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POTENTIAL HEALTH RISKS OF
SMOKELESS TOBACCO
AS USED IN WESTERN POPULATIONS

A SUMMARY OF THE EVIDENCE RELATING
TO ORAL CANCER AND CARDIOVASCULAR DISEASE

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Introduction

In the United States, smokeless tobacco has formed an important part of total tobacco consumption for many years. For example, chewing tobacco and snuff represented 12% of all tobacco products by weight in 1995. In most other economically developed countries, smokeless tobacco forms only an unimportant part of the market, the major exception being Sweden, where snuff (“snus”) has always formed a large proportion of total sales of tobacco (45% in 1995). Smokeless tobacco is also widely used in parts of Central and South-East Asia, in a variety of forms and in combination with other products such as betel nut quid, but this summary will concentrate on the evidence relating to the potential health risks of smokeless tobacco as used in Western populations.

Concerns about health risks associated with smokeless tobacco have mainly related to oral cancer (since smokeless tobacco is normally used orally) and to cardiovascular disease (since cigarette smoking is associated with an increased risk of the disease, smokeless tobacco involves an exposure to nicotine that is quite comparable to that from cigarette smoking, and nicotine has been implicated in several processes related to the disease). Accordingly, detailed reviews have been carried out of the evidence relating to both oral (including pharyngeal) cancer (Appendix 1) and cardiovascular disease (Appendix 2), the main conclusions being summarized below.

Oral cancer

27 case-control and 5 prospective studies were identified that provided relevant information. 23 of the studies were conducted in the USA, 5 in Sweden and one each in Puerto Rico, England, Norway and Brazil. Many of the studies involved small numbers of oral cancer cases who used smokeless tobacco, collected data from unreliable sources and failed to report their findings adequately, take account of potential confounding variables or conduct dose-response analyses. A few studies had gross weaknesses of design. Despite these problems, a number of conclusions can be drawn from the available data.

1. **Use of Swedish and snuff carries little or no increased risk of oral/pharyngeal cancer**

This conclusion derives mainly from two high quality studies published in 1998 which reported relative risks (for head and neck cancer and for oral cavity cancer respectively) that were close to unity after adjustment for relevant confounders, and partly from a smaller study of lip cancer which also found no association with snuff use. A combined relative risk estimate of 0.97 (95% confidence interval [CI] 0.72-1.30) can be derived from these 3 studies, findings which seem consistent with the results of a poorly reported study conducted over 40 years ago, and with results of a further prospective study for which detailed data are not available.

2. **There is no convincing evidence of an effect of chewing tobacco on the risk of oral/pharyngeal cancer**

This conclusion derives from 11 studies, mainly conducted in the USA. Though data on risk by detailed site of cancer within the mouth, on risk in nonsmokers and on dose-response are limited, the consistent lack of association of chewing tobacco with oral/pharyngeal cancer seen in studies published since 1969, which provide a combined relative risk estimate of 1.07 (95% CI 0.92-1.24), argues against earlier reports (in 1920, 1957 and 1962) of a significant association of chewing tobacco with, respectively, lip cancer, oral/pharyngeal cancer and mouth/pharynx/larynx cancer.

3. **Snuff use in the USA is associated with an increased risk of oral/pharyngeal cancer, particularly of the gum and buccal mucosa, but the evidence is extremely heterogeneous**

Meta-analysis of the evidence indicates a significantly increased risk, with the combined relative risk estimate 2.26 (95% CI 1.08-4.75). However, this conceals enormous variability between studies. While significantly increased relative risks of oral/pharyngeal cancer related to snuff use of 2.42, 2.67, 3.40, 4.22, 4.81 and 14.6 have been reported in six studies with a further study, of

dubious design, reporting a relative risk as high as 540), three other studies have reported non-significant relative risks of 0.42, 0.62 and 0.80, all with an upper 95% confidence limit below 2. Three of the studies showing a positive association reported large relative risks for cancer of the gum and buccal mucosa, where the snuff is typically held, but a much smaller increase in risk for cancers of other sites. Limited evidence suggests that risk estimates are higher in women than men and in never than ever smokers and increase with duration of snuff use. Although the reason for the between-study heterogeneity is unclear, the overall data show a clear relationship of snuff use in the USA to risk of cancer of the gum and buccal mucosa. A possible weaker relationship to risk of cancer of the pharynx or other sites in the mouth has not been so clearly demonstrated.

4. **Results relating oral/pharyngeal cancer risk to the unspecified use of smokeless tobacco also show evidence of an association**

This conclusion is based mainly on studies conducted in the USA. Relative risks are again heterogeneous, though less so than for snuff, the overall data giving a combined (random-effects) relative risk estimate of 1.93 (95% CI 1.41-2.64). The evidence is inconsistent regarding the cancer site showing the strongest relationship. Limited data suggest a higher relative risk in nonsmokers than in smokers, but provide no clear evidence of a dose-response relationship. The data for unspecified smokeless tobacco use, which take little account of potential confounding variables, taken on their own, do not provide completely convincing evidence of a true effect. However, snuff is part of unspecified smokeless tobacco use and it is reasonable to conclude that the observed increase is, at least in part, a real one.

5. **In summary, oral/pharyngeal cancer risk is increased by smokeless tobacco use in the USA. This increase is related mainly, if not wholly, to the use of oral snuff rather than to chewing tobacco, and predominantly arises where the snuff is held, typically, in the gingival buccal area. Limited evidence suggests that the risk is greater in never smokers and in women. Oral snuff, as used in Sweden, does not appear to increase the risk of oral/pharyngeal cancer**

Results from some relevant random-effects meta-analyses are given below:*

| Exposure/Studies considered | Studies | Estimates | Relative risk (95% CI) |
|--|---------|-----------|---------------------------|
| <u>Chewing tobacco</u> | | | |
| All studies | 11 | 14 | 1.29(0.99-1.68) |
| Studies published since 1969 | 8 | 11 | 1.07(0.92-1.24) |
| Studies of nonsmokers | 3 | 4 | 1.68(1.00-2.80) |
| All studies except two with major weaknesses | 9 | 12 | 1.27(0.96-1.69) |
| <u>Snuff</u> | | | |
| All studies | 14 | 14 | 2.31(1.23-4.32) |
| All studies except two with major weaknesses | 12 | 12 | 1.80(1.00-3.27) |
| - conducted in Sweden | 3 | 3 | 0.97(0.72-1.30) |
| - conducted in USA | 9 | 9 | 2.26(1.08-4.75) |
| <u>Smokeless tobacco use</u> | | | |
| All studies | 11 | 17 | 1.93(1.41-2.64) |
| All studies except two with outlying results | 9 | 13 | 1.59(1.30-1.95) |

*See Appendix 1 sections 4.2-4.4 for fuller details of these meta-analyses

Cardiovascular disease

Evidence has been reviewed relating use of smokeless tobacco to incidence of or mortality from cardiovascular disease, to risk of hypertension and to other cardiovascular risk factors. Where possible, smokeless tobacco users have been compared both with non-users of tobacco and with smokers.

1. **The epidemiological data do not demonstrate the existence of an association between smokeless tobacco and risk of cardiovascular disease incidence/mortality**

There are four relevant epidemiological studies. Two are case-control studies of myocardial infarction (MI) in Northern Sweden, one is a prospective study of Swedish construction workers and one a prospective study of a representative sample of the US population. All involve moderately large numbers of cases of cardiovascular disease and, though all have some potential limitations, they all provide some useful information. Endpoints considered vary from study to study, and include all MI, fatal MI and mortality from ischaemic heart disease (IHD), stroke, all cardiovascular disease and all circulatory disease, and the results predominantly relate to men.

As expected, the evidence of an increased risk in smokers (compared to non-users of tobacco) is generally clear. The evidence of an increased risk in smokeless tobacco users is much less compelling. The two studies in Northern Sweden and the US study show no significant increase in risk, and it is only the study of Swedish construction workers where a significant increase is seen, which even then is less than that seen in smokers. Combining estimates of the relative risk (RR) of smokeless tobacco users compared to non-tobacco users for MI from the two case-control studies and for IHD from the two prospective studies by random-effects meta-analysis gives an estimate of 1.09 (95% CI 0.80-1.49) for the sexes combined which is not significant. Similarly combining estimates for fatal MI from one of the Swedish case-control studies with those for all cardiovascular disease death from the Swedish construction workers study and for

all circulatory disease death from the US prospective study gives an estimate of 1.30 (CI 0.95-1.77) for the sexes combined. These two estimates are little changed if attention is restricted to males (1.04, CI 0.73-1.49 and 1.33, CI 0.91-1.95 respectively).

Combining estimates of the relative risk of smokers to smokeless tobacco users (here only available for males), in contrast, shows significant results, with RRs of 2.14 (CI 1.31-3.49) for MI/CHD and of 1.51 (CI 1.09-2.09) for fatal MI/cardiovascular disease/circulatory disease.

2. **There is adequate evidence of an effect of smokeless tobacco, as used in the USA, on blood pressure and other risk factors for cardiovascular disease**

The evidence consists of a number of case reports suggesting an acute effect of smokeless tobacco on blood pressure, a number of experimental studies which generally found an acute rise in blood pressure and/or in heart rate, a number of cross-sectional studies, all but one of which report an increased blood pressure in smokeless tobacco users, two case reports of Buerger's disease associated with smokeless tobacco and single reports of reduced exercise performance, increased tachycardiac response to exercise and increased hypercholesterolaemia in smokeless tobacco users. Though some of the cross-sectional studies fail to distinguish possible acute and chronic effects of smokeless tobacco, there certainly seems to be adequate evidence of an effect of US smokeless tobacco on the cardiovascular system. Some of the evidence allows comparison of effects in smokers and in smokeless tobacco users, with some studies on blood pressure and on cholesterol levels suggesting the possibility that effects might be greater in smokeless tobacco users. However, the evidence here is inconclusive.

3. **There is very limited evidence that Swedish snuff has any effect on blood pressure or other risk factors for cardiovascular disease**

Most cross-sectional studies found no real suggestion of an increased blood pressure in snuff users, and though one found clear increases in smokeless tobacco users in both blood pressure and a disability diagnosis of hypertension, this was the same study of construction workers which unusually found an association with cardiovascular mortality. Similarly, although there are two reports of an increase in Raynaud-like symptoms in smokeless tobacco users, the evidence generally shows little or no association with cardiovascular risk factors, including levels of fibrinogen, cholesterol and other lipids or antioxidant vitamins, sonographic evidence of atherosclerosis, markers of platelet activity, and response to exercise.

While one would certainly like to have an explanation of the unusual results from the study of Swedish construction workers, the overall data in relation to Swedish snuff provides little evidence that it has any effect at all on risk of cardiovascular disease or on factors that are generally associated with an increased risk. Even if it does have some effects, they are likely to be substantially less than those from smoking. The finding that effects of Swedish snuff on the cardiovascular system, if any, are far less than those of cigarette smoking, despite snuffers and smokers having comparable exposure to nicotine, is similar to findings based on comparison of pipe and cigarette smokers, and strongly suggests that the increased risk of cardiovascular disease associated with cigarette smoking is not a result of exposure to nicotine.