

Harm Reduction in Sweden – the case of snus

Karl Olof Fagerström

The Swedish smokeless tobacco product snus is a special product in the category of smokeless tobacco. The Federal Food and Drug Administration (FDA) in the US gave it, as the first product, a license as a less harmful tobacco product and in the EU the snus is banned. How can snus be so differently regulated? In this chapter the history of snus, its content, production, pharmacology, use and impact on public health in Sweden will be discussed.

Background.

Swedish snus is a grounded tobacco product that is put under the upper lip. Up until the end of last century it came in the form of loose tobacco and a pinch was formed by the thumb and index finger. Today it is pre-packed in small sachets of usually between 0,5 to 1 gram. It was invented during the early 1800s. Up until 1940s snus was the predominant form of tobacco used in Sweden. As in most other European countries more local products and habits went away partly by the wide and free distribution of cigarettes to soldiers during the two world wars but snus was not entirely wiped out in Sweden probably because Sweden was not a part of any of the wars. During the 1960s it became evident that smoking was very harmful, and the Swedish government acted accordingly with information to the public and started to promote snus the smokeless version of tobacco. At the time it was a state monopoly. From around 1970 when about 45% of Swedish men smoked snus started to increase its market share among men on the expense of cigarettes. During the early 1990s snus use became more prevalent than cigarette smoking. The women have never been attracted to the habit of using loose snus but the interest has grown somewhat with the portion packed sachets.

The product.

The Swedish snus is composed of sun or air cured tobacco and then sodium chloride, sodium carbonate, water, humectants and flavourings are added. Most smokeless tobacco products have been fermented with a risk of formation of bacterial nitrate and nitrosamines. Snus on the other hand is sieved to small particles mixed with water and sodium chloride in a closed system. The mixture is then subjected to a heat treatment – pasteurisation – to reduce the microbial

activity. Until the product is purchased it is kept cool in order to keep the product stable and reduce the risk of microbial nitrosamine formation. The Swedish Match company which nowadays produces most of the snus introduced a voluntary product standard Gothiatek that sets the following limits to potentially harmful constituents: nitrite 3,5 mg/kg, NNN+NNK 0,95 mg/kg, NDMA 2,5 µg/kg, B(a)P 1,25 µg/kg, aflatoxin 2,5 µg/kg, ochratoxin 10 µg/kg, formaldehyde 7,5 mg/kg, crotonaldehyde 0,75 mg/kg, cadmium 0,5 mg/kg, lead 1,0 mg/kg, arsenic 0,25 mg/kg, nickel 2,25 mg/kg, chromium 1,5 mg/kg, mercury 0,02 mg/kg and acetaldehyde 25 mg/kg.¹ The product is regulated by the Swedish Food Agency.

Pharmacology and toxicity.

Tobacco use is largely determined by nicotine delivery. Without nicotine the other factors would not be strong enough to motivate tobacco use (Fagerstrom 2012).

Two pharmacokinetic studies have looked into the nicotine delivery of modern snus. In these studies, the pouches were used for 30 min., which is a fairly normal use time for consumers. In the first study four snus products were used containing from 8,8 mg nicotine to 4,8 mg nicotine with an extracted dose of 1,1 to 2,7 mg nicotine. The maximum nicotine concentration ranged from 10,8 ng/ml to 29,0 ng/ml after eleven doses over 11 hours. The time to maximum concentration was 30 min for all products (Lunell/Lunell 2005). In the second, a single dose study, two snus products were studied that contained 9,9 mg and 8,7 mg nicotine. From these products 2,1 and 2,2 mg nicotine was extracted and resulted in nicotine blood maximum concentrations of 14,8 ng/ml and 13,7 ng/ml with a time to maximum concentration of 37 min for both products (Lunell/Curvall 2011).

Loose snus products, which are not in much use any longer, may deliver nicotine more effectively (Holm et al.1992) since the tobacco comes into contact with the oral mucosa better than with the pouched product where the tissue can be a barrier. The total uptake of nicotine from snus can match that of cigarettes although the speed of delivery cannot (Digard et al. 2013).

Health effects.

Snus and Cancer: There is some biological basis for proposing that nicotine may promote cancer based on mechanistic and experimental studies (Lee/Cooke 2012; Chen et al. 2008) but human evidence is lacking.

¹ <https://www.swedishmatch.com/Snus-and-health/GOTHIATEK/GOTHIATEK-standard/>

There are 69 identified carcinogens in tobacco smoke, but nicotine is not among them according to the International Agency for Research on Cancer (IARC 2021). If nicotine alone were to cause cancer, one would expect that long-term exposure to nicotine from snus would cause cancer. However, studies generally have seen no increased risk of cancer in either the oral cavity or the throat after snus use (Lee 2011a). Furthermore, a meta-analysis by Lee found no association between snus and cancer of the oropharynx, oesophagus, stomach, pancreas, lung or other sites (Lee 2011b). Some studies have reported suggestive evidence of an association between the use of snus and oesophageal squamous cell carcinoma, noncardia stomach cancer (Zendhdel et al. 2008) and rectal cancer (Araghi et al. 2017). A recent meta-analysis (Byhamre et al. 2021) found a very small increase in death from cancer among snus users (HR 1,1, 95% CI 1.0-1.3). If at all snus is causing cancer it is probably via mechanisms other than nicotine.

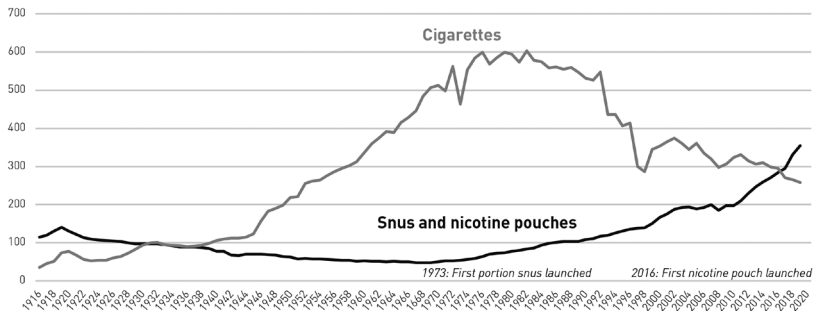
Cardiovascular disease: Although it is recognized that medicinal nicotine causes acute and temporary changes to the cardiovascular system epidemiological studies have not found the use of nicotine replacement (NR) to be linked to the development of cardiovascular disease (Hubbard et al. 2005; Benowitz/Hansson/Jacob 2002) and studies have shown that NR need not be contraindicated for smokers with heart disease. (Kimmel et al. 2001; Greenland/Satterfield/Lanes 1998) In a study that evaluated the safety of NR in 663 patients after acute coronary syndrome, NR use for 1 year was not associated with an increased risk of cardiovascular events (Joseph et al. 1996). Several epidemiological studies have been conducted in long term users of snus to evaluate the risk of cardiovascular heart disease, mostly myocardial infarction and stroke. Two meta-analyses concluded that snus use was not associated with acute myocardial infarction (Hansson/Galanti/Hergens 2012). However, it was suggested that snus use might slightly increase the risk for a more severe outcome in patients with stroke and a nonfatal myocardial infarction (Hergens et al. 2007). A recent meta-analysis (Byhamre et al. 2021) found a small increase in death from cardiovascular disease among snus users (HR 1,3, 95% CI 1.1-1.4).

Pregnancy: For adverse effects of pregnancy it is more clear that snus is one of many other substances that should be abandoned during pregnancy. Pregnant women who use snus are at higher risk of having babies of lower birth weight, still birth and elevated risks for premature delivery (Kreyberg et al. 2019). From animal work it seems likely that nicotine may also have adverse neuro-behavioural consequences (Pauly/Slotkin 2008).

Tobacco use in Sweden.

Swedish men have never had the same high smoking prevalence figures as in many other European countries. Again, probably due to not being part of any of the two wars. During the 1960s the top was reached by a smoking prevalence of about 50% and for the snus a low mark of a few percent was seen. However, after the insights into the harmful effects of smoking use of snus started to grow and smoking to fall as can be seen in fig. 1 where the amount of cigarette and snus sales are shown for the last 100 years.

Figure 1: Sales of cigarette packs and snus cans from 1916 to 2015.



Source: Swedish Match estimates, SMD Logistics.

In the most recent Eurobarometer (2020) it was found that 6% of the Swedish men were smokers and 20% were snus users. The Swedish official statistics figure for men using snus is 18%.² If the 6% smoking and 18% snus use is added around 24% of Swedish men use tobacco which is close to the average EU value for men of 26% according to the 2020 Eurobarometer. In order not to complicate matters too much the women's tobacco use is not discussed since they have hardly not used snus at all up until recently.

Tobacco related mortality attributed to tobacco use.

If we look at the mortality attributed to tobacco as calculated by WHO we see that Swedish men are singled out from men in the rest of EU.³ As can be seen in table 1 where we have the tobacco attributable death rate/100000 of

² <https://www.scb.se/hitta-statistik/artiklar/2018/farre-roker-fler-snusar/>

³ <https://apps.who.int/iris/handle/10665/44815>. Adapted by Lars Ramström

Swedish men compared with EU median and the EU country with the lowest and highest mortality we see that Swedish men are below the next best country on all disease categories.

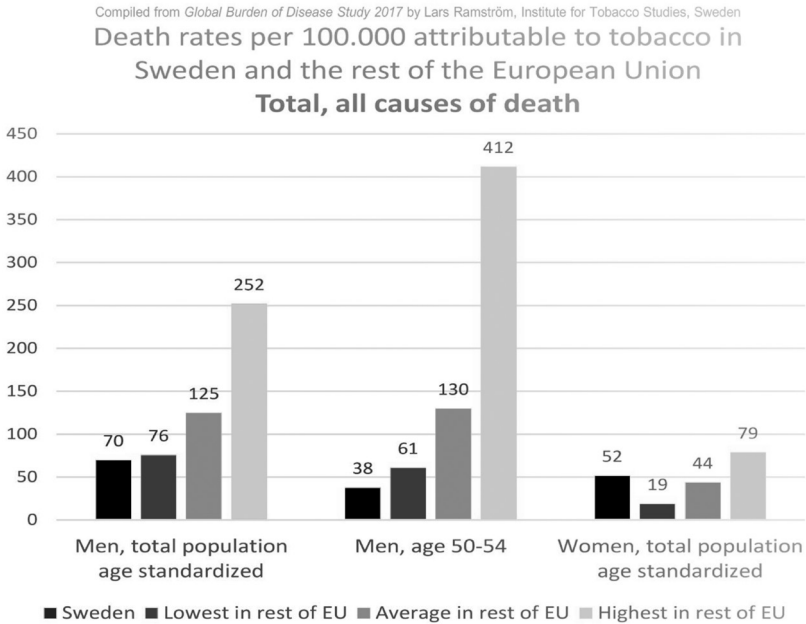
Table 1: Death rates (per 100,000) attributable to tobacco.

	Sweden	European Union Member States other than Sweden		
		Min	Median	Max
MEN (age 60-69)				
Lung cancer	87	91	220	399
Other cancer	36	41	105	217
All cardiovascular	72	107	170	618
All causes	222	378	550	1388
WOMEN (age 60-69)				
Lung cancer	61	5	39	127
Other cancer	17	1	10	39
All cardiovascular	63	5	50	222
All causes	173	14	115	690

For all causes the Swedish men's death rate is 40% of the average EU. In contrast the Swedish females have higher death rates than the EU average on all disease categories. The men's low death rate thus cannot be attributed to something special with the Swedish lifestyle (Ramstrom/Wikmans 2014).

The above WHO data are from 2004 and is somewhat old and therefore it is of interest to look at more recent data from the Global Burden of Disease report (GBD 2018). In Fig. 2 the tobacco related mortality from all causes has been compared with EU countries with the lowest, average and highest mortality for all adult men (the left part) and a more narrower and comparable cohort of men 50-54 years of age (middle panel) and all women for comparison (right panel). Again, Swedish men have lower tobacco attributable mortality than any other country in EU, 56% of the EU average for the entire population and 29% of the EU average for men 50-54 years. The Swedish women have a higher tobacco attributable death than EU.

Figure 2: Death rates per 100.000 attributable to tobacco in Sweden and the rest of the EU.



Smoking Cessation.

Snus has in a very direct way contributed to the very low smoking prevalence in Sweden, 6% for men (Eurobarometer 2020) and more recently in Norway where only 9% of the men smoke daily and 19 use snus.⁴ It is not just that many men start with snus instead of cigarettes but snus is used as a way to stop smoking. When smokers and former smokers are asked which aid they have used in their efforts to stop smoking snus comes out as the most used aid among men in both Sweden (Ramstrom/Borland/Wikmans 2016) and Norway (Lund/Lund 2014). It has also been reported from both Sweden (Ramström/Borland/Wikmans 2016) and Norway (Lund/Schaffels/McNeill 2011) that snus is more effective for stopping smoking than other aids e.g. nicotine patches. This is probably due to the nicotine concentrations that are obtained with snus,

⁴ <https://www.ssb.no/en/royk>

the price, availability and social acceptance. Complementing these kind of surveys are two randomized, double-blind placebo controlled trials with snus as a smoking cessation aid. In this clinical and more controlled situation active snus proved better than placebo snus (Rutqvist/Fry/Lee 2013).

Harm Reduction.

Sweden has record low smoking in the EU among men and Sweden also has record low tobacco attributable mortality. There is likely a casual effect so that the snus displacement of smoking among the men is the reason for the low tobacco attributable mortality. A common criticism has been that snus is a gateway to smoking. With the record low smoking rate in men that cannot have been the case with snus in Sweden.

For understanding how to reduce harm from tobacco products it is necessary to understand the role of and health effects of nicotine. While nicotine is the main cause of dependence it is by itself not contributing significantly to respiratory, cardio-vascular and cancer disorders (Benowitz/Burbank 2016). This is very well formulated by the former Commissioner of the US Federal and Food Administration (FDA) M.D. Scott Gottlieb when he said: “Nicotine, while highly addictive, is delivered through products on a continuum of risk, and that in order to successfully address cigarette addiction, we must make it possible for current adult smokers who still seek nicotine to get it from alternative and less harmful sources”.⁵

Swedish snus is obviously such a source and therefore FDA gave Swedish snus , as the first product a harm reduction designation stating “the available scientific evidence, including long-term epidemiological studies, shows that relative to cigarette smoking, exclusive use of these specific smokeless tobacco products poses lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis”.⁶

The Snus commission in Sweden⁷ has estimated that in the EU 561,000 men die every year from diseases attributable to tobacco. If the men in the whole of EU have had the same tobacco habits as in Sweden the figure would be 205,000.

⁵ <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-pivotal-public-health-step-dramatically-reduce-smoking>

⁶ <https://www.fda.gov/news-events/press-announcements/fda-grants-first-ever-modified-risk-orders-eight-smokeless-tobacco-products>

⁷ www.snuskommissionen.se

Thus, a reduction by about 355,000 deaths and just in Germany a reduction of 44,000, from 80,000 to 360,000 deaths per year.

The death and disease with its suffering among its users and the burden to the society would be less if tobacco and nicotine containing products were regulated similarly to e.g. alcohol containing beverages. For example, availability, marketing and taxation could be determined according to the harmfulness of the product to the user and society. The EU and FDA opposing positions on snus is hard to understand given the body of facts available in the literature.

References

- Araghi, M./Galanti, M.R./Lundberg, M./Liu, Z./Ye, W./Lager, A./Engström, G./Manjer, J./Alfredsson, A./Knutsson, A./Norberg, M./Palmqvist, R./Gylling, B./Wennberg, P./Lagerros, Y.T./Bellocco, R./Pedersen, N.L./Östergren, P.O./Magnusson, C. (2017): Smokeless tobacco (snus) use and colorectal cancer incidence and survival: Results from nine pooled cohorts. In: *Scand J Public Health* 45(8): 741-748. doi: 10.1177/1403494817714191.
- Benowitz, N./Burbank A. (2016): Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. In: *Trends Cardiovasc Med*. 26(6): 515-523. doi: 10.1016/j.tcm.2016.03.001.
- Byhamre, M./Gustafsson, P.E./Jansson, J.H./Wennberg, M./Hammarström, A./Wennberg, P. (2021): Swedish snus use is associated with mortality: a pooled analysis of eight prospective studies. In: *Int J Epidemiol* 49(6): 2041-2050. doi: 10.1093/ije/dyaa197.
- Chen, R.J./Ho, Y.S./Guo, H.R./Wang, Y.J. (2008): Rapid activation of Stat3 and ERK1/2 by nicotine modulates cell proliferation in human bladder cancer cells. In: *Toxicological Sciences* 104(2): 283–293.
- Digard, H./Proctor, C./Kulasekaran, A./Malmqvist, U./Richter, A. (2013): Determination of nicotine absorption from multiple tobacco products and nicotine gum. In: *Nicotine Tob Res*. 15(1): 255-261. doi: 10.1093/ntr/nts123.
- Eurobarometer (2020): Latest surveys & Publications. Online verfügbar unter: <https://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/Survey/getSurveyDetail/yearFrom/1974/yearTo/2021/surveyKy/2240> [Stand 26.07.2021].
- Fagerstrom, K. (2012): Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence. *Nicotine & Tobacco Research* 14(1): 75–78. <https://doi.org/10.1093/ntr/ntr137>.
- GBD (2018): Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017:

- a systematic analysis for the Global Burden of Disease Study 2017. In: *Lancet* 392(10159): 1923–94. doi: 10.1016/S0140-6736(18)32225-6.
- Greenland, S./Satterfield, M.H./Lanes, S.F. (1998): A metaanalysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. In: *Drug safety: an international journal of medical toxicology and drug experience* 18(4): 297–308.
- Hansson, J./Galanti, M.R./Hergens, M. (2012): Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. In: *European journal of epidemiology* 27(10):771-9. doi: 10.1007/s10654-012-9704-8. Online verfügbar unter: <http://www.ncbi.nlm.nih.gov/pubmed/22722951> [Stand 26.07.2021].
- Hergens, M.P./Alfredsson, L./Bolinder, G./Lambe, M./Pershagen, G./Ye, W. (2007): Longterm use of Swedish moist snuff and the risk of myocardial infarction amongst men. In: *J Intern Med.* 262: 351–359.
- Holm, H./Jarvis M.J./Russell M.A./Feyerabend C. (1992): Nicotine intake and dependence in Swedish snuff takers. In: *Psychopharmacology (Berl)* 108(4): 507-511. doi: 10.1007/BF02247429.
- Hubbard, R./Lewis, S./Smith, C./Godfrey, C./Smeeth, L./Farrington, P./Britton, J. (2005): Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. In: *Tobacco control* 14(6): 416– 421. doi: 10.1136/tc.2005.011387.
- IARC Monographs (2021): IARC monographs on the identification of carcinogenic hazards to humans, WHO. Online verfügbar unter: <https://monographs.iarc.fr/list-of-classifications> [Stand 24.02.2021].
- Joseph, A.M./Norman, S.M./Ferry, L.H./Prochazka, A.V./Westman, E.C./Steele, B.G./Sherman, S.E./Cleveland, M./Antonuccio, D.O./Hartman, N./McGovern, P.G. (1996): The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. In: *N Engl J Med.* 335(24): 1792-8. doi: 10.1056/NEJM199612123352402.
- Kimmel, S.E./Berlin, J./Miles, C./Jaskowiak, J./Carson, J.L./Strom, B.L. (2001): Risk of acute first myocardial infarction and use of nicotine patches in a general population. In: *Journal of the American College of Cardiology* 37(5):1297–302.
- Kreyberg, I./Nordhagen, L./Bains, K./Alexander, J./Becher, R./Carlsen, K./Glavin, K./Carlsen, K. (2019): An update on prevalence and risk of snus and nicotine replacement therapy during pregnancy and breastfeeding. In: *Acta Paediatr* 108(7): 1215-1221. doi: 10.1111/apa.14737.
- Lee, P. (2011a): Summary of the epidemiological evidence relating snus to health. In: *Regul Toxicol Pharmacol* 59(2): 197-214. doi: 10.1016/j.yrtph.2010.12.002.
- Lee P. (2011b): Summary of the epidemiological evidence relating snus to health. In: *Regul.Toxicol Pharmacol* 59(2): 197-214. doi: 10.1016/j.yrtph.2010.12.002.
- Lee, J./Cooke, J.P. (2012): Nicotine and pathological angiogenesis. In: *Life Sciences* 91(2122): 1058–1064.

- Lund, I./Lund, K.E. (2014): How has the availability of snus influenced cigarette smoking in Norway? In: *Int J Environ Res Public Health* 11(11): 11705-11717. doi: 10.3390/ijerph111111705.
- Lund, K.E./Scheffels, J./McNeill, A. (2011): The association between use of snus and quit rates for smoking: results from seven Norwegian cross-sectional studies. In: *Addiction* 106(1): 162-167. doi: 10.1111/j.1360-0443.2010.03122.x.
- Lunell, E./Lunell, M. (2005): Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 2-mg Nicorette chewing gum: a crossover study. In: *Nicotine Tob Res.* 7(3): 397-403. doi: 10.1080/14622200500125468.
- Lunell, E./Curvall, M. (2011): Nicotine delivery and subjective effects of Swedish portion snus compared with 4 mg nicotine polacrilex chewing gum. In: *Nicotine Tob Res.* 13(7): 573-578. doi: 10.1093/ntr/ntr044.
- Pauly, J.R./Slotkin, T.A. (2008): Maternal tobacco smoking, nicotine replacement and neurobehavioural development. In: *Acta Paediatr.* 97(10): 1331-1337. doi: 10.1111/j.16512227.2008.00852.x.
- Ramstrom, L./Wikmans, T. (2014): Mortality attributable to tobacco among men in Sweden and other European countries: an analysis of data in a WHO report. In: *Tob Induc Dis.* 12(1): 14. doi: 10.1186/1617-9625-12-14.
- Ramström, L./Borland, R./Wikmans, T. (2016): Patterns of Smoking and Snus Use in Sweden: Implications for Public Health. In: *Int J Environ Res Public Health* 13(11): 1110. doi: 10.3390/ijerph13111110.
- Rutqvist, L./Fry, J./Lee, P. (2013): Systematic review of Swedish snus for smoking cessation based on primary subject data from randomised trials. In: *J Smok Cessation.* doi 10.1017/jsc.2013.10.
- Zendejdel, K./Nyren, O./Luo, ./ Dickman, P.W./Boffetta, P./Englund, A./Ye, W. (2008): Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. In: *Int J Cancer* 122: 1095–1099.