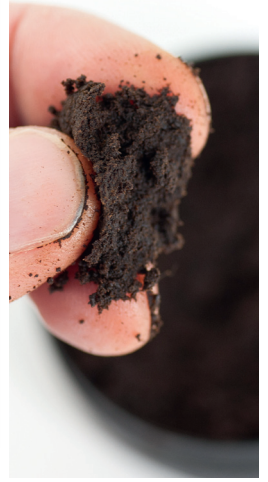
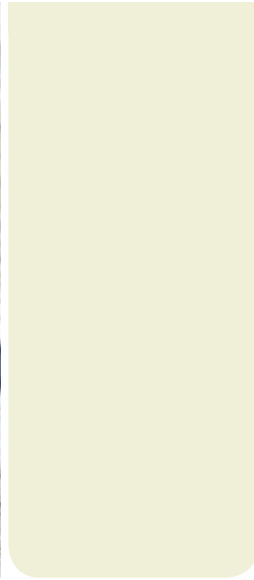


2014



# Health risks of Scandinavian snus consumption (English summary)

## Summary

### Introduction

In 2005, the health risks from using Scandinavian snus were evaluated in knowledge summaries from both the Norwegian Knowledge Centre for the Health Services, and in Sweden by the Swedish Institute of Public Health together with the Karolinska Institute. Since then, snus consumption in the Norwegian population has increased greatly, particularly among young people. Many have questioned whether the increased use of snus may have an impact on public health. Over the last ten years, significant new research on the impact on health from using snus has accumulated, emphasising the need for an update. In 2013, the Ministry of Health and Care Services commissioned the Norwegian Institute of Public Health to evaluate snus with the following mandate:

*A health risk assessment of snus consumption in Norway will be carried out. The work should be based on the Swedish report "Health risks of Swedish snus" from 2005, and will be supplemented by a review and analysis of recent, relevant scientific publications. An overview of potential health hazards from snus documented by various methods (epidemiological studies, clinical trials and animal studies) will be provided, including an assessment of exposure and associated risk. The Norwegian Institute of Public Health is free to organise its work as necessary, including the use of external expertise.*

An academic working group was established, including:

Jan Alexander, Prof. MD, PhD, Deputy Director-General, Per E Schwarze, PhD, Department Director, Rune Becher PhD, toxicologist and senior scientist and Elisabeth Øya MSc, toxicologist and scientist, all from the Norwegian Institute of Public Health.

The following people have also contributed:

Tom K. Grimsrud, MD, Senior Medical Officer at the Cancer Registry of Norway (methodological challenges, cancer, pregnancy outcomes, cardiovascular diseases, and diabetes and metabolic syndrome), Liv Grøtvedt PhD, senior scientist at the Norwegian Institute of Public Health (snus and risk for subsequent smoking, exposure), Jon Dahl, Dr. odont., Director, Nordic Institute of Dental Materials (oral health), Håkon Valen Rukke, dentist, PhD, senior scientist at Nordic Institute of Dental Materials (oral health), Wenche Jacobsen, librarian at the Norwegian Institute of Public Health (systematic literature search on snus), and Karin Melsom, senior adviser at the Norwegian Institute of Public Health (report editing).

Since the Norwegian and Swedish summary reports on snus were published in 2005, several summaries and comprehensive reviews on health risks posed by the use of snus or smokeless tobacco have been issued. In 2007, the New Zealand Health Technology Assessment published the report, "Systematic review of the health effects of modified smokeless tobacco products." In 2008, the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published a comprehensive review: "Health Effects of Smokeless Tobacco Products."

The working group summarised the conclusions from the four previous reports and has considered newer scientific literature. In 2007 and 2012, the International Agency for Research on Cancer (IARC), under the World Health Organization, evaluated smokeless tobacco, including snus and its components, with regard to cancer. When

assessing the cancer risk, the working group based its assessment on the IARC evaluations together with new scientific literature.

In 2014, the Surgeon General at the US Department of Health published a comprehensive report about tobacco: "The Health Consequences of Smoking - 50 Years of Progress." The report provides a general assessment of smoking, but also contains a chapter that describes the health effects from tobacco that are attributable to nicotine. This chapter is highly relevant for snus. The primary literature about nicotine is very extensive, and it would be outside the scope of the mandate to perform a comprehensive review based on original studies. Therefore, the working group has mainly based its opinions about nicotine on the information provided in the nicotine chapter of the US Surgeon General's report.

A systematic literature search on snus from 2004 to February 2014 was performed. A selection and critical review of the existing scientific evidence (both epidemiological and experimental studies) was made on the health effects of using Scandinavian snus/smokeless tobacco, the impact of snus/smokeless tobacco use among young people on later initiation of smoking, and the pattern of snus consumption in Norway.

Besides snus and nicotine, tobacco-specific nitrosamines (TSNA) in snus have also been evaluated. For TSNA, the report uses the IARC evaluations (IARC 2007 and 2012) as well as selected scientific articles from a PubMed literature search.

In total, 134 scientific articles from literature searches were included and evaluated. In addition, 6 articles funded by the tobacco industry were described.

In line with the decision taken by leading medical journals and the World Health Organization (WHO), and in consultation with the Ministry of Health and Care Services, the working group has decided to place little or no weight on the evaluations and opinions presented in publications funded by the tobacco industry.

## **Exposure**

Snus is a smokeless, ground tobacco product, which is held in the mouth between the gum and lip. To the best of our knowledge, snus is not produced in Norway. In 2013, the total import of snus and chewing tobacco was 1,815 tonnes, mostly from Sweden. In addition, there is private import from trade along the border.

Like other tobacco products, snus contains the biologically active and addictive substance, nicotine. Snus also contains carcinogenic tobacco-specific nitrosamines (TSNA) and other carcinogenic substances such as polycyclic aromatic hydrocarbons (PAH).

In 2013, snus was used daily by 9% of the adult population, while 4% used it occasionally. More men than women used snus. While 14% of men and 4% of women used snus daily, the figures for occasional snus use were 5% of men and 3% of women, respectively. Snus use was particularly high in the 16–24 year age group, where 33% of men used snus daily or occasionally compared to 23% of women. There was some geographical variation; Trøndelag and Nordland counties had the highest percentage of users, while Finnmark, Telemark and Aust-Agder had the lowest.

Snus consumption in the population is rising, and it has increased over the last 20 years for men and for the past 10 years for women from a few per cent to the current figures. This is reflected in the threefold increase in import of snus from 2009 to 2013.

The increase in the snus consumption is greatest in the youngest age groups among both men and women. The increase could almost be described as an epidemic, and there are no signs of it stopping. Snus consumption among eighth graders showed significant differences and was highest among those that perceived that their family had the poorest economy. However, there was little difference in snus consumption among adults in terms of education level. We have limited knowledge about the extent of snus consumption in pregnancy, but there are indications that it is increasing. Approximately 20% of users appeared to continue to use snus during pregnancy. The rapidly rising use among young women increases the risk that more pregnant women will use snus in the years to come.

In all the age groups, 5% both use snus and smoke. Half of the snus users also smoke. It is most common to use snus daily and smoke occasionally.

The amount of snus that is used varies and is on average 10.6 daily doses, where one dose is equivalent to 0.9 grams for portion snus. This corresponds to about 3 boxes per week (24 portions per box). The average user holds snus in the mouth for 11–14 hours per day.

The nicotine content in various snus products varies from a few milligrams/grams (mg/g) up to 20 mg/g snus in the strongest snus products on the market, but is typically 7–8 mg/g. The nicotine content is in the same order of magnitude as for smoking tobacco. Nicotine exposure is somewhat greater from one dose of snus than from one cigarette, but may vary with the nicotine content in the snus and how long it is kept in the mouth.

TSNA exposure will vary considerably with the type of snus and usage patterns. The level of TSNA in Swedish snus is 0.48 to 3.1 micrograms/g, ( $\mu\text{g/g}$ ). Assuming that the TSNA is released to the same degree as nicotine (60–90%), the local exposure in the oral cavity can, based on 10 snus portions per day, reach levels of 2.6 to 25  $\mu\text{g/day}$ , which may be absorbed directly or swallowed. In one study, the total levels of NNAL in the urine, which is a marker for TSNA intake, was similar or slightly higher in users of snus compared with smokers.

## **Health hazards**

### *Nicotine*

One of the main active ingredients in tobacco is nicotine. Nicotine absorption from moist snus is rapid, and the nicotine levels in the blood of snus users and smokers are shown to be relatively similar. Nicotine is quickly metabolised to inactive degradation products, so that half of the nicotine is gone after 2 hours. Nicotine acts primarily via the nicotinic acetylcholine receptors, causing the release of different signalling molecules. Besides the central and peripheral nervous system, these receptors are present in other organs and tissues such as muscle, lung, endothelium, kidneys, and skin. Nicotine has a significant addictive potential. In pharmacological literature, the lethal dose of nicotine has been reported to range from 30 to 60 mg in adults. The basis for these figures is unclear, and it is possible that the lethal dose for adults may be higher (~500 mg).

Nicotine has acute effects on the cardiovascular system and causes increased heart rate and increased blood pressure, but the long-term effects are less clear. Animal studies have shown that nicotine exposure in utero and in young animals leads to adverse structural and functional changes in the brain and behavioural changes.

Likewise, nicotine inhibits lung development and function in the foetus and later in life, in a similar way as that observed following tobacco smoking during pregnancy. It cannot be ruled out that nicotine from snus during pregnancy may have a similar effect in humans. Nicotine may also affect cellular processes that are involved in cancer development, but there is insufficient scientific evidence to determine whether nicotine can cause or promote cancer development in humans. Nicotine also appears to be both suppressive and stimulating to the immune system. However, it is unclear whether this has implications for health.

#### *Tobacco-specific nitrosamines (TSNA)*

Overall, the carcinogenic effects of tobacco-specific nitrosamines (NNK and NNN) in animal experiments have been convincingly documented, and exposure to these substances in animal studies have shown to be potent inducers of cancer in several organs. There is no new information to indicate that the IARC evaluations about NNK and NNN being carcinogenic to humans are no longer valid.

NNK / NNN have been shown to be carcinogenic and to damage genetic material (genotoxic). Therefore, cancer risk cannot be completely excluded, even at low exposure levels. The risk of developing cancer increases with increasing exposure. Since NNK/NNN are both carcinogenic and genotoxic, it should be assumed that any exposure is associated with some cancer risk.

#### *Snus*

The most comprehensive assessments of the carcinogenic properties of snus and other smokeless tobacco have previously concluded that snus is carcinogenic (Swedish Institute of Public Health 2005; IARC 2012). Few studies have been published since the IARC review in 2009 (IARC 2012). These do not contain information that modify previous conclusions that snus is carcinogenic. New information supports evidence that snus causes or may worsen cancer. Smokeless tobacco (including Scandinavian snus) is considered to be carcinogenic, based on epidemiological studies, experimental studies, the presence of carcinogenic tobacco-specific nitrosamines (TSNA) as well as other substances that may impact cancer development, e.g. PAH. There is convincing evidence that the use of snus increases the risk of cancer of the pancreas, oesophagus and oral cavity. There is some evidence that the use of snus increases the risk of cancer of the stomach, lung, colon and rectum. There is no reason to consider Swedish snus as essentially different in this respect.

Based on the present studies, it is impossible to determine how great the increased cancer risk would be with the use of snus. The degree of increased cancer risk will probably depend on when snus use began, how frequently and how much snus is used, how many years it has been used and the content of harmful substances in the snus product. There is some evidence that snus use gives a poorer cancer prognosis.

There is convincing evidence that snus consumption during pregnancy may lead to reduced birth weight, increased risk of premature birth and stillbirth. There are some indications that it may contribute to pre-eclampsia, and increase the risk of respiratory failure (neonatal apnoea) among new-born babies and lip/palate malformations.

There is little or no evidence that the snus consumption increases the risk of cardiovascular disease, myocardial infarction or stroke. There are indications that it may be associated with increased risk of heart failure. There is convincing evidence that it may lead to an increased risk of death after myocardial infarction or stroke. In

one study, quitting snus after a myocardial infarction halved mortality. The risk reduction is of the same magnitude as the effect of quitting smoking. The acute effects of snus consumption are increased heart rate and blood pressure, and cardiac function may also be affected. There is little or no evidence that long-term snus consumption is associated with a permanent increase in blood pressure.

There is evidence that a high consumption of snus is associated with an increased risk for diabetes mellitus type 2. This applies particularly to heavy users of snus (5 or more boxes per week). There is some evidence that snus consumption may be associated with increased risk of weight gain and overweight/obesity as well as lipid metabolism disorders.

Using snus causes changes in the oral cavity, most of which is seen as white and/or red mucosal lesions (spots). These are called snus-induced lesions. Some of these injuries have been classified as possibly pre-cancerous, but most of the lesions resolve when snus consumption ceases. There may be local permanent gum recession in the area where the snus is placed. This can lead to exposure of the neck of the tooth with subsequent tooth sensitivity. There is no evidence that using snus causes increased rates of general gum inflammation (gingivitis) and periodontal changes.

There are few studies of snus and neurological disorders, with the exception of stroke, but there are some indications that the snus consumption may be associated with a reduced risk of developing multiple sclerosis (MS).

There are some studies concerning use of snus and the possible impact on other health conditions. However, they are few and there is insufficient basis to make conclusions about any effects on risk.

The previous reports have not addressed the snus consumption and its possible impact on mental health. No new studies that discussed this topic were found in our literature search.

An important question is whether snus consumption among young people increases the risk for subsequent smoking. There have been several studies, but their results conflict. The weight of evidence suggests that it may increase the risk for subsequent smoking, but the studies have limitations. However, the evidence that it does not increase the risk for subsequent smoking is weak, and the studies suffer from major limitations.

#### *Dose-response considerations*

In only a few of the studies was there any attempt to characterise (and quantify) snus exposure. This applies to the content of nicotine and TSNA, how much snus has been used, when, and for how long. Apart from the risk of developing diabetes mellitus type 2, where an increased risk was observed for those with a consumption of 5 snus boxes or more per week, there was no information about doses in the studies.

## **Risk characterisation**

### *Cancer*

Of the three forms of cancer that are linked to snus consumption, pancreatic cancer is the most common. In the follow-up studies of snus users, it can be difficult to achieve sufficient statistical power when examining rare cancers. It is not possible to quantify the cancer risks associated with the use of snus. An increasing consumption will probably lead to a higher population risk of snus and TSNA-related cancers, resulting in an increased incidence. Meanwhile, several of the snus-related cancers are also related to the smoking habits of the population. Cancer risk will therefore be related to the combined use of snus and smoking in the population. In comparison, when tobacco is not used, the use of snus will increase the total cancer risk. However, the increase is probably less than the strong cancer risk associated with smoking, since smoking provides additional exposure to combustion products that could contribute to the development of lung cancer.

### *Adverse pregnancy outcomes*

The use of snus during pregnancy is associated with lower birth weight, increased risk of premature birth and stillbirth. Based on animal studies and knowledge of nicotine-related effects of smoking, it cannot be ruled out that snus could also interfere with foetal development at critical time points, although this has not been observed in epidemiological studies. With the rapidly increasing consumption among young women, the risk of more pregnant women using snus will increase in the coming years. The consequences could be an increase in adverse pregnancy outcomes and developmental disorders in the foetus and infant.

### *Cardiovascular diseases*

Despite a generally improved prognosis after myocardial infarction or stroke, cardiovascular diseases remain among the leading causes of disease and premature death in the population. Snus use seems to be particularly associated with an increased risk of early death after a stroke or myocardial infarction. Snus consumption among the older part of the population that is most likely to suffer from cardiovascular disease, is not increasing to the same extent as among the young. There is reason to discourage the use of snus as a means to quit smoking for those who have had a myocardial infarction or a stroke.

### *Diabetes mellitus type 2 (DMT2), obesity and other metabolic disturbances*

There is a particular risk of developing DMT2 with a consumption level of 5 or more snus boxes per week. This consumption level is significantly above the average consumption of about 3 boxes per week. We do not know the fraction of users that consume more than 5 boxes per week. However, if the effect of snus is related to nicotine exposure, the use of snus with a higher nicotine content, e.g. 20 mg/g, would also affect those with lower consumption. We do not know consumption patterns for these products.

### *Oral health*

In the long term, increased snus use in the population could lead to poorer oral health with snus-induced lesions in the oral mucosa, which in most cases will heal if usage stops. There can be permanent recession of the gums at the sites where the snus is placed.

*Risks of starting to smoke*

In this assessment, we addressed the risk for subsequent onset of smoking among young snus users. The results of the studies are not definitive but they indicate an increased risk. It cannot be ruled out that the significantly increased snus consumption among adolescents, and the resulting nicotine dependence, could lead to increased smoking.

The most common form of combined tobacco use is daily snus consumption and occasional smoking. We lack knowledge about whether snus might maintain smoking habits.