SMOKELESS TOBACCO

Smokeless tobacco was considered by a previous IARC Working Group in 2004 (IARC, 2007a). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Smokeless tobacco products

The term smokeless tobacco implies use of unburned tobacco in the finished products. A variety of smokeless tobacco products are available, for oral or nasal use. Products intended for oral use are sucked, chewed (dipped), gargled or applied to the gums or teeth, while fine tobacco mixtures are usually inhaled into the nostrils.

Table 1.1 summarizes for each smokeless tobacco product its mode of use, the main ingredients included, the WHO regions in which the product is used, and some specification of the countries is which the product is used most commonly or specifically (DHHS, 2001; IARC, 2007a; European Commission, 2008). Smokeless tobacco products that contain areca nut are commonly used in India, other countries in South Asia, and in migrant populations from these countries. These products may be mentioned here for comparison but are reviewed in the *Monograph* on Betel Quid and Areca Nut in this volume.

1.2 Chemical composition of smokeless tobacco

The tobacco used in a particular product has a decisive influence on its chemical composition, and varies with tobacco species, growing, curing, processing and storage. During product manufacture, tobacco is blended to achieve a specific nicotine content and pH. The pH strongly influences the concentration of unprotonated nicotine, the bioavailable form of nicotine, while the nitrite/nitrate content strongly influences the levels of carcinogenic nitrosamines in the product. Other tobacco components are alkaloids which include nicotine (85–95% of total alkaloids), terpenes, polyphenols, phytosterols, carboxylic acids, aromatic hydrocarbons, aldehydes, ketones, amines, nitriles, *N*- and *O*-heterocyclic hydrocarbons, pesticides, and metallic compounds. Flavour-type additives are also present (Bates *et al.*, 1999). Ammonia, ammonium carbonate and sodium carbonate are applied to control nicotine delivery by raising pH and subsequently the level of unprotonated nicotine which is most readily absorbed through the mouth into the bloodstream (Djordjevic *et al.*, 1995).

Table 1.1 Smokeless tobacco products, ingredients, and use by WHO region

Tobacco product	Mode of use	Ingredients	WHO Region					
			AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Oral use								
Betel quid with tobacco[a]	Chewing	Betel leaf, areca nut, slaked lime, tobacco in various forms			X		X	X
Chimó	Sucking	Paste of crushed and boiled tobacco leaves, sodium bicarbonate, sugar, wood ash, flavourings		X[b]				
Chewing tobacco	Chewing	See Tobacco chewing gum						
Chewing tobacco twist/ roll	Chewing	Dark, air- or fire-cured tobacco leaves treated with tobacco extract, flavourings		X[c]				
Creamy snuff	Other	Finely ground tobacco with aromatic substances (manufactured commercially)					X	
Dry snuff	Sucking	Fire- or air-cured, fermented powdered tobacco	X[d]	X[c]	X[e]	X[f]	X[g]	
Gudhaku	Other	Paste of powdered tobacco and molasses					X[g]	
Gul	Other	Powdered tobacco, molasses and other ingredients					X[g]	
Gutka[a]	Sucking	Sun-dried finely chopped tobacco, areca nut, slaked lime, catechu, flavourings, sweeteners (manufactured commercially)					X	
Iq'mik	Chewing	Fire-cured tobacco leaves with punk ash		X[h]				
Khaini	Sucking	Sun-dried or fermented coarsely crushed tobacco leaves					X[i]	
Khiwam	Chewing	Paste of tobacco extract, spices, additives					X[j]	
Loose leaf	Chewing	Small strips of air-cured, shredded cigar tobacco leaves (manufactured commercially)		X[c]		X		
Maraş	Sucking	Sun-dried powdered tobacco leaves, wood ash, water				X[k]		
Mawa[a]	Chewing	Sun-cured areca nut, crushed tobacco leaves, slaked lime					X[j]	
Mishri	Sucking	Tobacco toasted on hot metal plate and powdered					X[g]	
Moist snuff	Sucking	Air- or fire-cured tobacco, processed into fine particles (fine-cut) or strips (long-cut), with stem and seeds		X[c]		X[l]		
Naswar/nass	Sucking	Sun-dried, powdered tobacco, ash, oil, flavourings, colourings, slaked lime (optional)	X[d]		X[m]	X		
Plug chewing tobacco	Chewing	Heavy-grade or cigar tobacco top leaves immersed in liquorice or sugar, pressed into a plug		X[c]				
Red tooth powder	Other	Fine tobacco powder, many additional ingredients (manufactured commercially)					X	
Shammah	Sucking	Powdered tobacco, lime, ash, black pepper, oils, flavourings			X[n]	X		
Snus	-	See moist stuff		X[c]		X[l]		

Table 1.1 (continued)

Tobacco product	Mode of use	Ingredients	WHO Region					
			AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Saffa	-	*Toomback* rolled into a ball	X[q]					
Tobacco tablet	Sucking	Compressed powdered tobacco, mint, eucalyptus		X[c]				
Toombak	Sucking	Dried, fermented, ground and matured tobacco leaves, sodium bicarbonate	X[q]					
Tuibur	Other	Tobacco water					X[r]	
Zarda	Chewing	Tobacco leaves boiled with lime and spices until dry, colourings; chewed with areca nut and spices			X		X	
Nasal use								
Dry snuff	Sniffing	Fire-cured, fermented and powdered tobacco	X[s]		X	X[t]	X	
Liquid snuff	Sniffing	Powered tobacco mixed with ash from plants, oil, lemon juice, herbs	X[u]					

[a] These products contain areca nut and are reviewed in the *Monograph* on Betel Quid and Areca Nut in this volume.
[b] Specific to Venezuela, used by young boys and urban teenagers
[c] Used in the USA
[d] Used principally in South Africa; dry snuff is mostly inhaled.
[e] Common in North Africa, notably in Tunisia as *neffa*
[f] Used in Germany, Georgia and the United Kingdom
[g] Used as dentifrice, mostly by women, in various parts of India
[h] Specific to native American tribes of North-West Alaska
[i] Used in India, Bangladesh and Nepal
[j] Specific to India
[k] Specific to remote regions of Turkey
[l] Used in Sweden, Norway and Finland
[m] Common in Afghanistan, Islamic Republic of Iran, Pakistan and central Asia
[n] Common in the Middle East, particularly in Saudi Arabia and Yemen
[o] Used in Sweden and Denmark
[p] Specific to Japan (new product)
[q] Specific to Sudan, used by men
[r] Specific to eastern States of India
[s] Used by several tribes in South Africa, namely Bantus
[t] Used in the United Kingdom
[u] Specific to tribes in East Africa
AFRO, African Region; AMRO, Regions of the Americas; EMRO, Eastern Mediterranean Region; EURO, European Region; SEARO, South East Asian Region, WPRO, Western Pacific Region; the countries included in each region are available at http://www.who.int/about/regions/en/

1.2.1 Nicotine content in smokeless tobacco

The majority of commercial tobacco products are made from *N. tabacum* species, grown throughout the world with an alkaloid content that varies greatly. In randomly cultivated varieties examined, the alkaloid content ranged between 0.17 and 4.93%.

N. rustica species is cultivated in eastern Europe, Asia Minor and Africa, and the cured leaves may contain up to 12% nicotine. *Toombak* from Sudan, which contains *N. rustica* tobacco, had the highest reported levels of nicotine (Idris *et al.*, 1991; Prokopczyk *et al.*, 1995). In 17 brands of moist snuff from the USA, the nicotine content ranged from 0.47 to 3.43%.The nicotine content of Swedish snus ranges from 0.5–1.7% (Idris *et al.*, 1998; Stepanov *et al.*, 2008).

1.2.2 Carcinogenic compounds in smokeless tobacco

Multiple carcinogens have been identified in smokeless tobacco (IARC, 2007a) including:

(a) Tobacco-specific N-nitrosamines

Tobacco-specific *N*-nitrosamines include the carcinogens *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Tobacco-specific *N*-nitrosamines are formed from tobacco alkaloids (nicotine, nornicotine, anatabine, anabasine, and nitrite) primarily during tobacco curing, fermentation and ageing. The nitrate or nitrite content, the mode of curing and the various steps of processing are the main determining factors for the yields of tobacco-specific *N*-nitrosamines in tobacco.

IARC (2007a) compiled an international comparison of the concentrations of NNN and NNK in smokeless tobacco products. The ranges vary widely and are product- and country-specific. In some moist snuff brands in the USA, the highest concentrations of NNN and NNK measured were 135 and 17.8 µg/g tobacco, respectively. In home-made *toombak* from Sudan, values as high as 3085 and 7870 µg/g dry wt tobacco, respectively, have been reported (Idris *et al.*, 1991; Prokopczyk *et al.*, 1995).

(b) N-Nitrosamino acids

The amino acids present in tobacco, and probably also the proteins with secondary amino groups, are amenable to *N*-nitrosation. Since 1985, numerous studies have reported the presence of *N*-nitrosamino acids in smokeless tobacco products (IARC, 2007a).

To date, 11 *N*-nitrosamino acids have been identified in smokeless tobacco: *N*-nitrososarcosine (NSAR), *N*-nitrosoazetidine-4-carboxylic acid (NAzCA), 3-(methylnitrosamino)propionic acid (MNPA), 4-(methylnitrosamino) butyric acid (MNBA), *N*-nitrosoproline (NPRO), *N*-nitrosohydroxyproline (NHPRO), *N*-nitrosopipecolic acid (NPIC), *N*-nitrosothiazolidine-4-carboxylic acid (NTCA), *N*-nitroso-2-methylthiazolidine-4-carboxylic acid (MNTCA), 4-(methylnitrosamino)-4-(3-pyridyl)butyric acid (*iso*-NNAC) and 2-(methylnitrosamino)-3-phenylpropionic acid (MNPhPA) (Ohshima *et al.*, 1985; Tricker & Preussmann, 1988; Hoffmann *et al.*, 1995). Of these, NSAR, MNPA, MNBA and NAzCA have been established as carcinogens in experimental animals.

The concentration of *N*-nitrosamino acids depends on the nitrate or nitrite content of tobacco; they are formed during prolonged storage, particularly under adverse conditions of temperature and relative humidity. The concentrations reported in USA moist snuff samples were in the range of 5.7 to 13.45 µg/g dry wt. Highest amounts of MNPA were found in Indian *zarda* (up to 18 µg/g) and in moist snuff (up to 70 µg/g).

Table 1.2 PAHs in moist snuff brands marketed in the USA

Compound	Mean ± SD of 23 brands (ng/g dry weight)
Naphthalene	1726 ± 392.3
Acenaphthylene	110.5 ± 42.9
Acenaphthene	105.1 ± 53.8
Fluorene	826.5 ± 287.0
Phenanthrene	4700 ± 1571
Anthracene	844.2 ± 277.8
Fluoranthene	1404 ± 537.4
Pyrene	1292 ± 428.5
Benz[*a*]anthracene	193.6 ± 71.3
Chrysene	232.1 ± 109.8
Methylchrysenes	92.6 ± 35.0
Benzo[*b*]fluoranthene + Benzo[*f*]fluoranthene	107.0 ± 69.5
Benzo[*k*]fluoranthene	19.6 ± 6.6
Benzo[*e*]pyrene	52.4 ± 23.8
Benzo[*a*]pyrene	55.8 ± 21.5
Indeno[*c,d*]pyrene	20.5 ± 12.1
Benzo[*g,h,i*]perylene	18.0 ± 8.3
Dibenz[*a,h*]anthracene	7.5 ± 1.9

From Stepanov *et al.* (2010)

(c) *Volatile N-nitrosamines*

These include *N*-nitrosodimehtylamine (NDMA), *N*-nitrosopyrrolidine (NPYR) and *N*-nitrosopiperidine (NPIP).

Levels of volatile *N*-nitrosamines formed from volatile amines and nitrosating agents in smokeless tobacco products worldwide have been summarized (IARC, 2007a). The highest amounts were found in moist snuff (NDMA up to 265 ng/g dry wt and NPYR up to 860 ng/g dry wt).

(d) *PAHs*

These include benzo[a]pyrene, benz[a] anthracene, chrysene, benzofluoranthenes, and dibenz[a,h]anthracene.

Levels of various PAHs in 23 moist snuff brands marketed in the USA were determined by Stepanov *et al.* (2010) and are summarized in Table 1.2.

(e) *Other carcinogenic compounds and constituents*

Levels of the volatile aldehydes formaldehyde, acetaldehyde, acrolein and crotonaldehyde in smokeless tobacco products ranged from 0.207–10.6, 0.97–72.3, 0.27–7.85, and 0.55–19.4 µg/g dry weight tobacco, respectively (Stepanov *et al.*, 2010).

Uranium was reported in Indian snuff at a concentration of about 3 pCi/g tobacco (Sharma *et al.*, 1985). Levels of polonium-210 in commercial moist and dry snuff in the USA were reported to be 0.16–1.22 and 0.23–0.39 pCi/g, respectively.

In several parts of the world, smokeless tobacco is invariably chewed with lime which is responsible for highly alkaline pH (Nair *et al.*, 1990, 1992), facilitating absorption of nicotine in the oral mucosa.

1.2.3 *Comparison of new and traditional smokeless tobacco products*

Newer types of smokeless tobacco products are appearing on the market. These products are sold as small pouches and do not require spitting. Similar to Swedish snus, they have been manufactured with additional controls to inhibit nitrosamine formation, and are being promoted as reduced risk products. Levels of carcinogens in these newer products are compared to those in traditional products in Table 1.3 (Stepanov *et al.*, 2008).

1.3 Prevalence of use

1.3.1 *Prevalence of smokeless tobacco use among adults*

Several surveys have evaluated the prevalence of smokeless tobacco use at different times and targeting different populations in the WHO regions (AFRO, African Region; AMRO, Region of the Americas; EURO, European Region; EMRO, Eastern Mediterranean Region; SEARO,

Table 1.3 Mean levels of selected carcinogens in newer and traditional smokeless tobacco products

	Newer products (n = 12)	Traditional products (n = 5)
NNN (µg/g dry weight)	2.05	4.41
NNK (µg/g dry weight)	0.231	1.20
Benzo[*a*]pyrene (ng/g dry weight)	3.12	38.2
Fluoranthene	10.0	400
Benzo[*b*]fluoranthene + Benzo[*k*]fluoranthene (ng/g dry weight)	2.76	38.3
Formaldehyde (µg/g dry weight)	3.23	8.43
Acetaldehyde (µg/g dry weight)	6.16	35.7
Crotonaldehyde (µg/g dry weight)	9.12	2.98

NNN, *N′*-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
From Stepanov *et al.* (2008)

South-East Asian Region; WPRO, Western Pacific Region). The major surveys that form the basis of this report are (Table 1.4):

- the Global Adult Tobacco Survey conducted during 2009–10 among adults aged 15 years or more in 14 middle and low-income countries in AMRO, SEARO, EURO, EMRO and WPRO;
- the national level STEPS noncommunicable risk factor survey (2006–09) was conducted in 8 countries in AFRO, and a few countries in SEARO, EURO (Georgia), EMRO and WPRO (Mongolia), in adults aged 15–64 years, except for AFRO (age group, 25–64 years);
- the Demographic and Health Surveys (2003–10) provide prevalence on smokeless tobacco use among adults aged 15–49 years in countries in AFRO (16), EURO (4), EMRO (2), WPRO (8);
- some other surveys such as the Behavioural Risk Factor Survey, the National Smoking/Tobacco/Drug use Survey, health cost studies, and national health, public health or morbidity surveys.

The prevalence of smokeless tobacco use reported in the various surveys are not directly comparable because of the different methodologies and time periods; however, they provide a snapshot of the global smokeless tobacco burden. Large variations are observed between countries (Table 1.5), between sex within a country, and sometimes within a country (Table 1.6). Those countries with a high prevalence (≥ 10%) represent about 25% of the global adult population. They include, by WHO region:

- in AFRO: Benin (men, 13%), Madagascar (men 23%; women, 20%), Mauritania (women, 28%), South Africa (women, 11%);
- in EMRO: Yemen (men, 15%);
- in EURO: Norway (men, 17.0%; women, 5.0%), Sweden (men, 26%), Uzbekistan (men, 22.5%);
- in SEARO: Bangladesh (men, 26%; women, 28%), India (men, 33%; women 11–18%), Myanmar (men, 51.4%; women, 16.1%), Nepal (men, 31%), Sri Lanka (men, 24.9%);
- in WPRO: Cambodia (women, 12.7%).

A few countries have medium prevalence (between 5% and 10%); these include:

- in AFRO: Benin, Cape Verde, Malawi in women; Lesotho, Mali, Mauritania, Swaziland, Zimbabwe in men;
- in AMRO: USA in men;

- in EMRO: Tunisia in men; Yemen in women;
- in EURO: Finland, Iceland and Kyrgyzstan in men; Norway and Sweden in women;
- in SEARO: Sri Lanka and Thailand in women.

In most countries, current prevalence of smokeless tobacco use is higher among men than among women. Some exceptions are found at all levels of prevalence (in women and men, respectively): Bangladesh (27.9, 26.9), Barbados (0.6, 0), Cambodia (12.7, 0.7), Cape Verde (5.8, 3.5), Malaysia (3.1, 0.5), Mauritania (28.3, 5.7), South Africa (10.9, 2.4), Thailand (6.3, 1.3) and Viet Nam (2.3, 0.3).

Demographic health survey data indicate that in countries in AFRO and SEARO smokeless tobacco is more prevalent in rural compared to urban areas, and higher among low-income compared to high-income groups. Also, prevalence generally increases with increasing age.

Some countries warrant more detailed information of their pattern of smokeless tobacco use, and are presented below.

1.3.2 Country specific data

(a) India

The India Global Adult Tobacco Survey (2009–10) revealed that 26% of all adults use smokeless tobacco in some form, 21.4% daily and 4.5% occasionally. Prevalence in men (32.9%) is higher than in women (18.4%), and is higher in rural (29.3%) than urban areas (17.7%). Large variations are observed between States, from around 5% in Himachal Pradesh, Goa and Chandigarh to 49% in Bihar (India GATS Report, 2009–10).

Khaini is the most commonly used smokeless tobacco product (11.6%), followed by *gutka* (8.2%). Prevalence of *khaini* chewing is significantly higher among men (18%) than among women (5%); 13.1% men and 2.9% women chew *gutka*; 6.2% (7.5% men, 4.9% women) of adults use betel quid with tobacco; 4.7% (3.3% men, 6.3% women) use tobacco products such as *mishri, gul, gudakhu* for oral application (dentifrice); and 4.4% uses some other products, such as snuff for nasal application and some local products. The pattern of use of smokeless tobacco products also varies widely in different States of India (Table 1.6) (India GATS Report, 2009–10).

Proportion of dual tobacco users (smoking+smokeless) is 19.4% among men and 5.3% among women (Sinha *et al.*, 2011).

(b) Bangladesh

In Bangladesh the most prevalent form of smokeless tobacco is betel quid with tobacco (24.3%), followed by *gul* (5.3%), *sada pata* (1.8%), *khaini* (1.5%) and others (1.4%) (BAN GATS Report, 2009). Use decreases with increasing education and socioeconomic level in both men and women, by a steeper rate among women compared to men. Among current users, those with the highest prevalence of use of *gul* and *khaini* were labourers among men (7.5% and 2.8%, respectively) and homemaker among women (5.7% and 1.4%, respectively) (BAN GATS Report, 2009).

Proportion of dual tobacco users (smoking+smokeless) is 22.5% among men and 2.5% among women (Sinha *et al.*, 2011).

(c) Canada

Unchanged from surveys conducted in 2008 and 2009, 8% of Canadians aged 15 years and older reported having ever tried smokeless tobacco products in 2010. In 2009, 11% of young adults aged 20 to 24 years reported ever using smokeless tobacco and 1% having used it within the past 30 days. There has been a shift in the distribution of past-30-day smokeless tobacco users from youth towards older adults: in 2003, 23% of users were aged 15–19 years and 14% were older than 45 years, whereas in 2009, 16% of smokeless tobacco users were 15 to 19 years old and 33% were aged 45 and older.

Table 1.4 Surveys and articles used to compile the information presented*

Bangladesh GATS report Government of the People's Republic of Bangladesh, Ministry of Health and Family Welfare; World Health Organization, Country Office for Bangladesh. Global Adult Tobacco Survey: Bangladesh Report 2009. Dhaka, 2009. http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATSBAN_FullReport2009.pdf
Canada CTUMS Canadian Tobacco Use Monitoring Survey (CTUMS) 2010, http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_2010/ann_summary-sommaire-eng.php
Central Statistical Office (CSO) [Swaziland], and Macro International Inc. 2008. *Swaziland Demographic and Health Survey 2006–07.* Mbabane, Swaziland: Central Statistical Office and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR202/FR202.pdf
Central Statistical Office (CSO) [Zimbabwe] and Macro International Inc. 2007. *Zimbabwe Demographic and Health Survey 2005–06.* Calverton, Maryland: CSO and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR186/FR186.pdf
Central Statistical Office (CSO), Ministry of Health (health ministry), Tropical Diseases Research Centre (TDRC), University of Zambia, and Macro International Inc. 2009. *Zambia Demographic and Health Survey 2007.* Calverton, Maryland, USA: CSO and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR211/FR211[revised-05-12-2009].pdf
Department of Health, Medical Research Council, OrcMacro. 2007. *South Africa Demographic and Health Survey 2003. Pretoria: Department of Health.* http://www.measuredhs.com/pubs/pdf/FR206/FR206.pdf
Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF Macro. 2009. *Ghana Demographic and Health Survey 2008*. Accra, Ghana: GSS, GHS, and ICF Macro. http://www.measuredhs.com/publications/publication-FR221-DHS-Final-Reports.cfm
Global Tobacco epidemic report World Health Organization. World Report on the Global Tobacco Epidemic, 2009: Implementing Smoke-Free Environments. Geneva: WHO, 2009.
Global Tobacco epidemic report World Health Organization. World Report on the Global Tobacco Epidemic, 2011 Geneva: WHO, 2011.
India GATS report Government of India, Ministry of Health and Family Welfare. Global Adult Tobacco Survey: GATS India 2009–2010. Mumbai, 2010. http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATS_India.pdf
Institut National de la Statistique (INSTAT) et ICF Macro. 2010. *Enquête Démographique et de Santé de Madagascar 2008–2009.* Antananarivo, Madagascar: INSTAT et ICF Macro. http://www.measuredhs.com/pubs/pdf/FR236/FR236.pdf
Institut National de la Statistique et de l'Analyse Économique (INSAE) [Bénin] et Macro International Inc. 2007: *Enquête Démographique et de Santé (EDSB-III) – Bénin 2006*. Calverton, Maryland, USA: Institut National de la Statistique et de l'Analyse Économique et Macro International Inc. http://www.measuredhs.com/publications/publication-FR197-DHS-Final-Reports.cfm
Kenya National Bureau of Statistics (KNBS) and ICF Macro. 2010. *Kenya Demographic and Health Survey 2008–09*. Calverton, Maryland: KNBS and ICF Macro. http://www.measuredhs.com/publications/publication-FR229-DHS-Final-Reports.cfm
Liberia Institute of Statistics and Geo-Information Services (LISGIS) [Liberia], Ministry of Health and Social Welfare [Liberia], National AIDS Control Program [Liberia], and Macro International Inc. 2008. *Liberia Demographic and Health Survey 2007.* Monrovia, Liberia: Liberia Institute of Statistics and Geo-Information Services (LISGIS) and Macro International Inc. http://www.measuredhs.com/publications/publication-FR201-DHS-Final-Reports.cfm
Lund M, Lindbak R. *Norwegian Tobacco Statistics 1973–2006.* Oslo: Norwegian Institute for Alcohol and Drug Research; 2007. Sirus skrifter No. 3/2007.
Lundqvist G, Sandström H, Ohman A, Weinehall L. Patterns of tobacco use: a 10-yr follow-up study of smoking and snus habits in a middle-aged Swedish population, Scand J Public Health. 2009, 37:161–7
Ministry of Health and Social Services (MoHSS) [Namibia] and Macro International Inc. 2008. *Namibia Demographic and Health Survey 2006–07.* Windhoek, Namibia and Calverton, Maryland, USA: MoHSS and Macro International Inc. http://www.measuredhs.com/publications/publication-FR204-DHS-Final-Reports.cfm
Ministry of Health and Social Welfare (MOHSW) [Lesotho] and ICF Macro. 2010. *Lesotho Demographic and Health Survey 2009*. Maseru, Lesotho: MOHSW and ICF Macro. http://www.measuredhs.com/publications/publication-FR241-DHS-Final-Reports.cfm

Table 1.4 (continued)

MMWR August 27, 2010, 59(33), 487–92, Tobacco use among Middle and High school students –USA 2000–2009
MMWR August 6, 2010/59(30);946–950, Any tobacco use in 13 states-Behavioural Risk factor Surveillance System 2008
National Bureau of Statistics (NBS) [United Republic of Tanzania] and ICF Macro. 2011. *United Republic of Tanzania Demographic and Health Survey 2010*. Dar es Salaam, United Republic of Tanzania: NBS and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR243/FR243[24June2011].pdf
National Institute of Population Research and Training (NIPORT), Mitra and Associates, and Macro International. 2009. *Bangladesh Demographic and Health Survey 2007*. Dhaka, Bangladesh and Calverton, Maryland, USA: National Institute of Population Research and Training, Mitra and Associates, and Macro International. http://www.measuredhs.com/pubs/pdf/FR207/FR207[April-10-2009].pdf
National Population Commission (NPC) [Nigeria] and ICF Macro. 2009. *Nigeria Demographic and Health Survey 2008*. Abuja, Nigeria: National Population Commission and ICF Macro. http://www.measuredhs.com/publications/publication-FR222-DHS-Final-Reports.cfm
National Statistics Directorate (NSD) [Timor-Leste], Ministry of Finance [Timor-Leste], and ICF Macro. 2010. *Timor-Leste Demographic and Health Survey 2009–10*. Dili, Timor-Leste: NSD [Timor-Leste] and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR235/FR235.pdf
Sinha DN, Palipudi KM, Rolle I *et al*. (2011). Tobacco use among youth and adults in member countries of South-East Asia region: Review of findings from surveys under the global tobacco surveillance system. Indian J Public Health, 55:169–176. PMID:22089684
Statistics Indonesia (Badan Pusat Statistik—BPS) and Macro International. 2008. *Indonesia Demographic and Health Survey 2007*. Calverton, Maryland, USA: BPS and Macro International. http://www.measuredhs.com/pubs/pdf/FR218/FR218[27August2010].pdf
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Uganda Bureau of Statistics (UBOS) and Macro International Inc. 2007. *Uganda Demographic and Health Survey 2006*. Calverton, Maryland, USA: UBOS and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR194/FR194.pdf

*, Exceptionally, the most recent updates of well established ongoing surveys and reports, published after the meeting, were included in this *Monograph*. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

Table 1.5 Highest and lowest prevalence of smokeless tobacco use by WHO regions and by sex

	Men		Women	
WHO region	Lowest	Highest	Lowest	Highest
AFRO	0.8% in Gambia	22.6% in Madagascar	0.2% in Ghana	28.3% in Mauritania
AMRO	0.0% in Barbados	6.9% in USA	0.2% in Guyana & Dominican Republic	0.6% in Barbados
EMRO	1.3% in Saudi Arabia	15.1% in Yemen	0.1% in Libyan	6.2% in Yemen
EURO	0.2% in Switzerland & Latvia	26.0% in Sweden	0% in Switzerland & Ukraine	5% in Kyrgyzstan
SEARO	1.3% in Thailand	51.4% in Myanmar	0.3% in Indonesia	27.9% in Bangladesh
WPRO	0.3% in Viet Nam	2.8% in Mongolia & Philippines	0.1% in the People's Republic of China	12.7% in Cambodia

(d) USA

According to the Behavioural Risk Factor Surveillance System survey (2008), conducted in 13 States, prevalence varied from 0.5% (New Jersey) to 8.8% (West Virginia). Dual use of cigarette and smokeless tobacco products varied from 0.2% (Delaware) to 1.8% (West Virginia).

In an overall analysis of users' demographic characteristics, prevalence of smokeless tobacco use was higher among men (6.3%) than women (0.3%); more prevalent among non-Hispanic whites (4.1%) compared to other ethnic groups; highest in the youngest age group (18–24 years) and decreased steadily with age. Users of smokeless tobacco were almost equally distributed between the sextiles of annual income (3.0 to 3.8%).

(e) Europe

In Europe, countries with a high prevalence of smokeless tobacco use are Norway, Sweden and Uzbekistan.

In Sweden, a 10-year follow-up study of smoking and snus [Swedish moist snuff] habits in a middle-aged Swedish population showed that use of snus increased from 3.1% to 6.0% among women and from 24.6% to 26.3% among men. The number of people who used both snus and cigarettes was stable: 0.5% to 0.8% from baseline to follow-up for women and 4.1% to 3.3% for men. Whereas nearly all snus users in Sweden are daily users, almost half of snus users in Norway use it only occasionally.

1.3.3 Prevalence of smokeless tobacco use among youth

The Global Youth Tobacco Survey (GYTS) is a school-based survey of students aged 13–15 years that uses a two-stage sampling design. In a first stage, schools are selected based on the probability proportional to the enrolment of students in schools. In a second stage, classes are selected randomly. It uses standard questionnaire, field methodology and analysis. The Survey has core questions that spans seven thematic areas pertinent to tobacco. In addition, countries can include country-specific questions that allow assessment of tobacco unique to the country [smokeless tobacco use may include betel quid with tobacco.]

In AFRO, all countries surveyed reported a prevalence of smokeless tobacco use among youth above 5%, ranging from 5.4% in Swaziland to 16.4% in Congo. Among boys, it varied from 5.2% in Seychelles to 18.3% in Congo, whereas among girls, from 4.8% in Togo to 15.8% in Namibia. Prevalence was higher among boys than girls in most countries, except in Uganda where

Table 1.6 Highest and lowest prevalence of use of selected smokeless tobacco products in India, by State

	Lowest	Highest
Betel quid	0.5% in Punjab, Himachal Pradesh, Chandigarh and Uttrakhand	32.8% in Tripura
Dentifrice	0.4% in Tripura	28.35 in Chattishgarh
Khaini	0.5% in Tamil Nadu	32.6% in Jharkhand
Gutka	0.6% in Puducherry	17.0% in Madhya Pradesh

it was higher among girls (9.6% versus 8.6%) (Asma *et al.*, 2011). Four countries (Botswana, Congo, Lesotho and Namibia) are particularly noteworthy: these countries reported the highest prevalence in both sexes (11.3–16.4%), the highest prevalence in boys (11.3–18.3%), the highest prevalence in girls (11.4–15.8%), and similar prevalence in boys and girls.

In AMRO, prevalence of smokeless tobacco use among youth varied from 3.5% in Panama to 9.8% in Barbados. Among boys, it varied from 3.8% in Panama to 11.5% in Barbados, whereas among girls, it varies from 2.6% in Venezuela to 8.5% in Jamaica. Most notably, smokeless tobacco use among boys was above 10% in Barbados, Dominican Republic and Grenada. Girls in most countries used less smokeless tobacco than boys, except in Jamaica (8.5% for both) and Peru (boys, 4.3%; girls, 4.8%) where boys and girls had comparable prevalence (Asma *et al.*, 2011).

In SEARO, all countries surveyed reported a prevalence of smokeless tobacco use among youth above 5%, ranging from 4.9% in Bangladesh to 9.4% in Bhutan. Among boys, it ranged from 5.8% in Bangladesh to 14.1% in Bhutan whereas among girls, it varies from 2.7% in Myanmar to 6% in India. In all countries more boys than girls used smokeless tobacco products (Asma *et al.*, 2011).

In EURO, prevalence of smokeless tobacco use among youth is lower than in other WHO regions, ranging from 1.1% in Montenegro to 6.9% in Estonia. While it ranged from 1.1% in Montenegro to 9.4% in Estonia among boys, it varied from 0.7% in Serbia to 4.5% in Estonia among girls. Except for Estonia (6.9%), all countries reported a prevalence among youth below 5%. Also, in all countries boys used more smokeless tobacco than girls (Asma *et al.*, 2011).

In EMRO, prevalence of smokeless tobacco use among youth varied from 1.6% in Oman to 12.6% Djibouti. Among boys, it varied from 2% in Libyan Arab Jamahirya to 15.2% in Djibouti, whereas among girls, it varied from 0.9% in Oman and Tunisia to 9% in Djibouti. Prevalence of smokeless tobacco use among youth was highest in Djibouti (12.6%), where it is also highest among boys and girls separately. Boys generally used more smokeless tobacco than girls, except in Libyan Arab Jamahirya and Yemen where girl users slightly outnumbered boy users (Asma *et al.*, 2011).

In WPRO, prevalence of smokeless tobacco use among youth varies from 2.1% in Macau to 8.7% in Cook Islands. Among boys, it varies from 2.2% in Macau to 10.5% in Cook Islands, whereas among girls, it varies from 2.1% in Macau to 7.3% in Cook Islands. Prevalence of smokeless tobacco use among youth in Cook Island and Republic of Korea is above 5% for boys and girls combined, as well as separately for boys and girls. Prevalence among boys was generally higher than among girls (Asma *et al.*, 2011).

In summary, among the countries included in the GYTS survey 2007–2010, the prevalence of smokeless tobacco use among youth aged 13–15 years exceeds 5% in all or most countries in AFRO, AMRO and SEARO, in Djibouti, Islamic Republic of Iran, Qatar, Syrian Arab Republic and Yemen in EMRO, and in the Cook Islands and Republic of Korea in WPRO (Asma *et al.*, 2011).

In general, prevalence among boys was higher than among girls, although in several countries prevalence was similar, or higher among girls.

In several countries, smokeless tobacco use among 13 to 15 year-old men is higher than that among adult men (aged 15 years or more). These include Albania, Argentina, Brazil, the Dominican Republic, Guyana, Lesotho, Mexico, Namibia, Saudi Arabia, Tunisia and Uganda. Similarly, in Albania, Argentina, Barbados, Brazil, Dominican Republic, Guyana, Kyrgyzstan, Libyan Arab Jamahirya, Mexico, Saudi Arabia, Swaziland, Uganda and Yemen, smokeless tobacco use among 13–15 year women is higher than that in adult women.

2. Cancer in Humans

2.1 Oral use

2.1.1 Cancers of the oral cavity and pharynx

(a) Overview of studies

Studies of smokeless tobacco and oral and pharyngeal cancer have been conducted in North and South America, Europe, Asia, and Africa. All of the studies reported here examined oral cancer risks associated with use of unsmoked tobacco that was not part of a betel quid. Evidence regarding betel quid is presented in the *Monograph* on Betel Quid in this volume. This section focuses on the predominant smokeless tobacco products and behaviours in the countries in which the studies were conducted, for example on chewing tobacco and snuff in North America, snus in northern Europe, *shammah* in Saudi Arabia and Yemen, *toombak* in Sudan, and a variety of types in South Asia (see Table 1.1 for their mode of use, ingredients and region of use). The studies typically examine cancers arising in intra-oral sites, which are predominantly squamous cell in origin (Canto & Devesa, 2002), but some include other sites as well, such as the oropharynx, hypopharynx, or larynx. Studies involving smokeless tobacco and nasopharyngeal cancer are discussed in another chapter.

The previous *Monograph* (IARC, 2007a) concluded that there was *sufficient evidence* in humans that smokeless tobacco causes cancer of the oral cavity. Studies published since include updates on mortality and incidence for one of the cohorts reviewed previously (Accortt *et al.*, 2002, 2005), two new cohort studies (Luo *et al.*, 2007; Roosaar *et al.*, 2008); case–control studies from Sweden (Rosenquist, 2005; Rosenquist *et al.*, 2005) and India (Sapkota *et al.*, 2007); and three meta-analyses (Weitkunat *et al.*, 2007; Boffetta *et al.*, 2008; Lee & Hamling, 2009).

Because tobacco smoking is a risk factor for oral and pharyngeal cancers (IARC, 2004), and tobacco smoking is often positively correlated with smokeless tobacco use (Tomar, 2002), addressing confounding by smoking is important in the examination of causality related to smokeless tobacco. Heavy alcohol use is another important risk factor and can potentially confound the relationship between tobacco use and risk of oral and pharyngeal cancer (IARC, 2010, 2012).

While analysis restricted to non-smokers and non-alcohol drinkers eliminates the possibility of confounding due to smoking and alcohol drinking, the sample sizes can be small in study populations in regions where these behaviours are common. Adjusting statistically for smoking and alcohol can alternatively be used to address confounding by these factors in populations where these behaviours are common and can provide unbiased estimates that may be more stable if there is no residual confounding within smoking/drinking categories used in the adjustment. There is *sufficient evidence* that human papillomavirus (HPV) 16 causes oral cancer in humans (IARC, 2007b). Studies have shown that the prevalence of HPV DNA is negatively correlated with tobacco smoking and alcoholic beverage consumption (Gillison *et al.*, 2000), suggesting that positive confounding by HPV is

not likely to account for a spurious association between smokeless tobacco and oral cancer.

The specific name of the smokeless tobacco product will be used whenever available. In the USA, where moist snuff and chewing tobacco are both common, the term "smokeless tobacco" refers to use of either. Most publications provide data on "ever" versus "never" use of these products, usually defined as using the product or not for some minimal length of time such as a year. Due to the large body of evidence, this *Monograph* will focus on studies published since IARC (2007a).

(i) Cohort studies

Ever lifetime use or ever daily use of smokeless tobacco and risk of oral and pharyngeal cancers was examined in six cohort studies conducted in the USA (Zahm *et al.*, 1992; Accortt *et al.*, 2002, 2005; Henley *et al.*, 2005), Sweden (Luo *et al.*, 2007; Roosaar *et al.*, 2008), and Norway (Boffetta *et al.*, 2005). Mortality data were analysed in four studies (Zahm *et al.*, 1992; Accortt *et al.*, 2002; Henley *et al.*, 2005; Roosaar *et al.*, 2008), four (Accortt *et al.*, 2005; Boffetta *et al.*, 2005; Luo *et al.*, 2007; Roosaar *et al.*, 2008) analysed cancer incidence. None of the studies excluded persons diagnosed in the first 1 or 2 years of follow-up nor did they collect information on changes in behaviours, such as smokeless tobacco or smoking cessation or initiation, after the baseline (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.1.pdf).

Ever use of smokeless tobacco was associated with a statistically significant threefold increased risk of death from oral cancer and an 8.7 fold increased risk of death from pharyngeal cancer in one study from the USA (Zahm *et al.*, 1992). Risks were greater among those with more frequent use, but adjustment was not performed for tobacco smoking and therefore this study will not be considered further in this section.

Ever use of smokeless tobacco was not associated with risk for cancer in four cohorts (Accortt *et al.*, 2005; Boffetta *et al.*, 2005; Henley *et al.*, 2005; Luo *et al.*, 2007). In one cohort the age-adjusted standardized mortality ratio for oral cancer associated with ever smokeless tobacco use was not elevated (Accortt *et al.*, 2002) and the age-adjusted standardized incidence ratio for smokeless tobacco use and oral cancer was statistically lower than expected (Accortt *et al.*, 2005). The expected number of oral cancer deaths among ever smokeless tobacco users in this cohort was zero, suggesting limited statistical power to detect elevated risks.

In the Cancer Prevention Study I and II cohorts (Henley *et al.*, 2005; CPS-I and CPS-II, respectively), the hazard ratio (HR) for death from oral and pharyngeal cancer in CPS-I for current use of smokeless tobacco versus never use among men who never used any other form of tobacco was 2.0 (95%CI: 0.5–7.7), based on four deaths adjusting for alcohol consumption, fruit/vegetable intake and other factors. The corresponding HR in CPS-II was 0.9 (95%CI: 0.1–6.7), based on one death adjusting for similar factors as CPS-I.

In the Norwegian cohort (Boffetta *et al.*, 2005), the HR for ever use of smokeless tobacco was 1.1 (95%CI: 0.5–2.4), for oral, pharynx or salivary gland cancer after adjusting for age and smoking. Among non-smokers in a cohort of 280 000 Swedish male construction workers, the relative risk of developing oral cancer was 0.8 (95%CI: 0.4–1.7), adjusting for attained age and body mass index (BMI) (Luo *et al.*, 2007).

One cohort study in Sweden involved 9 860 men who participated in an oral examination (Roosaar *et al.*, 2008). An elevated relative risk (RR) of 3.1 (95%CI: 1.5–6.6) was found for ever daily use of snus compared to never daily use of snus controlling for calendar period, area of residence, alcohol consumption, smoking, and an interaction variable for age and smoking. Among

the never-smokers in the cohort, the relative risk for ever daily use of snus was 2.3 (95%CI: 0.7–8.3).

All cohort studies had at least 12 years of follow-up. No increased risk of oral cancer was observed for the three cohorts with 12–26 years of follow-up (Accortt *et al.*, 2002, 2005; Henley *et al.*, 2005; Luo *et al.*, 2007). One study with 35 years follow-up found no association of smokeless tobacco and oral cancer risk (Boffetta *et al.*, 2005) and another study with 27–29 years follow-up had significant positive findings among smokers only (Roosaar *et al.*, 2008).

(ii) Case–control studies

Many case–control studies examined smokeless tobacco and oral and pharyngeal cancer (Broders, 1920; Moore *et al.*, 1953; Wynder & Bross, 1957; Wynder *et al.*, 1957a, b; Peacock *et al.*, 1960; Chandra, 1962; Vogler *et al.*, 1962; Vincent & Marchetta, 1963; Martinez, 1969; Keller, 1970; Browne *et al.*, 1977; Jafarey *et al.*, 1977; Williams & Horm, 1977; Wynder & Stellman, 1977; Westbrook, 1980; Winn *et al.*, 1981a; Wynder *et al.*, 1983; Stockwell & Lyman, 1986; Young *et al.*, 1986; Blot *et al.*, 1988; Spitz *et al.*, 1988; Franco *et al.*, 1989; Goud *et al.*, 1990; Blomqvist *et al.*, 1991; Maden *et al.*, 1992; Marshall *et al.*, 1992; Mashberg *et al.*, 1993; Spitz *et al.*, 1993; Kabat *et al.*, 1994; Bundgaard *et al.*, 1995; Idris *et al.*, 1995a; Muscat *et al.*, 1996; Lewin *et al.*, 1998; Muscat & Wynder, 1998; Schildt *et al.*, 1998; Schwartz *et al.*, 1998; Wasnik *et al.*, 1998; Chelleng *et al.*, 2000; Merchant *et al.*, 2000; Rosenquist *et al.*, 2005; Rosenquist, 2005; Sapkota *et al.*, 2007). Two studies were of cancer of the salivary gland (Keller, 1969; Muscat & Wynder, 1998), one reported on hypopharyngeal cancer (Sapkota *et al.*, 2007), and one on nasopharyngeal cancer (Chelleng *et al.*, 2000). The same study was reported on twice in two instances (Wynder & Bross, 1957; Wynder *et al.*, 1957a; Rosenquist, 2005; Rosenquist *et al.*, 2005). Additionally, one cross-sectional study was conducted, but the comparability of the two surveys analysed to yield risk estimates was uncertain (Sterling *et al.*, 1992).

Nearly half the studies addressed potential confounding by tobacco smoking. In three (Broders, 1920; Stockwell & Lyman, 1986; Keller, 1970), smokeless tobacco information was probably obtained from medical records and, if ascertainment of smokeless tobacco use was more likely from cases than from controls, measurement error might account for the findings and these studies will not be considered further. The remaining 15 studies were conducted in the USA (Vogler *et al.*, 1962; Martinez, 1969; Williams & Horm, 1977; Winn *et al.*, 1981a; Blot *et al.*, 1988; Mashberg *et al.*, 1993; Kabat *et al.*, 1994), Sweden (Lewin *et al.*, 1998; Schildt *et al.*, 1998; Rosenquist, 2005; Rosenquist *et al.*, 2005), India (Chandra, 1962; Wasnik *et al.*, 1998; Sapkota *et al.*, 2007), Pakistan (Merchant *et al.*, 2000), and Sudan (Idris *et al.*, 1995a) (Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.2.pdf).

Five studies were population-based (Williams & Horm, 1977; Blot *et al.*, 1988; Lewin *et al.*, 1998; Schildt *et al.*, 1998; Rosenquist *et al.*, 2005); positive findings were observed in the majority of them (Williams & Horm, 1977; Blot *et al.*, 1988; Lewin *et al.*, 1998) and in all of the hospital-based studies except one (Mashberg *et al.*, 1993). One study (Winn *et al.*, 1981a) also included death certificate cases and controls.

Several case–control studies of oral cancer addressed potential confounding by tobacco smoking either by statistically controlling for tobacco smoking or by restricting to non-smokers. Odds ratios (OR) for ever versus never use of smokeless tobacco overall, or for at least one of the major cancer subtypes, was statistically significantly elevated in eight studies, with odds ratios for oral cavity cancer ranging from 3.9 to 34.5 (Vogler *et al.*, 1962; Martinez, 1969; Williams & Horm, 1977; Winn *et al.*, 1981a; Blot *et al.*, 1988; Kabat *et al.*, 1994; Idris *et al.*, 1995a; Wasnik *et al.*, 1998; Merchant *et al.*, 2000) and

in one study of hypopharyngeal cancer in India (Sapkota *et al.*, 2007). In case–control studies conducted in Sweden, there was no association with use of smokeless tobacco in 2 studies (Schildt *et al.*, 1998; Rosenquist, 2005) or in another study (Lewin *et al.*, 1998) that controlled for smoking and alcohol intake. However, when Lewin *et al.*, 1998 restricted the analysis to non-smokers the odds ratio for head and neck cancer associated with ever use of smokeless tobacco was 4.7 (95%CI: 1.6–13.8). [Rosenquist (2005) was based on a relatively small sample size of 132 cases and 320 controls.]

In one case–control study conducted in the USA (Vogler *et al.*, 1962) and another of *toombak* users in Sudan (Idris *et al.*, 1995a), neither statistical adjustment for tobacco smoking nor restriction to non-smokers was done. However, confounding by smoking was not likely to have a major effect on the risk estimates from these studies. The proportions of smokers in the case and control groups were low in the rural women in the study of Vogler *et al.* (1962) among whom positive findings were found. In the study in Sudan less than 10–12% of the two case groups and in a hospital-based control groups smoked; in the population-based control group 21% were smokers, but most had smoked for less than one year (Idris *et al.*, 1995a).

In a meta-analysis Boffetta *et al.* (2008) included studies published through 2007 that provided information about non-smokers and studies that adjusted for tobacco smoking. The summary estimate for the 11 studies of oral cancer (6 of them also including pharyngeal cancer) was 1.8 (95%CI: 1.1–2.9) overall. For the USA, it was 2.6 (95%CI: 1.3–5.2) and for northern European countries, 1.0 (95%CI: 0.7–1.3) (Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.3.pdf).

Another meta-analysis included 40 studies published through May 2008 (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.4.pdf) but excluded studies in Asian or African populations (Lee & Hamling, 2009). In addition to the studies in the meta-analysis by Boffetta *et al.* (2008), 15 other studies were included: (Moore *et al.*, 1953; Wynder & Bross, 1957; Wynder *et al.*, 1957, 1983; Peacock *et al.*, 1960; Vincent & Marchetta, 1963; Martinez, 1969; Keller, 1970; Browne *et al.*, 1977; Wynder & Stellman, 1977; Young *et al.*, 1986; Spitz *et al.*, 1988; Franco *et al.*, 1989; Blomqvist *et al.*, 1991; Maden *et al.*, 1992; Marshall *et al.*, 1992; Sterling *et al.*, 1992; Zahm *et al.*, 1992; Spitz *et al.*, 1993; Bundgaard *et al.*, 1995; Muscat *et al.*, 1996; Schwartz *et al.*, 1998) and one unpublished study by Perry and colleagues in 1993. Among never-smokers the odds ratio was 1.72 (95%CI: 1.01–2.94) based on 9 studies; further adjustment for alcohol in the three studies where this was possible yielded an odds ratio among never-smokers of 1.87 (95%CI: 0.82–4.27). The estimate for never-smokers among the studies conducted in the USA was 3.33 (95%CI: 1.76–6.32), and decreased with additional adjustment for alcohol drinking (1.58; 95%CI: 0.52–4.81), based on two studies among never-smokers. Corresponding estimates for snuff use in never-smokers in Scandinavia were 1.01 (95%CI: 0.71–1.45; 4 studies) and 2.30 (95%CI: 0.67–7.92; 1 study) adjusted for alcohol drinking. For studies published since 1990, the corresponding estimates were 1.24 (95%CI: 0.80–1.90; 7 studies) in never-smokers and 1.87 (95%CI: 0.82–4.27; 3 studies) adjusted for alcohol drinking.

Lee & Hamling (2009) updated an earlier meta-analysis (Weitkunat *et al.*, 2007) of 32 studies through 2005, excluding studies conducted in Asian populations. Weitkunat *et al.* (2007) did not include three studies (Rosenquist *et al.*, 2005; Luo *et al.*, 2007; Roosaar *et al.*, 2008), but provided sex- and tobacco type- specific estimates not reported by Lee & Hamling (2009). For smokeless tobacco, the overall smoking-adjusted relative risk was 1.35 (95%CI: 1.04–1.76), and for chewing tobacco and snuff, the estimates were 1.42 (95%CI: 0.99–2.03; 6 studies) and

1.28 (95%CI: 0.76–2.14; 7 studies). For men the smoking-adjusted estimate was 1.15 (95%CI: 0.97–1.37) and for women 2.51 (95%CI: 1.73–3.64). For case–control studies with hospital-based controls, the estimates were 1.41 (95%CI: 1.18–1.68) and for studies with population-based controls 0.99 (95%CI: 0.69–1.42). Smoking-adjusted relative risks for smokeless tobacco were elevated only for studies conducted before 1980: 2.02 (95%CI: 1.28–3.20) for earlier than 1969, 2.67 (95%CI: 1.83–3.90) for 1970–1979, compared with 0.97 (95%CI: 0.71–1.31) for 1980–1989, and 1.10 (95%CI: 0.88–1.37) for 1990 or later.

(b) Dose–response evidence

In this and subsequent sections, the relative risks and odds ratios are either among non-smokers or are adjusted for tobacco smoking. Dose–response relationships were observed in several studies.

(i) Duration and intensity

Williams & Horm (1977) found that the odds ratio for oral cavity cancers in men associated with heavy use of smokeless tobacco was higher than for moderate use. Lewin *et al.* (1998) also reported relative risks for head and neck cancer that increased with increasing intensity of oral snuff use. Of the case–control studies that examined duration, higher risks of oral cancer with greater numbers of years of snuff use were noted for cancers of the gum/buccal mucosa, but not for other cancers of the mouth/pharynx category (Winn *et al.*, 1981a). No increase with years of snus use was observed in two Swedish case–control studies (Lewin *et al.*, 1998; Rosenquist *et al.*, 2005). In a study in Sudan (Idris *et al.*, 1995a), the odds ratio for use of *toombak* for more than 11 years was greater than that for fewer years of use.

(ii) Cessation

In two cohort (Boffetta *et al.*, 2005; Luo *et al.*, 2007) and three case–control studies (Lewin *et al.*, 1998; Schildt *et al.*, 1998; Rosenquist *et al.*, 2005), risks were not significantly elevated in either current or former smokeless tobacco users. No studies provided information on time since stopping.

(c) Comparison of types of smokeless tobacco by geographical location

(i) Northern Europe

Four studies from this area found no overall association between use of snus and oral cancer (Lewin *et al.*, 1998; Schildt *et al.*, 1998; Boffetta *et al.*, 2005; Rosenquist, 2005). One case–control study (Rosenquist, 2005) examined users of fermented and not fermented snuff and observed no risk for either type. In Sweden before 1983, snuff was fermented as part of the manufacturing process, and this process is conducive to formation of tobacco-specific *N*-nitrosamines. In one cohort study (Roosaar *et al.*, 2008) the relative risk for ever daily use of snus was 3.1 (95%CI: 1.5–6.6, adjusted for smoking, calendar period, area of residence, alcohol consumption and a variable to account for the interaction between age and smoking) and 2.3 (95%CI: 0.7–8.3) among non-smokers with adjustment for calendar period, area of residence and alcohol consumption. In a case–control study, among non-smokers, the odds ratio for cancers of the oral cavity, pharynx and oesophagus combined was 4.7 (95%CI: 1.6–13.8) (Lewin *et al.*, 1998).

(ii) USA

In the USA chewing tobacco and moist snuff are the predominant forms of smokeless tobacco. In five case–control studies of oral cancer, the odds ratio for ever use of smokeless tobacco were statistically significantly elevated overall for use of one or other type, ranging from 4.2 to 34.5 (Martinez, 1969; Williams & Horm, 1977; Williams *et al.*, 1977; Winn *et al.*, 1981a; Blot *et al.*, 1988; Kabat *et al.*, 1994). No association with use of either of these products was observed in 2 cohort studies (Accortt *et al.*, 2002; 2005;

Henley *et al.*, 2005) and one case–control study (Mashberg *et al.*, 1993).

The odds ratio for chewing tobacco was not statistically significantly elevated in two studies (Mashberg *et al.*, 1993; Kabat *et al.*, 1994); but was in a third (Martinez, 1969). For snuff, one study found no association (Mashberg *et al.*, 1993) and in three others statistically significant elevated risks were observed, ranging from 4.2 to 34.5 (Winn *et al.*, 1981a; Blot *et al.*, 1988; Kabat *et al.*, 1994). In one case–control study in the southern USA positive associations were observed among non-smoking women who were snuff dippers, but a significant association was observed for white, but not black women; dry snuff was the predominant form of snuff used by women in that area (Winn *et al.*, 1981a). Elevated odds ratios persisted with control for poor dentition (Winn *et al.*, 1981b), use of mouthwashes (Blot *et al.*, 1983), fruits and vegetables (Winn *et al.*, 1984), type of respondent (self versus proxy), and alcohol consumption (Winn, 1986).

(iii) Africa, Middle East, and Asia

In Sudan the majority of a consecutively accrued series of oral cancer cases used *saffa*, an oral snuff, a moistened, powdered tobacco treated with sodium sesquicarbonate (Elbeshir *et al.*, 1989). Also, in Sudan *toombak* use was higher in oral cancer cases with squamous cell-carcinomas in sites with direct contact with the quid (e.g. floor of mouth) than cases with less or no contact (e.g. palate) (Idris *et al.*, 1995b). The odds ratio for *toombak* use was 7.3 (4.3–12.4) comparing hospital-based cases with oral cancers in direct contact with the quid versus hospital controls, and 1.4 (0.8–2.5) for cases with oral cancers not usually in direct contact with the quid (Idris *et al.*, 1995a), adjusting for age, sex, tribe and residence. Ten to twelve percent of the cases and hospital controls smoked. Twenty-one percent of population controls smoked, although most had smoked for less than one year.

Case series from Saudi Arabia have noted a high frequency of use of *shammah* or *al-shammah* in series of oral, pharyngeal, and laryngeal cancer cases (Amer *et al.*, 1985; Ibrahim *et al.*, 1986; al-Idrissi, 1990; Allard *et al.*, 1999).

In Pakistan, ever using *naswar* was associated with an odds ratio of 9.5 (95%CI: 1.7–52.5; adjusted for cigarette smoking and alcohol consumption) (Merchant *et al.*, 2000). Reports based on small series of users in which potential confounding by tobacco smoking could not be ruled out also noted higher frequencies of *naswar* use in oral cancer cases than controls or oral cancers among *naswar* users (Aleksandrova, 1970; Nugmanov & Baimakanov, 1970).

In India, a case–control study of buccal mucosa cancer observed an odds ratio of [2.7] for men and [2.5] for women associated with tobacco chewing among non-smokers (Chandra, 1962). In a cross-sectional survey, the period prevalence of oral and oropharyngeal cancer among persons who used *pattiwala*, sun-cured tobacco leaf only, was 1.17 per 100 persons compared to 0.36 among non-chewers of tobacco (Wahi, 1968) [tobacco smoking was not accounted for]. A case–control study of oropharyngeal cancer, using a smokeless tobacco product for teeth cleaning was associated with an odds ratio of 5.2 (95%CI: 2.5–11.8), adjusted for smoking (Wasnik *et al.*, 1998). In another case–control study in India, snuffing tobacco nasally or orally, generally using *naswar*, was associated with elevated odds ratios for hypopharyngeal cancer in never-smokers and in analyses adjusted for tobacco smoking and alcohol consumption (Sapkota *et al.*, 2007). [The Working Group noted that in the Sapkota *et al.* (2007) study, snuff use was nasal as well as oral so the role of oral use could not be separately determined.] In the same study, odds ratios for hypopharyngeal cancer among never-smokers were significantly elevated for *zarda* and non-significantly elevated for *khaini*, after adjusting for centre, age, sex, socioeconomic status, alcohol consumption and tobacco snuffing.

(d) Interactions

In one study in the USA that provided odds ratios for smokers only, smokeless tobacco users only, and smokers who also used smokeless tobacco, each compared to non-users of either, there was no evidence of an interaction between smokeless tobacco use and smoking (Winn *et al.*, 1981a), nor was there any evidence of an interaction between smokeless tobacco use and alcohol consumption in a similar analysis of that study population (Winn, 1986).

2.1.2 Precancerous lesions of the oral cavity

(a) Overview of studies

Studies on the natural history of oral cancer suggest that several types of potentially malignant lesions and conditions precede the development of cancer of the oral cavity. Oral precancerous lesions of relevance are leukoplakia and erythroplakia. The term leukoplakia will be used below to describe white lesions and erythroplakia to describe red lesions. Several classification systems for the lesions have been used (Axéll *et al.*, 1976; Pindborg, 1980, Greer & Poulson, 1983; Pindborg *et al.*, 1996), all involving visual inspection of the oral cavity and a diagnosis based on clinical appearance of the lesions to identify the causes of the white and red oral lesions. Smokeless tobacco use has previously been identified as a risk factor for oral premalignant lesions (IARC, 2007a). Histological and clinical changes occur in the mucosa of snuff users in as few as 2–7 days after initiation of use (Payne *et al.*, 1998). Furthermore, the location of the lesion in the mouth has been shown to correspond to where the smokeless tobacco is typically placed (Salem *et al.*, 1984; Zaridze *et al.*, 1986; Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Ayo-Yusuf *et al.*, 2000).

Since IARC (2007a) one cross-sectional study has been published in the USA (Fisher *et al.*, 2005), one from Sweden (Roosaar *et al.*, 2008), and one from Yemen (Scheifele *et al.*, 2007). Cross-sectional studies and case series from many parts of the world have reported that leukoplakia occurs more commonly among smokeless tobacco users and that persons with lesions are more frequently smokeless tobacco users. Many cross-sectional studies were conducted in the USA (Greer & Poulson, 1983; Poulson *et al.*, 1984; Offenbacher & Weathers, 1985; Wolfe & Carlos, 1987; Creath *et al.*, 1988; Cummings *et al.*, 1989; Stewart *et al.*, 1989; Ernster *et al.*, 1990; Grady *et al.*, 1990; Creath *et al.*, 1991; Daniels *et al.*, 1992; Sinusas *et al.*, 1992; Grasser & Childers, 1997; Tomar *et al.*, 1997; Martin *et al.*, 1999; Lee *et al.*, 2000; Shulman *et al.*, 2004; Fisher *et al.*, 2005; Sinusas & Coroso, 2006). The types of smokeless tobacco implicated are snus in Sweden (Salonen *et al.*, 1990; Rolandsson *et al.*, 2005), Finland (Jungell & Malmström, 1985), and Denmark (Roed-Petersen *et al.*, 1972; Roed-Petersen & Pindborg, 1973; Rolandsson *et al.*, 2005), chewing tobacco in the United Kingdom (Tyldesley, 1971) and India (Jacob *et al.*, 2004), *nass* (*naswar*) in Uzbekistan (Zaridze *et al.*, 1985, 1986; Evstifeeva & Zaridze, 1992), *toombak* in Sudan (Idris *et al.*, 1996; Ahmed *et al.*, 2003; Ahmed & Mahgoob, 2007), snuff (finely ground fermented tobacco leaf with the wet ash of an Amaranthus species plant) in South Africa (Ayo-Yusuf *et al.*, 2000), *shammah* in Yemen (Scheifele *et al.*, 2007) and Saudi Arabia (Salem *et al.*, 1984; Mani, 1985).

Table 2.5 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.5.pdf) includes cross-sectional and case–control studies of smokeless tobacco and leukoplakia, listed by country. Eight reports from the USA adjusted for tobacco smoking, either through statistical adjustment or restriction to non-smokers, one in schoolchildren (Tomar *et al.*, 1997) and the others in adults (Shulman *et al.*, 2004; Ernster *et al.*, 1990; Grady *et al.*, 1990; Daniels *et al.*, 1992; Greene *et al.*, 1992; Martin *et al.*, 1999; Fisher *et al.*, 2005). The prevalence rate ratio or odds ratio for oral leukoplakia in

current smokeless tobacco users exceeded those of non-users for smokeless tobacco overall in four studies from the USA (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Fisher *et al.*, 2005) for snuff in four studies (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Fisher *et al.*, 2005) and for chewing tobacco in two (Ernster *et al.*, 1990; Tomar *et al.*, 1997) but not in a third (Fisher *et al.*, 2005).

In Uzbekistan *nass* (*naswar*) use was positively associated with oral leukoplakia in non-smokers (Zaridze *et al.*, 1986) and after adjusting for smoking, alcoholic beverage consumption, and age (Evstifeeva & Zaridze, 1992). In India, oral precancerous lesions (oral leukoplakia, submucous fibrosis, erythroplakia, and multiple lesions) were associated with tobacco chewing after adjusting for age, sex, BMI, pack–years of smoking, and years of drinking alcohol (Thomas *et al.*, 2003; Jacob *et al.*, 2004).

(b) Dose–response evidence

(i) Duration and intensity

Strong dose–response relationships have been observed in studies in the USA with intensity and duration of use of smokeless tobacco, snuff or chewing tobacco. The prevalence odds ratio for mucosal lesions increased with increasing intensity (amounts used per day or week) and duration (months, years, minutes or hours per day with tobacco in the mouth; shorter time since last used) of use of smokeless tobacco (chewing tobacco and snuff) (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Fisher *et al.*, 2005). Baseball players who used smokeless tobacco only during the playing season had a lower prevalence rate of oral lesions than year-long users, but higher than non-users (Greene *et al.*, 1992).

In Uzbekistan there was a trend of greater odds ratios for pre-leukoplakia and leukoplakia with the number of times *nass* was used per day, earlier age at initiation of the habit, years used, and lifetime intake (Evstifeeva & Zaridze, 1992). In Yemen, there was a dose–response relationship with number of minutes *shammah* was kept in the mouth and the risk was reduced if the mouth was rinsed after using the product (Scheifele *et al.*, 2007).

(ii) Cessation

The prevalence or prevalence odds ratio for oral lesions were higher in current than in former users in studies in the USA (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Shulman *et al.*, 2004; Fisher *et al.*, 2005). Former users generally had higher prevalence or prevalence odds ratio (although not always statistically significantly elevated) than never users (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Fisher *et al.*, 2005). In Uzbekistan, both former (OR, 3.00; 95%CI: 1.08–8.32) and current users (OR, 3.86; 95%CI: 2.60–5.72) had statistically significantly elevated odds ratios associated with *nass* use (Evstifeeva & Zaridze, 1992).

(c) Severity of lesions

The percentage of more severe leukoplakia lesions (degree 3 and 4) was higher with increasing amount of use, longer duration of use, shorter time since last use of snuff, and exposure time in the mouth in studies in the USA (Ernster *et al.*, 1990; Grady *et al.*, 1990; Daniels *et al.*, 1992; Greene *et al.*, 1992; Tomar *et al.*; 1997; Martin *et al.*, 1999). Basal-cell hyperplasia was observed in 4% of 132 lesion biopsies from snuff users, while no hyperplasia was found in the 6 biopsies from chewing tobacco users (Daniels *et al.*, 1992). Severe epithelial atypia was observed in *toombak* users (38%) in a case series in Sudan (Ahmed *et al.*, 2003). Also in Sudan greater duration of *toombak* use was associated with greater severity of the lesions (Idris *et al.*, 1996). In a South African study, lesions were more severe among those with more minutes per day of use and the users of the commercial brand compared to home-made snuff (Ayo-Yusuf *et al.*, 2000).

(d) Types

The prevalence of lesions was higher among snuff users compared with tobacco chewers in several studies (Ernster *et al.*, 1990; Greene *et al.*, 1992; Tomar *et al.*, 1997; Martin *et al.*, 1999). Among snuff users, the prevalence of lesions and the relative risk varied depending on the brand used (Grady *et al.*, 1990; Greene *et al.*, 1992; Martin *et al.*, 1999). In Yemen (Scheifele *et al.*, 2007) the prevalence odds ratio was higher for using black *shammah* compared to white *shammah*. Greater frequency of more severe lesions has been found in users of loose snus compared to men using portion-bag snus (Andersson & Axéll, 1989; Andersson *et al.*, 1994; Rolandsson *et al.*, 2005).

(e) Reversal or progression of lesions

Table 2.6 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.6.pdf) provides information from studies that examined reversal or progression of lesions. In men with leukoplakia that were re-examined 1–21 days after the first examination, 15% of the lesions resolved and 18% improved by one degree (Grady *et al.*, 1991). Smaller lesions were most likely to have resolved in men who decreased or stopped smokeless tobacco use, among users of chewing tobacco compared with those of snuff, among light users, and among seasonal users only. Disappearance or regression of lesions was not associated with duration of smokeless tobacco use or the number of days between the initial examination and follow-up. In a study of military recruits, 97% of the oral lesions observed at the initial examination had completely resolved six weeks after they ceased using tobacco (Martin *et al.*, 1999). In a study in Denmark, there was a lower percentage of snuff users whose lesions transformed to dysplasia or malignancy compared to patients with leukoplakia who did not use snuff (Roed-Petersen & Pindborg, 1973).

Men in Sweden with snus-induced lesions followed over 27–29 years did not have a higher risk of oral cancer (not smoking adjusted) compared to the entire Swedish population (Roosaar *et al.*, 2006). A subset of men had a repeat oral examination 19–22 years after the baseline. Among those who stopped snus entirely or used it less than once per day, 6.1% had a lesion at the follow-up exam. Lesions were still present with the same or lesser severity in 91% of the men who continued use of loose snuff or changed to portion-bag snuff and 8.7% had a worse lesion. Of those who used snus for more hours per day at the follow-up than at baseline, 12.1% had a worse lesion. In an earlier study, after 3–6 months, snus users with oral lesions who used portion-bag snus were more likely to have less severe lesions and users who stopped using snus or who changed to portion bags and changed the placement of the snus in the mouth had no lesions at the original site (Larsson *et al.*, 1991). Snus users who changed to snus with a lower pH and lower nicotine concentrations had less severe lesions after 24 weeks (Andersson & Warfvinge, 2003).

In a 10 year follow up study in India, Gupta *et al.* (1980) reported significantly higher malignant transformation in a group of smokeless tobacco users with precancer.

2.1.3 Cancer of the oesophagus

(a) Overview of studies

Studies of smokeless tobacco and oesophageal cancer have been conducted in North America, Europe and Asia. All of the studies reported here examined oesophageal cancer risks associated with use of unsmoked tobacco that was not part of a betel quid. Evidence regarding betel quid is presented in the *Monograph* on Betel Quid in this volume. These studies generally focused on the predominant smokeless tobacco products and behaviours in the countries in which the studies were conducted.

Two studies (Zendehdel *et al.*, 2008; Nasrollahzadeh *et al.*, 2008) have been published since the previous *Monograph* (IARC, 2007a).

Major risk factors for oesophageal cancers are tobacco smoking, betel quid chewing, heavy alcohol consumption (only for squamous cell carcinomas of the oesophagus) (IARC, 2004, IARC, 2010) and BMI (for adenocarcinoma of the oesophagus) (Kubo & Corley, 2006), making these factors potential confounders in studies of smokeless tobacco. [The Working Group notes that betel quid chewing and smokeless tobacco use are nearly always mutually exclusive in certain geographic regions.]

In two cohort studies (Boffetta *et al.*, 2005; Zendehdel *et al.*, 2008) smokeless tobacco use and oesophageal cancer has been examined (Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.7.pdf); both addressed potential confounding by smoking and included incident cases occurring in the first few years of follow-up.

One of the cohort studies was conducted in Norway and study participants were followed for 35 years for cancer incidence (Boffetta *et al.*, 2005). The relative risk for oesophageal cancer was 1.4 (95%CI: 0.6–3.2) for ever use of snuff compared to never use, adjusted for age and smoking. In a Swedish cohort study (Zendehdel *et al.*, 2008) the relative risk for squamous cell carcinoma of the oesophagus among non-smoking men who used only snuff compared to never users of tobacco was 3.5 (95%CI: 1.6–7.6) adjusting for age and BMI.

Several case–control studies in the USA have been conducted that did not include odds ratio among non-smokers or did not adjust statistically for smoking behaviours (Wynder *et al.*, 1957; Wynder & Bross, 1961; Wynder & Stellman, 1977; Pottern *et al.*, 1981). Of the seven case–control studies of smokeless tobacco and oesophageal cancer that did so (Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.8.pdf), two were conducted in Sweden (Lewin *et al.*, 1998; Lagergren *et al.*, 2000), three in the USA (Martinez, 1969; Williams & Horm, 1977; Williams *et al.*, 1977; Brown *et al.*, 1988), one in India (Phukan *et al.*, 2001) and one in the Islamic Republic of Iran (Nasrollahzadeh *et al.*, 2008). Because the survival rate for oesophageal cancer is poor (Crew & Neugut, 2004), case–control studies may be susceptible to selection bias from not interviewing study cases who died before the time of interview or measurement error due to obtaining information from proxy interviews (Winn, 1986).

Three case–control studies from the USA (one from Puerto Rico) showed no association between use of smokeless tobacco and oesophageal cancer (Martinez, 1969; Williams & Horm, 1977; Williams *et al.*, 1977; Brown *et al.*, 1988) after adjusting for smoking or restricting the analysis to non-smokers. The proportion of proxy interviews needed to ascertain smokeless tobacco use in these studies was 45% (Williams & Horm, 1977; Williams *et al.*, 1977), at least 69% (Brown *et al.*, 1988), and 12% (Martinez, 1969).

Both of the Swedish case–control studies were population-based and adjusted the analyses for smoking and alcohol intake (Lewin *et al.*, 1998; Lagergren *et al.*, 2000). In one of them that involved both squamous cell and adenocarcinoma, no proxy interviews were permitted (Lagergren *et al.*, 2000). The odds ratio for users of smokeless tobacco only compared to non-users of tobacco was 1.4 (95%CI: 0.9–2.3) for squamous cell carcinoma of the oesophagus and 1.2 (95%CI: 0.7–2.0) for adenocarcinoma of the oesophagus adjusting for age, tobacco smoking, alcohol drinking and other factors. In the other Swedish study (Lewin *et al.*, 1998) on squamous cell carcinoma, most were interviewed about a month after the case's diagnosis date. The odds ratio for ever use of snuff was 1.2 (95%CI: 0.7–2.2), adjusting for age, region, tobacco smoking and alcoholic beverages.

In a hospital-based case–control study from India an association between smokeless tobacco and oesophageal cancer was found (Phukan *et al.*, 2001). Relative to persons who neither used smokeless tobacco nor smoked, the odds ratio for persons who used only *chadha* (a type of smokeless tobacco) but did not chew betel quid nor smoke was 3.2 (95%CI: 1.6–9.5) for men and 6.2 (95%CI: 2.4–12.1) for women, adjusting for alcohol. In a study in the Islamic Republic of Iran cases were interviewed at the time of diagnosis (there were no proxy interviews), and only histologically confirmed squamous cell carcinoma were included (Nasrollahzadeh *et al.*, 2008); when use of different tobacco products was examined in a multivariate model, there was a significant positive association with *nass* use only compared to never users of any tobacco product, after adjustment for education, ethnicity, and total intake of fruit and vegetables.

In a meta-analysis of studies published through 2007 (Boffetta *et al.*, 2008; Table 2.9, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.9.pdf), only studies from Europe and the USA that provided information about non-smokers and studies that included smokers but adjusted for tobacco smoking were included. The overall estimate of effect for the five studies of oesophageal cancer was 1.6 (95%CI: 1.1–2.3). In a second meta-analysis Lee & Hamling (2009) included studies from Europe and the USA of smokeless tobacco and oesophageal cancer through May 2008, including and two studies that did not adjust for smoking (Wynder & Bross, 1961; Wynder & Stellman, 1977; Table 2.10, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.10.pdf). The overall relative risk among never-smokers was 1.91 (95%CI: 1.15–3.17) and the smoking-adjusted relative risk 1.13 (95%CI: 0.95–1.36). For Scandinavian studies, the summary relative risk in never-smokers was 1.92 (95%CI: 1.00–3.68; one study) and 1.10 (95%CI: 0.92–1.33) when smoking adjusted. For studies from the USA, the relative risks restricted to never-smokers or adjusted for smoking were identical, 1.89 (95%CI: 0.84–4.25).

(b) Dose–response evidence

(i) Duration and intensity

In one case–control study (Lagergren *et al.*, 2000), there were no significant increases in risk for years of use up to 25 years, adjusted for smoking, alcohol, and other factors. For more than 25 years of use, the odds ratio for snuff use controlling for smoking, alcohol intake and other factors was 2.0 (95%CI: 0.9–4.1) for squamous cell carcinoma of the oesophagus and 1.9 (95%CI: 0.9–4.0) for adenocarcinoma of the oesophagus. The odds ratio for use of 15–35 quids per week for squamous cell carcinoma was 2.1 (95%CI: 1.0–4.4) and for adenocarcinoma, 2.0 (95%CI: 1.0–4.3). Corresponding estimates for using more than 35 quids per week were 1.0 (95%CI: 0.4–2.4) and 0.8 (95%CI: 0.3–2.0), respectively. In another case–control study (Lewin *et al.*, 1998), the odds ratio for smokeless tobacco users of more than 50 g per week was 1.9 (95%CI: 0.8–3.9) adjusting for smoking and alcohol intake among other factors. In the Islamic Republic of Iran study (Nasrollahzadeh *et al.*, 2008), there were significant positive exposure-response relationships for frequency of use per day of *nass*, cumulative use (frequency times duration), and duration of *nass* use. However, these findings were not controlled for tobacco smoking.

(ii) Cessation

In one case–control study of oesophageal cancer (Lewin *et al.*, 1998), there was no association with snuff use for former or current smokeless tobacco users compared to never smokeless tobacco users.

(c) Types

In northern Europe, the predominant form of smokeless tobacco is snus. Of the four studies from that geographic region – two cohort

(Boffetta *et al.*, 2005; Zendehdel *et al.*, 2008) and two case–control (Lewin *et al.*, 1998; Lagergren *et al.*, 2000) – all of the odds ratios were greater than 1.0, but statistically significantly elevated only in one study (Zendehdel *et al.*, 2008). The odds ratios in the three studies from the USA where snuff and chewing tobacco are used, were not statistically significantly elevated (Martinez, 1969; Williams & Horm, 1977; Brown *et al.*, 1988).

In India, among non-smokers, statistically significantly elevated odds ratios associated with chewing *chadha* were reported for both men and women adjusting for alcohol consumption (Phukan *et al.*, 2001). In a study in the Islamic Republic of Iran, *nass* users had a significantly increased risk of oesophageal cancer (Nasrollahzadeh *et al.*, 2008).

It was noted in a report on a case series in Sudan that use of tobacco in the form of *toombak* under the tongue or in the labiodental groove was common in an area where oesophageal cancer incidence rates were high (Babekir *et al.*, 1989).

(d) Histology

Two studies analysed squamous cell cancer and adenocarcinoma separately (Lagergren *et al.*, 2000; Zendehdel *et al.*, 2008); in the other studies (Brown *et al.*, 1988; Phukan *et al.*, 2001; Nasrollahzadeh *et al.*, 2008), most (if not all) of the cases had squamous cell carcinomas. Statistically significantly elevated odds ratios were found for ever use of smokeless tobacco and squamous cell carcinomas in one study (Zendehdel *et al.*, 2008), in another study (Lagergren *et al.*, 2000) for users of 15–35 quids per week, and in a third study of predominantly squamous cell carcinomas (Phukan *et al.*, 2001). In a fourth study from the Islamic Republic of Iran that assessed squamous cell carcinomas, *nass* use was found to have a significant positive association with oesophageal cancer (Nasrollahzadeh *et al.*, 2008).

Two studies provided odds ratios for use of smokeless tobacco and adenocarcinoma of the oesophagus; in one the odds ratio was statistically significantly elevated for ever users (Zendehdel *et al.*, 2008) and in the other (Lagergren *et al.*, 2000) users of 15–35 quids per week had an increased risk for adenocarcinoma of the oesophagus.

(e) Population characteristics

In the study in India (Phukan *et al.*, 2001), significantly elevated odds ratios were observed in both men and women.

(f) Subsites of cancers of the upper aerodigestive tract

In some studies smokeless tobacco-associated risks were examined only for oral cancer or provided oral cavity cancer-specific findings. Of these studies, statistically significantly elevated odds ratios for ever use of smokeless tobacco were noted in seven (Chandra, 1962; Williams & Horm, 1977; Blot *et al.*, 1988; Idris *et al.*, 1995a; Merchant *et al.*, 2000) but no association in two (Schildt *et al.*, 1998; Accortt *et al.*, 2002, 2005; Luo *et al.*, 2007). Some other studies provided estimates for the oral cavity plus one or more of the pharynx, lip, salivary gland, oesophagus, and larynx. Of these four had positive findings (Kabat *et al.*, 1994; Lewin *et al.*, 1998; Wasnik *et al.*, 1998; Roosaar *et al.*, 2008) and four had relative risks below one or close to approximately equal to one (Mashberg *et al.*, 1993; Boffetta *et al.*, 2005; Henley *et al.*, 2005; Rosenquist, 2005). In studies providing information separately for the pharynx, estimates were positive for women with 20 or more years of snuff use in the USA (Winn *et al.*, 1981a); for hypopharyngeal cancer, estimates were positive in one study in India (Sapkota *et al.*, 2007) and below one in two other studies (Williams & Horm, 1977; Lewin *et al.*, 1998).

2.1.4 Cancer of the pancreas

Three cohort studies (Zheng *et al.*, 1993; Boffetta *et al.*, 2005; Luo *et al.* 2007), three population-based case–control studies (Williams & Horm 1977; Farrow & Davis, 1990; Alguacil & Silverman, 2004) and two hospital based case–control studies (Muscat *et al.*, 1997; Hassan *et al.*, 2007) in North America and in Europe investigated the association between the use of smokeless tobacco and pancreatic cancer.

(a) North America

(i) Cohort study

In the Lutheran Brotherhood Insurance Society cohort with 20 years follow-up, a relative risk of 1.7 (95%CI: 0.9–3.1, based on 16 deaths) adjusted for age, alcoholic beverages and smoking was found for male ever users of smokeless tobacco (Zheng *et al.*, 1993).

(ii) Case–control studies

No association was found with smokeless tobacco in two population-based case–control studies (Williams & Horm 1977; Farrow & Davis, 1990). In a population-based case–control study that restricted analyses to lifelong non-smokers of cigarettes, a non-significantly 40% increase in risk for pancreatic cancer (95%CI: 0.5–3.6) was found in those who used smokeless tobacco regularly compared to non-users of tobacco (Alguacil & Silverman, 2004). Among tobacco chewers who were not current cigarette smokers, an elevated risk of 3.6 (CI: 1.0–12.8) was seen when compared to never-smokers and long-term quitters (≥ 20 years) in one hospital-based case–control study (Muscat *et al.*, 1997) and no association with chewing tobacco or using snuff was noted in an another hospital-based case–control study (Hassan *et al.*, 2007). None of the studies adjusted for BMI or alcohol, which are potentially important risk factors for pancreatic cancer (Table 2.11, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.11.pdf).

In a meta-analysis of four studies from the USA, the summary relative risk for pancreatic cancer among users of smokeless tobacco was 1.4 (95%CI: 0.7–2.7) (Boffetta *et al.*, 2008).

(iii) Duration and intensity

Only a few studies assessed risk in relation to duration and intensity of use, assessing oz per week or grams per day and duration of use. In one study (Alguacil & Silverman, 2004), the odds ratio for those who used > 2.5 oz of smokeless tobacco a week compared to non-users of tobacco was 3.5 (95%CI: 1.1–10.6) and for those who used smokeless tobacco for more than 20 years was 1.5 (95%CI: 0.6–4.0), adjusted for age, sex, race, cigar smoking and study area.

(b) Europe

In the Norwegian Cohort Study followed up for 35 years the relative risk for pancreatic cancer for ever use of snuff (snus) was 1.67 (95%CI: 1.12–2.50; 45 cases), adjusted for smoking and age (Boffetta *et al.*, 2005). Among ever users of snuff, the relative risk was 0.85 (95%CI: 0.24–3.07, based on three cases) in never-smokers. In the Swedish construction worker cohort study, analyses were restricted to never smoking men at the time of entry into the study (Luo *et al.*, 2007). Average follow-up was 20 years and 83 pancreatic cancers were recorded. Compared to never users of any tobacco product, and after adjustment for age and BMI, the relative risk for never smoking current users of snus was 2.1 (95%CI: 1.2–3.6; 18 cases) and in never-smokers who used ≥ 10 g/day snus was 2.1 (95%CI: 1.1–3.8) (Table 2.12, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.12.pdf).

A meta-analysis showed a summary relative risk for pancreatic cancer among users of smokeless tobacco based on the two above cohort studies of 1.8 (95%CI: 1.3–2.5) (Boffetta *et al.*, 2008).

2.1.5 Other cancers

(a) Cancer of the stomach

Four cohort studies (Kneller *et al.*, 1991; Chao *et al.*, 2002; Boffetta *et al.*, 2005; Zendehdel *et al.* 2008) and 4 case–control studies (Williams & Horm, 1977; Hansson *et al.*, 1994; Ye *et al.*, 1999; Phukan *et al.*, 2005) investigated the association between stomach cancer and use of smokeless tobacco. Phukan *et al.* (2005) also reported exposure to *tuibur* (Table 1.1).

(i) Cohort studies

In the USA, non-significantly elevated risks associated with smokeless tobacco use were observed among never-smokers compared to men who never used tobacco in the Lutheran Brotherhood cohort study with 20 years follow-up (Kneller *et al.*, 1991) and in the CPS-II cohort study with 18 years follow-up (Chao *et al.*, 2002). In the cohort study from Norway (35 years follow-up), a non-significantly elevated risk for snuff use was found (Boffetta *et al.*, 2005). A total of 343 822 men were analysed in the construction worker cohort study from Sweden (33 years follow-up) and a significant positive relative risk was seen among non-smoking snus users aged 70 and over for cancer in the non-cardia region of the stomach when compared to never users of any tobacco product (Zendehdel *et al.*, 2008; Table 2.13, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.13.pdf).

(ii) Case–control studies

Williams & Horm (1977), Hansson *et al.* (1994) and Ye *et al.* (1999) found no significant associations with the use of smokeless tobacco products or snuff. The study by Phukan *et al.* (2005) showed a significantly elevated risk for chewing tobacco alone among non-betel quid users (adjusted for tobacco smoking, alcohol drinking, *tuibur*, education, occupation, income) and for *tuibur* use (adjusted for tobacco smoking, alcohol drinking, education, occupation, income) (Table 2.14, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.14.pdf).

(iii) Dose–response evidence

In one study, risk increased with cumulative dose of tobacco chewing and for *tuibur* use (p for trend < 0.001), each adjusted for other confounding factors (Phukan *et al.*, 2005).

(iv) Cessation

Phukan *et al.* (2005) found that risk decreased with years of cessation of *tuibur* use, although the test for trend was not significant.

(b) Cancer of the colon and rectum

In the US Veterans' cohort study with 26 years follow-up (Heineman *et al.*, 1995), smokeless tobacco users had a relative risk of 1.2 (95%CI: 0.9–1.7; based on 39 deaths) for cancer of the colon and 1.9 (95%CI: 1.2–3.1; based on 17 deaths) for cancer of the rectum compared to those who had never used tobacco. No new data have been published since the previous *IARC Monograph* (IARC, 2007a).

(c) Cancer of the extra-hepatic bile duct

In a population-based case–control study in Los Angeles County, USA (Chow *et al.*, 1994) an odds ratio of 18 (95%CI: 1.4–227.7; based on 3 cases) was found for chewing tobacco and cancer of the ampulla of Vater. [All cases of cancer of the ampulla of Vater who chewed tobacco also smoked.] There have been no new studies published since the previous *IARC Monograph* (IARC, 2007a).

(d) Cancers of the digestive system combined

A reduced risk with use of smokeless tobacco was seen in the case–control study by Sterling *et al.* (1992) and in the National Health and Nutrition Examination Survey (NHANES I) follow-up study that analysed 6805 men and women aged

45–75 years at baseline (1971–75) (Accortt *et al.*, 2002). The entire NHANES I cohort was reassessed between 1982 and 1984 and analysed 7787 subjects aged 45 and over at baseline. The results showed non-significantly elevated risks for those aged 65 years and over in men and aged 45–64 years in women (Accortt *et al.*, 2005). [The analysis was limited to incident diseases that required an overnight stay in health care facility. Hence, there is a possibility of underrepresentation of the actual number of cancer cases that occurred in the cohort. Analysis was based on a small sample size, 414 exclusive smokeless tobacco users, and chewing tobacco and snuff use were not analysed separately. Pipe and cigar use was not controlled for in the analysis.]

The hazard ratio for men who reported current use of smokeless tobacco and never used other tobacco products was significantly elevated after adjustment for age, race, educational level, BMI, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use in the CPS I cohort but not in the CPS II cohort (additionally adjusted for status and type of employment) (Henley *et al.*, 2005).

(e) Cancer of the gall bladder

One case–control study in India found positive associations with chewing *khaini* [raw tobacco with lime] and cancer of the gall bladder (OR, 1.65; 95%CI: 0.78–3.49) or chewing tobacco alone (OR, 2.71, 95%CI: 1.22–6.02), unadjusted for other potential confounding factors (Shukla *et al.*, 2008).

(f) Cancers of the respiratory tract

(i) Nasal cavities

Brinton *et al.* (1984) in a case–control study found non-significant sex-adjusted odds ratios for tobacco chewers or snuff users while Stockwell & Lyman (1986) found an odds ratio for smokeless tobacco of 3.3 (95%CI,0.4–25.9), adjusted for age, race, sex and tobacco use. [The Working Group noted that information about tobacco use was obtained from medical records and ascertainment bias cannot be ruled out.] No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(ii) Larynx

In a case–control study in Florida, USA, a significantly elevated odds ratio for smokeless tobacco use, adjusted for age, race, sex and tobacco smoking was found (Stockwell & Lyman, 1986). [The Working Group noted that information about tobacco use was obtained from medical records and ascertainment bias cannot be ruled out.] From a case–control study in Sweden Lewin *et al.* (1998) reported no significant association for current and former use of snuff, adjusted for age, smoking and alcoholic beverages. No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(iii) Lung

The NHANES follow-up study ascertained incident cases (Accortt *et al.*, 2005) and deaths from lung cancer (Accortt *et al.*, 2002). Never-smoking women who ever used smokeless tobacco had significantly higher mortality compared to never tobacco users. In men, no deaths from lung cancer occurred among those who were never-smokers and used smokeless tobacco. Estimates of the relative risk were adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise and fruit/vegetable intake. The results for cancer incidence (Accortt *et al.*, 2005) showed significantly elevated risks in women aged 65 years and over, based on small numbers of cases among exclusive smokeless tobacco users ($n < 4$ cases). No incident cases of lung cancer occurred in men who used smokeless tobacco. Risk was adjusted for age, race and poverty index ratio. [The Working Group noted limitations to this study. See section on cancers of the digestive system *(d)*.]

In the Cancer Prevention Study I (CPS-I) in the USA, the hazard ratio for lung cancer for current smokeless tobacco users who never used other tobacco products was non-significantly elevated and the corresponding hazard ratio in the CPS-II cohort was significantly elevated, after adjusting for age, race, level of education, BMI, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake, aspirin use and status and type of employment (for CPS-II only) (Henley *et al.*, 2005). The magnitude of effect was similar for those who chewed tobacco but never used snuff and for those who used snuff but never chewed tobacco. In the Norwegian cohort study the relative risk adjusted for age and smoking was non-significantly reduced for ever users of snus compared to never users (Boffetta *et al.*, 2005). In the Swedish construction worker cohort study with 279 897 men followed for an average of 20 years there was no significant association for snus use among never-smokers (Luo *et al.*, 2007).

Henley *et al.* (2007) used CPS II data to compare mortality among former cigarette smokers who switched to smokeless tobacco (switchers) with those who quit using tobacco entirely (quitters), based on tobacco use ascertained at baseline and followed-up for 20 years. In a subset of the cohort that examined uptake of tobacco after baseline, the proportions of persons taking up cigarette smoking was very low. Compared with quitters, the relative risk of lung cancer was 1.5 (95%CI: 1.2–1.7) for all switchers, 1.3 (95%CI: 1.1–1.6) for switchers to tobacco chewing only, 1.8 (95%CI: 1.2–2.5) for snuff only, and 1.9 (95%CI: 1.2–2.9) for tobacco chewing and snuff combined. Compared with men who never used any tobacco product, the relative risk of lung cancer was 3.9 for quitters and 5.6 for switchers (statistically significant but 95% confidence intervals were not provided). Risk estimates were adjusted for age, number of cigarettes formerly smoked per day, number of years smoking cigarettes, age at which they quit smoking cigarettes, race, educational level, BMI, exercise level, alcohol consumption, employment type, employment status, fat consumption, fruit and vegetable intake and aspirin use. The analysis was restricted to men because women were not asked whether or not they used smokeless tobacco.

The case–control study of lung cancer by Williams & Horm (1977) reported non-significant risk for smokeless tobacco use in men, adjusted for age, race, and smoking.

(g) *Sarcoma*

In the US Veterans' cohort, the relative risk for soft-tissue sarcomas associated with smokeless tobacco use compared to persons who never used tobacco products was 1.5 (95%CI: 0.8–2.7) (Zahm *et al.*, 1992). In a population-based case–control study conducted in the USA, the unadjusted odds ratio for ever use of smokeless tobacco was 1.8 (95%CI: 1.1–2.9); the risk was highest for those diagnosed at age 80 years or above (3.2; 95%CI: 1.0–10.1). Risks were elevated but not significantly so when analysed by anatomical site of the soft-tissue sarcoma (upper gastrointestinal; lung, pleura and thorax; head, neck and face) or by cell type (fibromatous; adipose, myomatous) (Zahm *et al.*, 1989). No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(h) *Cancer of the breast*

Spangler *et al.* (2001, 2002) conducted a case–control study in Cherokee Native American women and reported a non-significant elevated risk of breast cancer for use of smokeless tobacco. [There was no medical verification of breast cancer and the time relationship between use of smokeless tobacco and breast cancer diagnosis was not reported.] A prospective cohort study of the US population (NHANES I) showed a positive but non-significant association with smokeless tobacco (snuff or chewing tobacco) in women aged 45 years and over based on five breast cancer cases, however the hazard ratios

were below one when stratified by age (Accortt *et al.*, 2005). [The Working Group noted limitations to this study. See Section on cancer of the digestive system, 2.1.5 *(d)*.]

(i) Cancer of the uterine cervix

In a population-based case–control study elevated risks for cervical cancer, adjusted for smoking, age and race, for use of chewing tobacco or snuff were reported (Williams & Horm, 1977). No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(j) Cancer of the prostate

In two cohort studies significantly elevated risks were found among users of smokeless tobacco compared to never users of tobacco (Hsing *et al.*, 1990, 1991). Putnam *et al.* (2000) reported no association with use of snuff and chewing tobacco. [The Working Group noted that data were not presented to support this.] In one case–control study (Hayes *et al.*, 1994) and one cohort study (Accortt *et al.*, 2005) non-significantly elevated risks of prostate cancer associated with chewing tobacco were found.

(k) Cancer of the penis

In a case–control study of cancer and the penis in India, the relative risk for snuff users was 4.2 (95%CI: 1.6–11.3), adjusted for smoking, tobacco chewing and phimosis (Harish & Ravi, 1995). [It was not clear whether snuff was used orally or nasally.] No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(l) Cancer of the urinary bladder

Population-based case–control studies conducted in three provinces of Canada (Howe *et al.*, 1980), in the USA (Hartge *et al.*, 1985; Slattery *et al.*, 1988) and in Alberta and Ontario provinces of Canada (Burch *et al.*, 1989) did not show a significant association between chewing tobacco and bladder cancer. No association with snuff use was seen in the Norwegian cohort (Boffetta *et al.*, 2005).

(m) Cancer of the kidney

Four case–control studies (Goodman *et al.*, 1986; McLaughlin *et al.*, 1995; Muscat *et al.*, 1995; Asal *et al.*, 1988) and one cohort study (Boffetta *et al.*, 2005) evaluated the risk associated with smokeless tobacco use. The adjusted risk for chewing tobacco in non-smokers was not significantly elevated in two case–control studies (Goodman *et al.*, 1986; McLaughlin *et al.*, 1995) and in one cohort study in Norway (Boffetta *et al.*, 2005). In two studies, a significant association was reported for ever use of smokeless tobacco (Asal *et al.*, 1988; Muscat *et al.*, 1995) but there was no adjustment for potential confounders in either study. A dose–response relationship was observed: odds ratio 2.5 (95%CI: 1.0–6.1) for chewing 10 times or fewer per week and 6.0 (95%CI: 1.9–18.7) for chewing 11 or more times per week (Muscat *et al.*, 1995), although there was no adjustment for smoking and other potentially confounding factors.

(n) Cancer of the brain

From a population-based case–control study in the USA (Zheng *et al.*, 2001), no significantly increased risk of brain cancer was reported for either men or women with the use of snuff or chewing tobacco. [Data to support this were not presented.] No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(o) Non-Hodgkin lymphoma

Two population-based case–control studies of non-Hodgkin lymphoma in men were conducted in the USA (Brown *et al.*, 1992a; Schroeder *et al.*, 2002). Schroeder *et al.* (2002) found an increased risk for t(14;18)-positive non-Hodgkin lymphoma cases who started chewing tobacco ≤ 18 years of age, after adjusting for age and state (OR, 2.5;

95%CI: 1.0–6.0). No significant associations were observed in the study by Brown *et al.*, (1992a) for any non-Hodgkin lymphoma subtype or overall.

Bracci & Holly (2005) from a population-based case–control study of non-Hodgkin lymphoma conducted in the USA reported significantly elevated risks for non-Hodgkin lymphoma and for follicular and diffuse large cell types in those who used smokeless tobacco. Risk estimates were adjusted for age, level of education and level of average weekly alcohol consumption. [The results are based on only seven cases and six controls.]

(p) Leukaemia

Brown *et al.* (1992b) conducted a population-based case–control study in the USA of chewing tobacco/snuff only and risk for leukaemia. Non-significant elevated risks were seen for all leukaemias, chronic myelogenous leukaemia, chronic lymphocytic leukaemia and myelodysplasia. In the Swedish construction worker cohort study (average follow-up 22.2 years), non-significantly elevated risks for acute lymphocytic and chronic myelogenous leukaemias and no association in men for snuff dipping and acute myelogenous leukaemia and multiple myeloma were found (Fernberg *et al.*, 2007).

(q) Myeloma

In a population-based case–control study in the USA, Brown *et al.* (1992a) compared users of smokeless tobacco only with never users of tobacco and found an odds ratio of 1.9 (95%CI: 0.5–6.6; based on 5 cases). A Swedish construction worker cohort study showed no association for myeloma in men with snuff dipping (Fernberg *et al.*, 2007).

(r) Cutaneous squamous cell carcinoma

Odenbro *et al.* (2005) analysed the Swedish cohort study and found a relative risk of 0.64 (95%CI: 0.44–0.95) for the association between snuff dipping and the incidence of cutaneous squamous cell carcinoma.

2.2 Nasal use

There are no cohort or case–control studies that examined the association between nasal snuff use and nasal cancer.

2.2.1 Cancers of the oral cavity and pharynx

(a) Overview of studies

Three case–control studies from India investigated the association between nasal snuff use and cancer of oral and pharyngeal subsites (Table 2.15, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.15.pdf).

Sankaranarayanan *et al.* (1989a) focused on cancer of the anterior two-thirds of tongue and floor of the mouth; the age-adjusted odds ratio was 4.27 (95%CI: 1.24–14.67; men only) for occasional nasal snuff users and 3.02 (95%CI: 0.94–9.60) for daily snuff users. For cancer of the gingiva the odds ratio for regular snuff use was 3.04 (95%CI: 0.67–12.65) after adjustment for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use (Sankaranarayanan *et al.*, 1989b). For cancer of the buccal and labial mucosa, the age-adjusted odds ratio was 3.98 (95%CI: 1.53–10.34) for regular nasal snuff users and 2.28 (95%CI: 0.74–7.03) for occasional nasal snuff users (Sankaranarayanan *et al.*, 1990a). After adjusting for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use, the odds ratio associated with ever snuff use was 2.93 (95%CI: 0.98–8.77).

In a multicentre case–control study of cancer of the hypopharynx in India, Sapkota *et al.* (2007) found an odds ratio of 2.85 (95%CI: 1.15–7.08) for tobacco snuffing among never-smokers who did not chew tobacco or a non-tobacco product, adjusting for alcohol use, and other factors [The Working Group noted that snuff use was oral as

well as nasal so the role of nasal use could not be determined separately.]

(b) Dose–response evidence

In the study of cancer of the gingiva (Sankaranarayanan *et al.*, 1989b), the age-adjusted odds ratio for daily nasal snuff use was 3.90 (95%CI: 1.19–12.70) and that for occasional use was 3.78 (95%CI: 1.05–13.54). When categories of high versus low defective nasal snuff use were compared, the odds ratios were significantly elevated for the category of lower intensity for cancers of the tongue (Sankaranarayanan *et al.*, 1989a) and of the buccal and labial mucosa (Sankaranarayanan *et al.*, 1990a).

2.2.2 Other cancers

No new studies were identified since the previous *IARC Monograph* (IARC, 2007a) for the sites listed except for cancer of the nostril.

(a) Cancer of the oesophagus

A case–control study of oesophageal cancer form India showed an age-adjusted odds ratio for daily snuff use of 2.39 (95%CI: 0.81–7.04) and that for occasional use of 3.59 (95%CI: 1.20–10.67) (Sankaranarayanan *et al.*, 1991). [Estimates were not adjusted for smoking or betel quid chewing.]

(b) Cancer of the paranasal sinuses

Shapiro *et al.* (1955) studied Bantu cases of paranasal sinus cancer from radiation therapy department records from 1949–51 of a group of hospitals in South Africa. The authors noted that a high proportion (80%) of the antral cancer cases reported 'prolonged and heavy' use of snuff in contrast to 34% of Bantu men with cancer at other sites. The product snuffed by Bantus typically contained powdered tobacco leaves and an ash from aloe plants or other species, with the occasional addition of oil, lemon juice and herbs; typical use was 'one teaspoonful' per day (Keen *et al.*, 1955). [The Working Group noted that the source and nature of the control group was not described.]

(c) Cancer of the larynx

A case–control study from India (Sankaranarayanan *et al.*, 1990b) of laryngeal cancer showed a non-significant risk for snuff use.

(d) Cancer of the lung

Hsairi *et al.* (1993) conducted a case–control study of bronchial cancer in Tunisia. The odds ratio for ever use of inhaled snuff ('tabac à priser'), adjusted for age, sex, cigarette use, water pipe and cannabis use was 2.2 (95%CI: 0.9–5.6).

(e) Carcinoma of the nostril

Sreedharan *et al.* (2007) reported a case of squamous cell carcinoma in the right nostril in a 69-year-old woman in Karnataka, south India, with a history of daily snuff usage of more than 2 g for a duration of 30 years.

2.3 Synthesis

2.3.1 Oral use

(a) Oral cavity and pharynx

Smokeless tobacco was positively associated with cancers of the oral cavity in a cohort study in northern Europe and several case–control studies, some of which that adjusted for smoking and others that adjusted both for smoking and alcohol. There were elevated risks for every type of smokeless tobacco studied: snuff and chewing tobacco in the USA, snus in northern Europe, *toombak* in Sudan, smokeless tobacco used as a dentifrice in India and *naswar* in Pakistan. Case series implicate *shammah* used in Saudi Arabia as a risk factor for oral cancer. Not all reports were positive, namely some studies in Scandinavia and the USA, including two cohorts with small sample sizes. The evidence is strongest for the

oral cavity, with some indication of increased risks for the hypopharynx, or oropharynx and hypopharynx combined. Dose–response relationships with intensity of use were noted in one study and with duration in another. It is unclear whether risks are elevated in former smokeless tobacco users. Three meta-analyses of studies from northern Europe and the USA were generally consistent. In one meta-analysis an overall relative risk of 1.8 (95%CI: 1.1–2.9) was computed for studies that adjusted for smoking or among non-smokers; in another the relative risk was 1.72 (95%CI: 1.01–2.94) among never-smokers and 1.87 (95%CI: 0.82–4.27) when further adjusted for alcohol among never-smokers. In conclusion, there is strong evidence in humans that smokeless tobacco causes cancer of the oral cavity.

(b) Precancerous lesions

Studies in many countries have observed that oral lesions are more common in smokeless tobacco users than non-users, regardless of the type of smokeless tobacco used. The types include snus, snuff, chewing tobacco, smokeless tobacco used as a dentifrice, *naswar*, *toombak*, and *shammah*. In many studies the oral lesions were observed to be in the place in the mouth where users in that geographic region typically place the smokeless tobacco. The prevalence of the lesions increased with various exposure metrics of increasing intensity and duration of use, such as amounts used per day, time kept in mouth, duration of use in months or years. Although some lesions in young persons resolve, the prevalence of lesions in older adult users of these products remains elevated even in former users. There is some evidence from three studies that a small proportion of the lesions among smokeless tobacco users can progress to oral cancer over a period of years, although the rates vary, are not adjusted for any medical intervention to remove the lesions, smoking has not been taken into account, and the follow-up periods are highly variable. Use of smokeless tobacco causes leukoplakia and erythroplakia, both considered precancerous, with a much higher risk of progressing to cancer than normal mucosa.

(c) Oesophagus

Nine studies evaluated the association between smokeless tobacco use and oesophageal cancer. The risks for ever use of smokeless tobacco compared to never use were statistically significantly elevated in one cohort study from Sweden and case–control studies from the Islamic Republic of Iran and India. In a Swedish case–control study, increased risks were observed with 15–35 quids used per week. Smoking could be ruled out as a potential confounder in all of the studies, as well as alcohol intake in two. No increased risk was observed in the three studies from the USA, which included a significant proportion of proxy respondents. Two meta-analyses found that, overall and for the Nordic countries, the estimates of effect for smokeless tobacco use were significantly elevated. The two studies published since the previous *Monograph* on Smokeless Tobacco showed a positive significant association with oesophageal cancer and were adjusted for major confounders. Four of five studies of squamous cell carcinomas and both studies of adenocarcinoma showed significantly positive results.

(d) Pancreas

In North America, 3 case–control studies showed no association, one cohort study and two case–control studies showed a non-significant increased risk and one case–control study showed a borderline significant increase in risk. While these studies accounted for smoking, none adjusted for BMI or alcohol, potentially important risk factors for pancreatic cancer. In Europe, two cohort studies showed a significant increase in risk of pancreatic cancer associated with snuff use. Both studies controlled for smoking; one study adjusted for BMI and also showed that the highest risks were seen in the highest exposure

Table 3.1 Carcinogenicity studies of application of smokeless tobacco to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mouse, CAF1 and Swiss (sex NR) Wynder & Wright (1957)	40, 30 controls Skin application 3 × /wk of unburnt cigarette tobacco 50% methanol extract, (dose NR), controls received whole tar extract; 24 mo	Skin (papillomas): CAF1–11/40 (27%), 16/30 (53%) in controls (8 converted to carcinoma) Swiss–3/40 (7%) (1 converted to carcinoma), 16/30 (53%) in controls (3 converted to carcinoma)	 NR NR	No adequate control groups

mo, month or months; NR, not reported

category. There is good evidence to support a causal association between smokeless tobacco use and pancreatic cancer.

(e) Stomach

One cohort study in Sweden showed a significantly higher risk among non-smoking snus users aged 70 years and over for cancer in the non-cardia region of the stomach, not adjusted for alcohol use. One case–control study in India showed significantly higher risks for chewing tobacco alone and for *tuibur* users, with dose-dependent increases in risk. Risk decreased with cessation of *tuibur* use. The risk was not statistically significant in the other studies. Despite some positive findings for chewing tobacco in two different countries and for tobacco smoke-infused water, it was not considered strong enough to conclude for a causal association.

(f) Lung

In summary, in two cohort studies significant positive associations between smokeless tobacco use and lung cancer were found while in three cohort studies and one case–control study there was no association. In one of the positive cohort studies switching from cigarette smoking to smokeless tobacco significantly increased the risk for lung cancer compared to never-tobacco users, and the risk was of greater magnitude than for quitting all together (RR, 3.9 versus 5.6).

2.3.2 Nasal use

Strong positive associations for cancers of the tongue and floor of mouth, gingiva and buccal and labial mucosa were observed in one study in India. In one positive study snuff use was oral as well as nasal so the role of nasal use could not be determined separately.

3. Cancer in Experimental Animals

Since the previous *IARC Monograph* on Smokeless Tobacco (IARC, 2007a), only one new study has been published. The collective evidence for the carcinogenicity of smokeless tobacco in experimental animals is summarized below.

3.1 Chewing tobacco, unburned cigarette tobacco, *mishri* and *naswar*

3.1.1 Mouse

Topical application of unburned cigarette tobacco induced skin papillomas in mice (Wynder & Wright, 1957; Table 3.1). Similar treatment with

Table 3.2 Carcinogenicity studies on administration of smokeless tobacco with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse, Paris albino XVII x 57 black (sex NR) Ranadive *et al.* (1963)	11–36 animals/ group Totally alkaloid free extract, twice/wk for 95 wk + croton oil/dose and duration not specified, controls received acetone	Papillomas: 22/35 (63%) Controls–3/19 (16%) Carcinomas: 10/35 (27%) Controls–0/19	$P > 0.001$ $P = 0.0097$
Mouse, ICR Swiss (F) Bock *et al.* (1964, 1965)	30 animals/group A single DMBA application of 125 µg DMBA in 0.25 mL acetone + 0.25 mL acetone extract of unburnt tobacco 2.5 from cigarettes/d, 5 × / wk; controls received a single application of DMBA 125 µg 36 wk	16 papillomas in 7/30 (23%) mice Controls–0/30	$P > 0.01$
Mouse, ICR Swiss (F) Van Duuren *et al.* (1966)	20 animals/group 150 µg DMBA in 0.1 ml acetone once + (after 2–3 wk) reconstituted extract of flue-cured cigarette tobacco leaf, 25 mg in 0.1 ml solvent, tobacco extract, 3 × /wk; 52 wk	Papillomas: 5/14 (36%) Controls–0/12	$P = 0.04$

d, day or days; F, female; NR, not reported; wk, week or weeks

chewing tobacco extract for 95 weeks followed by croton oil increased the incidence of skin papillomas and carcinomas in mice (Ranadive *et al.*, 1963; Table 3.2). Application of chewing tobacco extract to benzo[*a*]pyrene-initiated mouse skin promoted development of a few skin papillomas and carcinomas in mice (Ranadive *et al.*, 1963). In mice initiated with 7,12-dimethylbenz[a]anthracene (DMBA) applied topically, application of a barium hydroxide extract of unburned tobacco promoted skin papilloma development (Bock *et al.*, 1964; Table 3.2). Skin-tumour-promoting activity of unburned tobacco was reported in some DMBA-initiated mice in two additional studies (Bock *et al.*, 1965; Van Duuren *et al.*, 1966; Table 3.2). Application of brown or black *mishri* extracts to DMBA-initiated skin increased significantly the total incidence of papilloma and carcinoma in Swiss mice (Kulkarni *et al.*, 1989; Table 3.3). Administration of chewing tobacco extracts to the oral mucosa (Mody & Ranadive, 1959), skin painting with chewing tobacco extracts (Mody & Ranadive, 1959; Ranadive *et al.*, 1976), or intravesicular or intravaginal application of *jarda* (Randeria, 1972) did not induce tumours in mice.

Inhalation of powdered tobacco leaves led to a significant increase in the incidence of tumours of the lung and liver in strain A mice (Hamazaki & Murao, 1969; Table 3.4). Mice given chewing tobacco extract by oral intubation developed lung adenocarcinoma and hepatocellular carcinoma in one study [with incomplete reporting of the distribution of different neoplasms] (Bhide *et al.*, 1984). Adding black or brown *mishri* in the diet increased significantly the incidence of forestomach papilloma in Swiss mice (Kulkarni *et al.*, 1988; Table 3.5).

Table 3.3 Carcinogenicity studies of *mishri* alone or with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse Swiss (M) Kulkarni *et al.*, (1989)	30 animals Topical/a single application of 200 nmol DMBA; 24 mo	No tumours	
	29 animals 200 nmol DMBA + 2.5 mg per application of black *mishri* extract, 5 d/wk for 20 wk; 24 mo	Skin papillomas: 4/29 (14%)	$P < 0.05$
	30 animals Topical application of black *mishri* extract, 2.5 mg per application, 5 d/wk for 20 wk; 24 mo	No skin tumours	
	30 animals 200 nmol DMBA + 2.5 mg per application of brown *mishri* extract, 5 d/wk for 20 wk; 24 mo	Skin papillomas: 4/30 (13%)	$P < 0.05$

d, day or days; M, male; mo, month or months; wk, week or weeks

3.1.2 Rat

Administration of chewing tobacco extract by gavage to vitamin-A-sufficient rats induced benign tumours in the lung and forestomach while similarly treated vitamin-A-deficient rats developed benign tumours in the stomach and pituitary gland and "lymphoma" in the lung [extremely rare tumour in rats] (Bhide *et al.*, 1991; Table 3.6).

Administration of *mishri* by gavage to vitamin-A-sufficient or vitamin-A-deficient rats increased significantly the proportion of tumour-bearing rats in both groups. Lung adenomas and forestomach papillomas developed in vitamin-A-sufficient animals while multiple neoplasms including lung lymphoma [an extremely rare tumour in rats] pituitary adenoma and forestomach papilloma occurred in vitamin-A-deficient animals. Control animals did not develop tumours (Ammigan *et al.*, 1991; Table 3.5). No tumours appeared when chewing tobacco extract was applied to the oral mucosa (Gothoskar *et al.*, 1975). Adding black or brown *mishri* in the diet increased significantly the incidence of forestomach papillomas in male and female Sprague-Dawley rats (Kulkarni *et al.*, 1988; Table 3.5).

3.1.3 Hamster

Application of a chewing tobacco extract to the cheek pouch of Syrian golden hamsters produced squamous cell papillomas and/or carcinomas in a small number of animals (Rao, 1984; Table 3.7). Adding black or brown *mishri* in the diet significantly increased the incidence of forestomach papillomas (Kulkarni *et al.*, 1988; Table 3.5). Implantation of chewing tobacco in the cheek pouch (Peacock & Brawley, 1959; Peacock *et al.*, 1960; Dunham & Herrold, 1962; Summerlin *et al.*, 1992), or application of chewing tobacco extract (Suri *et al.*, 1971; Ranadive *et al.*, 1976) or *jarda* (Kandarkar *et al.*, 1981) to the cheek pouch did not induce tumours.

Application of *naswar* to the cheek pouch for life increased incidence of tumours in treated

Table 3.4 Carcinogenicity studies of inhalation of smokeless tobacco in experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mouse, Strain A (M) Hamazaki & Murao (1969)	80 animals/group Inhalation of powdered tobacco leaf, dose (NR), alternate days, controls were untreated; 30 mo	Treated– Lung tumours 12/75 (16%; alveologenic carcinomas 6, squamous cell carcinomas 3, malignant adenomas 3) Leukaemia 11/80 (15%) Hepatocellular carcinomas 3/75 (4%) Controls– Malignant lung adenomas 1/80 Leukaemia 2/80 Hepatocellular carcinomas 0/80 Controls– Malignant lung adenomas 1/80 Leukaemia 2/80 Hepatocellular carcinomas 0/80	Lung tumours: $P < 0.001$ Leukaemias: $P < 0.01$ $P < 0.01$	The incidence of lung tumours and leukaemia was significantly increased in treated animals, the incidence of lung and liver tumours in the untreated controls was unusually low

M, male; mo, month or months, NR, not reported

Table 3.5 Carcinogenicity studies of oral administration of *mishri* alone or with modifiers to experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse, Swiss (M, F) Kulkarni *et al.* (1988)	26 animals/sex/group Black *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–11/24 (46%) F–11/26 (42%)	$P < 0.01$ *vs* controls
	26 animals/sex/group Brown *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–14/26 (54%) F–11/26 (42%)	$P < 0.01$ *vs* controls
	27 M, 31 F (controls) No *mishri* tobacco, standard diet only; 25 mo	Forestomach (papillomas): M–3/27 (11%) F–1/31 (3%)	$P < 0.01$ *vs* controls
Rat Sprague Dawley (M, F) Kulkarni *et al.* (1988)	27 M, 24 F Brown *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–10/27 (37%) F–9/24 (37%)	$P < 0.01$ *vs* controls
	25 M, 30 F No *mishri* tobacco, standard diet only; 25 mo	Forestomach (papillomas): M, F–0%	$P < 0.01$ *vs* controls
Hamster Syrian Golden (M, F) Kulkarni *et al.* (1988)	23 M, 26 F Black *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–10/23 (43%) F–7/26 (27%)	$P < 0.01$ *vs* controls $P < 0.02$ *vs* controls
	28M, 20F Brown *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–12/28 (43%) F–5/20 (25%)	$P < 0.01$ *vs* controls $P < 0.01$ *vs* controls
	23 animals/sex No *mishri* tobacco, standard diet only; 25 mo	Forestomach (papillomas): M–2/23 (9%) F–1/23 (4%)	
Rat Sprague Dawley (M) Ammigan *et al.* (1991)	30 or 31 animals/group VitA sufficient diet + 3 mg *mishri* extract per application by gavage 5 × /wk; 21 mo Controls received VitA sufficient diet + 0.0.5 ml per application DMSO by gavage 5 × /wk; 21 mo	Lung (adenomas and stomach papillomas): 8/30 (27%) Controls–0/31	Total tumour incidence treated *vs* controls $P < 0.001$
	30 animals/group Vit A deficient diet + 3 mg *mishri* extract per application by gavage 5 × /wk; 21 mo Controls received Vit A deficient diet + 0.05 ml per application DMSO by gavage 5 × /wk; 21 mo	28/30 (93%) Controls–0/30	Total tumour incidence Vit deficient *vs* controls $P < 0.001$

F, female; M, male; mo, month or months; *vs*, versus; wk, week or weeks

Table 3.6 Carcinogenicity studies of oral administration of chewing tobacco in experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rat Sprague Dawley (M) Bhide *et al.* (1991)	29, 31 controls Diet containing shark liver oil + tobacco by gavage, 3mg tobacco extract (vaccum dried powder of 100 g tobacco extracted with 1L dichloromethane) in 0.05 ml DMSO, 5 × /wk; controls received diet containing shark liver oil + 0.05 ml DMSO 5 d/wk; 21 mo	Lung (adenomas):3/29 (10%) Forestomach (papillomas): 3/29 (10%) Controls–0/31	$P < 0.05$ χ^2 test	
	31, 30 controls Diet containing shark liver oil + tobacco by gavage, diet without shark liver oil + tobacco by gavage; controls received diet without shark liver oil + 0.05 ml DMSO, 5 × /wk; 21 mo	Lung (lymphomas): 22/31 (71%) Pituitary (adenomas): 19/31 (61%) Stomach (papillomas): 24/31 (77%) Controls–0/30	$P < 0.001$ χ^2 test	Primary lymphoma of the lung is extremely rare in rats

d, day or days; mo, month or months; wk, week or weeks

Table 3.7 Carcinogenicity studies of application of smokeless tobacco to the oral mucosa or cheek pouch of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Hamster Syrian golden (M) Suri *et al.* (1971)	11–12 animals/group Banarasi Tobacco-DMSO extract/not specified; application to the cheek pouch 3 × /wk for 21 wk; controls received DMSO; 21 wk	No tumours found in treated and control animals Leukoplakia: 8/12 (67%)		Short duration of exposure, tobacco/DMSO dose not specified
Hamster Syrian golden (F) Rao (1984)	20, 10 controls Topical application to the cheek pouch of lyophilised aqueous tobacco extract, 1 mg in 0.05 mL water twice/d for 6 mo; controls received topical application of 0.05 mL water; 12 mo	Squamous cell papillomas and carcinomas: 3/17 (18%) Controls–no tumours	NR	Statistics not provided

D, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.8 Carcinogenicity studies of administration of naswar with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	SSignificance	Comments
Hamster Syrian golden (M, F) Kiseleva *et al.* (1976)	33 M, 28 F *Naswar* introduced as dry powder in the left buccal pouch (mixture of tobacco 45%, lime 8%, ash 30%, plant oil 12% and water 5%, dose (NR); life time	13 animals with tumours: Liver–6 Mixed–1 Adrenal gland–3 Forestomach–1 Uterus/ovary–1 Skin (melanoma)–1 Large intestine–1	Tumour frequency higher than in controls $P < 0.05$	Dose of *naswar* not specified Tumour type not specified genderwise
	24 M, 13 F *Nas* introduced as sunflower oil suspension in the left buccal pouch	Liver: 1 Uterus/ovary: 2 Skin (Papilloma): 1	Tumour frequency higher than in controls, $P < 0.05$	
	46 M, 40 F *Nas* introduced as sunflower oil suspension in the left buccal pouch	13 animals with tumours: Liver–4 Mixed–1 Adrenal gland–3 Forestomach (papillomas)–4 Uterus/ovary–1 Skin (papilloma)–1 Pancreas–1	Tumour frequency higher than in controls $P < 0.05$	
	41 M, 9 F *Nas* suspension in sunflower oil introduced in oesophagus	No tumours		
	31 M, 19 F *Nas* suspension in sunflower oil applied to dorsal skin	3 animals with tumours: Liver–1 Adrenal gland–1 Forestomach (papilloma)–1		
	41 M, 69 F Untreated controls	2 animals with tumours: Stomach–1 Adrenal gland–1		

Table 3.8 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	SSignificance	Comments
Hamster Syrian golden (M, F) Milievskaja & Kiseleva (1976)	184 animals *Naswar* introduced in the buccal pouch as dry powder or 50% suspension in sunflower oil; life time	Buccal pouch: 0 Forestomach: 5 Liver: 13 Adrenal gland: 6 Others: 9	NR	The number of animals that survived at the time of first tumour appearance was small High mortality was seen even in control animals
	30 animals DMBA only introduced in the buccal pouch once	Buccal pouch: 1 Stomach: 2		
	30 animals 0.1 g DMBA only + *naswar* introduced in the buccal pouch as dry powder or 50% suspension in sunflower oil; life time	Buccal pouch: 0 Stomach: 5 Others: 1		
	110 untreated controls	Stomach: 1 Adrenal gland: 1		

F, female; M, male; NR, not reported

Table 3.9 Carcinogenicity studies of oral administration of snuff to experimental animals

Reference Species, strain (sex)	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Stenström *et al.* (2007)	5.9% snuff diet (snus mixed with powdered standard mouse show); 6 mo	Gastric carcinoma in situ		
Mouse, wild type, FVB (M)	8, 11 controls	0/8 Controls: 0/11	NR	
Wild type, FVB *Helicobacter pylori* infected (M)	20, 8 controls	9/17 Controls: 0/11	NR	Gastric carcinoma in situ invading the mucosa and submucosa
INS-GAS (M)	8 animals/group	4/8 Controls: 2/8	NR	
INS-GAS (M) *Helicobacter pylori*-infected (M)	22, 8 controls	12/12 Controls: 2/8	NR	Gastric carcinoma in situ invading the mucosa

M, male; mo, month or months; NR, not reported

Table 3.10 Carcinogenicity studies of snuff to the oral mucosa or cheek pouch of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rat, Sprague Dawley (M) Johansson *et al.* (1989)	30 animals/group Snuff insertion in lip canal, 100 mg per application twice/d, 5 d/wk, controls received cotton pellet dipped in saline; 108 wk	Squamous cell carcinomas: 5 (lip–1, hard palate–2, nasal cavity–1, forestomach–1) Squamous cell carcinomas in situ: hard palate–1 Squamous cell papillomas: 3 (lip–1, hard palate–1, nasal cavity–1) Undifferentiated lip sarcomas: 2 Controls: no tumours	All squamous cell tumours $P < 0.01$ Malignant squamous cell tumours $P < 0.05$
Rat, Sprague-Dawley (M) Johansson *et al.* (1991)	38, 30 controls Snuff inserted in surgically created lip canal, moist snuff,150–200 mg/ application twice/d, 5 d/wk for 104 wk, controls received a cotton pellet dipped in saline once/d 5 d/wk for 100 wk	Sarcoma of the lip: 10/38 (26%) Squamous cell carcinomas and papillomas of the oral cavity: 3/38 (8%) (lip palate and buccal mucosa), Controls–1/30 (3%) sarcoma of the lip	Comparison of sarcoma $P < 0.01$ Comparison of all tumours $P < 0.01$

d, day or days; M, male; wk, week or weeks

hamsters compared to controls (Kiseleva *et al.*, 1976; Milievskaja & Kiseleva, 1976; Table 3.8).

3.2 Snuff

3.2.1 Mouse

Addition of snuff (snus) to the diet induced stomach tumours in gastrin transgenic mice but not in wild-type mice unless they were infected with *Helicobacter pylori* (*H. pylori*). Feeding snuff to *H. pylori*-infected transgenic mice increased gastric carcinoma incidence 2-fold versus control transgenic mice (Stenström *et al.*, 2007; Table 3.9).

3.2.2 Rat

Application of snuff to the oral mucosa (Chen, 1989) or swabbing of lips and oral cavity with a snuff extract (Hecht *et al.*, 1986) did not induce tumours.

In one study, the administration of snuff in a surgically created lip canal did not induce tumours in the oral cavity (Hirsch *et al.*, 1984) while a squamous cell carcinoma of the oral mucosa developed in one rat in another study (Hirsch & Johansson, 1983). Insertion of snuff in a surgically prepared lip canal induced a squamous cell carcinoma in the lip canal, a papilloma in the oral cavity and an olfactory tumour (Hecht *et al.*, 1986).

Insertion of snuff in a surgically prepared lip canal induced squamous cell carcinoma in the lip, hard palate, nasal cavity and forestomach and a carcinoma in situ in the hard palate. In addition, the treated animals developed squamous cell papillomas in the lip, hard palate and nasal cavity and two undifferentiated lip sarcomas. The incidence of all squamous cell tumours, squamous cell carcinomas and the total number of tumours in the treated group were significantly greater than in controls (Johansson *et al.*, 1989; Table 3.10).

In another independent study, the insertion of snuff in the surgically prepared lip canal induced two squamous cell papillomas in the lip,

Table 3.11 Carcinogenicity studies of snuff with known carcinogens or modifiers to experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rat, Sprague-Dawley (M) Johansson *et al.* (1991)	40 animals/group with surgically created lip canal Group 1: DMBA in mineral oil – 70 mg solution + a cotton pellet containing saline 1 × /d, 5 d/wk + snuff 150–200 mg/application. Group 2: DMBA initiation as for control group + snuff in the lip canal twice/d, 5 d/wk. Group 3: Controls initiated with cotton pellets containing 0.1% DMBA in mineral oil in lip canal 3 × / wk for 4 wk only, 104 wk	Sarcomas of the lip: 9/40 (22%) Squamous cell carcinomas and papillomas of the oral cavity (lip, palate, and buccal mucosa): 3/40 (7%) Controls: 0/40	Significant increase in lip sarcoma over Group 1
	38, 40 controls Group 4: Initiation with 4 NQO as for control group + snuff in the lip canal twice/d, 5 d/wk, 70 mg 4NQO sol + cotton pellet containing saline 1 × /d, 5 d/wk + snuff 150 – 200 mg/application. Group 5: Controls initiated with 4 NQO (0.5% in propylene glycol) in cotton pellet placed in lip canal 3 × / wk for 4 wk only, 70 mg 4NQO sol + cotton dipped in saline inserted in the lip canal once/d, 5d/wk; 100 wk	Sarcoma of the lip: 25/38 (66%) Controls–1/40 (2%) Squamous cell carcinomas and papillomas of the oral cavity (lip, palate, and buccal mucosa): 8/38 (21%) Controls–9/40 (22%)	Significant increase in lip sarcoma over control
Hamster Syrian golden (M) Park *et al.* (1986)	15–20 animals/group Cheek pouches inoculated with HSV1 or HSV2 (groups 1 and 1'), once/mo for 6 mo (no snuff); 6 mo	No tumours 0/19 (HSV1) No tumours 0/16 (HSV2)	
	Cheek pouches inoculated with HSV1 once/mo + snuff 150 mg/pouch, in both pouches twice/d, 5 d/wk for 6 mo; 6 mo (Group 2)	Invasive squamous cell buccal pouch carcinomas: 10/20 (50%)	Increase in carcinoma $P < 0.05$ Group 2 *vs* Group 1
	Cheek pouches inoculated with HSV2 once a mo + Snuff 150 mg/pouch in both pouches twice/d, 5 d/wk for 6 mo; 6 mo (Group 3)	Invasive squamous cell buccal pouch carcinoma: 11/20 (55%)	Increase in carcinoma $P < 0.05$ Group 3 *vs* Group 1'

Table 3.11 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Hamster Syrial golden (M) Gijare *et al.* (1990)	15 or 20 animals/group Application of 0.125 mg DMBA in 50 µl oil, twice/wk for 1 mo to both cheek pouches 0.25% in liquid paraffin; 6 mo	Cheek pouch tumours: 10/15 (66%) Forestomach tumours: 15/15 (100%)	NR
	Application of 0.125 mg DMBA in 50 ml oil, twice/wk for 1 mo + 50 µl snuff in liquid paraffin 20 mg per cheek pouch twice/wk to both cheek pouches 0.25% in liquid paraffin + Manglorian snuff; 6 mo	Cheek pouch tumours: 3/20 (15%) Forestomach tumours: 20/20 (100%)	NR
	Application of 50 µl snuff in liquid paraffin, 20 mg per cheek pouch twice/wk to both cheek pouches; 6 mo	Cheek pouch tumours: 0/20 Forestomach tumours: 17/20 (85%)	NR
	Application of 0.125 mg DMBA in 50 ml oil, twice/wk for 1 mo + 50 µl scented snuff in liquid paraffin 20 mg per cheek pouch twice/wk to both cheek pouches 0.25% in liquid paraffin + Scented snuff; 6 mo	Cheek pouch tumours: 2/20 (10%) Forestomach tumours: 19/20 (95%)	NR
	Untreated controls	No tumours	

d, day or days; M, male; mo, month or months; NR, not reported; *vs*, versus; wk, week or weeks

10 lip sarcomas and three squamous cell carcinomas in the hard palate. In the control group, a lip sarcoma occurred in one rat. The total incidence of epithelial and mesenchymal tumours of the lip and oral cavity and the incidence of lip sarcoma was significantly greater in snuff-treated rats than in controls (Johansson *et al.*, 1991; Table 3.10).

In one study, animals were repeatedly administered snuff extracts by the subcutaneous route. No local tumours developed in either treated or control groups (Schmähl, 1965).

Application of snuff to the surgically created lip canal of rats infected with HSV 1 resulted in the development of squamous cell carcinoma of the oral cavity in 2/7 (28%) rats and a retroperitoneal sarcoma developed in one rat. In the group exposed to snuff alone, one rat each developed a squamous cell carcinoma of the anus and a retroperitoneal sarcoma (Hirsch *et al.*, 1984).

In animals whose hard palate was treated with 4-Nitroquinoline 1-oxide (4NQO), repeated application of snuff did not enhance the incidence of benign and malignant oral cavity tumours over that in animals treated with 4NQO alone (Johansson *et al.*, 1989). However, in another study, application of snuff to a 4NQO-treated surgically created lip canal increased the incidence of lip sarcoma (Johansson *et al.*, 1991; Table 3.10).

3.2.3 Hamster

In hamsters infected with HSV1 or HSV2, insertion of snuff in the cheek pouch increased significantly the incidence of squamous cell carcinoma over that in animals infected with HSV1 or HSV2 and not administered snuff (Park *et al.*, 1986; Table 3.11). Application of a snuff suspension alone to the cheek pouch resulted in the development of stomach papillomas but did not increase the forestomach papilloma incidence in animals initiated with DMBA (Gijare *et al.*, 1990). In one study, chronic feeding of snuff and calcium hydroxide induced a pancreatic carcinoid in one animal only (Dunham *et al.*, 1975) but did not induce any tumours in another study (Homburger *et al.*, 1976). Snuff instillation in the cheek pouch did not induce tumours in six studies (Peacock & Brawley, 1959; Peacock *et al.*, 1960, Dunham & Herrold, 1962; Dunham *et al.*, 1975; Homburger *et al.*, 1976; Park *et al.*, 1986).

3.3 Synthesis

In animals administered various smokeless tobacco preparations, consistent increases were observed for forestomach, lung, oral cavity and nasal tumours in rats; lung, skin, forestomach and liver tumours in mice; and oral cavity (cheek pouch) and forestomach tumours in hamsters.

4. Other Relevant Data

See Section 4 of the *Monograph* on Tobacco Smoking in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity, oesophagus and pancreas.

There is *sufficient evidence* in experimental animals for the carcinogenicity of smokeless tobacco.

Smokeless tobacco is *carcinogenic to humans (Group 1).*

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* Exceptionally, the most recent updates of well-established ongoing surveys and reports, published after the meeting, were included in this Monograph. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.