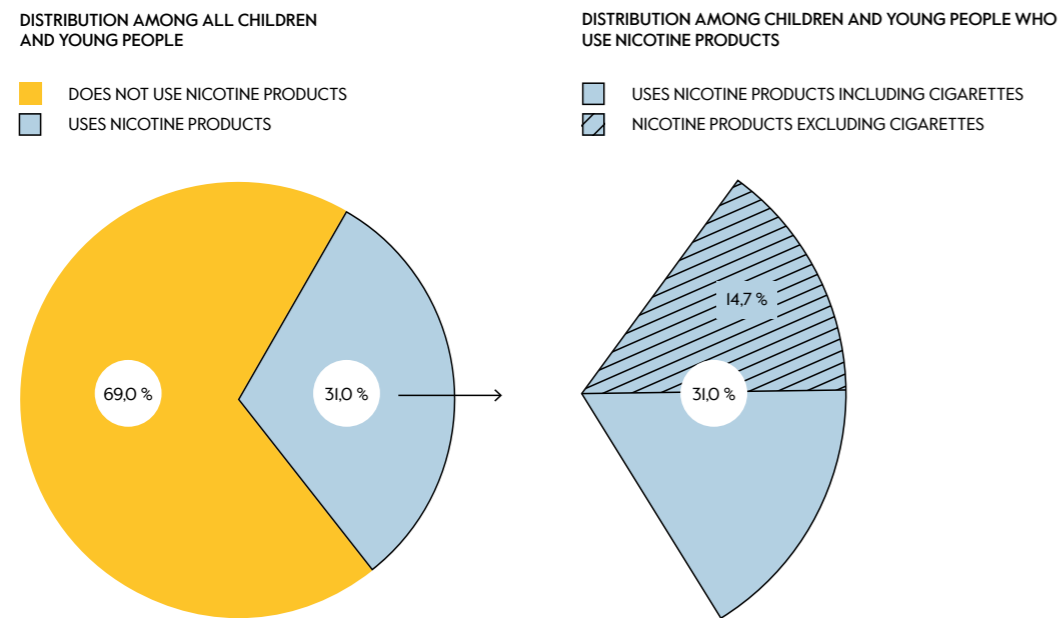
'§SMOKE - A study of tobacco, behaviour and regulations'

A Danish nationwide survey on children and young people's consumption of tobacco, behaviour and regulations. The aim is to monitor developments in tobacco and nicotine consumption of children and young people and to evaluate the Danish Government's tobacco action plan for the 2020-2025-period. At present, a total of three surveys have been completed as part of the §SMOKE study; the first in early 2020; i.e. before the first measures of the action plan came into force. Data from the survey made in the autumn of 2021 are used in the present report. The data comprise answers from more than 10,500 children and young people aged 15-29 years.

The §SMOKE study is conducted by the National Danish Institute of Public Health in collaboration with the Danish Cancer Society, the Danish Heart Association (Hjerteforeningen) and the Danish Lung Association (Lungeforeningen) and financed by TrygFonden.

Figure 1

Use of nicotine products among children and young people aged 15-29 years (2)



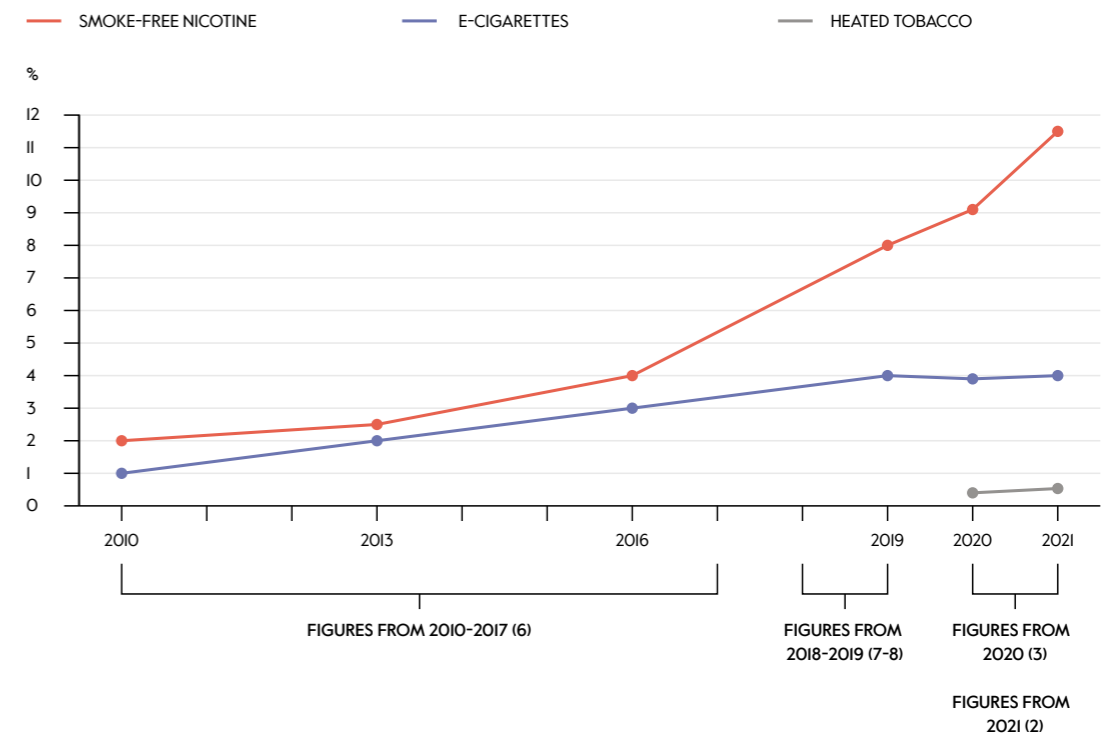
nicotine product (1), corresponding to around 165,500 children and young people in the age group. For the total consumption of tobacco and nicotine products including cigarettes, the corresponding share is 31% (2), or approximately 350,000 15-29-year-olds in absolute numbers. In other words, around half of the children and young people who consume nicotine products only use other nicotine products than cigarettes (see Figure 1).

In early 2020, 12.5% used nicotine excluding cigarettes (1), whereas 27% used at least one tobacco- and/or nicotine-containing product, including cigarettes (3). In other words, the total share of children and young people who use nicotine products, including or excluding cigarettes, has increased since 2020.

Thus, we see that the products are gaining popularity among children and young people in Denmark. A third of all children and young people use at least one nicotine product, whereof half of the consumption originates from other products than cigarettes, i.e. e-cigarettes, heated tobacco, Swedish snus, chewing tobacco, nicotine pouches, tobacco pods, or tobacco powder.

Figure 2

Development of nicotine use among children and young people aged 15-29 years



2.3 Prevalence of smoke-free nicotine products

In recent years, smoke-free nicotine products have gained popularity among Danish children and young people (2,4). The most frequently used smoke-free nicotine products are Swedish snus, chewing tobacco, and nicotine pouches. Swedish snus and chewing tobacco have been available for a long period of time even though selling Swedish snus is illegal in Denmark, whereas nicotine pouches have only lately arrived at the Danish market. When nicotine products were first launched, they were not comprised by Danish tobacco legislation and could therefore be marketed freely, including online.

A study among children and young people shows that they often employ the term “snus” about any of these products (5). Therefore, the consumption figures for each individual product should be interpreted with caution; and for the same reason, joint consumption figures for the three smoke-free nicotine products are often reported, as in this report.

Looking back in time, smoke-free nicotine products were not used very frequently by children and young people in Denmark. As presented in Figure 2, in 2010 approximately 2% of children and young people used smoke-free products. As nicotine pouches have been marketed only in recent years, the figures on smoke-free nicotine products until 2020 describe only Swedish snus and chewing tobacco. By 2016, consumption had increased to 4% (still without nicotine pouches), whereas the latest figures from the autumn of 2021 (including nicotine pouches) show that the consumption of smoke-free nicotine products has risen to 11.4% among Danish children and young people (2) (see Figure 2 and Fact Box I).

Divided into daily and occasional consumption, 6.9% of children and young people used smoke-free nicotine products daily in 2021, whereas 4.5% used these products occasionally; i.e. weekly or more seldom. Additionally, 27.4% had tried smoke-free nicotine products, and 2.9% were previous users (2). As also previously described, children and young people themselves do not distinguish between the products but generally report most use as snus. However, results from a recent study show that the majority of the consumption among children and young people in Denmark is comprised by nicotine pouches (5).

Thus, recent years have brought a considerable increase in the share among children and young people in Denmark who regularly use smoke-free nicotine products; from approximately 2% in 2010 to 11.4% in 2021 (see Figure 2). The majority of this consumption is due to the new nicotine pouches that have been launched on the Danish market in the past few years.

2.4 Prevalence of e-cigarettes

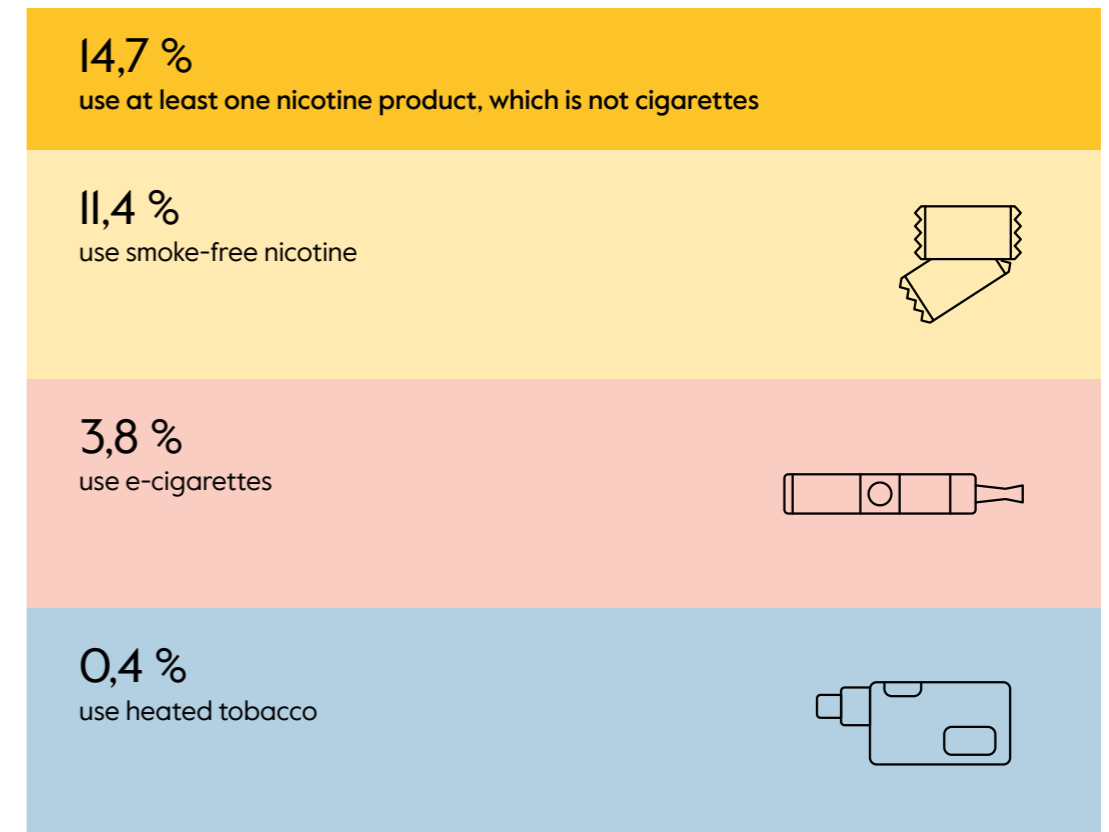
The consumption of e-cigarettes among children and young people in Denmark is relatively limited (in the autumn of 2021). E-cigarettes were introduced on the Danish market around 2010. Since then, the consumption of e-cigarettes among children and young people has remained around 2-4% (2,3,6) (see Figure 2). Figures show that 3.8% of the 15-29-year-olds used e-cigarettes daily or occasionally in the autumn of 2021 (see Fact Box I) (2). Around every fourth (27.3%) of the 15-29-year-olds say that they have tried using e-cigarettes and 7.1% that they are previous users of e-cigarettes (2).

E-cigarettes may be used with or without nicotine. The latest figures from the autumn of 2021 show that the overwhelming majority of children and young people who use e-cigarettes state that they always or occasionally use e-cigarettes with nicotine (2).

In summary, we may conclude that e-cigarettes is one of the more established nicotine products in the market and that many children and young people have tried it. Despite the fact that consumption seems to have remained stable in the past few years, an increase has occurred over time; e.g., a 4-fold increase since 2013.

Fact Box I

Consumption of nicotine products among children and young people aged 15-29 years (2)



2.5 Prevalence of heated tobacco products

Heated tobacco was introduced in Denmark only a few years ago. The first measurements of consumption among children and young people are therefore from early 2020 (3). At that point in time, 3.2% stated having tried heated tobacco, whereas 0.3% used heated tobacco daily or occasionally. The latest figures, from the autumn of 2021, show that 3.7% state having tried heated tobacco, whereas 0.4% state that they use heated tobacco either every day or occasionally (see Fact Box I). A total of 0.5% have previously used heated tobacco (2).

Currently, heated tobacco is not a frequently used product among children and young people (see Figure 2), but we cannot exclude that heated tobacco will gain popularity with time. We have seen a trend towards smoke-free nicotine products being more widely used by Danish children and young people lately, and we therefore need to monitor closely this consumption.

2.6 Gender, age and education

The use of nicotine products is not equally distributed among all children and young people and varies by product type, gender, age and educational level. To take an example, the use of nicotine products is characterised by considerable gender differences. Among boys and young men aged 15-29 years, 15.7% use smoke-free nicotine products daily or occasionally. When divided by gender, 10.4% of boys and young men use these products daily, and 5.3% of boys and young men use the products occasionally. In contrast, among girls and young women of the same ages, the total share is 7.3% (3.5% daily and 3.8% occasionally) (2). Around two thirds of boys and young men use smoke-free nicotine products daily, whereas the distribution among girls and young women between daily and occasional users is around 50/50. Furthermore, age differences apply to the use of smoke-free nicotine products. For both genders, the most frequent daily use is recorded among the 18-year-olds (see **Figure 3.A** and **Figure 3.B**). Here, it is 18.4% of 18-year-old young men and 8.6% of 18-year-old women who use smoke-free nicotine products daily. Among boys and young men, the 17-26-year-olds, in particular, use smoke-free nicotine, whereas the consumption among girls and young women peaks among 17-21-year-olds (5).

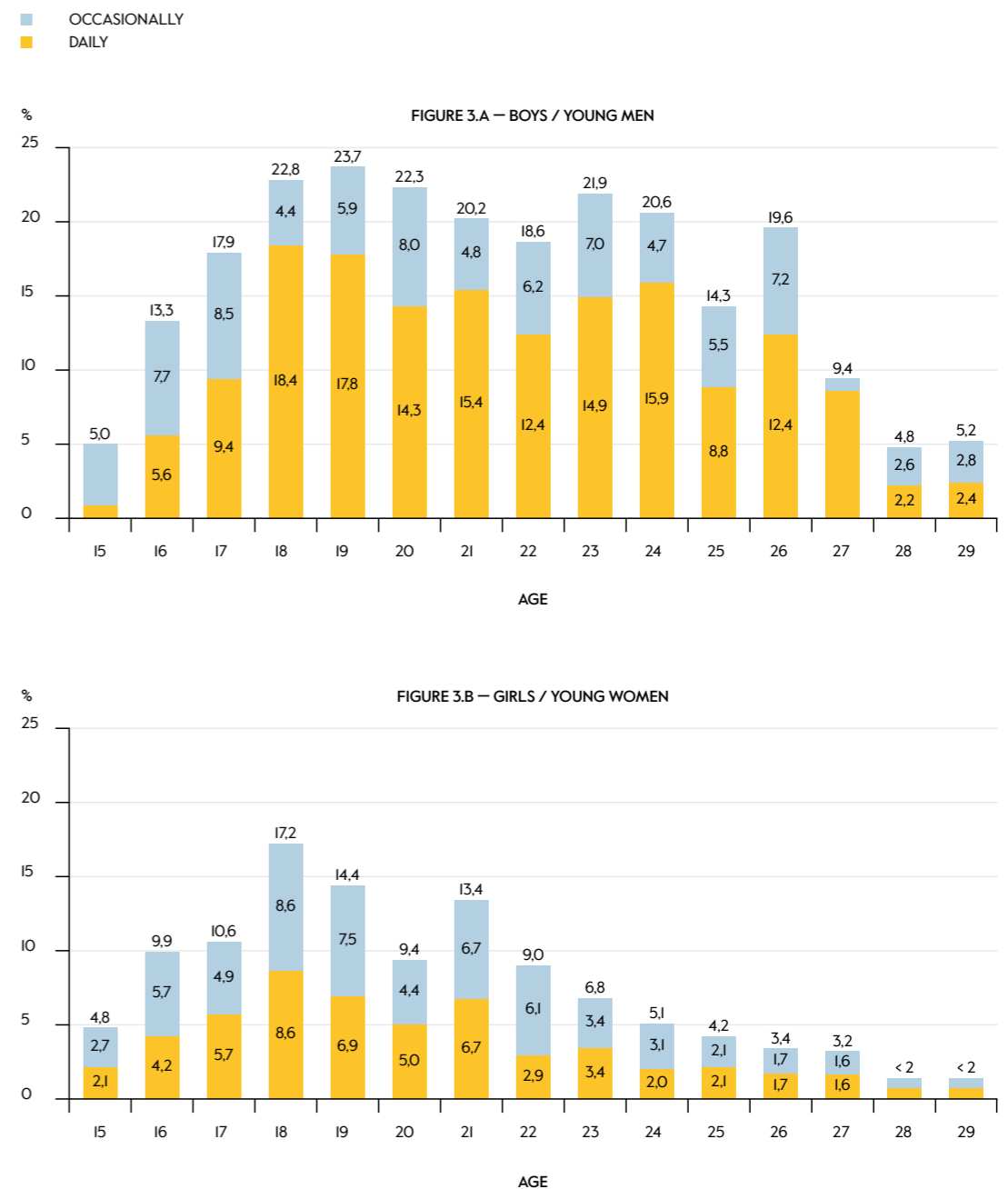
Similar marked gender or age differences do not apply to the use of e-cigarettes, even though there are indications that boys and young men have a slightly higher consumption of e-cigarettes than girls and young women. To take an example, more boys and young men have tried using e-cigarettes or are previous users than are girls and young women (2). The consumption of heated tobacco is too limited to explore differences related to gender or age.

Furthermore, variation exists in the consumption of nicotine products by educational level (3) even though the differences are not consistent across product types. For example, 11.0% of the students in vocational training or initial vocational training stated that they use e-cigarettes daily or occasionally, whereas this applies to nearly 2% of young people who attend medium-length or long higher education programmes (3). The smoke-free nicotine products are popular among children and young people who attend an initial or standard vocational training programme (16.1%), upper secondary education (17.0%), a short-term higher training programme (17.7%) and among those who are working and have either no or only a short education (12.4%) (see **Figure 4**) (5). The consumption of heated tobacco is too limited to study any differences by level of education.

We see a clear trend that smoke-free nicotine products appeal more to children and young people around the age of 18 years, many of whom are attending vocational training or short-term higher education. It should be noted that these figures are a snapshot of the consumption in the autumn of 2021. The coming years will show if the consumption in these groups is maintained while they grow older, and if the next birth cohorts will adopt the same consumption pattern.

Figures 3.A and 3.B

Consumption of smoke-free nicotine products among children and young people aged 15-29 years (5)



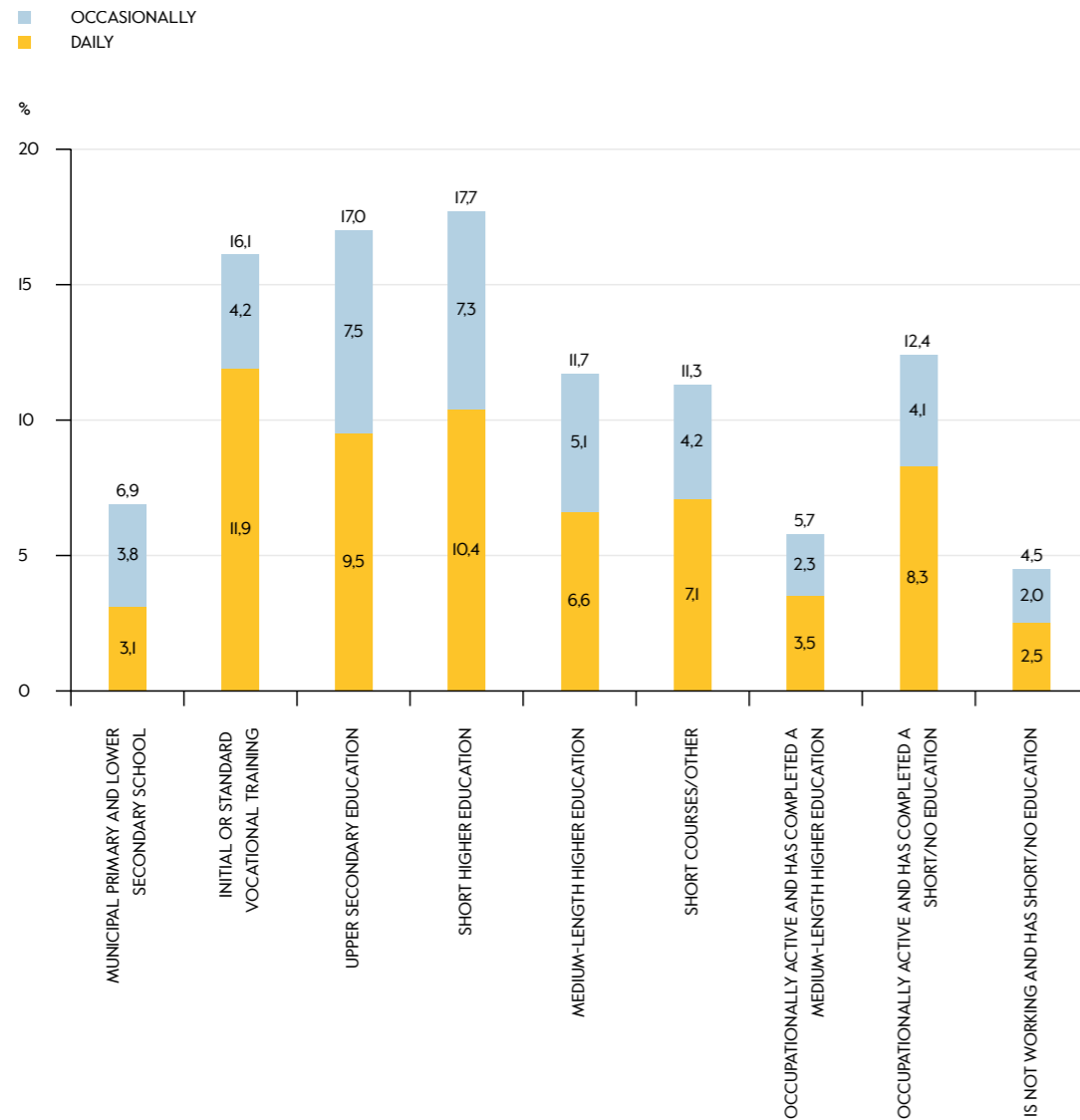
* In some groups, the number of respondents is too limited to provide %.

** In some groups, the number of respondents is relatively low why column heights should be interpreted with caution.

The columns were included to illustrate variations between the various ages.

Figure 4

Consumption of smoke-free nicotine products by ongoing education or occupational status for children and young people aged 15-29 years of age (5)



2.7 Use of multiple nicotine products

Differences also exist in terms of how the nicotine products are used. Many children and young people use a single product, whereas some children and young people use two or more nicotine products - which we have termed double or multiple use (2). The share of children and young people in Denmark who use two or more products, including cigarettes, is 4.1%, corresponding to around 46,000 children and young people aged 15-29 years of age (2). In this group, most (89.2%) use two products, whereas a limited share use three or more products (10.8%). Typically, cigarettes and smoke-free nicotine products like Swedish snus, chewing tobacco and nicotine pouches are used in combination with each other (60.7% of those who use more than one product). The combination of cigarettes and e-cigarettes is also rather frequent (28.8%) (2).

Most children and young people use only a single tobacco or nicotine product, however some do use more than one product. Here, the most frequently observed combination is cigarettes and a smoke-free nicotine product. It is therefore decisive that measures aiming to reduce children and young people's consumption of tobacco

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3

Health consequences of nicotine use among children and young people

This chapter initially describes what nicotine is and how it affects the brain. Next, we discuss studies that have investigated how nicotine affects the development of the brain during youth and explain why children and young people are particularly vulnerable to the effects of nicotine. Furthermore, we refer to studies to describe other health effects that may occur when nicotine products are used among children and young people.

This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

3.1 Background

In the following sections 3.2-3.5, we describe scientific literature addressing the health consequences of nicotine use in the young brain. The literature described is based on a wide range of different research methods, including knowledge from animal studies. Even though results from animal studies cannot always be transferred directly to humans, many biological processes are the same in all mammals. Decades of animal experiments have shown that disease conditions found in mice and rats that have been exposed to nicotine or tobacco smoke are very much in line with the smoking-related conditions found in humans. If findings from animal, cell, and human studies point in the same direction, a causal relation may be underpinned. Figure 5 summarises the health risks of nicotine consumption for children and young people. The health effects are described in the chapter below.

Nicotine is a toxin formed in the tobacco plant as a defence against insects. Previously, nicotine was used as an insecticide and as a pesticide in agriculture. Nicotine is absorbed in the body via the lungs, mucous membranes and skin, and is quickly transported via the blood flow to the brain and the rest of the body. Nicotine is strongly addictive and heavily affects the brain and the nervous system. Nicotine also affects the rest of the body, increasing heart rate and blood pressure. Nicotine is a potent substance, i.e. effects can be measured even at low doses. High doses of nicotine may cause poisoning with symptoms such as malaise, nausea, vomiting, vertigo, palpitations and abdominal pain, etc. Furthermore, nicotine activates many biological mechanisms that increase the risk of disease (1).

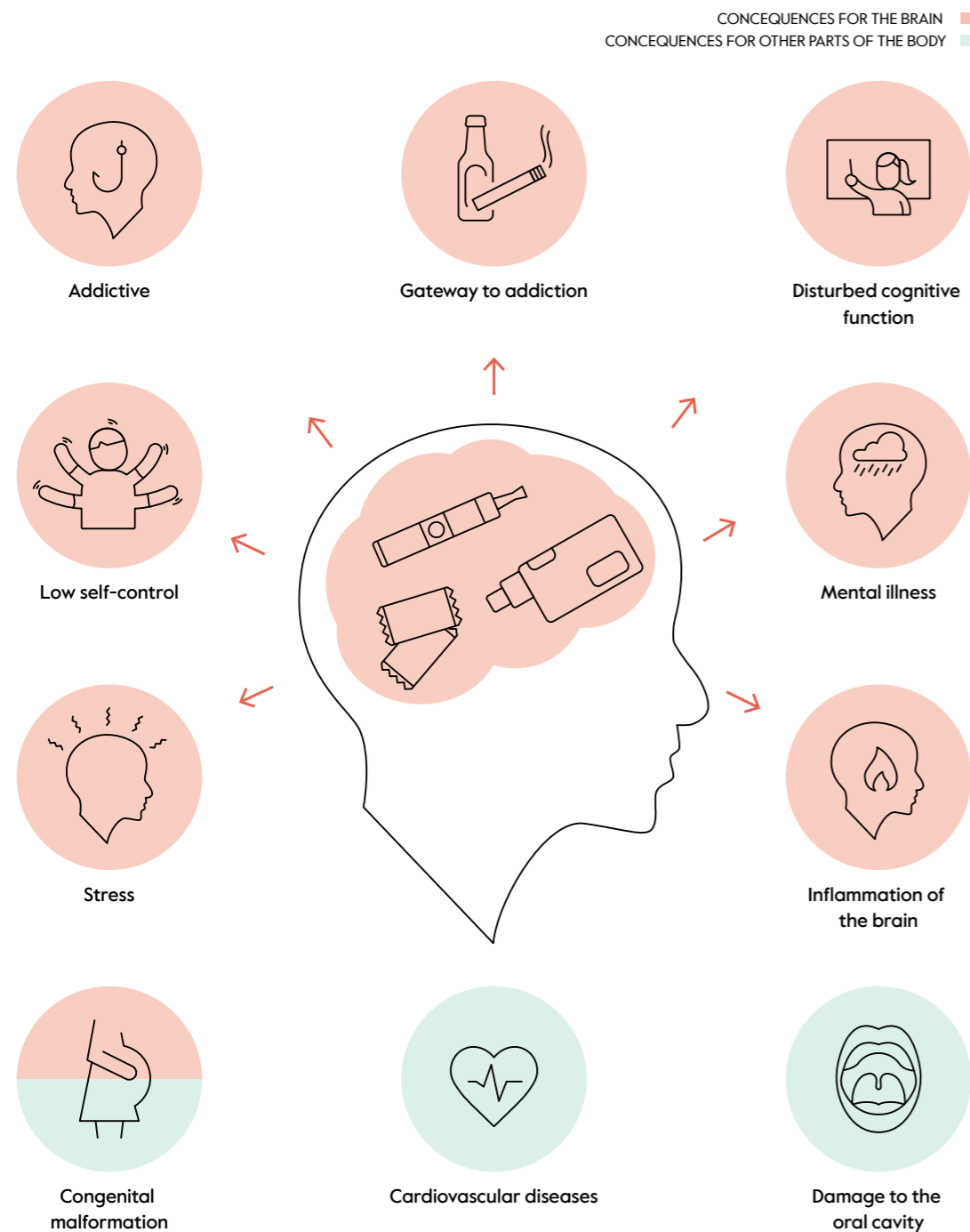
3.2 Dependence and addiction

In the brain, nicotine promotes release of dopamine, which triggers a feeling of well-being and mild euphoria. In nicotine addiction, the brain expects to receive nicotine regularly. If you try to stop taking nicotine, withdrawal symptoms will appear within a few hours. Nicotine is a so-called psychostimulant as activation of nicotine receptors stimulates the dopamine and noradrenaline systems of the brain. Nicotine has many effects, several of which are immediate and experienced as appealing.

The immediate effects of nicotine are, among others, improved concentration and attention (6,7), reduced jitteriness and anxiety (8-11), reduced appetite (12) and a stimulating and rewarding effect (13). Nicotine is experienced as energising, and it elevates mood and the capacity for enjoyment, which may produce a feeling that life is now more intense (13,14). The positive effects, however, taper off following frequent use, and nicotine withdrawal is associated with the opposite effects including difficulty concentrating, increased tension, poor mood, and a low energy level (15,16).

Figure 5

Health risks associated with nicotine use among children and young people



Nervous system communication

The nervous system primarily communicates via nerve connections, called synapses. A nerve cell in the nervous system releases a chemical substance (also known as a neurotransmitter) and this substance is detected by its binding to specific receptors on other nerve cells. To some extent, nicotine mimics the body's own signal substance acetylcholine by activating a group of receptors that are normally affected by acetylcholine. The receptors have therefore been coined nicotinic acetylcholine receptors (also known as nicotine receptors). When acetylcholine is released in the synapses, it binds to nicotine receptors and activates them. Acetylcholine is present only for a very short period of time (less than a second) as it is quickly metabolised by enzymes. As is the case for all other signal substances in the brain, acetylcholine is released specifically into the brain areas that are relevant at any point in time. In this sense, where and when acetylcholine is released to activate the nicotine receptors is tightly controlled. Nicotine works differently. Once nicotine reaches the brain, it binds to the nicotine receptors instead of acetylcholine and thereby disturb acetylcholine signals. In contrast to the short duration and precise timing of acetylcholine, nicotine has a longer-lasting effect on the receptors. Frequent use of nicotine also causes the number of nicotine receptors to increase (2). In this way, nicotine has effects that last long after the presence of nicotine in the body (the half-life of nicotine is about two hours). This disturbs the signalling pattern of acetylcholine, thereby affecting the development of the brain. As the young brain is still developing, it is particularly vulnerable to such disturbances (3-5). This means, among others, that the ability to handle stress is disturbed and that the brain fails to develop a sufficient ability to control impulses and emotions (see Section 3.4.6).

3.2.1 The context

In all forms of drug addiction, the consumption of the drug is associated with specific situations or emotional conditions, i.e. use becomes context-dependent. In addition to the dopamine released by the drug, so-called conditioned learning occurs (conditioning) after which the context in and of itself increases dopamine release and triggers the craving to use the drug. This phenomenon is particularly prominent in the case of nicotine use (13,22,23). If you, e.g., usually use nicotine in social contexts or when you are stressed, then these contexts will release dopamine, simply because of the expectation that nicotine will soon be taken, and that will trigger a craving for nicotine. The context-triggered craving is a key element in addiction. By increasing dopamine, among others, nicotine can make other forms of enjoyment seem more satisfying, including everyday activities (22,24). In case of prolonged

Dependence and addiction

Our understanding of drug dependence and addiction in general and nicotine in particular has two components: (physical) dependence and (psychological) addiction.

Dependence, the physical component, is due to the fact that the brain and the rest of the body gradually become accustomed to having the drug available and therefore do not work optimally without the drug. Abstinence causes transitory withdrawal symptoms, which vary depending on the drug and the daily dose ingested previously. For nicotine, the withdrawal symptoms last from a few days to weeks. Nicotine withdrawal syndrome comprises the following symptoms: sadness, fatigue, irritability, jitteriness, anxiety, increased stress sensitivity, sleep disturbances and difficulty concentrating. Furthermore, the withdrawal symptoms are associated with a craving to ingest nicotine (15,16). Withdrawal symptoms comprise bodily and psychological symptoms alike. The bodily symptoms are described as dependence, an umbrella term comprising any type of physiological dependence.

Addiction, the psychological component, addiction, comprises the psychological changes that may ensue following prolonged drug use. Addiction comprises, among others, the habit-forming effect of drugs and manifest as behavioural changes and inflexible thoughts about the drug. The feeling of not functioning properly without the drug is essential in this context and means that thoughts and behaviours circle around the drug, particularly if the person is in a context where the drug is habitually ingested. The thought of not being able to consume the drug may provoke anxiety and lead to physical and psychological distress, even in the absence of withdrawal symptoms. The psychological craving for the drug is characterised by irritability, restlessness and jitteriness. Over time, withdrawal symptoms and the craving for nicotine may lead to ritualised and compulsive behaviour (17-19). Stress strengthens the craving and the ritualised behaviour. Conversely, both the craving and the feeling of stress are reduced briefly when the drug is ingested. This strengthens the experience that the drug is helpful and that the drug is necessary to reduce stress.

The faster a drug stimulates the dopamine system, the more addictive it is (20). The fastest effects of nicotine are achieved if it is inhaled or adsorbed through mucous membranes. In these cases, it reaches the brain within seconds to minutes. In contrast, uptake is slower and less addictive if nicotine is used in the form of a patch as is the case for medicinal nicotine products (20,21)

nicotine use (months), satisfaction experienced from natural rewards and everyday activities is increasingly contingent upon the presence of nicotine, i.e. these situations do not produce quite the same satisfaction and enjoyment without nicotine. Subconsciously, this leads to an excessive focus on nicotine as a necessary enhancer to experience satisfaction (14).

To conclude, nicotine is appealing because it increases dopamine release, which has an energising effect and elevates mood. Nicotine is one of the most addictive drugs we know of because it is quickly absorbed through the mucous membranes and thereby quickly activates the dopamine system. Additionally, consumption becomes context conditioned, i.e. you develop a craving for the drug in situations in which you normally ingest nicotine. The Working Group is therefore concerned that the use of nicotine products among children and young people places them at a risk of becoming addicted to nicotine already before reaching adulthood.

3.3 The young brain

Nearly everyone who is addicted to tobacco started using nicotine during adolescence – an age period where the brain is still developing and is therefore very susceptible to addictive effects of drugs (25,26). Youth is characterised by substantial hormonal changes and developmental changes of the brain, and this period is particularly important for the development of psycho-social and cognitive skills (27). It is therefore relevant to describe how the young brain is particularly vulnerable to nicotine, including how it is affected more in the long term than the brain of an adult.

3.3.1 How the brain evolves in youth

The brain undergoes considerable changes during adolescence. The most fundamental changes occur in the first part of adolescence, corresponding to the 12-17-year age range, but the brain keeps maturing until 25-30 years of age (28,29). Among others, the amount of gray matter is reduced, which is the area where the bodies of the nerve cells and their synapses with other nerve cells are located. The gray matter shrinks because the number of synapses (nerve connections) is gradually reduced during adolescence to reach around half of the number that were present at 12 years of age. By contrast, the connections that survive are strengthened. Concurrently, there is an expansion of the white matter, i.e. the nerve pathways that connect different areas of the brain. The electrical impulses of the brain travel via these pathways. The expansion of white substance results from a process called myelination. Myelination of the nerve pathways is similar to electrical isolation of an electrical cable and allows electrical signals to travel faster between the areas of the brain, while requiring less energy (30,31).

Maturation of the brain therefore gradually makes the networks of the brain more fixed into specific communication pathways that are more effective but also less flexible. As the brain is tuned to effectively follow specific thought and behavioural patterns, but it also becomes less flexible than in younger years. Adolescence can therefore be considered a period that has a strong bearing on how the brain will be in adulthood. It causes concern that so many children and young people use nicotine, since this disturbs the development of their brains.

3.3.2 Development of self-control

In the deeper parts of the brain, the centres for reward, motivation, and emotional reactions (the limbic system, also coined the reptilian brain) are found. These include the amygdala and the parts of the dopamine system that are important for reward and motivation. The limbic areas mainly mature in the early and mid-teenage years, and these years are therefore characterised by a lower degree of emotional self-control and lack of emotional stability. Impulsive or sensation-seeking behaviours are also more pronounced (32). The activity of both the limbic system and the frontal lobe is regulated by a variety of signalling molecules in the brain. The balance between the signal substances differ in youth and adulthood.

Development of the frontal lobe

The frontal lobe is, among others, responsible for assessing own behaviour and for rational decision-making, control of emotions and impulsive or sensation-seeking behaviour. In this manner, the frontal lobe may be important in relation to self-control. The frontal lobe matures later than the rest of the brain, and it keeps maturing until the age of 25-30 years (28). In the early teenage years, the frontal lobe has limited control over the deeper-set systems, but its control strengthens as the connections between the frontal lobe and the deeper-set areas of the brain are strengthened. In this way, the frontal lobe gradually develops an improved control over impulses and emotions (33,34), which explains why children and young people are more impulsive and have less control over their emotions than adults have. Studies in humans and animals alike have shown that nicotine inhibits the maturation of the frontal lobe, causing it not to develop as effective a control over the deeper systems of the brain, and causing a limited development of control of attention, planning and self-evaluation (3,35,36). This damage is more pronounced if nicotine use starts in early youth (37).

The development of the dopamine and serotonin system

The dopamine system is a central element of the reward system and changes markedly during the teenage years. The change is dynamic, i.e. it depends on the exposures that the brain receives in that period of life. This makes the reward system particularly sensitive to the effects of nicotine (26,38). The dopamine system is important for motivation and drive, whereas the serotonin system contributes, among others, to self-control, adaptiveness, regulation of mood and emotions, tolerance to

stress, and also, to some extent, controls the dopamine system. In youth, the dopamine system is relatively more active than the serotonin system, which reflects that youth compared with adulthood is a period characterised by considerable initiative, less self-control and increased sensitivity to stress.

Development of the GABA system

The primary activating signal substance of the brain, glutamate, is more active in youth, whereas the most important inhibitory system, the GABA system, has not yet been fully developed. Glutamate and GABA may - in simple terms - be considered the "accelerator" and the "brake" of the brain, and the balance between the two is decisive for most of the brain's functions. The inhibitory role of GABA is strengthened in the course of youth, which is reflected in the fact that youth is a period during which you gradually learn to control your impulses and emotions. Dopamine plays an important role in maturing the interaction between GABA and glutamate (39,40). Therefore, affection of the dopamine system by drugs in youth will not only affect maturation of the dopamine system itself but will also affect the maturation of the critical interaction between glutamate and GABA, thereby affecting a wide range of the functions of the brain, including the ability to control impulses and emotions. Therefore, the young brain is particularly vulnerable to exposure to nicotine (3,26,41).

Development of the reward system

In youth, the reward system is more sensitive to enjoyment and reward (including those produced by drugs), making you more outgoing, willing to take risks and more impulsive, until the frontal lobe establishes some degree of control of this driving force. The reward system of the brain is therefore more sensitive in the teenage years as the various networks of the brain are not as well-established as they are in adult life. Thus, young teenagers are more open to new impressions and to follow the actions of friends, etc. When you add to that the fact that the frontal lobe only has limited impulse control at this stage, it makes sense that teenagers' behaviour is more controlled by satisfaction and they are more risk tolerant than adults. This contributes to making the teenage years a period during which the risk of experimenting with nicotine and other drugs is high (42, 43).

Thus, maturation of the brain means that interconnections between nerve cells gradually become more fixed in specific functional networks that are more effective, but also less flexible than is the case in the young brain. In youth, the reward system matures, and while this development occurs, the young person is more outgoing, risk tolerant and impulsive and will therefore be more prone to seeking nicotine or other drugs. Therefore, it is essential what the brain is presented to during this period. Nicotine exposure in youth will affect maturation of the ability to regulate emotions and impulsivity (self-control), posing a risk that the brain will lock into a more seeking condition. If the young brain is presented to nicotine, the very synapses and pathways that are specialised in drug-related behaviours will be strengthened, thereby making the brain more nicotine seeking.

3.3.3 The young brain

In the past 20 years, animal studies have shown that adults and young people respond very differently to nicotine, and that the young brain in various ways is more sensitive to the effects of nicotine (44). Following occasional or frequent nicotine use, young animals have a considerably higher risk of nicotine addiction than adults have (25, 45). Young rats react to the rewarding effect of nicotine at ten-fold lower nicotine doses than those needed to trigger a reaction in adult rats, and young rats have a higher tolerance of the unpleasant effects of nicotine, even at high doses (46). Young rats also more rapidly develop addictions and ingest larger amounts of nicotine than adult rats do, if given the possibility to self-administer nicotine (47, 48). Prolonged nicotine treatment of adult rats causes permanent sensitisation of the dopamine system and makes the rats more sensitive to the addictive effects of nicotine later in life, even after prolonged discontinuation of nicotine use (49). In young rats, a single high dose of nicotine may be sufficient to trigger a long-term preference for the environment in which the nicotine was given, whereas repeated nicotine doses are required to trigger this effect in adult rats (50).

Young rats experience less intense nicotine withdrawal symptoms than adult rats and therefore experience relatively more positive effects of nicotine (51-53). Studies in mice show that very young mice, corresponding to the early teenage period in humans, drink more of a nicotine solution than mice whose age corresponds to the late teenage period, and also more than adult mice. When the nicotine concentration was reduced, the mice in early adolescence drank more to compensate. This behaviour was not seen in mice in late adolescence or in adult mice (54). This indicates that the rewarding effect is more potent in very young animals.

The above-mentioned animal studies show moderate evidence that young brains are more susceptible to the rewarding effects of nicotine and may therefore have a higher propensity to develop addiction than adults. Similar human studies have not yet been conducted. However, based on animal studies, it is likely that young brains are affected more by the rewarding effects of nicotine, and that children and young people develop addiction more rapidly.

3.3.4 Nicotine affects the development of the brain

The development of the brain is highly dependent on what it is exposed to in the teenage period. Nerve connections and neural pathways that are frequently activated are preserved and strengthened, whereas neural connections and pathways that are less active are weakened. Thus, the young brain is shaped by the exposures it receives. Therefore, it is absolutely decisive what the young brain is exposed to and experiences, as these factors contribute to determining how your brain will work as an adult. If, e.g., you spend much time ice skating or playing music when you are young, your brain will develop and strengthen the neural pathways that are

important to those activities, which will then seem more straight-forward later in life. In line herewith, a brain that has ingested nicotine will develop and strengthen the neural pathways that are important for this particular behaviour and these experiences. Thus, an attentiveness is developed towards nicotine and an increased tendency to seeking nicotine as an adult (26, 41).

This means that youth is not simply a period during which the risk of addiction to nicotine is increased; it is also a particularly sensitive period with respect to permanent harmful nicotine effects. Exposure to nicotine during the teenage period causes a variety of permanent changes in the deep areas of the brain and in the control that the frontal lobe exerts over the corresponding functions (55). This means that the maturation of the dopamine system is inhibited and to some extent remains at an immature stage where it is more sensitive towards the rewarding effects of drugs (26).

3.4 Permanent harmful effects of nicotine use in youth

Studies of the effect of nicotine products on the human brain primarily comprise studies of the effect of tobacco smoking, whereas studies focusing on e-cigarettes and smoke-free nicotine products are still lacking or limited. Brain scans in persons who smoke and persons who do not smoke have shown that several areas of the brain are smaller in persons who smoke than in persons who do not, and the differences correlate with the daily smoking dose and with the number of years of smoking (56). Differences in grey substance have been found in several areas of the brain, and differences in the functional connections between different regions of the brain have also been observed (3, 25, 34, 57). Corresponding structural and functional changes were observed in rodents, and the changes were associated with changed behaviour in adulthood. Among others, nicotine treatment of young animals causes permanent changes in the reward system and, due to close connection between the reward system and the brain's network for emotional regulation, this is also reflected in anxiety and depressive-like behaviour when the animals are subsequently tested in adulthood (26). Such differences may, in part, have been caused by other factors than tobacco smoking, e.g., genetic or environmental factors that both predisposing towards becoming a smoker and which are also related to the development and function of the brain. The authors of a systematic literature review found solid evidence that the observed effects are indeed caused by smoking itself, as tobacco smoke contains several thousand chemical compounds, several of which trigger toxic processes in the brain (58). The role of nicotine in these effects cannot be established based on these studies, but studies in rodents have explored the specific harmful effect of nicotine on the brain.

3.4.1 Nicotine as a gateway to addiction

The earlier tobacco smoking begins, the higher the risk of becoming addicted to tobacco as an adult (45); a risk that is up to ten-fold higher than if a person starts smoking in adulthood (25). Smoking and nicotine use alike are also associated with an increased risk of subsequent abuse and addiction to other drugs (59, 60). To take an example, smoking is associated with an eight-fold increased risk of addiction to opioids (e.g., morphine, heroin, fentanyl), and the association was more pronounced following early initiation of smoking (61). A recent study, which employed a genetic method to establish the likelihood of causal relations, found that the risk of opioid addiction increases by approx. 17% for each cigarette ingested daily (61).

Use of nicotine-containing products like e-cigarettes and smoke-free tobacco is associated with nicotine addiction (16,62). A study conducted among e-cigarette users found that e-cigarettes were considerably more addictive than cigarette smoking (63). Some studies following young non-smoking e-cigarette users over time concur that teenagers who use e-cigarettes have a 3-4-fold increased risk of subsequently starting to smoke tobacco (64-67). Some studies also show that e-cigarette use increases the risk of using cannabis (68) and that e-cigarette use is associated with more frequent abuse of other drugs (69, 70). Without further evidence, such associations are not sufficient to conclude that the increased risk is due to tobacco smoking or nicotine. The association may also be explained by other non-biological factors, e.g., socioeconomic conditions and living conditions, etc. However, studies have shown that young people who experimented with nicotine-free e-cigarettes did not have an increased risk of starting to smoke normal cigarettes, and that young people using e-cigarettes with a low nicotine content had a lower risk of being smokers six months later than young people using e-cigarettes with a high nicotine content (62, 71, 72). This supports the role of nicotine in the tobacco-free products as a gateway to cigarette smoking.

The causal relation has also been explored in studies in rats and mice. A study comparing rats that had access to self-administering nicotine as young “teenage” rats with rats that did not have access to nicotine until adulthood showed that early experience with nicotine led to a higher nicotine consumption if the rats were subsequently given access to self-administering nicotine (73). It is well-known from a wide range of animal and human studies that prolonged nicotine use increases the number of nicotine receptors, and that this increase is associated with nicotine addiction (13, 74). Normally, the number of nicotine receptors will gradually down-regulate again once nicotine consumption stops, but this effect seems to depend on age. An rat study showed that chronic addition of nicotine produced a more substantial receptor increase in young than in adult rats, and the increase persisted for a longer time period in young rats (75). Nicotine use in youth seems to increase the risk of nicotine addiction later in life, and also enhances the effects of other drugs and generally increases the tendency to become addicted to drugs (76-80).

Studies in mice and rats have shown that nicotine affects the development of the young brain, among others by changing which nerve connections persist and which are eliminated (3, 34)). To take an example, the maturation of the dopamine system is impeded and therefore the higher susceptibility to drugs that characterises youth is prolonged, stretching far into adulthood (81-83).

Use of nicotine is frequently associated with use of alcohol, and this link is particularly clear among young people. A study showed that persons who started smoking before 13 years of age have double the risk of developing an alcohol addiction as persons who started smoking at 17 years of age or later (84). An study in rats that explored the interaction between nicotine and alcohol, found that alcohol consumption of young rats increased 2-3 fold if they were concurrently given nicotine. In contrast, nicotine given to adult rats did not affect their alcohol consumption. Furthermore, nicotine treatment in young rats caused them to develop a prolonged preference for alcohol, and these rats ingested more alcohol as adults than rats that had not been given nicotine when they were young (85). This trend is confirmed by another study in rats showing that the increased alcohol intake in adulthood was associated with permanent changes in the reward system because they had received nicotine when they were young (86). This seems to indicate that nicotine pushes the young brain more than the adult brain towards an increased alcohol intake. Among young people in Denmark, an association was found between binge-drinking (i.e. consuming large amounts of alcohol on a single occasion) and using smoke-free nicotine. For example, 26% of the 15-17-year-olds who frequently engage in binge drinking also use Swedish snus or other smoke-free nicotine products. For comparison, the corresponding proportion is 7.5% of 15-17-year-olds who never or rarely engage in binge drinking (87). The same trends have been confirmed by other Nordic studies (88, 89).

A comparison of results from epidemiological studies in humans with animal studies in mice and rats shows moderate to strong evidence that nicotine increases the likelihood of becoming addicted, not only to cigarettes but to drugs in general, and that nicotine therefore has a so-called gateway effect. The Working Group does not find that the increasing use of nicotine among children and young people should simply be accepted, when the use of nicotine in youth may lead to subsequent abuse of other drugs.

3.4.2 Effects on cognitive function

Several studies have explored the effects of smoking on cognitive function. One study found reduced memory among children who smoked, regardless of when they had last smoked, and also after accounting for differences in intelligence, reading skills and their parents' educational level. This indicates that smoking may lead to learning disabilities. The observed difference was largest for persons who had started smoking at a young age, and it was more pronounced when the affected

persons were undergoing nicotine withdrawal symptoms (90). A young age of smoking initiation is also associated with issues related to attention and reduced impulse control when smokers are later tested as adults (91). Another study showed similar differences between young smokers and young non-smokers and also found that the difference was less pronounced for young people who had previously been smokers, which may indicate that some harmful cognitive effects are reversible (92). A longitudinal study of monozygotic twins showed that twins who had smoked tobacco in their teenage years showed more cognitive problems than their non-smoking twin when they were compared adulthood (93).

The above-mentioned studies underpin the association between smoking and cognitive function. The studies indicate that early smoking onset is associated with harmful cognitive effects. However, based on these studies, it is not possible to draw firm conclusions about the isolated role nicotine plays in the harmful effects. Therefore, these findings need to be considered in conjunction with animal studies exploring this topic. For example, studies in mice and rats have shown that nicotine use in animals causes permanent dysfunction of the neural pathways that regulate attention and impulse control (94, 95). Behaviourally, this is reflected by permanent disturbances in the animals' attention (81, 96), motivation (96) and ability to learn (97-99), and in increased impulsivity (35, 81). The behavioural effects are also reflected in permanent cellular, molecular, and neurochemical changes in the frontal lobe, including a prolonged increase in the number of nicotine receptors in the brain (5, 75, 81, 96, 100). In the above-mentioned animal studies, no permanent effects were found when nicotine was only given to the animals after they had reached adulthood. This supports the notion that the young brain is much more sensitive to permanent harmful effects from nicotine than the adult brain is.

Difficulty concentrating and other cognitive difficulties are a well-known symptom of nicotine withdrawal (101). However, withdrawal symptoms were shown to be less pronounced in early youth among rats than in rats that were slightly older or adults (51-53). Withdrawal symptoms are probably also dependent on age in humans. Early onset of nicotine use will often mean that addiction was established before reaching late youth and adulthood, when withdrawal symptoms are associated with more pronounced cognitive problems. In this manner, the motivation for using nicotine is changed. Thus, the young brain will be motivated to use nicotine because of the rewarding effects of the drug, whereas later in youth and during adulthood, motivation to keep using nicotine increases because nicotine withdrawal symptoms cause cognitive difficulties such as difficulty concentrating (52,102-104).

Overall, the Working Group concludes that there is moderate evidence that nicotine has a harmful effect on cognitive function. In case of early nicotine debut, studies show that nicotine use impairs attention, motivation and impulse control. These harmful effects seem not to occur if the nicotine use is initiated in adulthood. Based on the above-mentioned studies, it is of concern that nicotine use already starts in early youth.

3.4.3 Mental health effects

The association between nicotine and mental illness is very well studied and is primarily based on studies on tobacco smoking. The existing studies indicate that the association may, in part, be explained by the fact that mental illnesses lead to nicotine use because nicotine may briefly be experienced as symptom limiting (the self-medication hypothesis), and in part because nicotine may, in the longer term, trigger and aggravate mental illness (the toxicity hypothesis). The latter seems to be the more powerful of the explanations, particularly because nicotine use starts while the brain is developing in youth.

In persons who are addicted to nicotine, use of nicotine may briefly reduce anxiety, stress and depressive symptoms (10, 14, 105) and increase the ability to concentrate (106). Among persons with symptoms of anxiety or depression, the experience that nicotine increases positive, and reduces negative, moods is typically stronger than in other people (10, 14, 105). Furthermore, symptoms of anxiety or depression are also associated with a more rapid development of nicotine addiction (107). Persons with depression often reduced ability to experience ability to pleasure (anhedonia), which contributes to a more powerful nicotine craving (108), and in young people anhedonia is a risk factor for smoking initiation (109). Furthermore, people with social anxiety who smoke may use smoking as a so-called false safety behaviour in social situations (8).

Anxiety and depression are associated with a higher risk of developing nicotine addiction (10, 105). Most studies have not adjusted sufficiently for so-called confounders that may lead to incorrect conclusions, e.g., social and demographic factors, addiction to other drugs, the educational level of parents, etc. This raises some doubt as to whether the association is causal, i.e. if the association is seen because symptoms of anxiety or depression are a truly contributory cause of smoking. In a ten-year prospective study, which adjusted for the occurrence of other mental illnesses and social and demographic factors, albeit not for addiction to other drugs, anxiety disorders were associated with a nearly doubled risk of smoking initiation and an approx. 30% increased risk of nicotine addiction. Depression was associated with an approx. 40% increased risk of starting to smoke and of becoming addicted to nicotine (110). This indicates that anxiety-related and depressive conditions are a direct contributory cause of smoking. Even after adjusting for other factors, smoking in the teenage years is tightly associated with subsequent development of depression and anxiety. For example, a nearly four-fold higher risk was found of subsequently developing depression (111), whereas the risk of subsequently developing generalised anxiety disorder was about five-fold increased, and the risk of panic disorder was increased by around 15-fold when occurrences were studied at follow-up 5-7 years after smoking initiation (112). The studies did not find evidence to support that these conditions independently increased the risk of smoking initiation.

Animal studies support that nicotine may have a direct role in contributing to the development of conditions characterised by anxiety and depression. In young rats that were given nicotine for a period of their adolescence, the maturation of the frontal lobe and its pathways to the amygdala and the dopamine system were affected (3, 26). The amygdala becomes more sensitive and therefore reacts more to stress, while changes in the dopamine system cause a generally increased sensitivity to addictive drugs (26, 82). Thereby, nicotine causes prolonged changes in pathways of the brain that are important for stress handling (113). Nicotine dosing of young rats also causes changes in molecular markers, corresponding to those seen in anxiety, depression and drug addiction (82, 83). Brain scans from rats that have been given nicotine at a young age show permanent structural and functional changes in the brain corresponding to those found in humans who smoked as teenagers (3). Adult rats that had been given nicotine in adolescence present with an increased anxiety and depressive-like behaviour (82, 83). These behavioural and molecular changes were not observed when nicotine was given chronically to adult rats.

The association between nicotine, anxiety conditions and depression may therefore be considered a vicious circle. Persons with depression or anxiety may experience that nicotine provides brief symptom alleviation. In the longer term, however, nicotine may contribute to triggering or aggravating symptoms of anxiety or depression. Particularly during nicotine withdrawal, symptoms of anxiety and depression may be prominent and contribute to nicotine cravings (15).

Overall, the Working Group concludes that there is moderate indicating that nicotine has harmful effects on mental health and may contribute to symptoms of anxiety and depression. The Working Group finds that this is a cause for concern, particularly because many children and young people use nicotine.

3.4.4 Addiction and emotional instability

The amygdala is overactive during anxiety and depression and generates emotions like fear, stress, self-reproach, pessimism and irritability. The amygdala is also part of the reward system and in close contact with the dopamine system. Therefore, the amygdala may effectively connect negative emotions with the dopamine effect (“the rush”) experienced when using drugs. This is a form of conditional learning that is particularly strong in the case of nicotine and which means that future negative emotions will trigger a craving to smoke (10,14,105).

As addiction evolves, the pleasure from everyday activities will increasingly be contingent on the presence of nicotine, i.e. will be experienced as less satisfactory without nicotine. Thus, addiction contributes to aggravating anhedonia (14), and the young brain is particularly vulnerable to such changes (3, 26). Conversely, anhedonia, anxiety and stress will increase the craving for nicotine (10, 14, 105).

It is a characteristic of nicotine and other drugs that drug-seeking behaviour is motivated by stress and anhedonia. Nicotine withdrawal symptoms contribute to this by virtue of their similarity to symptoms of anxiety and depression. Withdrawal symptoms are alleviated by nicotine, and this strengthens the experience and belief that nicotine alleviates stress, anxiety, and anhedonia. However, fluctuating between withdrawal symptoms and nicotine use will, in the longer term, render the amygdala hypersensitive and contribute to emotional instability and reduced sensitivity to natural rewards (10, 11).

This means that a vicious circle is established by which addiction leads to emotional instability as everyday pleasurable experiences become conditioned by nicotine use. Concurrently, emotional instability will increase nicotine cravings. The growing number of children and young people who use nicotine products is worrying if the everyday activities that normally make them feel joy become contingent on the presence of nicotine.

3.4.5 Inflammation in the brain

Higher inflammation marker levels have been observed in the brain in persons who smoke than in persons who do not smoke (114). This may be explained by the fact that nicotine and other compounds contained in smoke damage the integrity of the blood-brain barrier and trigger inflammation-like conditions in the brain (115). In the young brain, these processes will affect the maturation of pathways that are important to the regulation of emotions, cognitive function, and the experience of pleasure and reward (3, 25).

The brain contains a type of cells called microglia that are important to the development of the brain and for maintenance of its pathways (116). Most addictive drugs activate microglia in a way that makes them initiate an inflammatory state changing the activity in the brain, particularly in the reward system and in the amygdala (34, 80). Microglia activation increases the amount of so-called free radicals, which stress the nerve cells and accelerate brain aging (117). Microglia activation and increased levels of free radicals are shared traits between depression and nicotine dependence, and free radicals are associated with emotional instability (58, 115). Nicotine’s contribution to these changes is also underpinned by animal studies showing that chronic nicotine dosing produces changes in the brain that match those found in people who smoke (118). Nicotine treatment of rats also activates microglia, and the degree and duration are considerably larger in young rats than in adult rats (119). By affecting the reward system, microglia furthermore contribute to triggering the anxiety symptoms associated with nicotine withdrawal (120). Finally, microglia activation increases the rewarding effect of cocaine, as seen in rats that have been treated with nicotine as young rats (119).

Overall, the Working Group concludes that there is moderate evidence that nicotine consumption at a young age can lead to the development of an inflammatory state of the brain, and it seems that this inflammation is involved in the disturbances of the maturation of the brain that cause an increased risk of depression, anxiety disorders, and addiction. The inflammation disturbs the development of normal cognitive function, the ability to experience pleasure, and regulation of emotions.

3.4.6 Nicotine and stress

The interplay between nicotine, stress and impulsivity leaves children and young people particularly vulnerable. On the one hand, stress is a risk factor for nicotine use, and the rewarding effect of nicotine is intensified by stress. On the other hand, prolonged use of nicotine reduces the ability to cope with stressful experiences. A vicious circle is therefore established, in which nicotine and stress are mutually reinforcing factors. When considering this effect in combination with the combined effect of nicotine and stress for the development of the young brain, the resulting synergistic effect is especially alarming. In addition, impulsivity and stress are independent risk factors for experimenting with drugs (I21, I22), and nicotine increases impulsivity in the young brain (35, 81).

Studies have shown that young people experience more stress factors on a daily basis, and that these stress factors are experienced as being more stressful in young people than they are in children or adults (I23). Young people who experience an increased stress load have a higher risk of smoking initiation. (I24). Several studies show that stress is one of the most frequent causes of nicotine use, since short-term use of nicotine can alleviate stress (I0, I4, I05, I25). This may, however, seem paradoxical, as one of the biological effects of nicotine is to increase the levels of the body's stress hormones, cortisol and adrenalin, thereby mimicking the effect of acute stress (I26). A study in rats has shown that the rewarding and addictive effect of nicotine are strengthened if the rats are stressed (I27). This demonstrates that nicotine increases the sensibility to stress, and, conversely, that stress renders nicotine more appealing.

When the brain is repeatedly affected by stress, an adaptation will normally occur, meaning that the effect of the stress on stress hormone levels is gradually reduced. However, rat studies have shown that prolonged nicotine exposure disturbs this adaptation (I28). In rat studies, repeated exposure to nicotine was shown to augment the acute stress reaction (I29) and increase the level of stress hormone during acute stress (47).

Stress also reduces the ability to control impulsive actions. It was shown that young people find it more difficult to control their impulsive actions if they experience a daily stress load (I23).

Overall, stress and nicotine affect each other negatively. During stress, the risk of initiating a nicotine use is increased, and simultaneously nicotine use increases the body's susceptibility to stress. This means that when children and young people feel stressed, this may increase their impulsivity and therefore their risk of starting to use nicotine. Nicotine reduces stress tolerance. Therefore, nicotine use in children and young people who are not initially stressed may increase their risk of subsequently developing an increased stress sensitivity. Early consumption of nicotine may therefore trigger a vicious circle in which stress and nicotine cravings are mutually reinforcing factors.

This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

The below section focuses on the remaining health-related consequences of nicotine use. Here, we present effects on the heart and blood circulation, cancer risk, effects on pregnancy and on the foetus, effects on the fertility of young men and women, damage to the oral cavity and effects on the immune system.

In the following sections 3.5-3.12, we describe the scientific literature exploring health consequences of nicotine use. We frequently cite the UA Surgeon General's Report as this report is the latest joint knowledge source on the effects of nicotine.

Surgeon General

The Surgeon General is appointed by the US government (for a four-year period) and is given responsibility for public health.

The Surgeon General and his or her civil servants are organised in the Office of the Surgeon General under the auspices of the US Ministry of Health. Their overall objective is to protect and promote prevention and safety in the US population. The Surgeon General disseminates the best available scientific knowledge to the population in reports, etc. The Surgeon General also supervises the U.S. Public Health Services' (USPHS) advisory corps, an elite corps counting more than 6,000 public healthcare professionals. The objective of the USPHS is to protect and promote health in the USA.

3.5 Effects on the heart and blood flow

Nicotine increases the heart rate and blood pressure, the latter through contraction of the blood vessels (1). Nicotine has acute effects that may aggravate the outcome of, e.g., a blood clot in the heart or brain, and you do not necessarily need to have been exposed to nicotine long term for this to be case (1). A very extensive

body of literature from experimental medicine and animal models shows that nicotine has a persisting harmful effect on a wide range of cell types, the composition of lipids in the blood, the blood vessel wall in vessels of various sizes, the composition of connective tissue, etc., all important for the development arterial stiffness and other cardiovascular conditions (130, 131). Part of this information has been confirmed for e-cigarettes (132-134). Current research on animal models indicates that nicotine contributes to stiffening of arteries (135-138). From a cardiovascular viewpoint, there is thus no doubt that new ways of using nicotine have harmful health effects. This is best known from e-cigarettes; however, in that context the effect of nicotine may be difficult to separate from the effect of, e.g., solvents and taste additives (133, 139). A range of human studies have shown that high blood pressure is associated with smoking and use of nicotine-containing e-cigarettes, but not with e-cigarettes without nicotine (140), which strongly indicates that nicotine is causing the increased blood pressure. In animal models and small human studies, stiffening of the arteries was found following use of e-cigarettes with nicotine (130). Arterial stiffness is a risk factor for subsequent cardiovascular disease, and it therefore seems reasonable to assume that use of e-cigarettes with nicotine may lead to cardiovascular disease (134, 140).

Moderate evidence has also been found that Swedish snus increases the risk of high blood pressure among men (no studies have been conducted in women) and increases the risk of death if you suffer from a blood clot in the heart or brain (141). This increased risk is attributed to nicotine. Presumably, other nicotine products will be associated with the same risk. Even though the effect in young people is uncertain, the Working Group estimates that the effect of nicotine in the blood vessel wall and connective tissue in general will have harmful late consequences, particularly when combined with very early use of nicotine. It is therefore worrying to observe that a growing number of children and young people use nicotine products.

In summary, the Working Group assesses that strong evidence exists that nicotine is harmful to the heart and blood vessels, that moderate evidence exists of an increased risk of death due to existing heart disease/blood clot and that an association between early exposure to nicotine and subsequent cardiovascular disease is likely. The level of the increased risk of developing cardiovascular disease cannot be specified.

3.6 Cancer risk and nicotine use

The Surgeon General has assessed the quality of evidence to be insufficient to determine if nicotine is a direct cause of or contributes to the development of cancer (in adults) (142). Large human longitudinal studies are lacking as are studies of the role of nicotine in the risk of cancer in children and young people. However, some experimental cell and animal studies indicate that nicotine has an effect on cancer

development and spread (I43,I44). As an example, recent studies have shown that nicotine may promote new formation of vessels and metastasising of cancer (I37, I45-I50).

Overall, the Working Group assesses that currently no evidence supports a cancerogenic effect of the exposure of children and young people to nicotine, but the field is so poorly studied that a risk cannot be excluded.

3.7 Effects on pregnancy and the foetus

The quality of the evidence provided by the Surgeon General is assessed as sufficient to conclude that nicotine plays a role in how smoking affects pregnancy and the foetus (I42).

The harmful effect of nicotine during pregnancy comprises, among others, premature birth and still birth (I51). As an example, it was shown that use of e-cigarettes during pregnancy increases the risk that the child will be affected by low growth in relation to the age of the foetus and low birth weight(I52). In line herewith, an epidemiological study of more than 16,000 women found no signs of a reduced risk of too low a birth weight in women who shifted from cigarettes to e-cigarettes with nicotine during pregnancy (I53), which indicates that a shift from cigarettes to e-cigarettes with nicotine during pregnancy has no effect and does not change the risk of a too low birth weight. A Swedish study has shown an association between use of Swedish snus and low birth weight (I54). A systematic review of nicotine substitution as part of smoking cessation measures found no effect on the above markers for affection of the foetus, which may be due to the more limited nicotine dose used (I55). However, the review was based on only five studies of sufficient quality, and the Working Group finds that it is difficult to conclude clearly on the joint body of current knowledge.

It is well-documented that smoking causes serious harm to the foetus (I42). Animal studies indicate that nicotine probably plays an important role in long-term damage such as reduced fertility, type 2 diabetes, obesity, high blood pressure and neurological defects as well as decreased airway function among children who are exposed to nicotine during pregnancy (I56, I57). It is well documented that children to smoker mothers have a reduced lung function, an increased risk of high blood pressure in pulmonary circulation and more frequently experience early infections (I42). It is not possible to estimate how large a role nicotine has as an independent factor in these effects, but as the lungs and airways have a considerable number of nicotine receptors, it is very likely that exposure to nicotine during pregnancy may cause damage in the lungs and airways of the neonate (I58). Smoking during pregnancy also increases the risk of asthma in the child (I42). However, a Swedish register-based cohort study including nearly 800,000 children failed to detect this

association among users of Swedish snus during pregnancy (I59). Studies also show that exposure of the foetus to nicotine is associated with a permanent negative impact on the development of the child's cardiovascular system, that no periods during pregnancy are safer than others with respect to use of nicotine, and that no nicotine products may be used safely (I60).

In summary, the Working Group assesses that moderate to strong evidence exists that nicotine during pregnancy leads to reduced foetal growth, premature birth and still birth, and that exposing the foetus to nicotine in the womb causes disease, not least in terms of future lung and cardiovascular disease. Based on the above, the Working Group finds that the current warnings against smoking during pregnancy must be extended to also comprise all other nicotine products.

3.8 Effects on male fertility

Some evidence supports that smoking is associated with a reduced sperm count and motility in men (I61), and that women who are treated with assisted reproductive techniques more rarely become pregnant if their partner smokes cigarettes than if their partner does not smoke cigarettes (I62, I63). Animal studies have also indicated that nicotine may explain the reduced fertility. Rats or mice given pure nicotine deposit the nicotine in the seminal fluid, which reduces the sperm count and sperm motility (I64). Animals that are exposed to nicotine develop smaller testicles and have lower testosterone levels than animals that are not exposed to nicotine (I65, I66).

Overall, the Working Group assesses that scientific evidence is very weak in relation to drawing any conclusions, but an association between nicotine and the fertility of men cannot be excluded.

3.9 Effects on female fertility

Strong evidence shows that smoking reduces the fertility of women (I42). The role of nicotine remains unclear, but several studies indicate a harmful effect. Thus, animal studies have shown that nicotine impedes ovulation (I67). Nicotine was also found to cause cell death in the ovaries of human foetuses (I68), and animal studies found that nicotine causes cell death in the ovaries, and reduces the weight of the uterus (I69, I70). Some animal studies have found that females who are exposed to nicotine in the womb take longer to become pregnant as adults, whereas other studies have shown that nicotine does not inhibit the ability of adult females to become pregnant (I71, I72).

Overall, the Working Group assesses that scientific evidence is very weak in relation to drawing any conclusions, but an association between nicotine and the fertility of women cannot be excluded.

3.10 Effects on the oral cavity

A few animal studies have detected an increased occurrence of caries after exposure to nicotine (173, 174). The Association of Danish Dentists informs that Swedish snus may cause the gums to retract thereby exposing the neck of the tooth, and that it irritates the mucosa of the mouth, which forms a kind of hardened skin in the form of translucent-to-white, wrinkly patches where the Swedish snus is placed (175). If this is due to nicotine or is a mechanical effect cannot be determined. Additionally, Swedish snus may cause discolouration of the teeth and cause saliva to turn brown (176). We also hear from dentists and dental technicians that nicotine causes mouth dryness and sensible oral mucous membranes, including reddening and irritation. A recently conducted literature review comprising nine cohort studies which included more than 400,000 men concluded that no association has presently been found between use of Swedish snus in Swedish men and cancer of the oral cavity (177). A literature review of the effect of e-cigarettes has documented a harmful effect on the teeth, gums, and the oral microbiome (178). A recent systematic literature review studied inflammatory reactions that might explain the role of nicotine in some of these harmful effects (179). Two other literature reviews, based on cell studies, concluded that it seems unlikely that nicotine causes cancer in the oral cavity at the concentrations found in, e.g., e-cigarettes (180, 181).

In conclusion, the Working Group assesses that the available evidence is very weak in relation to drawing conclusions, and that it seems likely that no increased risk exists of cancer of the oral cavity. However, based on information provided by Danish dentists, we assume that nicotine has a harmful effect on the gums, the oral mucosa, and teeth.

3.11 Effects on the immune system

As described in the section on cardiovascular diseases, nicotine seems to play an important role in the development of stiffened arteries, to some extent due to chronic inflammation (131). However, it remains unknown which other effects nicotine has on the immune system in adults and children and young people (142). On the one hand, cell studies have shown that nicotine exposure causes an increase in pro-inflammatory cells and cell death among white blood cells, whereby auto-antigen compounds are excreted, which indicates that harmful effects may ensue when the immune system is exposed to nicotine. However, other studies have found that

nicotine has a protective, anti-inflammatory effect (182, 183), which runs counter to results of the above-mentioned studies. An experimental animal model demonstrated that nicotine either aggravated or had no beneficial effect on inflammatory bowel disease (184).

In summary, the Working Group assesses that the harmful effect of nicotine on hardening of the arteries is likely, to some degree, to be due to chronic inflammation caused by nicotine. However, the evidence is too weak to draw any conclusions on the overall effect of nicotine on the immune system.

3.12 Effects on physical performance

In 2012, the World Anti-Doping Agency (WADA) started monitoring nicotine. It could not be confirmed that nicotine enhances sports performance, and therefore nicotine was not banned among elite athletes (185-187). A literature review concluded that no evidence exists that nicotine has a performance-enhancing effect but also stated that too few studies had been conducted to conclude firmly on this topic (188). The review explored the effects of nicotine given to young persons who were engaged in intensive sports and who had not previously used nicotine or tobacco products (188). Nicotine was given to the participants at a moderate or high dose as, e.g., nicotine patches or bubble gum. A limited number of studies have detected some positive effects, e.g., increased concentration and ability to hit the ball among athletes who had not previously used nicotine products when they were taking nicotine (189-191). The positive effect of nicotine experienced by people who have not previously used nicotine recedes when the person starts using nicotine regularly, after which withdrawal symptoms will dominate, including concentration difficulties (192).

To summarise, studies that have explored the acute effect of nicotine in athletes who have not previously used nicotine have found no or only a weak performance-enhancing effect. No studies have aimed to determine if nicotine has any harmful long-term effects on the functional capacity of the body, and no scientific performance studies exist on persons who use nicotine regularly. Based on the above, the Working Group assesses that no evidence exists that nicotine use has a performance-enhancing effect among persons who use nicotine regularly.

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4

Prevention of nicotine use among children and young people

In this chapter, we summarise current literature on the prevention of nicotine product use among children and young people.

This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

4.1 Background

We have documented that the use of nicotine products among children and young people follows an increasing trend and that the products have several harmful health consequences on their brains and their developing somatic health. Youth, perceived as a phase of life, is an important factor for initiating nicotine use. As described in Chapter 3, the reward system in children's and young people's brains is susceptible. Therefore, children and young people are more open to new impressions and, e.g., to what their friends or trendsetters on social media do. Furthermore, the frontal lobe, which, among others, handles impulse control, is not yet fully developed in children and young people. The immature brain does not, to the same degree as the adult brain, understand the long-term consequences of any choices made. This means that the behaviour of children and young people is more controlled by a desire for satisfaction and that they are considerably more willing to take risks than adults are. Youth is, therefore, a period during which openness to experimenting with nicotine products is high (1,2).

Preventive measures are needed to protect children and young people against nicotine products. The current literature indicates that the most effective prevention of risk behaviour is achieved through multi-level measures. Moderate to strong evidence demonstrates the effectiveness of multi-component measures that comprise a combination of structural national-level measures limiting the availability by establishing, e.g., drug-free environments, price increases, enforced age limits, and bans in combination with school-based measures focusing on relations, social competencies, and parent involvement through teaching, introduction of a shared drug policy and a drug-free community.

Many nicotine products are still relatively new on the Danish market. Consequently, knowledge of preventing the more recently introduced types of nicotine products is limited (3,4). It is most likely important that the nicotine products may be used more discretely, that the new products are marketed differently from cigarettes, that the products have a wide range of flavours, and that our knowledge of the extent of the harmful effects of the new nicotine products is still imperfect (5,6). However, The Working Group assesses that strong parallels can be drawn between traditional tobacco prevention and the prevention of nicotine products and that the prevention of nicotine products is not fundamentally different from tobacco prevention. In the sections below, we review the literature on how nicotine use can be prevented among children and young people by drawing parallels to our knowledge about prevention in the tobacco field (7).

4.2 Structural measures

Overall, measures aiming to affect society primarily focus on making a framework and structures available to make healthy choices easier. This approach is termed structural prevention. Structural, national-level measures against tobacco comprise, among others, taxes, bans against selling to children and young people, smoke-free environments, warnings on cigarette packages, advertising bans, and neutral packaging (7). Below, we summarise current knowledge on the effect of structural measures.

4.2.1 Taxes

Price and availability are essential in determining the use of most goods, including tobacco and other substances (7). A high tobacco price is one of the most successful measures for preventing smoking among children and young people. Hence, strong evidence has been established that a higher price limits use, and the effect of this measure is more pronounced among children and young people with limited financial possibilities (8). However, a higher cigarette price may lead to increased use of other nicotine products if the price does not reflect the price of cigarettes (9). If this applies specifically to children and young people has yet to be documented.

In April 2020, the taxes levied on tobacco products were increased, but not the taxes levied on tobacco-free nicotine products. If taxes are placed on the nicotine content rather than on the individual product, it will be possible to affect all nicotine products equally, which will very likely limit the use of nicotine products among children and young people.

Generally, measures that regulate the availability, price, and marketing of nicotine products will very likely affect nicotine product use among children and young people.

4.2.2 Advertising

Today, an enhanced marketing ban is in place. This means promoting tobacco and nicotine products in Denmark is illegal. Furthermore, a total tobacco display ban has been implemented, meaning nicotine products are visible only in connection with their purchase. In the field of tobacco prevention, advertising bans, including bans on indirect advertising, were found to be effective (7). One study found that cartoon figures were depicted in cigarette ads in more than 20% of cases (10), which may indicate that children and young people are typically the target group for these ads. Furthermore, a randomized controlled study showed that young people with no smoking history who were exposed to e-cigarette ads were more likely to start using e-cigarettes and have more positive attitudes towards e-cigarettes than those who

had not been exposed to such ads (11). A similar pattern was found for smoke-free nicotine products (8). Policies limiting exposure to nicotine products are therefore important in preventing nicotine use. However, data from the Danish Safety Technology Authority show that every third nicotine product sales outlet fails to enforce current legislation on the sales of tobacco and nicotine products (12). Furthermore, children and young people are exposed to nicotine products on social media (13-15), and the state now supervises social media in addition to its physical monitoring efforts (16), which contributes to enforcing existing legislation, particularly the advertising ban, the presentation ban, and the age limit. Additionally, it was agreed that the Minister of Health and the Minister of Industry, Business, and Financial Affairs would establish a monitoring task force to strengthen the authorities' control of the tobacco and nicotine area and to ensure that any new trends and challenges are handled rapidly across the control authorities (17).

4.2.3 Availability - outlets

In addition to limiting advertising through the act on the ban of tobacco advertising and the tobacco display ban, it is necessary to further restrict the availability of nicotine products for children and young people. A study conducted in the UK showed that most e-cigarette ads were placed close to shops targeting children and alongside products like sweets, etc. (18). Another study found that young people living in an area with many tobacco outlets are more prone to start using a tobacco or nicotine product (19). By regulating which sales outlets may handle nicotine products, e.g., by introducing a licensing system for sales of nicotine products, it is possible to reduce the availability of nicotine products, which is very likely to reduce the use among children and young people.

4.2.4 Availability - age limit

Selling nicotine products to children below 18 years of age is illegal. Shops selling nicotine products are required to check valid photo identification if the retailer doubts whether the client is 18 years old. The Danish Safety Technology Authority supervises that shops enforce the age limit, and any violations of the regulations will be reported to the police. More intense enforcement of the age limit would prevent nicotine use among children and young people. To ensure that the age limit is enforced, the state can regulate which shops can sell nicotine products, as was introduced in Norway (20).

In 2019, the US decided to increase the age limit for tobacco sales to 21 years of age. The higher age limits introduced in the state of Oregon have reduced smoking initiation among the youngest and among young people who are close to turning 21 years old. Furthermore, fewer 18-20-year-olds stated that it was easy to buy tobacco products (21). Subsequently, a decline was seen in California in the proportion

of young people who smoked (21). In Hawaii, a considerable reduction was observed in the sale of cigarettes, particularly menthol cigarettes, which are the most commonly used cigarettes among children and young people (22). Raising the age limit will very likely prevent nicotine use among children and young people.

4.2.5 Availability - smoke- and nicotine-free environments

Legislation on smoke-free environments, including workplaces, restaurants, bars, and other public spaces, only applies to cigarettes and other more traditional tobacco products. Introducing legislation on smoke-free environments strengthens an anti-tobacco norm but can also prompt the use of nicotine products that serve as substitutes for cigarettes in situations in which smoking is not allowed (8). By expanding the legislation to include all nicotine products, more smoke-free and nicotine-free spaces will be achieved, which will likely affect nicotine use among children and young people.

According to Danish legislation on smoke-free school hours, all students attending primary and secondary education shall remain both smoke- and nicotine-free at school and beyond the school premises during school hours. Whereas it is relatively easy to see and smell cigarettes, the use and visibility of the various nicotine products vary considerably. When it comes to, e.g., smoke-free nicotine pouches, nicotine use may be harder to detect, and therefore, it may be more challenging to enforce the nicotine ban. All institutions must ensure that all students and employees are aware that smoke-free school hours comprise all nicotine products and that the ban is also in place beyond the school premises during school hours. At educational institutions, teachers and other adults are role models to their students. Strong evidence exists that visible smoking increases the students' risk of starting to smoke (23). By extending the legislation on smoke- and nicotine-free school hours to include employees and not only students, the visible use of nicotine at schools will be reduced, which will likely reduce the use of nicotine among children and young people.

4.2.6 Taste and packaging

In 2020, adding menthol flavour to cigarettes became illegal, and cigarettes can no longer taste of anything other than tobacco. A ban on menthol flavour in cigarettes was found to effectively reduce smoking (Levy et al. 2011). Recently, it also became illegal to add any other flavour than tobacco and menthol to e-cigarette liquid. Taste additives in nicotine products, e.g., in nicotine pouches, can increase use among children and young people (24), and menthol can increase addiction (25, 26). Cigarettes, chewing tobacco, water pipe tobacco, and e-cigarettes can be sold only in neutral standardised packages. This would make the packages less attractive to children and young people (27, 28). For e-cigarettes, studies in children and young people have shown that the most frequent reasons for experimenting with or using

e-cigarettes are the taste of fruit, sweets, or menthol, curiosity, influence from and use among friends, and that they consider the products to be cool and relatively harmless (5, 29-33). This indicates that the regulation of flavour additives in nicotine products, in line with cigarettes, may have a preventive effect on the use of nicotine products in children and young people. If all nicotine products, rather than only individual products, must follow legislation on neutral, standardised packaging, this will likely also reduce the motivation among children and young people to use nicotine products.

4.3 Information campaigns

Information campaigns can be implemented by the state, municipalities, schools, interest organisations, leisure time organisations, etc. Campaigns can target not only children and young people but also parents, teachers, pedagogues, trainers, etc. Contrary to smoking, from which most people are aware of the harmful effects, neither children and young people nor their parents know much about the harmful effects of nicotine. Various myths and misunderstandings are in circulation about nicotine products in the population (34). This underlines that knowledge is lacking about how nicotine affects the brain and the rest of the human body. Campaigns focusing on information have modest effects on smoking prevention because the initial knowledge level is high, whereas it is clear that many Danes are unaware of the risks of nicotine use. Therefore, information may form part of a multi-tiered measure. However, information measures alone are insufficient because they do not have an effect when implemented as individual measures but need to supplement structural measures relating to nicotine products (7).

4.3.1 School-based information campaigns

One example of a preventive school-based campaign against e-cigarettes is the 'Catch-my-breath' campaign implemented in the US. The intervention focuses on increasing knowledge about the health-damaging effects of using e-cigarettes through activities provided by similarly aged peers (peer-led teaching approach) (35). The approach was proven effective in reducing the use of e-cigarettes and in strengthening knowledge of the risks associated with e-cigarette use (36, 37). Many nicotine products are so new in the Danish market that we do not yet have any studies exploring the effect of information campaigns on children and young people. However, based on knowledge about e-cigarette campaigns, schools may contribute to increasing knowledge about the health consequences of nicotine use of children and young people by implementing information campaigns targeting pupils and teachers.

4.3.2 Family-based information campaigns

Many parents are unaware that their children or young adult offspring use tobacco or nicotine products apart from cigarettes. This is a result of the latest arriving nicotine products being novel, articulated by young people using slang, not accompanied by a smell of tobacco, and not visible during use (38). Furthermore, a study showed that it may be difficult for parents to keep up with the introduction of new products and keep updated on which products they should be aware of (39). To allow parents to help their children, information for parents is needed about the health consequences of nicotine products and the fact that nicotine products are illegal to sell to children below 18. Finally, parents must know that an illegal market exists.

4.4 Measures at school and during leisure time

Schools have traditionally been the context in which tobacco-preventive measures were implemented. Various measures have been implemented at schools, including information-based teaching, competence-building teaching, class competitions, agreements not to start smoking, smoking ban enforcement, and peer-to-peer measures. The evidence for and effect of the measures varies. However, these preventive measures work best overall if multi-component measures are used concurrently using several of the abovementioned measures (7). Until now, the prevention of newer nicotine products has formed part of the existing measures to prevent tobacco use (3). The scientific literature in the field comprises interventions targeting the prevention of e-cigarette use rather than the more recent types of nicotine products.

4.4.1 Culture, norms and role models

One of the main factors that increase the risk of starting to smoke is the perception of smoking as normal, i.e., when the social norm in schools and among friends and acquaintances is positive towards smoking. A broad consensus exists among professionals that smoking rules and the culture at school affect smoking among children and young people (7). Schools can improve their culture by ensuring that it becomes as unacceptable for children and young people to bring nicotine products to school as it is unacceptable to bring alcohol to school. It can therefore have a preventive effect if schools contribute to creating a positive social norm about not using nicotine products at school or during leisure time. Older pupils may be used as role models who may serve to make it attractive to remain nicotine free. Adults are also role models to children and young people. Therefore an extension of smoke-free school hours, which also includes employees, may contribute to creating a smoke-free and nicotine-free environment for children and young people.

4.4.2 Measures including young people

We know from the tobacco field that measures implemented by young people for young people may have a preventive effect by limiting the number of young people who start to smoke (7). We may therefore tap into an unexploited potential by including young people in preventing nicotine products. Young people know best what is going on among their peers on social media and how to act on social media. Young people may serve as non-nicotine-using role models or assist in developing campaigns targeted at young people.

4.5 Family-based measures

Involving parents makes a difference in the substance use behaviour of children and young people. Several studies have shown that the risk that children and young people start using e-cigarettes increases if their parents use e-cigarettes and are positive towards or have no opinion about using e-cigarettes (40-43). In the field of tobacco prevention, efforts have been made to prepare, e.g., family-based programmes and smoke-free homes, to mention some home-based measures (7). However, family-based programmes have limited effects on smoking among children and young people. In contrast, having a smoke-free home has a substantial impact on whether children and young people start smoking themselves. We know that parents who take a clear stand against smoking by stressing its harmful effects and telling their children that they should not begin smoking are important for smoking among children and young people (7). A study including approx. 9,000 American young people and their parents found that strict rules regarding the use of all forms of tobacco- and nicotine-containing products reduced the risk that the young people started using any form of tobacco or nicotine product (44). Therefore, the Working Group assesses that including parents and ensuring their commitment are important to prevent the use of nicotine products among children and young people.

4.6 Monitoring the use of and the market for nicotine products

4.6.1 Use

Cigarette smoking is closely associated with educational level, also among young people. However, the social gradient is less clear among users of nicotine products, including e-cigarettes, snuff, and nicotine pouches (24). It is important to remember that this was also the case for smoking. In the early phases of the smoking epidemic, well-educated people started smoking; they made smoking popular. Next, people

with short educations followed, and gradually the social gradient changed. People with a higher educational level started to quit smoking, and in the late stage of the smoking epidemic (where we are now in Denmark), relatively few people with a high educational level smoke, whereas many of those who still smoke have a short education (45, 46). Therefore, the Working Group cannot exclude that the same development may be expected for smoke-free products in the longer term. Thus, it is important to monitor developments in the use of nicotine products regularly; and if the development starts to look like the one observed for smoking, it will be necessary to adapt preventive measures.

4.6.2 The market

As smoking declines worldwide (47, 48), numerous new nicotine products are being marketed (49). The differences between the new nicotine products and traditional cigarettes are: 1) that they are often taxed less heavily than cigarettes (50), 2) that nicotine products are not regulated to the same extent as cigarettes through, e.g., smoking bans, advertising bans, health warnings, bans on taste additives, etc. (51), and 3) that nicotine products are marketed as harm-reducing products (52). According to manufacturers, the products target addicted adults who are unable or unwilling to stop smoking (53). Even so, the marketing efforts clearly demonstrate that the nicotine products are targeted at children and young people, as was initially the case for the marketing of cigarettes in the early phases of the cigarette epidemic (54-56). Today, marketing often occurs on social platforms, where nicotine products are marketed by influencers (14, 15, 57). Therefore, it is important to monitor market trends regularly and assess if it may be necessary to adapt preventive measures.

4.7 Treatment of addiction

To help children and young people overcome nicotine addiction, knowledge is needed about where you can get professional help to quit nicotine. Pupils and parents alike need to know more about and have easy access to addiction treatment. Therefore, tobacco prevention and quit-smoking programmes must also be adapted to comprise the new nicotine products available in the market as they are quickly gaining popularity among children and young people (58, 59). All adults with contact with children and young people who have started using nicotine products may help by actively encouraging them to seek professional help to become free of nicotine use.

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5

Courses of action

Whereas tobacco prevention is based on strong evidence for a wide range of measures that prevent the use of cigarettes among children and young people, research on prevention of smoke-free nicotine products is limited as many products are new in the market, when seen from a research perspective. In the available literature, nothing indicates that prevention of children and young people's use of nicotine products should be approached in a way that is fundamentally different from smoking prevention.

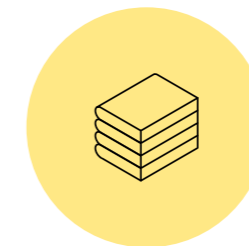
This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

The Working Group recommends linking prevention of smoking to prevention of nicotine products rather than only focusing on prevention of smoking among children and young people. Additionally, we need to combine national level structural measures with local initiatives while including as many stakeholders as possible to increase the probability of reducing the total nicotine use among children and young people in Denmark.

In this chapter, we summarise the courses of action for each stakeholder. The courses of action provided below are divided into three levels according to the strength of evidence we have for each measure:



Courses of action for which evidence already established from the field of smoking prevention is strong and the measures will therefore very likely also have a preventive effect on children and young people's use of nicotine.



Courses of action for which evidence for an effect is moderate, but which will likely also contribute to reducing the use of nicotine among children and young people.



Courses of action which the Working Group assesses will have an effect even though no strong or moderate evidence exists in support hereof.

5.1 The state



The state may ensure that any statutory provisions in place in the field of tobacco comprise all nicotine-containing products, including:

- **Taxes:** If duties are levied on the nicotine content rather than on the individual product as is currently the case, it is possible to ensure that all current and future nicotine products are regulated in the same manner.
- **Neutral packaging:** Requirements on neutral packaging may comprise all nicotine products rather than individual products as is currently the case.
- **Flavours:** All nicotine products can be comprised by a ban on flavours including menthol rather than designing flavour bans for individual products as is currently the case.
- **Smoke-free environments:** All smoke-free environments may include all products that contain nicotine and expose others to aerosol or smoke.



The state may ensure that current legal provisions comprising all nicotine products are observed, including:

- **Presentation bans**
- **Smoke-free and nicotine-free schools**
- **Age limits on the sale of nicotine products**
- **Advertising bans**



The state may also raise the age limit for nicotine product sales.



The state may introduce smoke-free and nicotine-free working hours: Smoke-free schools may be extended to comprise both pupils/students and employees at schools and other organisations where children and young people spend time.



The state may implement information campaigns: It is necessary to inform children and young people, their parents, teachers, lecturers and others who come into contact with children and young people.



The state may regulate nicotine product outlets.

5.2 Municipalities



Municipalities may ensure that current law on smoke-free school hours is observed: Smoke-free school hours include use of all nicotine products and apply on as well as beyond the school premises.



Introduce smoke-free and nicotine-free working hours: Smoke-free school hours may be extended to comprise both pupils/students and employees at schools and other organisations where children and young people spend time.



Implement information campaigns targeting children, young people, parents and employees: Municipalities may implement information campaigns informing about the health consequences and handling of nicotine use and inform of professional support to quit nicotine.



Introduce more smoke-free and nicotine-free environments: Municipalities may encourage all their stakeholders to ensure that smoke-free environments on municipal premises are also nicotine-free, e.g., squares, parks, stadiums, beaches and other places where children and young people spend time.



Inclusion of young people: Municipalities may implement youth-to-youth measures including young role models who engage in dialogues with children and young people.








Help to quit nicotine addiction: Municipalities may ensure that support is available to quit nicotine products and that support measures target children and young people.





5.3 Primary and secondary schools, leisure-time initiatives, youth clubs and vocational training facilities





Institutions may enforce smoke-free and nicotine-free school hours: Institutions must ensure that children, young people and employees are adequately informed that smoke-free school hours comprise all nicotine products and ensure that no children and young people smoke or use nicotine products in school hours.


-  **Institutions may introduce smoke-free and nicotine-free working hours:** Institutions may ensure that their employees do not use any form of nicotine products.
-  **Institutions may endeavour to include parents:** Institutions that discover that children and young people below 18 years of age use nicotine products may inform their parents and include parents in the preventive measures implemented by the school.
-  **Institutions may endeavour to include young people:** Children and young people may be included in the preventive work so that they participate in developing measures to reduce nicotine use among children and young people.
-  **Institutions may strive to establish positive social norms of not using nicotine products:** Institutions may adopt clear values relating to not using nicotine products and work actively to promote their culture.
-  **Refer children and young people for professional help to quit nicotine.**

5.4 Sports clubs



-  **Sports clubs may introduce smoke- and nicotine-free sports clubs and leisure time clubs for children, young people and employees.**
-  **The clubs may use trainers as role models who do not use nicotine products:** Clubs may ensure that children and young people do not see their trainers using nicotine products.
-  **Clubs may endeavour to include parents:** Clubs may notify parents if a trainer discovers that children under 18 years of age are using nicotine products.
-  **Clubs may endeavour to include young people:** Children and young people may be included in the preventive work so that they participate in developing measures to reduce nicotine use among children and young people.

-  **Clubs may strive to establish positive social norms of not using nicotine products:** Clubs may adopt a clear value set that nicotine products are incompatible with sports and health, and they may promote their culture.
-  **Clubs may inform their members that nicotine products do not enhance performance and that they are harmful.**



5.5 Interest organisations

-  **Interest organisations may participate in partnerships:** Organisations with an interest in preventing the use of nicotine products among children and young people may partner with other organisations who may share their vision of protecting children and young people against nicotine products and the health consequences of nicotine use. In Denmark, no single organisation currently holds responsibility for this task. Therefore, it would probably strengthen the prevention of nicotine use if a single organisation assumed the responsibility for coordinating this task.

5.6 Retailers

-  **Observe the age limit for nicotine product sales.**
-  **Observe presentation bans.**

5.7 Social media owners

-  **Observe marketing bans on nicotine products.**
-  **Make it easy and convenient to report any violations of the law.**

6

Overall conclusion

This report documents that nicotine is harmful to children and young people. Nicotine affects their brain, is highly addictive, has harmful effects on attention and motivation and on the development of self-control, among others. In the longer term, nicotine increases a risk of becoming addicted to other drugs and developing stress and anxiety. Additionally, nicotine damages the cardiovascular system, and use of nicotine among pregnant women is harmful to the foetus.

This report is a translation of a Danish report on nicotine and its effect on children in young people. The report is therefore written for a Danish audience and many of the recommendations are aimed at Danish stakeholders and decision makers. Some of the statements and recommendations may therefore not be directly applicable elsewhere.

Use of nicotine among children and young people is rising, and the group of children and young people with nicotine addiction is growing. If, as a society, we want to prevent any further addiction and harmful effects due the use of nicotine among children and young people, we need to act quickly by implementing effective measures.

The Working Group recommends implementing structural measures, for which the evidence from tobacco prevention is strong. These measures will therefore very likely also have preventive effects on the use of other nicotine products among children and young people. This applies, in particular, to the opportunities of the state to ensure that current legal provisions in the tobacco field apply to all products that contain nicotine, including that the state introduces neutral packaging and smoke-free environments, places duties on all nicotine products, introduces a ban on all taste additives and enforces any current legal provisions. Measures need to be underpinned by information campaigns that may be implemented by a variety of stakeholders and which should target children and young people, but also their parents, teachers, pedagogues, sports trainers, etc. The Working Group recommends that, in future, we perceive prevention of use of tobacco and nicotine products in conjunction rather than simply focusing on prevention of smoking among children and young people. This applies to legislation and measures affecting school hours and public spaces alike, not least the places where children and young people spend time.

The Working Group provides a range of action courses for stakeholders who may engage in limiting the nicotine use of children and young people. The evidence supporting these measures in the prevention of smoking is not as strong as the structural measures the state may employ, and therefore it is also less certain that these measures are effective in preventing nicotine use. However, we do know from drug prevention among children and young people that the more effective approaches are structural and evidence-based measures that the state may implement in collaboration with local measures that comprise the local community, parents and the children and young people themselves. The more concurrent measures are implemented, and the more stakeholders are involved, the more effective will the measures presumably be in preventing use of nicotine among children and young people.

The report reviews scientific literature on the health consequences of use of nicotine products among children and young people, including how nicotine affects their brains and their somatic health. Additionally, the report reviews which measures may be considered effective in preventing nicotine use among children and young people. The objective of the report is to contribute to the scientific bases for work to prevent the use of nicotine in children and young people while ensuring that politicians and decision makers have at their disposal a research-based foundation for any decisions made in this field.
