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SUPREME COURT

SLP (C) No. 16308/2007-Ankur Gutkha Vs Indian Asthama Care Society & Ors-regarding.

F.No.NIHFW/SLP(C)/16308/2007/2010
11th February, 20111.

Mr. R.S. Negi
Under Secretary
Min. Of Health & Family Welfare
Room No. 425-C
Nirman Bhavan
New Delhi – 110011.

Subject: SLP(C) No. 16308/2007 – Ankur Gutkha V. Indian Asthama Care Society & Others – regarding.

Sir,

With reference to the letter No. 16017/15/2011-PH-I dated 23rd Dec. 2010, please find enclosed herewith the final report with index and list of members.

Yours faithfully,

(Deoki Nandan)

Encl: as above.

Copy to: Mr. Ranjit Singh, Legal Consultant, NIHFW, Nirman Bhavan, New Delhi

National Institute of Health and Family Welfare, Munirka, New Delhi.

Evidence assessment: Harmful effects of consumption of gutkha, tobacco, pan masala and similar articles manufactured in India

BACKGROUND INFORMATION

The Central Government had been directed 'to undertake a comprehensive analysis and study of the contents of gutkha, tobacco, pan masala and similar articles manufactured in the country, and harmful effects of consumption of such articles'. The National Institute of Health and Family Welfare (NIHFW) had been asked to compile the national and International studies already done on this issue.

RESEARCH QUESTION

In view of the above, the following questions were drafted for assessment:

1) What are the contents of gutkha, tobacco, pan masala and other similar articles manufactured in the country?
2) What are their harmful effects on humans?

METHODOLOGY

The evidence assessment was carried out in two parts:

a) Formation of a Committee of technical experts for helping with scientific literature on the topic
b) Analysis of contents of gutkha, tobacco, pan masala and other similar articles with the help of scientific literature provided by technical experts
c) Review of research studies on harmful effects of these articles which were identified following a comprehensive literature search

a) Committee of Technical Experts

A committee of technical experts was constituted to provide guidance on technical issues and help in collecting relevant scientific literature. The members of this committee are mentioned in Annexure A.

b) Scientific literature on contents of articles

The scientific literature on the contents of gutkha, tobacco, pan masala and other similar articles manufactured in the country was provided by the above mentioned committee of technical experts. In addition to the scientific literature, these experts also provided letters from Directors of various Regional Cancer Centers of the country and these have been appended at the end of this report *Annexure B*.

c) Review of research studies on harmful effects

Literature search

To identify relevant published evidence for the harmful effects of these articles, a comprehensive literature search was conducted in PubMed – a highly respected electronic database of peer-reviewed journals and online books with 20 million citations for biomedical literature. The search strategy combined relevant controlled vocabulary and natural language or free-text words to search for relevant English language studies conducted in humans from the year 1990 onwards. Studies published prior to 1990 were not searched since these studies were included in the two monographs developed by the International Agency for Research in Cancer (IARC) of WHO which have been appended as evidence for this review *(Annexure 1 (a), 4 (a))*. Additionally, technical experts were invited to submit any study for consideration provided it met the selection criteria. No attempt was made to hand search journals not indexed in the database or search for grey literature (conferences, abstracts, theses and unpublished studies).

Study selection criteria

The abstracts identified from the literature search were reviewed and the following criteria were defined for selecting the studies:

a) Studies conducted with an objective of evaluating harmful effects of these products in humans.

b) Studies based on primary as well as secondary research.

RESULTS

I. CONTENTS OF ARTICLES

The term 'smokeless tobacco' includes a large variety of commercially or non-commercially available products and mixtures that contain tobacco as the principal constituent and are used

either orally (through the mouth) or nasally (through the nose) without combustion *(Annexure 1 (a))*.

Oral use of smokeless tobacco is widely prevalent in India and different methods of its consumption include chewing, sucking and applying tobacco preparations to the teeth and gums *(Annexure 2)*. According to the monograph developed by the International Agency for Research in Cancer (IARC) of the World Health Organization *(Annexure 1 (a))*, the three forms of smokeless tobacco which are commonly used orally include:

a) *Tobacco alone* (with aroma and flavourings) – e.g Creamy or dry snuff, Gudakhu, Gul, Mishri, Red tooth powder
b) *Tobacco with other components* (lime, sodium bicarbonate, ash) – e.g Khaini, Zarda, Maras, Naswar
c) *Betel quid with tobacco* (includes areca nut, slaked lime, catechu and tobacco with spices) – e.g Betel quid, Gutkha, Mawa

For nasal use, a small quantity of very fine tobacco powder mixed with aromatic substances called dry snuff is inhaled. This form of smokeless tobacco use, although still practiced, is not very common in India. Snus is a form of snuff using moist tobacco powder, consumed by placing it under the lip for extended periods of time *(Annexure 2)*.

The brands and common names of different products of chewing tobacco (smokeless tobacco) used in India have been enumerated in the proceeding of a prestigious meeting conducted by the National Cancer Institute, USA and the Centre for Disease Control, USA *(Annexure 3)*.

In addition to the above mentioned smokeless tobacco products used orally, various mixtures of *betel-quid without tobacco* are also commonly used in India. A *'betel quid'* (synonymous with 'pan' or 'paan') generally contains betel leaf, areca/betel nut (or supari) and slaked lime, and may or may not contain tobacco. In other words, it usually contains at least one of the two basic ingredients **tobacco** or **areca nut**, in raw or any manufactured or processed form. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners, are added to betel quid according to local preferences. *(Annexure 4 (a))*

Pan masala is very similar to a betel quid except that all its ingredients are in dehydrated and granular/powdered form. *Gutkha* is a mixture of Pan masala and chewing form of tobacco.

Chemical composition

There are 3095 chemical components in smokeless tobacco products (including gutkha), among them 28 are proven carcinogen. The major and most abundant group of carcinogens is the tobacco-specific *N*-nitrosamines (TSNA) and no safe level of this chemical has been ascribed so far *(Annexure 1 (b))*. Other carcinogens reportedly present in smokeless tobacco include volatile *N*-nitrosamines, certain volatile aldehydes, polynuclear aromatic hydrocarbons, certain lactones, urethane, metals, and radioactive polonium. The two monographs published by the IARC of WHO have listed all these toxic ingredients along with their specific health implications *(Annexure 1 (b), 4 (b))*.

Results from various studies have found high levels of Nitrosamines in the branded Indian smokeless tobacco products available in the market *(Annexure 5-7)*. A detailed laboratory report on the constituents of different brands of smokeless tobacco available in India had reported substantive quantities of two potent carcinogens (nitrosamines and benzo-a-pyrene) and heavy metals in most of these products *(Annexure 8)*. Other studies have also demonstrated presence of high levels of heavy metals (Lead, Cadmium, Chromium, Arsenic and Nickel) in these products *(Annexure 7 – 9)*, with one study reporting almost 30% of gutkha brand samples exceeding the permissible levels of heavy metals Lead and Copper, when compared to the provisional tolerable intake limits determined by the FAO/WHO *(Annexure 9)*.

II. REVIEW OF EVIDENCE ON HARMFUL EFFECTS

The two key ingredients of smokeless tobacco and betel-quid products are tobacco and areca nut, and the chemical composition and effects of these two ingredients are quite different. Hence the evidence on the harmful effects of smokeless tobacco and areca/betel nut (or supari) has been reviewed under separate sections.

Section I deals with smokeless tobacco and includes evidence on harmful effects from 105 studies from India and abroad. Section 2 is a compilation of harmful effects of areca nut and includes 93 Indian and International studies. Altogether 184 scientific articles have been included in this review.

Effort has been made to include all the relevant studies identified from literature search and which met the pre-defined selection criteria. Due to time constraint, it was not possible to search other electronic databases and evaluate the included studies for their methodological quality.

SECTION I: SMOKELESS TOBACCO (OR CHEWED TOBACCO)

Prevalence in India

The Global Adult Tobacco Survey India (GATS India) is the global standard for systematic monitoring of adult tobacco use (smoking and smokeless) in the country. The survey, conducted in 2009-10 by the International Institute for Population Sciences (IIPS) Mumbai, covered about 99.9 % of the total population of India. Its findings revealed that more than one-third (35%) of adults in India used tobacco in some form or the other. Among them, 21 % adults used only smokeless tobacco, 9 % only smoke, and 5 % smoke as well as smokeless tobacco. Based on these, the estimated number of tobacco users in India was 274.9 million, with 163.7 million users of only smokeless tobacco, 68.9 million only smokers, and 42.3 million users of both smoking and smokeless tobacco. The prevalence of overall tobacco use among males was 48 % and among females 20 %, while the use of smokeless tobacco products among males (33%) was higher than among females (18%). The quit ratio for the use of smokeless tobacco use was 5% *(Annexure 10)*.

Studies from different parts of the country have found high prevalence of smokeless tobacco use in the Indian population *(Annexure 11 – 22)*. This has been endorsed in the monograph developed by the International Agency for Research in Cancer (IARC) of WHO *(Annexure 1 (c)*. Many studies have also reported on the popularity of smokeless tobacco products amongst children and youth of the country *(Annexure 1 (c), 23 – 38)*. An annotated bibliography of research on smokeless tobacco in India published by the Human Development Network of the World Bank also provides evidence of its widespread use in India *(Annexure 28)*.

Harmful effects

CANCERS

Oral pre-malignant lesions/conditions

Several studies, majority of them from India, have reported a strong association between smokeless tobacco use and oral premalignant/precancerous lesions like leukoplakia, erythroplakia, submucous fibrosis or lichen planus (either alone or in combination) *(Annexure 1*

(d), 39 – 45). The risk of these lesions has been found to increase with the duration and frequency of smokeless tobacco use *(Annexure 1 (d), 39, 42)*.

Oral cancer

A large number of studies from India provide consistent results of an increased risk of oral cancer with the use of different forms of smokeless tobacco used in the country (Gutkha, mishri, gudaku, khaini, etc) *(Annexure 46 – 55)*. Similar results are seen in International studies and reviews including the IARC monograph *(Annexure 1 (d), 56, 57)*. There is also good evidence to suggest that the risk of developing oral cancer is directly associated with the duration and frequency of tobacco usage *(Annexure 1 (d), 46 – 48, 52, 53)*.

Oesophageal cancer

Smokeless tobacco use or tobacco chewing has been reported as an important risk factor for the cancer of the oesophagus by multiple studies from India and abroad *(Annexure 1 (d), 54, 58 – 62)*. Moreover study results suggest an increased risk of oesophageal cancer with increase in the duration and frequency of smokeless tobacco usage *(Annexure 60 – 62)*.

Stomach cancer

Few Indian and International studies were identified which have reported an increased risk of stomach cancer with the usage of smokeless tobacco *(Annexure 1 (d), 59, 63)*.

Pancreatic cancer

All the relevant studies identified for this topic have been conducted outside India and their results indicate a strong association between smokeless tobacco and pancreatic cancer *(Annexure 1 (d), 58, 64 – 66)*. The association was significant even after adjustment for other variables.

Throat (pharynx and larynx) cancer

Results from different studies suggest an increased risk of pharyngeal cancer and/or laryngeal cancer with the use of different forms of smokeless tobacco *(Annexure 47, 53, 54, 67 – 69)*. Two studies also observed a strong dose-response relationship between chewable tobacco and risk of pharyngeal cancer *(Annexure 54, 68)*.

Renal cancer

Most of the studies included in the IARC monograph have reported an increased risk of renal cancer of about 2-3 times with the use of smokeless tobacco *(Annexure 1 (d)*

MORTALITY

Results from some studies indicate an increased risk of all-cause mortality or all-cancer mortality in smokeless tobacco users compared to non-users *(Annexure 70 – 73)*, and the increased risk was seen predominantly in female users. In addition, one Swedish study has reported an increased risk of dying from cardiovascular disease among the users *(Annexure 74)*.

NON-CANCEROUS DISEASES/CONDITIONS

Oro-dental health

All the Indian studies identified under this section have shown a close association between smokeless tobacco usage and different types of periodontal diseases (inflammation, gingival recession and bleeding, staining, tooth loss) and/or caries *(Annexure 75 – 80)*. A review of oral mucosal disorders associated with gutkha usage also found an increased risk of peri-odontal inflammation *(Annexure 43)*.

Hypertension & Cardiovascular diseases

Results from several studies indicate that regular use of smokeless tobacco increases the risk of hypertension *(Annexure 81 – 86)* and that of cardiovascular disease *(Annexure 82, 84, 86, 87)*. A systematic review of observational studies from Sweden and USA has also shown an increased risk of fatal myocardial infarction *(Annexure 88)*.

Nervous system diseases

Two large studies have found a significant association between the use of smokeless tobacco and the risk of fatal cerebrovascular stroke (or stroke) *(Annexure 89, 90)*.

Metabolic abnormalities

A study from Sweden reported significant association between high-dose consumption of snus/snuff and metabolic syndrome which is defined as 3 or more abnormalities of abdominal obesity, high cholesterol level, high triglycerides level, hypertension, and diabetes or hyperglycemia *(Annexure 91)*. Another study has found increased triglyceride and cholesterol levels among smokeless tobacco user *(Annexure 86)*.

Reproductive health

Multiple studies have reported adverse effects of smokeless tobacco on the reproductive health of men and women and during pregnancy. A study of Indian men attending an infertility clinic reported a strong association with decrease in sperm quality and sperm count (*Annexure 92*), while another study found an increased risk of cervical lesions in women (*Annexure 93*). Its use during pregnancy is reported to be associated with increased incidence of birth complications and anemia (*Annexure 94, 95*), increased risk of fetal loss (*Annexure 96, 97*), and a higher incidence of preterm babies and low-birth weight babies (*Annexure 98 – 100*).

Other diseases (Gastro-intestinal and Respiratory)

Results from few studies have found increased prevalence of benign gastrointestinal diseases (oesophagitis, sub-mucous fibrosis) in smokeless tobacco users (*Annexure 101, 102*). Moreover it has been associated with chronic bronchitis and impaired lung function with chronic use (*Annexure 103, 104*).

ECONOMIC COSTS

Using healthcare expenditure data from the National Sample Survey of India, a study found direct medical costs for treating smokeless tobacco associated cancers and diseases as USD 285 million, while indirect morbidity costs (including costs of caregivers and work loss due to illness) amounted to USD 104 million. The total economic cost of tobacco use was reported as USD 1.7 billion which was many times more than the annual government expenditure on tobacco control and about 16% more than the total tax revenue generated from tobacco (*Annexure 105*).

Evidence summary

Most of the relevant studies identified are from India, Sweden and USA with studies from India making the biggest contribution. There is strong and consistent evidence from a number of studies to indicate significant risk of oral cancer and pharyngeal cancer, oesophageal cancer, and pancreatic cancer with smokeless tobacco use. The risk of these cancers is found to increase with increasing dosage and frequency of smokeless tobacco use.

Results from several studies suggest presence of strong and consistent evidence that smokeless tobacco is significantly associated with poor oro-dental health, risk of hypertension and cardiovascular diseases, and adverse effects on reproductive health (especially during pregnancy with birth complications, fetal loss, low birth weight, prematurity). The evidence available for other diseases/conditions is limited but consistent in reporting increased risk of ill-

cause mortality and all-cause cancer mortality in female users, and increased risk of cerebrovascular stroke, metabolic abnormalities, oesophageal dieases, and respiratory diseases among all users.

There is also some evidence to suggest that the total healthcare economic cost of tobacco use in India is many times more than the annual government expenditure on tobacco control and about 16% more than the total tax revenue generated from tobacco

II. ARECA NUT OR BETEL NUT (OR SUPARI)

Prevalence

Studies have found nearly one-third of the population to be chewing areca nut in form of betel quid (*Annexure 4 (a), 10, 11, 28, 106, 107)*. Areca Nut usage has also been reported amongst school children (*Annexure 108 – 110)*. Some studies including the IARC monograph has reported widespread use of areca nut/betel nut chewing across many countries, especially the South East Asian countries (*Annexure 4 (a), 111, 112)*.

Harmful effects

CANCERS

Oral pre-malignant lesions/conditions

All the relevant studies identified for this topic have reported strong association between chewing of areca nut/betel quid and oral premalignant lesions (leukoplakia, erythroplakia, submucous fibrosis, lichen planus). These studies have been conducted in various parts of India (*Annexure 4 (d), 39, 42, 43, 113 – 119)* and across the world (*Annexure 120 – 124)*. Follow-up studies have also shown a high risk of malignant transformation of these lesions with continued areca nut usage (*Annexure 43, 121, 122)*.

Oral Cancer

IARC's monograph and several studies from Indian have shown areca nut chewing to be a significant risk factor for the development of oral cancer in humans (*Annexure 4 (d), 53 – 55, 122, 125 – 127)*. Moreover the risk has been found to increase with the duration and frequency

of areca nut usage *(Annexure 55, 122, 125, 126)*. These findings have been confirmed from studies conducted in Taiwan and other countries *(Annexure 128 – 133)*.

Oesophageal cancer

The risk of oesophageal cancer was significantly increased among the chewers of areca nut as reported in studies from India and Taiwan *(Annexure 54, 60, 134 – 136)*. The increased risk was found to persist even after controlling for smoking and alcohol intake. Study results also suggest that the risk of oesophageal cancer is directly associated with the duration and frequency of areca nut usage *(Annexure 54, 60, 134)*.

Liver cancer

Studies from Taiwan have reported areca nut/betel quid chewing as an independent risk factor for the development of liver (hepatocellular) cancer in humans, and the risk increased with the duration and frequency of its usage *(Annexure 137 – 140)*.

Throat cancer

Few studies have shown an increased risk of pharyngeal cancer with the use of areca nut *(Annexure 54, 69, 141)*.

MORTALITY

Results from two large cohort international studies have reported an increased risk of all-cause mortality among areca nut chewers compared to persons who had never chewed areca nut *(Annexure 142, 143)*. In addition, one of these studies found increased mortality risk due to cardiovascular disease while the other one reported increased mortality risk due to cerebrovascular disease.

NON-CANCEROUS DISEASES/CONDITIONS

Oro-dental health

Several studies have been conducted in South-East Asia on this topic, especially in India, Sri Lanka and Bangladesh. All of them have shown a close association between areca nut usage and different types of periodontal diseases (inflammation, gingival recession and bleeding, staining, tooth loss, and/or caries *(Annexure 75, 79, 144 – 148)*.

Hypertension & Cardiovascular diseases

A systematic review of observational studies found areca nut chewing (with or without tobacco) to be significantly associated with the risk of cardiovascular disease in Asia *(Annexure 149)*. It also observed a strong dose-response relationship between the two. Other relevant studies identified in search *(Annexure 143, 150, 151)* have been included in the above mentioned review and they reported similar results. Areca nut chewing was also found to be associated with hypertension *(Annexure 152)* and sub-clinical Ischemic Heart Disease in diabetic patients *(Annexure 153)*.

Nervous system diseases

Limited numbers of studies found under this section have reported adverse effects of areca nut usage on central and autonomic nervous systems *(Annexure 154 – 156)*. A case study has reported its indulgence as a probable cause of epilepsy *(Annexure 157)*.

Metabolic abnormalities (including obesity and diabetes)

Various metabolic abnormalities have been reported with areca nut usage. Studies have found a significant association between areca nut chewing and metabolic syndrome *(Annexure 158, 159)*, while an increased risk of this syndrome has also been reported among children exposed to paternal chewing *(Annexure 160)*. Other studies have found close association of its use with obesity *(Annexure 161 – 163)*, risk of hyperglycaemia and diabetes *(Annexure 163, 164)*, and poor glycaemic control in diabetic patients *(Annexure 165)*. There are reports that it adversely affects calcium and Vitamin D metabolism *(Annexure 166 – 168)* and appetite *(Annexure 169)*.

Addiction and Psychological disorders

Two studies have shown areca nut usage (more so with tobacco additives) to be associated with dependence syndrome *(Annexure 170, 171)*. On the other hand some studies have reported its therapeutic effect in patients of schizophrenia by producing less severe symptoms of the disease *(Annexure 172 – 174)*.

Reproductive health

Areca nut chewing during pregnancy has been reported to be significantly associated with adverse birth outcomes like prematurity, lower birth weight and reduced birth length in babies, even after adjustment for other variables *(Annexure 175 – 178)*.

Liver disease & Kidney disease

Two studies each have found areca nut use associated with significantly increased risk of development of liver cirrhosis *(Annexure 179, 180)*, chronic kidney disease, *(Annexure 181, 182)*, and urinary stone disease *(Annexure 183, 184)*.

Evidence summary

Majority of the identified studies are conducted in India and Taiwan. Results from multiple studies show strong and consistent evidence suggestive of areca/betel nut being a significant risk factor for the development of cancers of the oral cavity, oesophagus and liver. The risk of these cancers is found to increase with increased duration and frequency of areca/betel nut usage. Sufficient evidence has also been found for the development of oral pre-malignant lesions with a high risk of malignant transformation, while few studies have reported close association between areca nut usage and pharyngeal cancer.

Strong and consistent evidence was found for a significant association between areca/betel nut usage and peri-odontal diseases, cardiovascular diseases, metabolic abnormalities (including obesity and diabetes), and adverse birth outcomes. Though limited evidence is available for other diseases/conditions, results were consistent in implicating its use with increased risk of all-cause mortality, and for causing liver cirrhosis, chronic kidney disease, urinary stone disease, addiction, and nervous system diseases. There is also some evidence to suggest betel nut's therapeutic effect in patients with schizophrenia.

आत्मवत् सर्वभूतेषु

National Institute of Health and Family Welfare
Munirka, New Delhi-110067

Annexure-A

List of the members of the Core Group SLP (C) No. 16308/2007/2010

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Annexure-B

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SR NO	NAME OF THE INSTITUTE	PLACE/STATE	LETTER SIGNED BY	NAME OF THE PERSON
1	Tata Memorial Center	Mumbai, Mahrashtra	Director	Rajan A Badwe
2	ACHARYA TULSI REGIONAL CANCER TREATMENT AND RESEARCH INSTITUTE	BIKANER, RAJASTHAN	DIRECTOR	DR. R.K. CHAUDHARY 9414314294
3	THE GUJRAT CANCER AND RESEARCH INSTITUTE	AHMEDABAD, GUJRAT	HON. DIRECTOR	DR. PANKAJ M. SHAH 9426006244
4	REGIONAL CANCER CENTRE: PT. B.D. SHARMA, PGIMS	ROHTAK, HARYANA	HEAD OF SURGICAL ONCOLOGY	DR. R.K. KARWASRA 9215050301
5	RASHTRA SANT TUKDOJI REGIONAL CANCER HOSPITAL (AND RESEARCH CENTRE)	NAGPUR, MAHARASHTRA	DIRECTOR	DR. S. CHAUDHURI 9823073992
6	DR. BHUBANESWAR BOROOAH CANCER INSTITUTE	GUWAHATI, ASSAM	DIRECTOR	DR. A.C. KATAKI 9864096972
7	CHITTARANJAN NATIONAL CANCER INSTITUTE	KOLKATA, WEST BENGAL	DIRECTOR	DR. JAYDIP BISWAS 9830026696
8	CANCER INSTITUTE (WIA)	CHENNAI, TAMILNADU	DIRECTOR	DR. T. G. SAGAR 9840083780
9	CANCER HOSPITAL AND RESEARCH INSTITUTE	GWALIOR, MADHYA PRADESH	DIRECTOR	PROF. DR. B.R. SHRIVASTAV 9425109174
10	KIDWAI MEMORIAL INSTITUTE OF ONCOLOGY	BANGALORE, KARNATAKA	DIRECTOR I/C	DR. VIJAYAKUMAR 9448467765
11	M N J INSTITUTE OF ONCOLOGY & REGIONAL CANCER CENTER	HYDERABAR, ANDHRA PRADESH	DIRECTOR	DR. T. MANDAPAL 9963104040
12	REGIONAL CANCER CENTRE	RAIPUR, CHATTISHGARH	DIRECTOR	PROF. VIVEK CHOUDHARY 9826064727
13	REGIONAL CANCER CENTRE	AGARTALA, TRIPURA	MEDICAL SUPERINTENDENT	DR. GAUTAM MAJUMDAR 9436131423
14	ACHARYA HARIHARA REGIONAL CANCER CENTRE	CUTTACK, ORISSA	DIRECTOR	DR. U.R. PARIJA 9437023451
15	REGIONAL CANCER CENTER	Trivandrum, Kerala	Director	Paul Sebastian 9847124165
16.	INDIRA GANDHI INSTITUTE OF MEDICAL SCIENCES	Patna Bihar	DIRECTOR	Dr Arun Kumar 9431044957

Hos EPBX : 2226334-38
Institute : 2226329
FAX : 2226329

Gram : BIKMEDC
College : 2226300-0
Hospital : 2226304

1

(A GOVT. OF RAJASTHAN UNDERTAKING)

ACHARYA TULSI REGIONAL CANCER TREATMENT AND RESEARCH INSTITUTE, BIKAN

(REGIONAL CANCER CENTER)

ASSOCIATED GROUP OF HOSPITALS, S.P. MEDICAL COLLEGE, BIKANER-334 003 (RAJ.)

Ref. No. RT/ATR/BKN/ 04

Date 02/01/2001

To,

The Hon'ble Prime Minister of India
New Delhi

Sub: Appeal for ban on sale of Gutka and other tobacco products.

Your Excellency,

This is true and hard fact that habit of Gutka is increasing day by day in our population specially in younger population due to its easy availability at all kinds of shop. Gutka is a preparation of crushed areca nut (betel nut), tobacco, eatechil, paraffin, lime and sheet or savoury flavourings. It is consumed much like chewing tobacco and is considered to be responsible for oral cancer and other severe negative health effects. The most serious side effect associated with prolonged Gutka use is a risk of cancer, Gutka is suspected to elevate the risk of cancers of the gum, mouth, throat, lung, liver, stomach, prostate and oesophagus.

Gutka can also lead to abrupt changes in blood pressure, dizziness, blurring of vision and even palpitation cardiac arrhythmias. It increases the risk of heart attack and stroke.

Our institute Acharya Tulsi Regional Cancer Treatment & Research Institute, S.P. Medical College, Bikaner is situated in North-West Part of the Rajasthan. Patients from Delhi, Punjab, Haryana, Uatter Pradesh also approach for treatment at this center. Oral cavity is one of the commonest malignancies at our center contributing 10% of all malignancy. 70-80% of all malignancy are tobacco related in our centre. In view of these ill effects of tobacco, we appeal to you to take necessary steps for complete ban on Gutka and impart education programme for people about ill effect of tobacco.

Sir, our government is spending huge amount of money for cancer control programme and on the other hand we are not removing the root causes of cancer i.e. Tobacco and Gutka which are known causes of cancer development. We expect from government to ban such products completely and strictly to save the population of our country from ill effects of these products.

Yours,

(Dr. R.K. Chaudhary)
Director
Acharya Tulsi Regional Cancer
Treatment & Research Institute,
Bikaner (Raj.)

Copy to:
The Hon'ble Union Minister of Health & Family Welfare, Government of India, New Delhi

(1)

(Dr. R.K. Chaudhary)
Director

ANNE-II

2

A joint venture of Govt. of Gujarat & Gujarat Cancer Society

THE GUJARAT CANCER & RESEARCH INSTITUTE

[M. P. Shah Cancer Hospital]

REGIONAL CANCER CENTRE

(Recognized by Ministry of Health & Family Welfare, Govt. of India)

No. GCRI/EST/D/ 1650
January 4 ,2011

To
Dr. Manmohan Singh
Hon'ble Prime Minister of India
Prime Minister's Office
South Block, Raisina Hill,
New Delhi - 110 101.

Dear Sir,

Gutka sold in small pouches across the country has become a very serious health hazards to citizens of our nation. Easy availability of this mixture of toxic substance which include tobacco, Betel nut (Supari), Lime etc. is available very freely and many time at cost of less than 1 rupee. It has affected health of many people and cause cancer, anemia, Sub Mucous Fibrosis etc. The trend of cancer after introduction of this oral cancer including mixture of toxins has changed dramatically. As per the records of our Institute before two decades cancer of the throat was number 1 type of head and neck cancer. Now it is cancer of mouth, particularly oral cavity and cheek is number 1 type of cancer in head and neck region. It also affects age group of 20 to 40 years. This causes cancer earlier than cancer caused by smoking previously. This Gutka affects the prime of the life of our citizens where their need to the society of the country is maximum. Our Institute has done many pioneering studies on this and effect of the Gutka on Buccal Mucosa also. We also appeared before the High Court of Gujarat to give the expert opinion in the petition filed against Ahmedabad Municipal Transport Service and Gujarat State Transport Service to display the Pan Masala and Gutka advertisement. I am happy to inform you that the High Court of Gujarat has disposed off the application of the AMTS and GSRTC and now asked them not to display advertisements on the city and State buses.

Sir, we firmly believe that Gutka is poison for health and its distribution in any form is to be banned in our country. I would like to emphasis that the country need good human resource.

As a Director of the Regional Cancer Centre and also in my personal capacity, I have observed for last 4 decades about the hazards of the tobacco and Gutka. I would like to join hands with all the tobacco control organizations in the country and recommend that the strict action should be taken in this issue.

Thanking you,

(ii)

Yours sincerely,

Dr. Pankaj M. Shah
Hon. Director

ANNEX-III

3

DEPARTMENT OF SURGICAL ONCOLOGY

REGIONAL CANCER CENTRE : PT. B.D. SHARMA, PGIMS, ROHTAK – 124001, Haryana.

Dr. R.K. Karwasra MBBS, MS, FIAS, FICS, FACS (USA)
Head of Surgical Oncology
Pt. B.D. Sharma, PGIMS, Rohtak.

Sub : The Gutka related Health Hazard.

Gutkha is a preparation of crushed areca nut (also called betel nut), tobacco, catechu, paraffin, lime and sweet or savory flavorings. It is consumed much like chewing tobacco, and like chewing tobacco it is considered responsible for oral cancer and other severe negative health hazards. India has 75,000 to 80,000 new cases of oral cancers a year. According to WHO Country profiles, India has one of the highest rates of oral cancer in the world and rates are still increasing. This disproportionate incidence of oral cancer has been related to the high proportion of tobacco, gutkha, khaini or pan masala chewers, a habit unique to Indians. This is true across a broad spectrum of people, rich and poor, male and female, old and young. Gutkha use begins at a very young age. It is highly addictive and a known carcinogen Due to its often flavorful taste, easy availability and cheapness, it is popular with poor children, who can exhibit precancerous lesions at a very early age as a result. Symptoms of cancer often appear by high school or college age.. At our center we have seen similar trend and have diagnosed oral cancer in as young as 15 year old.

Gutka causes chronic irritation and needs to submucous fibrosis, leucoplakia & ora cancer. Apart from this it is also responsible for chronic sore throat & poor hygiene. In th absence of Cancer registry it is not possible to quantify the exact burden of the gutk related diseases at Regional Cancer Centre, Rohtak. However Oral cancer accounts fc one-third of the total cancer cases and 90% of the patients are tobacco/gutkha/khaini c pan masala chewers.

(111)

In any educated society such habits should be shunned but rather than this strangely the habit has a high degree of social acceptability in India. A popular advertisement showed the parents of a bride and groom agreeing to greet guests with pan masala. Due to such publicity People who would not dream of smoking, have no such qualms about consuming several packets of pan masala every day, simply because they are unaware of the dangers involved. While packets of these products do bear health warnings, they are rendered almost invisible by the bright shiny packaging and the small size of the warnings.

Proliferation of companies producing these products reflects failure of our governance as a welfare state. Mumbai's annual film festival - the Bollywood Oscars - is sponsored by one of the main producers of Gutkha. What is this? We are actually exploiting our fellow human beings simply because they are illiterate and poor and we want to use them as slaves. No body wants the growth about which we keep on discussing all the time.

The government should be prepared to ban the production of these products. This will mean loss of revenue but we have to do it. The cost should be increased many fold so that they are out of reach for most of people. The children should be taught about the harmful effects of Gutkha etc. The people working in this huge industry should be rehabilitated.

(Dr. R.K. Karwasra)

ANNE – IV

4

RASHTRA SANT TUKDOJI REGIONAL CANCER HOSPITAL

(AND RESEARCH CENTRE)

Dr.(Prof.) Santanu Chaudhuri

MBBS (Cal.) DMRT (Bom.), PGD (Hosp. Management) MD (Com) Dub

DIRECTOR - RST REGIONAL CANCER HOSPITAL

Head, Dept. of Radiation Oncology, RCHRC

Honorary Professor [illegible]

Speciality Teacher [illegible]

UICC Scholar

FORMER ATTACHMENT - [illegible]

Ex- Member - Standing Committee (R.C.H.)

Ministry of Health & Family Welfare, Govt. of India

Visiting Fellow - [illegible]

Ref. No. RST/RCC/Dir/01/2011 Date 3rd January 20

To
The Hon'ble Prime Minister of India
New Delhi

Sub : Appeal for ban on sale of Gutkha and other tobacco products

Your Excellency,

I would like to draw your attention regarding the dimensions of ill effect of tobacco in In Administrative measures which have been taken in Europe and USA, have shown a downw trend in tobacco related cancers in the western world effectively. Tobacco is one of the single m important risk factor for cancer, cardio-vascular and chronic respiratory diseases. There is alarming rise of tobacco related cancers in young age groups and even in school going yo adults in Central India as seen in our Hospital based Cancer Registry.

We would request the Government of India to take urgent steps for completely ban the sal Gutkha and all other forms of tobacco products along with planning of effective rehabilitatio the people who are working for this industry.

I shall be grateful if the above facts are taken into consideration and an effective tobacco co policy is framed out.

Thanking you.
Yours sincerely,

(Dr. S Chaudhuri)
Director
RST Regional Cancer Hospital

Copy for information & n/a to:
1. The Hon'ble Union Minister of Health & Family Welfare
Government of India,
New Delhi

ANNE - V

5

DR.BHUBANESWAR BOROOAH CANCER INSTITUTE

(REGIONAL INSTITUTE FOR TREATMENT AND RESEARCH)
GOPINATH NAGAR, GUWAHATI – 781016
ASSAM, INDIA

No.BBCI/Misc-136/Dir/ 2766 /2010

December 29, 2010

To
The Hon'ble Prime Minister of India
New Delhi

Sub : Appeal for ban on sale of Gutka and other tobacco products

Your Excellency,

You may be aware that the lives of far too many people in the world are being blighted and cut short by chronic diseases such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes. Tobacco is one of the single most important risk factor for cancer, cardio-vascular and chronic respiratory diseases. The Population Based Cancer Registry of National Cancer Registry Programme of ICMR has revealed that the incidence of cancer in India is highest in the State of Mizoram followed by Urban Kamrup district of Assam. This is largely due to high prevalence of tobacco consumption in the North Eastern Region. Fifty five to sixty percent of all cancers in the region are tobacco related. As per information available, in the city of Guwahati alone, Gutka worth Rs.12.00 lakhs are sold daily. 6.5 lakhs sachet of gutka and 3.2 lakhs packet of cigarette are sold every day in Assam. As per Global School Personnel Survey (GSPS-2006), 34.3% of children in the age group of 13-15 years consume tobacco in the North Eastern Region. Tobacco products are sold freely in and around educational institutions, hospital and office premises.

Considering the health hazards of the tobacco products, it is very important that the Government of India takes necessary steps for complete ban on sale of Gutka and other forms of tobacco products. The Government should promote economically viable alternatives to those persons who will be adversely affected by the Government policy to ban production and sale of tobacco products.

I shall be highly obliged if the above facts are taken into consideration for evolving an effective tobacco control policy.

Thanking you.

Yours sincerely,

29/12/10

(**Dr. A. C. Kataki**)
Director
Dr B Borooah Cancer Institute
Guwahati-781016

☎ (91)0361-2472364, 2472366, 2472636 Fax (91)0361 – 2472636 Website : www.bbcionline.org
E-mail : bbci_info@yahoo.co.in PAN No.AAALB0017E

DR.BHUBANESWAR BOROOAH CANCER INSTITUTE

(REGIONAL INSTITUTE FOR TREATMENT AND RESEARCH)
GOPINATH NAGAR, GUWAHATI – 781016
ASSAM, INDIA

Memo No.BBCI/Misc-136/Dir/ / 2010

December 29, 2010

Copy for information & n/a to:

1. The Hon'ble Union Minister of Health & Family Welfare
   Government of India,
   New Delhi

(Dr. A. C. Kataki)
Director
Dr B Borooah Cancer Institute
Guwahati-781016

(VII)

☎: (91) 0361-2472364, 2472366, 2472636 Fax: (91) 0361 – 2472636 Website : www.bbcionline.org
E-mail : bbci_info@yahoo.co.in PAN No.AAALB0017E

ANNE-VI

6

DR. JAYDIP BISWAS
MBBS,MS,DMRT,FICS,FAIS
DIRECTOR
&
HEAD OF THE DEPARTMENT (SURGICAL & MEDICAL ONCOLOGY, CLINICAL RESEARCH & TRANSLATIONAL RESEARCH)

CNC
Chittaranjan National Cancer Instit
(An Autonomous Body under Ministry of He
and Family Welfare, Government of Ir
37, S.P. Mukherjee Road, Kolkata – 7(
Phone : 2475-9313; 2476-5101(Extr
Fax : 2475-7606; email cncinst@vsn
http ://www.cnci.

No.D-18(37)/95(1)/ 2689

To
The Hon'ble Prime Minister of India
South Block
Raisina Hill
New Delhi-110101

January 3, 2011

Subject : *Appeal for ban on sale of Gutka and other tobacco products*

Hon'ble Sir,

I would like to draw your kind attention to a serious pressing problem that confront us directly. You are aware that cancer takes a heavy toll of human life every year. But presently we have sufficient knowledge, ways and preventive measures that can help to control and fight this dreadful disease. It is high time we take up this aspect more seriously. In view of this, the following appeal is submitted for your kind perusal and consideration.

Gutka is a tobacco product and tobacco contains several chemicals, some of which are carcinogenic. Thus gutka is a potential threat to human health. Apart from cancer. The available data shows that consumption of gutka and other tobacco products are also responsible for several chronic medical ailments viz. like Hypertension, cerebrovascular accident, myocardial ischemia, diabetes, chronic respirations diseases etc.

Cancer of oral cavity is frequent among patients attending the OPD of Chittaranjan National Cancer Institute, Kolkata. A common finding among the cancer patients is addiction to gutka and other tobacco products. Hence, gutka seems to have a major contribution to oral cancer in eastern India. On an average annually more than 1000 new patients suffering from oro-pharyngeal cancer, many of which are related to gutka use, are registered at CNCI, Kolkata. It is observed that magnitude of tobacco related cancer in average is on an upward trend in Eastern India. This is largely due to high prevalence of tobacco consumption in the Eastern Region.

Contd...p/2

(VII)

The available data in this regard is furnished below :

State	2005—2006%	2006—2007%
Kolkata	45.8(Male) 13.8 (Female)	44.4(Male) 12.3 (Female)
Dibrugarh District	56.3 (Male) 26.4(Female)	57.0 (Male) 26.3 (Female)
Kamrup Urban District	59.7(Male) 26.1(Female)	56.2(Male) 25.5(Female)
Mizoram State	37.3 (Male) 21.6 (Female)-	38.2(Male) 20.9 (Female)
Aizwal District	41.6(Male) 20.7(Female)	43.1(Male) 22.1(Female)
Mizoram State Excl aizwal	33.3 (male) 22.6(Female)	33.4(Male) 19.6(Female)

Inspite of the magnitude of tobacco related cancer is on an upward trend, unfortunately there is practically not much control on production and selling of gutka. It is sold everywhere. No sensible person can be happy with this. Unfortunately, the focus on tobacco control activities is much more on smoking rather than on chewable tobacco products though the second one is much more prevalent in India.

It is felt by all concerned that the regulatory mechanisms imposed on smoking also need to be imposed on sale of gutka as well. The mechanism of implementing the laws banning production, sale and use of gutka should be properly laid down and monitored stringently. A broad based IEC campaign highlighting the ill effects of gutka need to be launched involving all stake holders.

It will be deeply appreciated if this opinion and suggestions on the above mentioned matters are taken into consideration to launch a campaign to regulate the production, sale and use of gutka in the greater interest of the public. At the same time it is imperative that Govt. should promote economically viable alternatives to those persons who will be adversely affected by the Government policy to ban production and sale of tobacco products in order to ensure fruitful outcome in this regard.

Thanking you,

With my best personal regards.

Yours sincerely,

3/1/2011

Dr. Jaydip Biswas
Director

ANNE – VII 7

CANCER INSTITUTE (WIA)
REGIONAL INSTITUTE FOR CANCER RESEARCH AND
TREATMENT OF GOVT. OF INDIA
ADYAR, CHENNAI – 600020-INDIA.

PHONE: 2491 0754; 24911526
2235 0131; 22350241
FAX NO. 91 – 44 – 491 2085
E-mail: caninst@md2.vsnl.net.in
31.12.2010

To

The Hon'ble Prime Minister of India,
New Delhi

Your Excellency,

Sub: Appeal for ban on Tobacco Products (Gutkha, Cigarettes, Bidi and other Tobacco related products)

India unfortunately occupies a very special place in the World Tobacco map. As all of us are aspiring to achieve a 'Super Power Nation' status for India, it is estimated that India would lose 13.2% of its population to tobacco terrorism by 2020. Currently, there is one tobacco related death in every eight seconds in India. According to the Madras Metropolitan Tumor Registry, the tobacco related cancers together constituted 44% and 16% of the total male and female cancers respectively. 96% of the oral cancers in India are related to chewing tobacco (Gutkha). According to MMTR oral cancer is the third commonest cancer among men and fourth among women. Mouth cancer is on the rise due to more youngsters getting addicted to Gutkha and 40% of the tobacco users are in the smokeless form in India. Unlike western countries, chewing is a major public health threat to India and it needs special attention.

Tobacco related diseases such as cancer, cardiac and pulmonary problems etc are not contagious, and however, the tobacco habit is contagious due to various psycho-socia and environmental factors. In Chennai, 18.9% of the 11 year old children are using tobacco whereas 25.5% of the college students are tobacco users. 40.9% of the children in Chenna are exposed to passive smoking at home. Despite the law in place, 35.8% of the 11-13 yea old children are procuring tobacco from the shops either for them or family members. 87% o the children reported that there are 5- 30 shops around their educational institutions sellir tobacco.

Reversing this entirely preventable tobacco epidemic must now rank as a top priority for public health and for political leaders in every country of the World -

Dr. Margaret Chan, WHO Director General

In a study conducted in Chennai city by Cancer Institute (WIA), 60.2% of shopkeepers reported that out of the total profits earned; only 10-20% was attributed to tobacco sale, implying that the percentage of profit earned by selling tobacco products is far less compared to selling other commodities. Moreover, 31.3% of the shopkeepers mentioned that they are contemplating to stop tobacco sale completely. However, the tobacco industry makes false representation that the retailers will be affected by ban. 75.7% of the shopkeepers insisted complete ban on tobacco products comparing with the lottery ban in Tamil Nadu and 60% of the Heads of Educational institutions also insisted for complete ban in addition to stringent punishments to the violators.

Moreover, 53% of the tobacco use is in the form of bidi and it causes 6 lakh deaths annually. In a study conducted in the Southern Districts of Tamil Nadu, 99.6% of the bidi rollers are earning less than Rs. 1000/month and 96.2% readily expressed their willingness to shift their occupation since it is not remunerating and causing health problems.

It is reported by ICMR, the health care costs are multiple times more than the revenue earned from the tobacco industry. It is evident; the killer tobacco is no way beneficial to the users, sellers, farmers and the Government.

Considering the above facts, I request the Government of India to take necessary steps to rehabilitate the workers involved in tobacco and ban all the tobacco products completely in India.

Thanking you

Yours Sincerely,

Dr. T. G. Sagar,
Director,
Cancer Institute (WIA)
Chennai

Reversing this entirely preventable tobacco epidemic must now rank as a top priority for public health and for political leaders in every country of the World -

Dr. Margaret Chan, WHO Director General

ANNE-VIII 8

CANCER HOSPITAL & RESEARCH INSTITUTE

Regional Centre For Cancer Research & Treatment

(JAN VIKAS NYAS), GWALIOR

Cancer Hill (Mandre Ki Mata), Gwalior, (M.P.) 474 009 INDIA

Tel. : 2336502, 2336503, 2336504, 2336505 Fax : 0751-2336506

E-mail : raju_chri@dataone.in, chri_gwl@gmail.com

Ref. No. 2499 Date 3 Jan.

To,
Hon'ble Dr. Manmohan Singh Ji
Prime Minister of India
India

Sub :- Regarding health hazard of Gutka chewing

Respected Sir,

Habit of Gutka chewing is going to be very dangerous health hazard for the people of India as this habit is acquired by people of all ages. Even school going children they are using Gutka very frequently & when they reach at the age of Twenty to Twenty five years they develop disease in mouth as oral submucous firbrosis and oral cancer.

The ingredients in Gutka like lime, betelnut, camfor & others are toxic to mucosa of oral cavity & produces severe changes in the form of leukoplakia (Pre Cancerous condition)

At Regional Cancer Centre, Gwalior we see about 500 to 800 cancer cases every year related to the habit of Gutka chewing.

Big Companies they advertised for the sale of Gutka in such a way they all class of people & all age of people they get attracted for this hazardous product & get habit of consuming this.

It is my request to your goodself that advertisement & sale of Gutka should completely banned in India so future of our generation can be saved from the harmful effects of Gutka.

With Warm Regards !

Prof. Dr. B.R. Shrivastav
Director

Copy to :- Sh. Gulam Nabi Azad, Minister of Health & Family Welfare
Govt. of India, New Delhi (India)

ANNEX-IX

9

ಕಿದ್ವಾಯಿ ಸ್ಮಾರಕ ಗಂಥಿ ಸಂಸ್ಥೆ
KIDWAI MEMORIAL INSTITUTE OF ONCOLOGY

ಪ್ರಾದೇಶಿಕ ಅರ್ಬುದ ಸಂಶೋಧನೆ ಮತ್ತು ಚಿಕಿತ್ಸಾ ಕೇಂದ್ರ
ಯು.ಐ.ಸಿ.ಸಿ. ಸದಸ್ಯ ಸಂಸ್ಥೆ (ಅಂತರರಾಷ್ಟ್ರೀಯ ಅರ್ಬುದ ರೋಗ ನಿವಾರಣಾ ಸಂಘಟನೆ)

Grams : KIMO
Phone : 26560722 (Director)
: 26094000
Fax : 91 - 80 - 26560723

ಡಾ II ಎಂ. ಎಚ್. ಮರೀಗೌಡ ರಸ್ತೆ -
ಬೆಂಗಳೂರು- 560 029
ಕರ್ನಾಟಕ, ಭಾರತ
Dr. M.H. Marigowda Road,
Bangalore - 560 029
KARNATAKA, INDIA.

NO:PER/CAB-II/D-2-146/2011 4.1.2011

To :

The Hon'ble Prime Minister
Government of India
NEW DELHI

Your Excellency,

It has been well researched and understood that chewing Gutka is very Injurious to health. It causes oral cancer and has many other severe health effects. It also is responsible for vast number of cases of oral sub mucous fibrosis, a precancerous condition. Where in the muscles in the mouth eventually lose their ability to stretch.

The contents of Gutka include tobacco, betal nut, catechu, arsenic, lime, paraffin, magnesium carbonate (used beyond prescribed limits). Most of these ingredients are well known carcinogens and warrants ban under prevention of Food Adulteration Act and other similar provisions. The tobacco in Gutka releases cancer causing chemicals called nitrosamines in the mouth.

Although the burden of cancer only due to the use of Gutka is still not known, the tobacco related cancers at Kidwai Memorial Institute of Oncology (Premier Regional Cancer Centre for treatment and Research on Cancer in Bangalore) accounts for 47 % of all cancers in males and 20 % of all cancers in females.

India has the highest number of Oral cancers in the world and the use of Gutka is increasing mainly due to a group of entrepreneurs "Gutka Barons" tuned 400 years old. Tobacco product hand-rolled in betel leaves into a spicy blend and sold for a small price on street corners from Bangalore to New Delhi. Sales of tobacco chewing products worth 210.0 billion Rupees in 2004

ಕಿದ್ವಾಯಿ ಸ್ಮಾರಕ ಗಂಥಿ ಸಂಸ್ಥೆ
KIDWAI MEMORIAL INSTITUTE OF ONCOLOGY
ಪ್ರಾದೇಶಿಕ ಅರ್ಬುದ ಸಂಶೋಧನೆ ಮತ್ತು ಚಿಕಿತ್ಸಾ ಕೇಂದ್ರ
ಯು.ಐ.ಸಿ.ಸಿ. ಸದಸ್ಯ ಸಂಸ್ಥೆ (ಅಂತರರಾಷ್ಟ್ರೀಯ ಅರ್ಬುದ ರೋಗ ನಿವಾರಣಾ ಸಂಘಟನೆ)

Grams : KIMO
Phone : 26560722 (Director)
: 26094000
Fax : 91 - 80 - 26560723

ಡಾ॥ ಎಂ. ಎಚ್. ಮರೀಗೌಡ ರಸ್ತೆ,
ಬೆಂಗಳೂರು- 560 029
ಕರ್ನಾಟಕ, ಭಾರತ
Dr. M.H. Marigowda Road,
Bangalore - 560 029
KARNATAKA, INDIA.

are on track to double by 2014 according to Data Monitor, a branch of the international research firm based in Hyderabad, India.

In spite of stringent laws/ rules on sale of Gutka, there has been no control in the sue of Gutka and is disturbing as many of the studies in our country has shown that Street vendors crowd around schools, breaking the law which prohibit the sale of tobacco products within 100 yards of educational Institutional and the use of Gutka in the younger age groups is increasing as evidenced by Devika Chadha, a program Director at Salman Bombay Foundation working with schools to educate children about tobacco dangers.

The facts mentioned above calls for the most stringent action to curb the menace. It is time for all of us who have been witnessing the caused by use of Gutka in our day to day professional work to raise our voice so as to dim the noise caused by the powerful Gutka industry.

As cancer care provides and public health advocates, we extend all the necessary support to strengthen the efforts of Ministry of Health and Family Welfare to wage a War by projecting a strong case against Gutka.

Yours sincerely,

(M. VIJAYAKUMAR)
Director I/c

ANNEX-X

M N J INSTITUTE OF ONCOLOGY & REGIONAL CANCER CENTER

AUTONOMOUS INSTITUTE OF GOVT. OF ANDHRA PRADESH

Red Hills, Hyderabad - 500 004. A. P.
Fax : 040 - 23314063. E-mail : dirmnjiorcc@yahoo.com

Dr.T. MANDAPAL, M.D., FICR
DIRECTOR

+91(40)23318414, 2331
+91(40)23318424, 2339

Rc. No . / MNJ IO&RCC/ 2010/502 Date: 3 -01 - 2011

To
Dr. Pankaj Chaturvedi
Head and Neck Surgeon
45, Head & Neck Services
Tata Memorial Hospital
MUMBAI -- 400012

Dear Sir,

Sub: - MNJIO&RCC, representing a short and succinct opinion for sale of Gutka to be Banned in our Country and to save the life of adductors and their family.

Ref: E-mail , dated, 28th December, 2010.

****

With reference to the E-mail, 28-12-2010 MNJIO&RCC, representing a short and succinct opinion for sale of Gutka to be banned in our Country and to save the life of adductors and their family. Please find the points covered in the enclosures as requested in your letter.

Wish you a favorable Judgment in favor of the Public Health.

Thanking you,

Yours Sincerely

(Dr. T. MANDAPAL)
DIRECTOR

Encl: as above.

MNJ INSTITUTE OF ONCOLOGY
& REGIONAL CANCER CENTER HYDERABAD

The MNJ Institute of Oncology & Regional Cancer Centre was established in 1955 and inaugurated by the late Pandit Jawaharlal Nehru, the Hon'ble first Prime Minister of India on 8th December 1955. The Govt. of India has conferred the status of Regional Cancer Center on 13th March 1996 as a 12th center in the country. It is the sole referral hospital of Andhra Pradesh offering free comprehensive cancer care to the poor patients. It is also serving a number of cancer patients coming from surrounding states of Maharashtra, Madhya Pradesh, Karnataka and Orissa. After making a humble beginning as a 40 bedded hospital we have grown into the institution with occupancy of 350-400 in patients.

More than 11,000 new cancer patients are registered per year and about 80,000 patients come for follow-up. 1500 major surgeries and 1000 minor surgeries are performed per year. 300 patients are being given radiotherapy and 300 patients are being given chemotherapy every day. More than 1.5 lakh cancer-related investigations are done every year.

The institution has the following Departments:

1. Radiation Oncology, 2. Surgical Oncology, 3. Medical Oncology, 4. Plastic & Reconstructive Surgery, 5. Nuclear Medicine, 6. Radiology, 7. Anesthesiology, 8. Pathology, 9. Dental Surgery, 10. Radiation Physics, 11. Molecular Oncology, 12. Biochemistry, 13. Pediatric Medical Oncology, 14. Pain & Palliative Care and 15. Tobacco Cessation Clinic

The MNJ Institute of Oncology & Regional Cancer Center, Hyderabad is a teaching institute affiliated to Osmania Medical College/NTR University of Health Sciences, Vijayawada. The institute is offering the postgraduate and paramedical courses .

- Gutka constitutes of Nicotine in the form of tobacco and other ingredients which is detrimental to the human health particularly Oral Cancers such as Tongue Cancer, Cheek, Floor of mouth, Palate and Tonsils etc.

- Gutka consumption is more common among youth. As smoking Cigarettes, Bidi is obvious to persons in the nearby environment hence youth take the gutka in the palm and put into the mouth and slowly chew it and this will make tobacco consumption invisible. However as tobacco is hazardous to health in this form of consumption becomes invisible to the neighbors. Hence particularly drivers of Auto rickshaws, Transport vehicles, petty vendors and even white color employees in the offices where smoking is prohibited chew the Tobacco which is not obvious to the Authorities. This is a more dangerous form of Tobacco consumption which is surreptous. hence Gutka is very bad in our opinion. The habitués is also encourages spitting within the premises of offices , banks, hospitals and Public Places which spoils the surrounding environment and causes infection to all.

- The cancer cases are 10 – 20% of the Tobacco related Cancers are due to Gutka Consumption in our center, MNJIORCC, Hyd.

- Gutka is sold all over the country and through the Metropolitan cities. Gutka is available in all shops near Schools, Colleges, Work places, Public places within 10 yards vicinity. This is sold to minors too. This is available even in Religious Places where smoking is banned.

- The Government should take steps to ban not only smoking but also Gutka consumption in Public Places.

- Selling of Gutka near Schools, Colleges, Public Places and Religious places should be banned.

- The Pan shops were selling Cigarettes with Gutkas (tobacco related products) are usually attached to Restaurants, Hotels, Cinema theaters and Bars. We are unhappy with the way the gutka is sold and advertised. This should be banned.

- Health awareness campaigns should be conducted in the Schools, Colleges with particular importance to the tobacco consumption. Display the slides on health hazards of tobacco use in Cinema theaters. Sign boards should be displayed banning Smoking and Gotka consumption as well in the Public Places and stringent action should be taken on violation.

ANNE-XI

11

REGIONAL CANCER CENTRE RAIPUR
PARTMENT OF RADIOTHERAPY
Pt. J. N. M. Medical College and
Dr. B. R. Ambedkar Memorial Hospital
Raipur (C.G.) 492 001
Phone No. 0771- 2886661, 2890084 Fax. No 4028150,
E-mail – rccraipur@yahoo.com

Rt. No. **584** Dated **31/12/2010**

To,

The Hon'ble Prime Minister of India
New Delhi

Sub : Appeal for ban on sale of Gutka and other tobacco products.

Your Excellency,

1. How bad is gutka for health such as oral cancer ?

   Oral cancer is the 6th most common cancer in India. Most of the oral cancers . are related to gutka eating. Beside oral cancer, gutka causes other health hazards like erosive gastritis, oesophagitis, heart diseases, lung diseases. For oral cancer , person who is chewing tobacco is having 2-4 folds more risk, 8- 10 folds more risk who smokes as well as chew and person who keeps tobacco gutka through out night is 60-65 fold more at risk comparative to non chewer.

2. What makes Gutka bad in your opinion?

   Gutka by all means bad for person, society & country. From ancient time Indian morning starts with gutka . this smokeless tobacco is slow poison forPerson, family & society. As a rule of thumb where ever chronic friction isthere, it is genesis of cancer. And tobacco spiting over walls is uniqueFeature of our country.

3. what is the burden of gutka related diseases in your center?

   Head & neck cancers are most common cancer in our registry. In year 2009 out of 2868 newly registered patients 521(18%) are of head & Neck cancer. Out of them about 59% constitutes Oral cancer .other cancer Caused by gutka are oropharangeal, esophageal ,lung, stomach cancers.

(xviii)

4. Are you happy with the way gutka is sold and advertised?

No, it is hazardous for person , society & country. It should be banned by the society in the society for the society,

5. How would you like the government to tackle this issue?

By banning gutka by strict legislation without if & buts. It should be strictly prohibited despite of lot of revenue losses to government. I shall be highly obliged if the above facts are taken into consideration for evolving an effective tobacco control policy.

Thanking you.

Yours sincerely

Prof. Vivek Choudhary
Director, Regional Cancer Centre
Pt. J.N.M. Medical College &
Dr. B.R. Ambedkar Memorial Hospital
Raipur (C.G.)

Copy for information & n/a to:

1. **The Hon 'ble Union Minister of Health &Family Welfare Government of India.**

Yours sincerely

Prof. Vivek Choudhary
Director, Regional Cancer Centre
Pt. J.N.M. Medical College &
Dr. B.R. Ambedkar Memorial Hospital
Raipur (C.G.)

ANNE-XII

12

GOVERNMENT OF TRIPURA
OFFICE OF THE MEDICAL SUPERINTENDENT
REGIONAL CANCER CENTRE,
KUNJABAN, AGARTALA, PIN-799 006
Telephone No (0381) 235-3407 Fax No (0381) 235-9002
E-mail : rcc.agartala@yahoo.co.in, rcc_agartala@rediffmail.com

No F.3(225)-CH/MS/COPTA/2010/5[illegible] Dated, Agartala, the 30th Dec., 2010

To
The Hon'ble Prime Minister
Government of India
South Block, Raisina Hill,
New Delhi-110 011

Sub :- An appeal for ban on sale of Gutka and other tobacco products.

Respected Sir,

In North-Eastern States there are approximately 250 different tribes which contribute 50% of total tribes in the country. The simple reason behind the origin of such huge number of tribes was geographical terrain lack of connectivity since time immemorable. Since the inception **of DONER** and **Look East projects** the area is now gradually developing. It is exciting to have railways & airways communication in all these states. Before these new developments culture and beliefs of these people were different. Surprisingly all superstitions, all religions faith of these people were with Tobacco and alcohol which they used to produce locally.

With the advent of "Gutka pouch", Paan Masala pouch, Zarda pouch the sale of old fashioned Tobacco i.e. Tobacco leaves, Betel, Betel leaves to earlier-older customer and the sale of Gutka pouch to youngster have increased tremendously. **As a result the consumption of Tobacco items has increased double folds.** Consequence to the use of these old fashioned tobacco and new fashioned Gutka the older as well as newer generation are equally suffering from various health hazards including oral cavity and lung cancers.

Though awareness programme through Govt. Organization and Non Govt. Organization has already curtailed the use of Tobacco in public places I think sale of these products in open market should be banned like alcohol.

Yours Sincerely,

30/12/10

[Dr. Gautam Majumdar]
Medical Superintendent
Regional Cancer Centre,
Agartala.

Enclosures :-
1. Tobacco Related Cancer Sites in Tripura
2. Tobacco Related Cancer in North East India

(X)

ANNE-XIII

13

RESOURCE CENTRE FOR TOBACCO CONTROL

(W. H. O. PROJECT)

HARIHARA REGIONAL CANCER CENTRE, CUTTACK - 753007

Tel: 0671 – 2302536

Email: ranjanparija@sify.com

ranjanparija@yahoo.in

Dr. U. R. Parija

Prof. Head & Neck Oncology

Tel: 0671-2311040(R)

Mob: 94370 23451

To,

Dr Pankaj Chaturvedi
Tata Memorial Hospital,
Mumbai

Sub: Tobacco & Cancer

Sir,

With reference to the discussion we had regarding 'Smokeless Tobacco' & 'Oral Cancer', it is pertinent to mention here that the incidence of oral cancer is mostly due to 'Chewing of Gutkha (with tobacco)

It has been observed that the hour of contact of the quid with the oral mucosa is of vital importance for causation of oral lesions for smokeless tobacco users. The incidence of pre-cancer lesions is at an increasing trend among the smokeless tobacco i.e. different forms of Gutkha users.

Hence, adequate necessary steps requires to be implemented for prohibiting the increasing status of oral cancer.

With Regards

Thanking You

Dr.U.R.Parija

Director & Principal Investigator

Resource Centre for Tobacco Control (RCTC)

& Regional Cancer Centre, Cuttack

ANNE – XIV

14

REGIONAL CANCER CENTRE

Phone: +91 471 2443128 / 2522222
Fax: +91 471 2447454 / 2522500
E-mail: director@rcctvm.org
PO Box 2417 Medical College Campus
Thiruvananthapuram 695 011 India
www.rcctvm.org

No.Dir/72/2011/RCC
Date: 07/01/2011

The Hon'ble Prime Minister of India
South Block-11
Raisina hill
NEW DELHI - 110 101

Hon'ble Sir,

Subject: Appeal for ban of Gutka and other tobacco products

This letter has reference to the current Supreme Court ruling on gutka sold in plastic pouches by virtue of its allegation that the plastic pouch containing gutka can be disastrous to the environment. In this context, I would like to draw your kind attention to some of the facts related to gutka use and its implications on public health in general.

In the state of Kerala, smokeless tobacco sold in sachets are called by the generic name 'panmasala'. The term panmasala itself is a misnomer because many of the brands may not contain their prime ingredient pan or betel nut. Moreover, panmasala comes in two forms ie, panmasala with gutka (it contains tobacco) and without gutka. It is a combination of many ingredients and most of them are unknown to the consumer. The flavoring agents are trade secrets and hence the consumer is denied of the right to know the ingredients other than tobacco and arecanut.

(XXII)

It is estimated that 35% of the Indian population use tobacco of which 21% use only smokeless tobacco. This is a matter of serious public health concern as the use of tobacco is are responsible not only for cancer but also for coronary artery disease, hypertension, cerebrovascular accidents, chronic obstructive airway disorders etc. There is irrefutable evidence to show the association between gutka use and oral cancer.

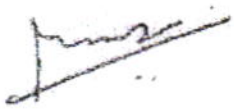
Among gutka users, oral cancer usually arises from a precancerous condition called oral submucos fibrosis. If one does not quit the habit or if left untreated, the cancer occurs 5 to 10 years after the advent of oral submucos fibrosis. In our country, oral cancer is a major public health problem accounting for nearly 10% of all cancers. Due to the increase in gutka use among adoloscents and young adults, a change in trend in the occurrence of oral cancer is expected to occur with more number of oral cancers in young adults.

The Hospital Based Cancer Registry of the Regional Cancer Centre, Thiruvananthapuram has information on tobacco related cancer patients arriving at the Centre. However, data on incident cancer cases due to gutka use alone is currently not available. While looking into tobacco related cancers occurring among males, it was observed that the number of cases registered in the year 2009 were higher when compared to previous years. For instance, 5730 tobacco related cases (directly or indirectly related to tobacco use) were reported among males in the year 2009 whereas in the year 2005, it was 4555. While looking at the age specific cancer cases (up to 34 years of age), 41 tobacco related cancer cases were reported at RCC, Trivandrum in the year 2009 when compared to 26 cases in the year 2008. This upward trend in the occurrence of tobacco related cancers has been observed in many other Indian states also.

Though we have hard evidence that tobacco related cancers are on the increase, very little has been done to control the production and sale of gutka in our country. Banning of advertisements on tobacco products in the print and electronic media will have little impact if the main provisions mentioned in the Cigarettes and Other Tobacco products Act, 2003 are not being effectively implemented. For example, the main provisions of the act like prohibition of sales to minors [section 6(a)] and prohibition of sales of tobacco products near educational institutions [section 6(b)], has not become fully operational in Kerala State. Strict enforcement of this act is necessary to check gutka use among adolescents. The Government can also make consumption of gutka unattractive by imposing hefty taxes similar to what was done for cigarettes. In addition to all these, a broad based IEC campaign by the Government against gutka needs to be launched.

Thanking you,

Yours faithfully,



Paul Sebastian

(x IV)

ANNEX XV

TATA MEMORIAL CENTRE
टाटा स्मारक केन्द्र
TATA MEMORIAL HOSPITAL
टाटा स्मारक अस्पताल

312802

Date [illegible]

To,

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Copy to : Hon'ble Minister for Health and Family Welfare, Government of India, New Delhi.

[illegible]

(XXV)

ANNE- XVI

INDIRA GANDHI INSTITUTE OF MEDICAL SCIENCES

An Autonomous Institute of Government of Bihar
(Not a Deemed University Created by an Act of State Legislature)

Dr. Arun Kumar

SHEIKHPURA, PATNA - 800 014 (INDIA)
Ph. (0091-0612-2297634, 2297099) Fax: 239 2296329 (Direct) (O), 2547325 (R)
Mobile: 09431044957, E-mail: patrauni@hotmail.com

To
The Hon'ble Prime Minister of India
New Delhi

Sub : Appeal for ban on sale of Gutka and other tobacco products

Your Excellency,

You may be aware that the lives of far too many people in the world are being blighted and cut short by chronic diseases such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes. Tobacco is one of the single most important risk factor for cancer, cardio-vascular and chronic respiratory diseases. The Population Based Cancer Registry of National Cancer Registry Programme of ICMR has revealed that the incidence of cancer especially tobacco related such as head and neck, lung, cervical cancers in India is highest in the North Eastern States. This is largely due to high prevalence of tobacco consumption in the North Eastern Region. Tobacco use including smoking is very high among 13-15 year old students in Bihar. According to Global School Personnel Survey, GSPS, 77.4% were ever tobacco users; of them 48.9% had used tobacco before 10 years of age. Seventy to seventy five percent of all cancers in the region are tobacco related. Tobacco products are sold freely in and around educational institutions, hospital and office premises.

Considering the health hazards of the tobacco products, it is very important that the Government of India takes necessary steps for complete ban on sale of Gutka and other forms of tobacco products. The Government should promote economically viable alternatives to those persons who will be adversely affected by the Government policy to ban production and sale of tobacco products.

I shall be highly obliged if the above facts are taken into consideration for evolving an effective tobacco control policy.

Thanking you.

Yours sincerely,

(Dr. Arun Kumar)
Director
IGIMS, Patna

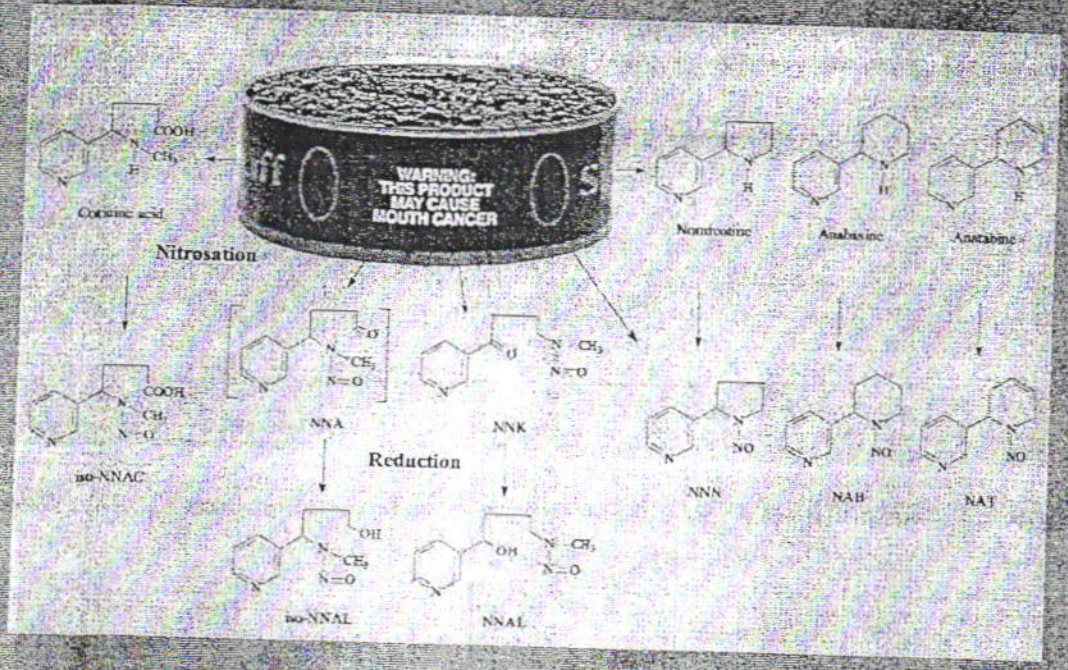
(XXVI)

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 89

Smokeless Tobacco and Some Tobacco-specific *N*-Nitrosamines



LYON, FRANCE
2007

GENERAL REMARKS

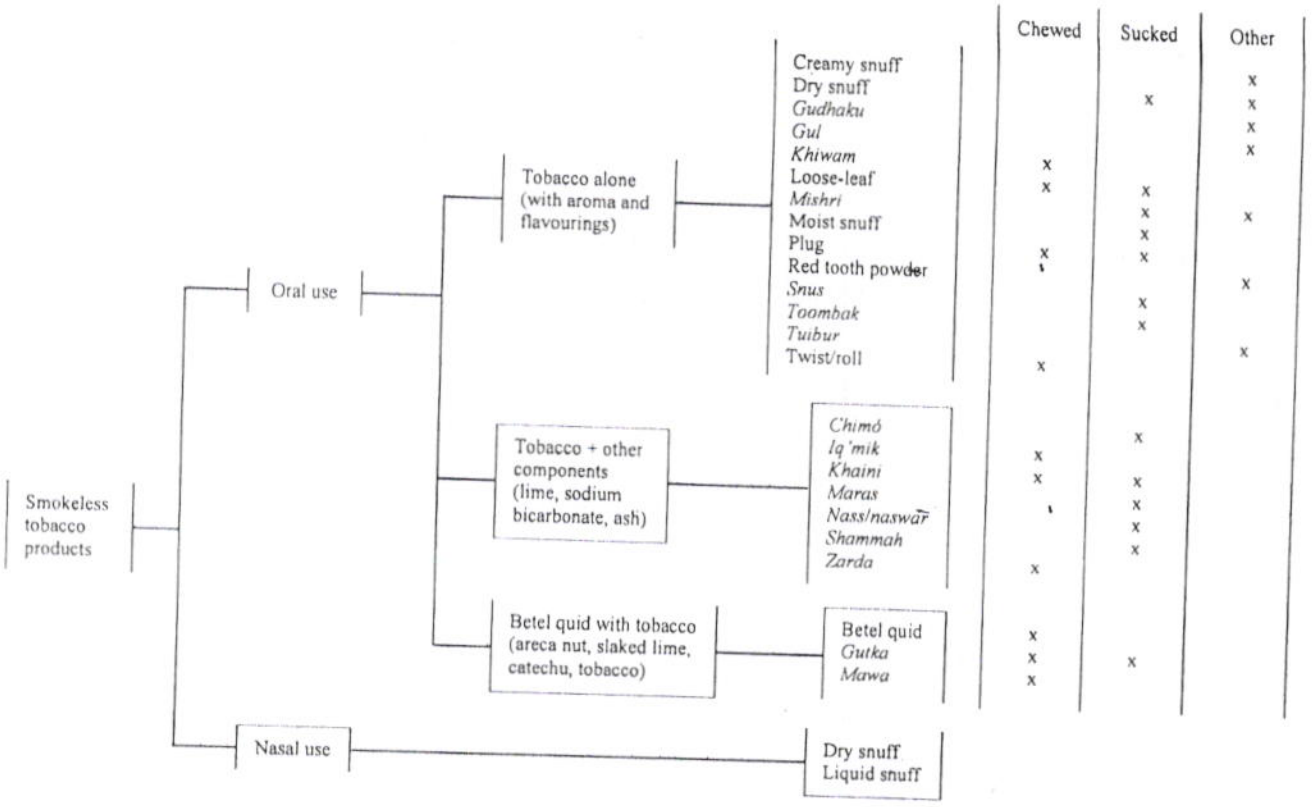
This eighty-ninth volume of the *IARC Monographs* is the third and last of a series on tobacco-related agents. Volume 83 reported on the carcinogenicity of tobacco smoke and involuntary smoking (second-hand smoke or environmental tobacco smoke) (IARC, 2004a). Volume 85 summarized the evidence on the carcinogenic risk of chewing betel quid with and without tobacco (IARC, 2004b). That volume explored the variety of products chewed in South Asia and other parts of the word that contain areca nut in combination with other ingredients, often including tobacco. In this eighty-ninth volume, the carcinogenic risks associated with the use of smokeless tobacco, including chewing tobacco and snuff, are considered in a first monograph. The second monograph reviews some tobacco-specific nitrosamines. These agents were evaluated earlier in Volume 37 of the *Monographs* (IARC, 1985), and information gathered since that time has been summarized and evaluated.

The agent termed 'smokeless tobacco' includes a large variety of commercially or non-commercially available products and mixtures that contain tobacco as the principal constituent and are used either orally or nasally without combustion. Figure 1 presents the forms of smokeless tobacco that are evaluated in this volume and their mode of use. For all products, except those that contain areca nut, the only known source of carcinogenic agents is the tobacco. (For tobacco chewed with betel quid or areca nut, see IARC, 2004b). The expression 'smokeless tobacco' was preferred to other terms such as 'non-smoking tobacco', 'non-smoked tobacco', 'unsmoked tobacco' and 'uncombusted tobacco', despite the imprecision of this term in the English language and the potential difficulty in its translation (see IARC, 1985).

The oral and nasal use of tobacco, either in leaf form for chewing or finely powdered as snuff, is as old as its use for smoking in pipes, cigars and cigarettes. In the first half of the twentieth century, the use of chewing tobacco and snuff in Europe and North America was overtaken by a huge increase in the smoking of cigarettes. In some parts of the world, particularly in South Asia, however, smokeless tobacco is still widely used. In addition, there has been a resurgence in the use of chewing tobacco and snuff in some European countries and in the USA during the last few decades.

In recent years, tobacco manufacturing companies have developed smokeless tobacco products with potential reduced exposure, also know as PREPs. These products are promoted and marketed by industry with claims that imply reduced risks and, subsequently,

Figure 1. Forms of smokeless tobacco evaluated in this volume



harm. The issue regarding the use of PREPs in the reduction of harm caused by tobacco has been reviewed (Henningfield *et al.*, 2002; Tomar, 2002; Hatsukami *et al.*, 2004).

Some health scientists have suggested that smokeless tobacco should be used for smoking cessation, and claim that its use would reduce the smoker's exposure to carcinogens and risk for cancer. They also attribute declines in smoking in Sweden to increased consumption of moist snuff in that country. However, as discussed in Section 1 of the monograph on Smokeless Tobacco, these claims are not supported by the available evidence.

Occupational exposure to unburnt tobacco may occur during tobacco manufacture, particularly in *bidi* factories in India, which are often very small-scale industries that have poor working conditions. The workers are mainly women and are exposed to tobacco by dermal contact, and also have airborne exposure to tobacco dust and volatile components. Studies of such industries have mainly reported on the concentration of tobacco dust and particulate matter in the ambient air in the factories, as well as biomonitoring of the workers, but no epidemiological studies on tobacco-related health risks in these workers have been carried out.

While in the Americas, Europe and Oceania, the leading cancers are those of the lung, breast, prostate and colorectum, cancer of the oral cavity is one of the leading malignancies in India and many other countries in South-East Asia, and ranks first in incidence among men and third among women, after cancer of the cervix and of the breast (IARC, 2003).

Oral leukoplakia is considered to be a precursor stage of oral cancer and is also prevalent in South Asia; this precancerous lesion is therefore also discussed in Section 2, Studies of Cancer in Humans. The term 'snuff-induced lesions', which is sometimes used in research articles, is avoided because of the ambiguity in the type of lesions to which it refers.

Tobacco-specific *N*-nitroso compounds have been detected at high concentrations in snuff and chewing tobacco and were evaluated in a previous monograph (IARC, 1985). New tobacco-specific nitrosamines have been identified and isolated since that time. However, only those for which there are sufficient mechanistic data to be able to draw a conclusion on their carcinogenicity were evaluated. Many other known carcinogens have been identified in various forms of tobacco (IARC, 2004a), including smokeless tobacco. The identification of nitrosamines as carcinogenic agents does not rule out the likelihood that other compounds present in tobacco may also contribute to their carcinogenicity.

References

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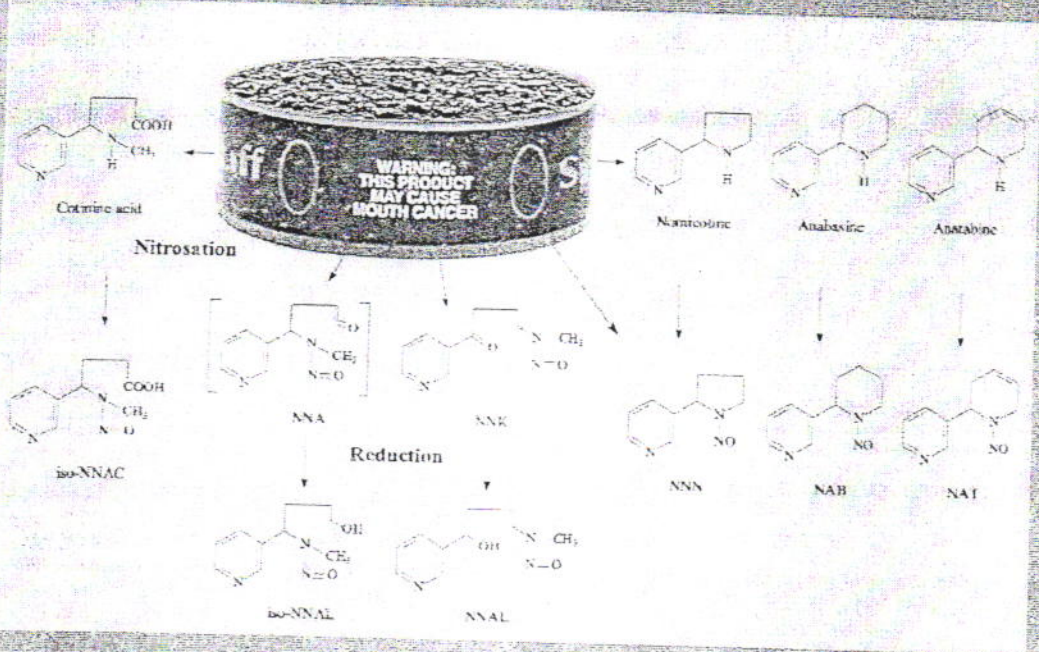
Tomar, S.L. (2002) Snuff use and smoking in U.S. men. Implication for harm reduction. *Am. J. prev. Med.*, **23**, 143–149

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 89

Smokeless Tobacco and Some Tobacco-specific *N*-Nitrosamines



LYON, FRANCE
2007

(b) Liquid snuff

Liquid snuff was reported to be used by the Nandi tribe in East Africa. It is used nasally (Hou-Jensen, 1964).

1.3 Chemical composition of smokeless tobacco

1.3.1 *General overview*

The type of tobacco used in a particular product has a decisive influence on its chemical composition. That of leaf tobacco varies with genetic make-up, environmental conditions and every step of production and handling (Tso, 1990). The classification of leaf tobacco commonly used in smokeless tobacco products is primarily based on curing methods (e.g. air-, flue- and fire-cured tobacco) and tobacco types (e.g. Burley, Wisconsin, Pennsylvania air-cured tobacco, dark fire-cured tobacco, Virginia flue-cured tobacco).

The first summary of chemical components found in tobacco and tobacco smoke was prepared by Stedman in 1968. Since then, frequent additions have been made to the list and, in 1988, the number of compounds identified in tobacco totaled 3044 (Roberts, 1988). The latter count has not been confirmed by independent research. Moreover, Roberts (1998) does not list many of the constituents that are currently known to be present in tobacco (e.g. volatile *N*-nitrosamines, tobacco-specific *N*-nitrosamines, *N*-nitrosamino acids). Hoffman *et al.* (2001) expanded the list to include 23 *N*-nitrosamines and 28 pesticides, which brought the number to 3095 constituents in tobacco. The identification of each single compound is an arduous task and requires a vigorous confirmation protocol that uses state-of-the-art instrumentation as well as synthesis.

During preparation for product manufacture, tobacco leaves, stems and other ingredients are blended to achieve a specific nicotine content, pH, taste, flavour and aroma. These features are critical for acceptance of the product by the user. For cigarettes, it has been demonstrated that the type of tobacco blend significantly affects these features as well as the toxicity of the product (Abdallah, 2003; Baker & Smith, 2003). The pH strongly influences the concentration of unprotonated nicotine, the bioavailable form of nicotine (Djordjevic *et al.*, 1995; Henningfield *et al.*, 1995; Richter & Spierto, 2003), while the nitrite content influences the levels of nitrosamines in the product (Fischer *et al.*, 1989; Burton *et al.*, 1994; Hoffmann *et al.*, 1995).

A choice of 60 *N. tabacum* species and 100 varieties of tobacco can be blended. However, the majority of commercial tobacco products use *N. tabacum* species, which are grown in North America and throughout the world. The alkaloid content in *N. tabacum* species varies greatly. From a random examination of 152 cultivated varieties, a range of alkaloid content between 0.17 and 4.93% was found. Tobacco types, plant parts, cultural practices, degree of ripening and fertilizer treatment are among some prominent factors that determine the level of alkaloids in *Nicotiana* plants. Every step in tobacco production that affects plant metabolism influences the level of alkaloid content to a certain degree. Cured tobacco lines can contain between 0.2 and 4.75% nicotine by weight, depending on

plant genetics, growing conditions, degree of ripening, fertilizer treatment and leaf position on the stalk (Tso, 1990; Stratton *et al.*, 2001).

N. rustica species is cultivated in some parts of eastern Europe, Asia Minor and Africa, and the cured leaves may contain up to 12% nicotine. In greenhouse-grown plants, *N. rustica* can accumulate up to 5.3 mg nicotine/g tobacco (98.2% of total alkaloids) and in field-grown plants up to 24.8 mg nicotine (97.1% of total alkaloids) (Sisson & Severson, 1990). *Toombak*, which contains *N. rustica* tobacco, was reported to contain the highest levels of nicotine (up to 102.4 mg/g dry wt) and nicotine-derived tobacco-specific nitrosamines ever measured in consumer products (Idris *et al.*, 1991; Prokopczyk *et al.*, 1995).

The chemical composition of tobacco undergoes substantial changes during growing, curing, processing and storing (Burton *et al.*, 1983, 1989a,b; Peele *et al.*, 1995; Walton *et al.*, 1995; Wiernik *et al.*, 1995; Peele *et al.*, 2001; Bush *et al.*, 2001). The purpose of curing is to produce a dried leaf of suitable physical properties and chemical composition. At the beginning of curing, a tobacco leaf is metabolically active and continues to live until biochemical processes are arrested by thermal effects or desiccation. In curing, the starch content of the leaves declines drastically, while the amount of reducing sugars increases by 100%. Protein and nicotine contents decrease slightly. The bulk of the processed tobacco leaf before fermentation consists of carbohydrates (about 50%) and proteins. Fermentation of cured tobacco causes the contents of carbohydrates and polyphenols in the leaves to diminish. Other major components are alkaloids (0.5–5.0%), which include nicotine as the predominant compound (85–95% of total alkaloids), terpenes (0.1–3.0%), polyphenols (0.5–4.5%), phytosterols (0.1–2.5%), carboxylic acids (0.1–0.7%), alkanes (0.1–0.4%), aromatic hydrocarbons, aldehydes, ketones, amines, nitriles, *N*- and *O*-heterocyclic hydrocarbons, pesticides, alkali nitrates (0.01–5%) and at least 30 metallic compounds (Brunnemann & Hoffmann, 1992; IARC, 2004b).

Because of the disappearance of carbohydrates and polyphenols during fermentation, heavy casings [additives applied during processing] such as molasses, liquorice and fruit extracts are added to tobacco to meet the consumer's requirements (e.g. they improve taste, flavour and aroma, and prolong shelf-life). Many smokeless tobacco formulations use plant extracts or chemicals as flavouring agents (Mookherjee & Wilson, 1988; Roberts, 1988; Sharma *et al.*, 1991). Tobacco additives may include methyl or ethyl salicylate, β-citronellol, 1,8-cineole, menthol, benzyl benzoate, eugenol and possibly coumarin, among others (LaVoie *et al.*, 1989; Stanfill *et al.*, 2006). Eugenol (ranging from < 0.00005 to 25 706 µg/g in Dentobac Creamy Snuff sold in India; Gupta, 2004) and menthol are used to numb the throat and facilitate tobacco use (Ahijevych & Garrett, 2004; Wayne & Connolly, 2004). Ascorbic acid is added to tobacco as an antimicrobial agent whereas the addition of sodium propionate serves as a fungicide. Other additives, such as ammonia, ammonium carbonate and sodium carbonate, are applied to control nicotine delivery by raising pH and subsequently the level of unprotonated nicotine which is the form of nicotine that is most readily absorbed through the mouth into the bloodstream (Djordjevic *et al.*, 1995; Henningfield *et al.*, 1995). However, the formulation of most of the additives, including flavours, remains a trade secret.

1.3.2 *Carcinogenic compounds in smokeless tobacco*

To date, 28 carcinogens have been identified in smokeless tobacco (Table 3; adapted from Brunnemann & Hoffmann, 1992). The major and most abundant group of carcinogens are the non-volatile alkaloid-derived tobacco-specific *N*-nitrosamines (TSNA) and *N*-nitrosoamino acids. Other carcinogens reportedly present in smokeless tobacco include volatile *N*-nitrosamines, certain volatile aldehydes, traces of some polynuclear aromatic hydrocarbons such as benzo[*a*]pyrene, certain lactones, urethane, metals, polonium-210 and uranium-235 and -238 (see Brunnemann & Hoffmann, 1992 for review).

There are three major types of nitroso compounds in smokeless tobacco: (*a*) non-volatile TSNA, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN); (*b*) *N*-nitrosamino acids, including *N*-nitrososarcosine (NSAR), 3-(methylnitrosamino)propionic acids (MNPA) and 4-(methylnitrosamino)butyric acids (MNBA); and (*c*) volatile *N*-nitrosamines, including *N*-nitrosodimethylamine (NDMA), *N*-nitrosopyrrolidine (NPYR), *N*-nitrosopiperidine (NPIP) and *N*-nitrosomorpholine (NMOR).

TSNA are present in fresh green tobacco leaves in *N. tabacum* species, at levels of up to 0.39 μg/g NNN and 0.42 μg/g NNK in the top leaves of tobacco (flue-cured type) grown in the USA (Djordjevic *et al.*, 1989a), up to 0.035 μg/g NNN and 0.0115 μg/g NNK in *N. tabacum* grown in India (Bhide *et al.*, 1987a) and up to 46.1 μg/g NNN and 2.34 μg/g NNK in *N. rustica* species grown in India (Bhide *et al.*, 1987a). However, TSNA are formed primarily during tobacco curing, fermentation and ageing, from their alkaloid precursors (namely, nicotine, nornicotine, anatabine and anabasine) and from nitrite/nitrate. The nitrate or nitrite content, the mode of curing and the various steps of processing are therefore the determining factors for the yields of TSNA in tobacco (Burton *et al.*, 1989a,b; Fischer *et al.*, 1989; Chamberlain & Chortyk, 1992; Djordjevic *et al.*, 1993a; Burton *et al.*, 1994; Peele *et al.*, 2001; Li & Bush, 2004). NNN, *N*′-nitrosoanatabine (NAT) and *N*′-nitrosoanabasine (NAB) are formed primarily from the corresponding secondary amines in the early stages of tobacco processing; some NNN and the majority of NNK are formed from the tertiary amine nicotine at the later stage of tobacco curing and fermentation (Spiegelhalder & Fischer, 1991).

In addition to these three groups of compounds, smokeless tobacco contains *N*-nitrosodiethanolamine (NDELA), which is formed from diethanolamine, a residual contaminant in tobacco. In 1981, the levels of NDELA were up to 224 ng/g in chewing tobacco and up to 6840 ng/g in fine-cut moist snuff. Treatment of Burley leaves with the sucker growth inhibitor maleic hydrazide significantly increased the hydrazine content. Although a tolerance of 80 ppm for maleic hydrazide was established in at least three European countries and the USA, concentrations up to 269 ppm were reported for the flue-cured tobacco harvested in Georgia, USA, in 1990 (Sheets, 1990). As the use of maleic hydrazide–diethanolamine as a sucker growth-controlling agent was gradually reduced, the concentration of NDELA decreased to less than 100 ng/g in 1990 (Brunnemann & Hoffmann, 1991).

Table 3. Chemical agents identified in smokeless tobacco products

Agent	Type of tobacco where it has been detected	Concentration (ng/g)	*IARC Monographs* evaluation of carcinogenicity			*Monographs* volume, year
			In animals	In humans	IARC Group	
Benzo[*a*]pyrene	NT, MS, DS, MI[a]	> 0.1–90	S	I	1	Vol. 92 (in prep.)
α-Angelica lactone	NT	Present	–	–	–	–
β-Angelica lactone	NT	Present	–	–	–	–
Coumarin	NT	600	L	I	3	Vol. 77 (2000)
Ethyl carbamate (urethane)	CT	310–375	S	I	2A	Vol. 96 (in prep.)
Volatile aldehydes						
Formaldehyde	NT, MS, DS	1600–7400	S	S	1	Vol. 88 (2006)
Acetaldehyde	NT, MS, DS	1400–27 400	S	I	2B	Vol. 71 (1999)
Crotonaldehyde	MS, DS	200–2400	I	I	3	Vol. 63 (1995)
Volatile N-*nitrosamines*						
N-Nitrosodimethylamine (NDMA)	CT, MS	ND–270	S	I	2A	Suppl. 7 (1987)
N-Nitrosopyrrolidine (NPYR)	CT, MS	ND–860	S	I	2B	Suppl. 7 (1987)
N-Nitrosopiperidine (NPIP)	CT, MS	ND–110	S	I	2B	Suppl. 7 (1987)
N-Nitrosomorpholine (NMOR)	CT, MS	ND–690	S	I	2B	Suppl. 7 (1987)
N-Nitrosodiethanolamine (NDELA)	CT, MS	40–6800	S	I	2B	Vol. 77 (2000)
N-Nitrosamino acids						
N-Nitrososarcosine (NSAR)	MS	ND–6300	S	I	2B	Suppl. 7 (1987)
3-(*N*-methylnitrosamino) propionic acid (MNPA)	CT, MS	200–70 000	–	–	–	–
4-(*N*-methylnitrosamino) butyric acid (MNBA)	CT, MS	ND–17 500	–	–	–	–
Nitrosoazetidine-4-carboxylic acid (NAzCA)	CT, MS	4–140	–	–	–	–

Table 3 (contd)

Agent	Type of tobacco where it has been detected	Concentration (ng/g)	*IARC Monographs* evaluation of carcinogenicity			*Monographs* volume, year
			In animals	In humans	IARC Group	
Tobacco-specific N-nitrosamines (TSNA)						
N'-Nitrosonornicotine (NNN)	CT, MS	400–3 085 000	S	–	1	Vol. 89
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	CT, MS	ND–7 870 000	S	–		Vol. 89
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	MS	0.07–22 900	–	–	–	Vol. 89
N'-Nitrosoanabasine (NAB)	ST, MS	Present–2 370 000	L	I	3	Vol. 89
Inorganic compounds						
Arsenic	NT	500–900	L	S	1	Suppl. 7 (1987)
Nickel compounds	ST, MS	180–2700	S	S	1	Vol. 49 (1990)
Radioelements		*(pCi/g)*				
Polonium-210	NT, MS, DS	0.16–1.22	S	I	1[b]	Vol. 78 (2001)
Uranium-235	MS	2.4	L	I		Vol. 78 (2001)
Uranium-238	MS	1.91	L	I		Vol. 78 (2001)
Beryllium	NA	NA	S	S	1	Vol. 58 (1993)

Updated from Bhide *et al.* (1984a), Nair, U.J. *et al.* (1987); Idris *et al.* (1991), Brunnemann & Hoffmann (1992)
CT, chewing tobacco; DS, dry snuff; I, inadequate; L, limited; MI, *mishri*; MS, moist snuff; NA, not available; ND, not detected; NT, natural tobacco; S, sufficient; ST, smoking tobacco

[a] Concentrations up to 119 000 ng/g in *mishri* (Nair, U.J. *et al.*, 1987)

[b] Evaluation of internally deposited α-particle-emitting radionuclides

Polycyclic aromatic hydrocarbons (PAHs) originate primarily from polluted air and perhaps from fire-curing of some tobaccos.

Formaldehyde, acetaldehyde and crotonaldehyde, which are themselves probable or known human carcinogens, probably contribute to the carcinogenic potential of smokeless tobacco. It is known that tobacco contains a large spectrum of alkyl aldehydes that contribute to its aroma and are formed from amino acids and sugars by heating during tobacco processing (Coleman & Perfetti, 1997).

The α- and β-angelica lactones have been reported in natural tobacco (Weeks *et al.*, 1989). A minor group of polyphenols in tobacco are coumarins, of which scopoletin is the major representative. The presence of urethane in fermented Burley tobacco (up to 400 ng/g) is not unexpected since the fermentation of food and beverages leads to the formation of this compound. Both air- and flue-cured tobaccos contain hydrazines.

Radioactive polonium-210, which decays to radon, originates from soil that is fertilized with phosphates rich in radium-226 (Tso *et al.*, 1966).

1.3.3 *Smokeless tobacco products*

(*a*) *Nicotine, pH and unprotonated nicotine*

All smokeless tobacco products contain nicotine as a major constituent, which is addictive (Henningfield *et al.*, 1997; Hatsukami & Severson, 1999). The level of unprotonated nicotine affects the rate and degree of nicotine absorption (see Section 4.1).

Djordjevic *et al.* (1995) analysed 17 brands of moist snuff purchased in Westchester County, New York (USA) in 1994. In addition, samples of the five leading brands were purchased in six areas of the USA (Alameda, CA; Boston, MA; Denver, CO; Lansing, MI; Lexington, KY; Westchester, NY) and analysed separately to determine geographic variations. The nicotine content in 17 brands ranged from 0.47% dry wt (in Hawken Wintergreen) to 3.43% (in Skoal Long Cut Mint), which corresponds to 3.4 mg/g and 14.5 mg/g, respectively; the pH ranged from 5.39 (in Skoal Bandits Classic) to 7.99 (in Kodiak Wintergreen); unprotonated nicotine ranged from 0.23% of total nicotine (in Skoal Bandits Classic) to 48.3% (in Kodiak Wintergreen). The average values for the five best-selling brands of moist snuff in the USA in 1994 are summarized in Table 4.

Similar findings were reported by Henningfield *et al.* (1995) for products purchased at three locations (Baltimore, MD; Boston, MA; Lansing MI; Table 4). Both studies show that nicotine-dosing capability varies remarkably between products and that it is governed predominantly by nicotine content and pH level.

The Centers for Disease Control and Prevention (CDC) carried out an analysis of 18 smokeless tobacco products (eight brands of moist snuff and 10 of loose-leaf chewing tobacco) (Richter & Spierto, 2003). Among moist snuff brands, Timber Wolf Long Cut Straight contained the highest amount of nicotine (13.54 mg/g) followed by Copenhagen snuff and Skoal (12.71 mg/g and 12.94 mg/g, respectively). Consistent with the findings by Djordjevic *et al.* (1995), the highest pH was measured for Kodiak Wintergreen (pH, 8.28), which also had the highest quantity of unprotonated nicotine (64.5%; 5.81 mg/g).

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Table 4. Nicotine content and pH of the five leading brands purchased at different locations in the USA

Constituents	Skoal Bandits Straight	Hawken Wintergreen	Skoal Original Fine Cut Wintergreen	Copenhagen Snuff	Kodiak Wintergreen
Djordjevic et al. *(1995)*[a]					
pH	5.37 ± 0.12	5.71 ± 0.1	7.46 ± 0.14	8.00 ± 0.31	8.19 ± 0.11
Nicotine (% dry wt)	2.29 ± 0.46	0.46 ± 0.02	2.81 ± 0.34	2.91 ± 0.18	2.5 ± 0.22
Nicotine (mg/g)	10.1 ± 0.8	3.2 ± 0.2	11.9 ± 1.3	12.0 ± 0.7	10.9 ± 0.8
Unprotonated nicotine (%)[b]	0.23 ± 0.05	0.5 ± 0.11	22.0 ± 5.73	49.0 ± 16.7	59.7 ± 6.01
	Skoal Bandits				
Henningfield et al. *(1995)*	Wintergreen				
pH	6.9		7.6	8.6	
Nicotine (mg/g)	7.5		10.4	11.4	
Unprotonated nicotine (%)[b]	7.05		27.55	79.17	
Unprotonated nicotine (mg/g)	0.53		2.87	9.03	

[a] All values are mean ± standard deviation.
[b] The percentage of unprotonated nicotine was calculated according to the Henderson-Hasselbach equation and by using a pKa value of 8.02 for nicotine (Henningfield *et al.*, 1995).

The lowest pH and amount of free nicotine were reported for Hawken Wintergreen (pH, 5.35; 0.20% free nicotine or 0.01 mg/g).

Another CDC study (CDC, 1999a) also reported that Copenhagen snuff and Kodiak Wintergreen had the highest pH (8.18 and 8.35, respectively) and the highest concentration of unprotonated nicotine (6.23 and 5.83 mg/g tobacco, respectively); Skoal Bandits Straight and Hawken Wintergreen had the lowest pH (5.52 and 5.24, respectively) as well as the lowest concentration of unprotonated nicotine (0.025 and 0.007 mg/g tobacco, respectively).

In 1996, Massachusetts enacted a tobacco product disclosure law which required manufacturers of cigarettes and smokeless tobacco products to disclose the ingredients and nicotine content by brand for average consumers. The Massachusetts Department of Public Health (MDPH) promulgated regulations in 1996 that required cigarette and smokeless tobacco manufacturers to file annual reports on nicotine yield by brand (MDPH, 2004). The requirements for reporting on smokeless tobacco were based on federal rules published by the CDC, adopted in 1996 and revised in 1999 (CDC, 1999b). Unlike Massachusetts, where disclosure of nicotine is a public record, data reported to the CDC remain private. Annual reports submitted by all smokeless tobacco manufacturers who sold products in Massachusetts from 1997–2003 contributed the most comprehensive data base on the levels of total nicotine (expressed as % and mg/g adjusted for moisture), tobacco pH and the levels of unprotonated nicotine (expressed as % of total nicotine and mg/g dry wt) in smokeless tobacco. Tables 5–7 list the pH, and total and unprotonated nicotine content of individual brands of, respectively, chewing tobacco, dry snuff and moist snuff sold in the Common-

Table 5. Chemical composition of chewing tobacco sold in Massachusetts (USA) in 2003

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
Conwood Company	Bloodhound	Plug	21.10	1.72	13.54	5.37	0.22	0.03
	Bull of the Woods	Plug	20.73	2.12	16.78	5.16	0.14	0.02
	Cannon Ball	Plug	20.62	1.68	13.37	5.23	0.16	0.02
	Cotton Bowl Twist	Chewing Tobacco	14.57	4.65	39.74	5.21	0.15	0.06
	Cumberland Twist	Chewing Tobacco	22.35	1.56	12.12	5.70	0.48	0.06
	Hawken	Wintergreen Smokeless Tobacco	28.57	0.60	4.31	5.77	0.56	0.02
	HB Scott	Loose Leaf	23.95	0.60	4.53	6.09	1.16	0.05
	Levi Extra	Loose Leaf	23.85	0.67	5.13	6.13	1.27	0.07
	Levi Garrett	Plug	22.48	0.84	6.51	5.93	0.81	0.05
		Loose Leaf	24.13	0.71	5.40	6.02	0.99	0.05
	Lieberman's	Loose Leaf	19.58	1.12	8.99	6.76	5.21	0.47
	Mammoth Cave Twist	Chewing Tobacco	16.77	3.88	32.28	5.10	0.12	0.04
	Morgan's	Loose Leaf	23.97	0.45	3.41	6.00	0.95	0.03
	Peachey	Loose Leaf	24.02	0.62	4.68	5.73	0.51	0.02
	Taylor's Pride	Plug	22.15	0.79	6.18	5.94	0.82	0.05
		Loose Leaf	23.82	0.62	4.76	5.79	0.59	0.03
	Union Workman	Loose Leaf	23.53	0.52	3.97	5.89	0.74	0.03
National Tobacco	Beech-Nut	Regular	24.36	0.77	7.71	5.83	0.64	0.05
		Wintergreen	25.25	0.55	5.54	5.97	0.88	0.05
	Durango	Regular	24.61	0.59	5.93	5.96	0.86	0.05
	Havana Blossom	NR	22.43	1.64	16.37	5.95	0.84	0.14
	Trophy	NR	24.04	0.56	5.58	6.02	0.99	0.06
RBJ Sales Inc	24-C	Course Cut	23.34	0.49	4.93	5.70	0.51	0.02
	757	Sweet Chew	22.71	0.56	5.59	5.94	0.82	0.05
	Black Wild Cherry	Loose Leaf	24.32	0.49	4.85	5.64	0.42	0.02
	Butternut	Loose Leaf	22.75	0.53	5.25	5.99	0.53	0.05

Table 5 (contd)

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
RBJ Sales Inc (contd)	Fred's Choice	Chewing Tobacco	27.79	0.50	5.05	5.78	0.59	0.03
	L-50	Mellow Chew	22.11	0.50	4.98	5.62	0.41	0.02
	Stoker's	Apple Loose Leaf	24.10	0.51	5.14	5.67	0.74	0.35
		Peach Loose Leaf	22.47	0.54	5.43	5.96	0.88	0.05
		Red Course Cut	25.31	0.49	4.89	5.72	0.55	0.03
		Tequila Sunrise Chew	26.96	0.49	4.87	5.76	0.57	0.03
	Tennessee	Chew	25.31	0.49	4.89	NR	0.55	0.03
	Tropical Chew	Chewing Tobacco	25.13	0.46	4.63	5.87	0.73	0.03
Swedish Match North America	Apple	Thick Plug	16.98	1.45	12.00	5.33	0.21	0.03
		Thin Plug	16.81	1.36	11.28	5.28	0.18	0.02
	Browns	Mule Plug	20.89	1.23	9.73	5.34	0.21	0.02
	Cup	Plug	23.83	2.68	20.43	5.07	0.11	0.02
	Day's Work	Plug	21.40	1.53	12.00	5.24	0.17	0.02
	Exalt Original Snuff	NR	23.87	3.32	25.30	6.80	6.13	1.54
	Exalt Peppermint Snuff	NR	20.46	2.22	17.65	6.91	9.52	1.77
	Granger	Select Loose Leaf	24.35	0.74	5.60	6.07	1.13	0.06
	J D 's Blend	Loose Leaf	27.16	0.61	4.48	6.41	2.47	0.11
	Original Natural Leaf	Plug	17.99	1.51	12.35	5.70	0.49	0.06
	Pay Car	Loose Leaf	25.41	1.13	8.45	5.90	0.76	0.06
	Red Horse	Loose Leaf	25.68	1.06	7.85	5.94	0.82	0.07
	Red Man	Plug	21.45	1.00	7.87	5.89	0.74	0.06
		Loose Leaf	25.83	1.17	8.70	6.01	1.01	0.09
		Select Loose Leaf	26.27	0.52	3.83	6.35	2.11	0.08
		Golden Blend Loose Leaf	25.84	1.05	7.75	6.22	2.12	0.17
		Golden Blend Totems	19.45	0.51	4.10	6.33	2.25	0.10
	Southern Pride	Loose Leaf	25.76	0.75	5.55	6.23	2.20	0.13
	Spark	Plug	20.07	1.18	9.45	5.95	0.85	0.08
	Tinsley	Plug	18.82	1.48	12.05	5.52	0.31	0.04
	Union Standard	Plug	16.88	0.98	8.18	5.80	0.67	0.06
		Loose Leaf	25.22	1.11	8.30	5.94	0.84	0.07
	WNT	Thick Plug	18.10	1.50	12.30	5.56	0.35	0.04
	Work Horse	Loose Leaf	25.24	1.10	8.23	5.86	0.71	0.06

Table 5 (contd)

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
Swisher International	Best Buy	Chewing Tobacco	25.04	0.94	7.06	5.83	0.67	0.05
	Bowie	Chewing Tobacco	24.60	0.91	6.88	5.86	0.71	0.05
	Chattanooga	Chewing Tobacco	24.88	1.06	7.97	5.77	0.69	0.05
	Earl Caulfield's Country Flavors	Classic Bourbon	24.44	0.97	7.30	5.57	0.41	0.03
		Orchard Blend	24.60	0.91	6.88	5.86	0.71	0.05
	Jackson's Apple Jack	NR	25.29	0.91	6.81	5.74	0.54	0.04
	Lancaster Premium	NR	25.04	0.94	7.06	5.83	0.67	0.05
	Old Reliable Elephant Butts	NR	19.22	2.96	23.97	5.79	0.59	0.14
	Penn Cigar Clippings	NR	18.65	3.23	26.23	5.71	0.50	0.13
	Silver Cup	NR	21.88	1.69	13.17	5.62	0.41	0.05
	Standard Clippings	NR	20.07	2.08	16.65	5.81	0.62	0.10
	Starr Value	Chewing Tobacco	25.04	0.94	7.06	5.83	0.67	0.05
	Superior	Quality Chew	25.04	0.94	7.06	5.83	0.67	0.05
	Swisher Sweets	Chewing Tobacco	25.04	0.94	7.06	5.83	0.67	0.05
	Whalen Plain Scrap	NR	18.65	3.23	26.23	5.71	0.50	0.13
	XX Black	NR	18.65	3.23	26.23	5.71	0.50	0.13

NR, not reported
From MDPH (2004)

Table 6. Chemical composition of dry snuff sold in Massachusetts (USA) in 2003

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
Conwood Company	Dental	Scotch Dry Snuff	6.00	1.82	17.12	6.27	1.75	0.30
		Sweet Dry Snuff	6.11	1.70	15.99	5.82	0.63	0.10
	Honest	Scotch Dry Snuff	5.93	1.94	18.27	6.25	1.67	0.31
	Peach	Sweet	6.10	1.31	12.29	6.05	1.06	0.13
	Tube Rose	Sweet Dry Snuff	6.61	1.59	14.82	5.89	0.74	0.11
	W.E. Garrett	Sweet	6.13	1.66	15.58	5.79	0.59	0.09
		Dry Scotch Snuff	5.38	2.25	21.33	5.92	0.79	0.17
Swisher International	Buttercup[a]	Sweet Scotch Snuff	7.30	1.57	14.54	5.96	0.89	0.13
	Dixie[a]	Sweet Snuff	8.20	1.36	12.45	5.41	0.24	0.03
	Ladies Choice	Extra Strong Scotch Snuff	7.84	2.51	23.17	6.22	1.58	0.36
	Lorillard	High Toast Scotch Snuff	7.00	1.88	17.53	6.39	2.31	0.41
		Sweet Scotch Snuff	7.17	1.61	14.88	6.09	1.20	0.18
	Navy	Sweet Scotch Snuff	7.59	1.83	16.91	6.28	1.80	0.31
		Plain Scotch Snuff	7.61	2.69	24.84	6.60	3.87	0.97
	Railroad Mills	Sweet Scotch Snuff	7.12	1.79	16.61	6.28	1.81	0.30
		Plain Scotch Snuff	7.61	2.69	24.84	6.60	3.87	0.97
	Ralph's	Scotch Snuff	8.56	2.34	21.42	6.16	1.41	0.30
	Society	Sweet Scotch Snuff	7.30	1.57	14.54	5.96	0.89	0.13
	Square	Snuff	8.56	2.34	21.42	6.16	1.41	0.30
	Starr	Scotch Snuff	7.70	1.14	10.48	7.51	29.56	3.08
	Strawberry	Sweet Snuff	7.17	1.61	14.88	6.09	1.20	0.18
	Superior	Scotch Snuff	7.84	2.51	23.17	6.22	1.58	0.36
	Three Thistles	Sweet Scotch Snuff	7.12	1.79	16.61	6.28	1.81	0.30
		Strong Scotch Snuff	8.56	2.34	21.42	6.16	1.41	0.30
	Tops	Sweet Snuff	7.35	1.55	14.31	5.99	1.08	0.15
		Mild Scotch Snuff	8.38	1.78	16.30	5.50	0.31	0.05
	Wild Cherry	Sweet Scotch Snuff	8.15	2.55	23.38	6.20	1.48	0.35

Table 6 (contd)

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
US Tobacco	Bruton	White Label	7.55	1.20	11.14	7.61	28.48	3.12
	Carhart's	NR	7.20	1.33	12.38	7.23	14.07	1.74
	Choice							
	Devoe	Sweet	7.20	1.33	12.38	7.23	14.07	1.74
		Eagle	7.55	1.20	11.14	7.61	28.48	3.12
	Red Seal	Scotch	7.44	1.47	13.70	7.29	19.76	2.51
	Revel[a]	Mild	5.89	0.49	4.70	7.96	46.46	2.18
		Regular	5.71	1.06	10.11	7.67	30.91	3.13
	Rooster	Scotch	7.23	1.33	12.51	6.82	5.92	0.74

From MDPH (2004)

[a] Reported as moist snuff in original article

Table 7. Chemical composition of moist snuff sold in Massachusetts (USA) in 2003

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
Conwood Company	Cougar	Fine Cut Natural	55.12	2.35	10.53	8.14	56.86	5.99
		Long Cut Natural	55.17	2.30	10.32	8.13	56.30	5.81
		Long Cut Wintergreen	55.48	2.64	11.75	8.03	50.58	5.94
		Wintergreen	55.72	3.04	13.46	7.98	47.70	6.42
	Grizzly	Fine Cut Natural	54.73	3.39	15.35	7.83	39.23	6.02
		Long Cut Wintergreen	53.85	2.56	11.81	8.23	61.86	7.31
	Kodiak	Wintergreen	53.90	2.30	10.60	8.33	67.12	7.12
		Ice	54.30	2.49	11.36	8.09	54.02	6.14
		Straight	54.30	2.49	11.36	[8.19][a]	59.66	6.78
	Xtreme	Wintergreen	54.47	2.52	11.49	8.38	69.61	8.00
RBJ Sales Inc	Stoker's	Smokeless Regular Moist	45.67	2.29	22.93	5.49	0.44	0.10
	Yukon	Fine Cut	49.52	2.06	20.55	7.06	10.27	2.13
		Long Cut	51.30	1.86	18.55	6.85	6.57	1.22
Swedish Match North America	Longhorn Fine Cut	Natural	51.18	3.35	16.35	8.08	53.39	8.57
	Longhorn Long Cut	Wintergreen	53.45	3.14	14.60	7.94	45.26	6.71
	Renegades	Moist Snuff	54.22	3.31	15.18	7.35	17.60	2.73
	Sequoia	Cinnamon Ice Snuff	51.62	3.13	15.15	7.44	20.84	3.15
		Mountain Cider Snuff	51.90	3.04	14.60	7.08	11.00	1.58
	Sequoia Artic Wintergreen	Wintergreen Snuff	54.63	2.82	12.80	8.09	54.02	6.92
	Timberwolf	Fine Cut Natural	52.41	3.66	17.43	7.84	39.90	6.98
		Long Cut Natural	52.03	3.46	16.60	7.91	43.94	7.36
		Long Cut Wintergreen	54.72	3.64	16.50	7.94	45.60	7.59
		Cool Wintergreen	53.91	3.46	15.95	7.89	42.49	6.79
		Fine Cut Wintergreen	54.83	3.65	16.47	7.96	46.42	7.88
		Long Cut Mint	54.09	3.50	16.08	7.77	36.15	5.83
		Long Cut Straight	54.58	3.70	16.83	7.87	41.40	7.02

Table 7 (contd)

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
Swisher International	Best Buy	Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Natural	54.48	2.83	12.96	7.91	44.46	5.75
		Long Cut Straight	54.86	2.29	10.30	7.33	18.86	1.98
		Long Cut Cherry	54.20	2.17	9.94	7.64	30.48	2.93
	Bowie	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Natural	54.48	2.83	12.96	7.91	44.46	5.75
	Cheyenne	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Natural	54.48	2.83	12.96	7.91	44.46	5.75
	Cooper	Long Cut Wintergreen	54.93	2.21	9.93	7.15	13.04	1.33
	Finest Quality	Long Cut Wintergreen	54.93	2.21	9.93	7.15	13.04	1.33
		Natural	54.50	2.80	12.74	8.01	49.78	6.38
		Long Cut Mint	53.40	2.09	9.71	7.23	17.10	1.65
		Long Cut Cherry	54.10	2.27	10.42	7.52	24.74	2.56
	Gold River[b]	NR	23.92	1.50	11.41	5.71	0.58	0.06
	Hunter	Long Cut Wintergreen	55.40	2.43	10.84	7.59	27.51	2.98
		Natural	54.50	2.80	12.74	8.01	49.78	6.38
	Kayak	Fine Cut Natural	54.50	2.80	12.74	8.01	49.78	6.38
		Long Cut Wintergreen	55.31	2.40	10.71	7.62	28.87	3.08
	Lorillard	Maccoboy Snuff	41.70	2.13	12.42	6.80	5.76	0.73
	Mail Pouch	NR	21.58	1.76	13.80	5.73	0.56	0.08
		Country Blend	25.04	0.94	7.06	5.83	0.67	0.05
		Select	25.04	0.94	7.06	5.83	0.67	0.05
	Our Best	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Natural	54.48	2.83	12.96	7.91	44.46	5.75
		Fine Cut Wintergreen	54.04	2.58	11.86	7.49	24.60	2.88
	Our Pride	Natural	54.48	2.83	12.96	7.91	44.46	5.75
		Fine Cut Wintergreen	54.04	2.58	11.86	7.49	24.60	2.88

Table 7 (contd)

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
Swisher International (contd)	Railroad Mills	Long Cut Straight	54.86	2.29	10.30	7.33	18.86	1.98
		Maccoboy Snuff	41.82	2.08	12.14	6.73	4.94	0.59
		Checkerberry Snuff	40.80	1.21	7.18	7.21	18.57	1.33
	Redwood	Fine Cut	54.48	2.83	12.96	7.91	44.46	5.75
		Long Cut	54.63	2.64	11.96	7.75	38.17	4.53
	Silver Creek	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Fine Cut Wintergreen	54.04	2.58	11.86	7.49	24.60	2.88
		Long Cut Straight	54.86	2.29	10.30	7.33	18.86	1.98
		Long Cut Cherry	54.20	2.17	9.94	7.64	30.48	2.93
	Silverado	Natural Pouches	48.90	2.47	12.58	6.95	8.23	1.03
		Wintergreen Pouches	50.87	2.42	11.87	7.08	10.91	1.29
	Starr Value	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Natural	54.48	2.83	12.96	7.91	44.46	5.75
	Superior Value	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Natural	54.48	2.83	12.96	7.91	44.46	5.75
		Long Cut Cherry	54.20	2.17	9.94	7.64	30.48	2.93
	Swisher Sweets	Long Cut Wintergreen	54.80	2.16	9.75	7.35	19.88	1.94
		Long Cut Straight	54.86	2.29	10.30	7.33	18.86	1.98
	Tub[b]	NR	20.07	2.08	16.65	5.81	0.62	0.10
US Tobacco	Copenhagen	Fine Cut	54.35	2.87	13.12	7.87	43.03	5.56
		Long Cut	54.60	2.95	13.42	7.54	26.12	3.51
		Long Cut Black	54.17	2.91	13.42	7.18	13.35	1.79
		Pouch	53.78	2.16	9.99	7.63	31.04	3.01
	Husky	Long Cut Wintergreen	54.75	3.14	13.96	7.33	16.80	2.35
		Natural	54.37	3.04	13.70	7.71	32.88	4.50
	Red Seal	Long Cut Natural	55.76	3.01	13.50	7.51	24.71	3.33
		Long Cut Wintergreen	54.43	2.95	13.62	7.42	20.61	2.82

Table 7 (contd)

Manufacturer	Brand name	Sub-brand	Moisture content (%)	Nicotine (% dry wt)	Nicotine (mg/g)	pH	% unprotonated nicotine	Total unprotonated nicotine (mg/g)
US Tobacco (contd)		Natural	55.01	2.93	13.35	7.52	25.61	3.40
		Fine Cut Wintergreen	54.59	2.90	13.37	7.44	21.35	2.86
		Long Cut Mint	55.10	3.05	13.89	7.51	24.85	3.42
		Long Cut Straight	54.81	3.02	13.84	7.35	17.83	2.48
	Rooster	Wintergreen	55.77	2.81	12.62	7.43	20.79	2.62
		Berry	55.24	2.75	12.47	7.44	21.34	2.67
		Mint	55.73	2.80	12.51	7.54	25.19	3.16
	Skoal	Long Cut Wintergreen	54.52	3.00	13.82	7.48	22.75	3.15
		Fine Cut Wintergreen	54.45	2.81	12.98	7.38	19.17	2.47
		Long Cut Mint	54.62	2.97	13.69	7.44	21.06	2.88
		Long Cut Straight	54.84	2.99	13.69	7.54	25.64	3.52
		Long Cut Cherry	54.03	2.90	13.51	7.44	21.00	2.85
		Pouch	55.53	2.62	11.68	7.60	27.96	3.25
		Bandits Mint	49.00	1.75	8.96	7.00	8.79	0.79
		Bandits Straight	48.60	1.94	9.99	5.50	0.31	0.03
		Bandits Wintergreen	48.56	1.77	9.11	6.80	5.72	0.52
		Fine Cut Key	54.88	3.00	13.68	7.64	32.42	4.40
		Fine Cut Straight	54.56	2.88	13.29	7.41	20.42	2.71
		Long Cut Berry	54.27	2.94	13.59	7.16	12.29	1.67
		Long Cut Classic	55.18	3.18	14.45	8.03	49.96	7.18
		Long Cut Spearmint	54.68	3.08	13.79	7.33	18.03	2.50
		Long Cut Vanilla	55.16	2.92	12.93	7.50	23.61	3.05
		Pouch Berry	54.55	2.96	13.29	7.40	19.81	2.63
	WB Cut	Long Cut Cherry	34.61	3.68	24.29	5.50	0.30	0.07

From MDPH (2004)

[a] Reported as 0.0819 in original document

[b] Reported as dry snuff in original document

wealth of Massachusetts in 2003; Table 8 presents the mean values for each type of tobacco product.

Table 8. Ranges of pH and nicotine concentration in smokeless tobacco products sold in Massachusetts (USA) in 2003

Constituent	Chewing tobacco (n = 74) Mean (range)	Dry snuff (n = 33) Mean (range)	Moist snuff (n = 106) Mean (range)
Moisture (%)	22.8 (14.57–28.57)	8.2 (5.38–23.9)[a]	52.6 (21.58–55.77)[b]
Nicotine (%, dry wt)	1.22 (0.45–4.65)	1.82 (1.14–2.69)	2.58 (0.49–3.70)
Nicotine (mg/g product)	9.9 (3.41–39.74)	16.8 (10.48–24.84)	12.6 (4.70–24.29)
pH	5.82 (5.07–6.91)	6.36 (5.50–7.61)	7.43 (5.41–8.38)
Unprotonated nicotine (mg/g product)	0.11 (0.02–1.77)	0.71 (0.05–3.12)	3.52 (0.03–8.57)

From MDPH (2004)

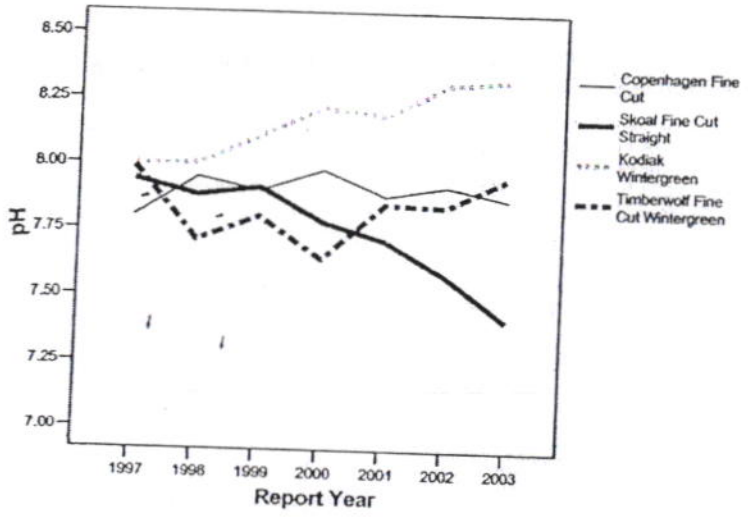
[a] Two Swisher International products contained over 20% moisture.

[b] Four moist snuff brands contained 5.71–8.2% moisture and were therefore excluded from the statistical analysis.

On average, moist snuff contained the highest percentage of moisture (mean, 52.6%; range, 21.58–55.77%) and nicotine (mean, 2.58% dry wt; range, 0.49–3.7%) (Table 8). Dry snuff had the lowest moisture content (mean, 8.2%; range, 5.38–23.9%) but middle range of nicotine (mean, 1.82%; range, 1.14–2.69%). Chewing tobacco had the lowest nicotine content (mean, 1.22%; range 0.45–4.65%). Moist snuff had, on average, the highest pH (7.43 versus 6.36 and 5.82 in dry snuff and chewing tobacco, respectively). Because of the high pH, the levels of unprotonated nicotine in moist snuff averaged 3.52 mg/g product (range, 0.03–8.57 mg/g); this is fivefold higher than that in dry snuff and 32-fold higher than that in chewing tobacco. The highest concentration of unprotonated nicotine was reported for Longhorn Fine Cut Natural, which is marketed by Swedish Match North America (Table 7).

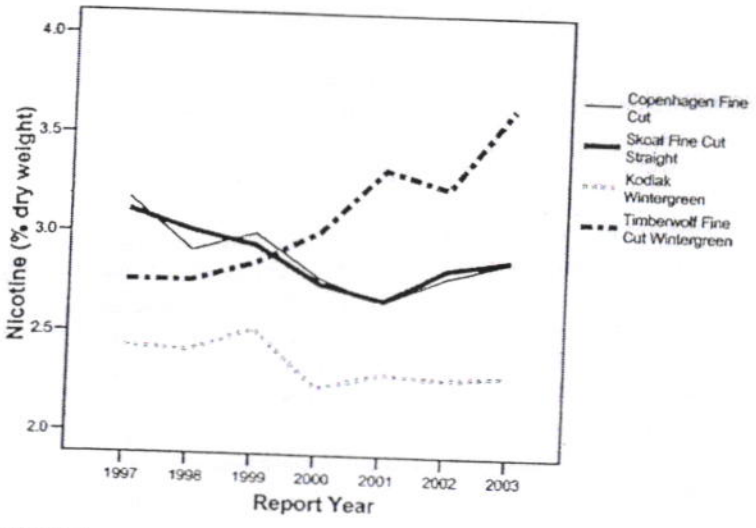
Regular and comprehensive reporting on the chemical composition of smokeless tobacco products to the MDPH enables analysis of trends in chemical composition over time and comparison of the levels of specific constituents between different brands or types of products. The trends for pH and nicotine content (both total and unprotonated) in the four leading brands of moist snuff in the USA (Copenhagen Fine Cut, Skoal Straight Fine Cut, Kodiak Wintergreen and Timberwolf Fine Cut Wintergreen) (Maxwell Tobacco Facts Book, 2002) from 1997 to 2003 are presented in Figures 1–3 (MDPH, 2004). Nicotine content (% dry wt) in three of the brands did not change notably between 1997 and 2003, while it increased steadily in Timber Wolf from 2.8 to 3.6% during the same period.

Figure 1. The pH of leading US moist snuff products (1997–2003)



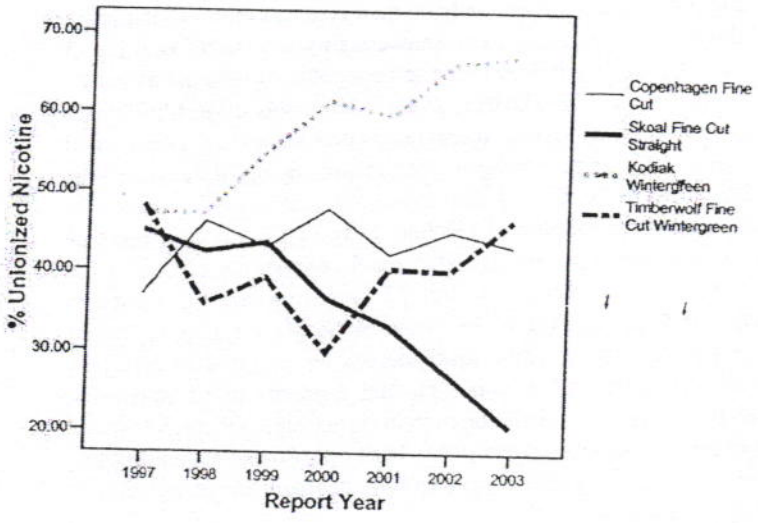
From MDPH (2004)

Figure 2. The nicotine content (% dry weight) in leading US moist snuff products (1997–2003)



From MDPH (2004)

Figure 3. The unprotonated nicotine content (% of the total nicotine) in leading US moist snuff brands (1997–2003)



From MDPH (2004)

The pH values for Copenhagen fine cut were constant between 1997 and 2003 (Figure 2), while the pH of Skoal Fine Cut Straight dropped significantly during the same period. Of the four brands, Kodiak has had the highest pH since 1999, and the pH of the Timber Wolf fluctuated between 7.6 and 8.0. The latter observation underlines the importance of monitoring the composition of all products rather than using one brand as a proxy for different types of smokeless tobacco product, or sub-brands of a brand family.

As shown in Figure 3, the levels of unprotonated nicotine were the highest in Kodiak Wintergreen, and increased from 35.19% total nicotine in 1997 to 60.27% total nicotine in 2003. This pattern parallels the trend in pH. On average, the levels of unprotonated nicotine in Copenhagen and Skoal brand families decreased steadily overtime. However, for the individual brands, this trend was only true for Skoal Fine Cut Straight, and not for Copenhagen Fine Cut, similar to the observation regarding pH. The percentage of unprotonated nicotine for Timberwolf also parallels the pH (Figures 2 and 3). As a result of the constant interplay of pH, nicotine content and moisture in tobacco products, the levels of unprotonated nicotine vary from product to product and from year to year.

In summary, the data from the MDPH show that pH and unprotonated nicotine content are brand- and company-specific. pH appears to be the primary determinant of nicotine absorption (Tomar & Henningfield, 1997). Among the 562 components reported on the list of additives for smokeless tobacco products (House of Representatives, 1994), several salts (e.g. ammonium, sodium and potassium salts) may alter the pH of smokeless

tobacco. Moreover, smokeless tobacco contains components that are intended to control delivery of nicotine to the body (Food and Drug Administration, 1996). However, exposure of users to tobacco toxins does not depend only on their concentration in a particular product but also how the product has been used. Smokeless tobacco users who dip or chew eight to 10 times a day may be exposed to the same amount of nicotine as individuals who smoke 30–40 cigarettes a day (DHHS, 1986). Lemmonds *et al.* (2005) examined the relationship between topographical measures of oral smokeless tobacco and biomarkers of exposure to tobacco and carcinogens. The major finding of the study was that frequency and duration measures of smokeless tobacco use are significantly correlated with total cotinine, a major metabolite of nicotine. Fifty-four male snuff users of 2.8 tins/week (6.1 dips/day) excreted on average 20.1 nmol cotinine/mg creatinine (or 3.3 nmol cotinine per dip) in urine compared with 27 nmol cotinine/mg creatinine excreted by smokers who consumed on average 27.9 cigarettes/day (or 1.07 nmol creatinine per cigarette) (Hecht *et al.*, 2005). Thus, snuff dippers are exposed to 3.08-fold higher amounts of nicotine than cigarette smokers. This high exposure to nicotine needs to be taken into consideration when recommending nicotine replacement therapy to those who contemplate quitting snuff use. Moreover, it has been shown that increasing the nicotine concentration in the presence of alcohol significantly increases the penetration of NNN across the oral mucosa (Du *et al.*, 2000).

The latest information on the chemical composition of 14 varieties of smokeless tobacco products used in India, including pH and nicotine content, was made available in a report to the WHO South-East Asian Regional Office (Gupta, 2004; Table 9). Some products had a pH of up to 10.1 and a nicotine content of up to 10.2 mg/g.

Ayo-Yusuf *et al.* (2004) reported on the pH and nicotine content of moist snuff products consumed in South Africa. The pH ranged from 7.1 to 10.1, the nicotine content from 0.8 to 1.6% wet wt [11.6–29.3 mg/g dry wt, as adjusted for moisture content] and from 10.1 to 99.1% in the unprotonated form.

A new product that is on the market, tobacco tablets, also referred to as Ariva® or Cigalett®, contain 1.3 mg nicotine per tablet and have a pH of 8.4. The 'buffering capacity' of Ariva® is sufficient to control the acidic pH of human saliva (Nguyen *et al.*, 2002).

(*b*) *Tobacco-specific N-nitrosamines (TSNA)*

Hoffmann *et al.* (1995) provided the most comprehensive insight into the levels of major tobacco carcinogens in the leading brands of moist snuff sold in the USA. The purpose of the study was threefold: (*a*) to determine the concentrations of major carcinogenic TSNA and *N*-nitrosamino acids in each of the five most popular brands of moist snuff (Table 10); (*b*) to analyse quantitative differences in selected snuff components (e.g. NNK and NNN) between two major categories of moist snuff: a category that comprised those brands known to have high levels of unprotonated nicotine (Copenhagen, Skoal Fine Cut and Kodiak) versus a category that comprised those brands known to have low levels (Hawken and Skoal Bandits); and (*c*) to compare the concentration of nicotine, NNN, NNK and total TSNA between these two categories. Concentrations (mean ± standard deviation

Table 9. Chemical composition of smokeless tobacco products used in India

Constituent	Minimum value	Brand	Maximum value	Brand
pH	5.21	Baba Zarda 120	10.1	Lime Mix – Miraj Tobacco
Ammonia (μg/g)	4.04	Baidhyanath Red Tooth Powder	5280	Gai Chhap Zarda
Total carbonate (μg/g)	140	Dabur Red Tooth Powder	2040	Baba Zarda 120
Nicotine (mg/g)	1.24	Raja Khaini[a]	10.16	Dentobac Creamy Snuff
NNN (μg/g)	ND	Click Eucalyptus[b]	7.36	Baba Zarda 120
NNK (μg/g)	ND	Click Eucalyptus[b]	4.88	IPCO Creamy Snuff
Benzo[*a*]pyrene (μg/g)	< 0.0001	Click Eucalyptus	0.94	IPCO Creamy Snuff
Cadmium (μg/g)	0.03	Click Eucalyptus	0.5	Baba Zarda 120
Arsenic (μg/g)	0.07	Click Eucalyptus	1.53	Shahin Mishri
Nitrate (μg/g)	< 0.1	Dabur Red Tooth Powder	13.85	Lime Mix – Miraj Tobacco

From Gupta (2004)

ND, not detected; NNK, 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N*'-nitrosonornicotine

[a] *Tuibur* contained no detectable amounts of nicotine.

[b] Click Eucalyptus and six other compounds in this report contained nitrosamines other than tobacco-specific *N*-nitrosamines.

[SD]) of nicotine, NNN, NNK and total TSNA in the two categories were as follows: nicotine, 11.6 ± 1.06 mg/g versus 6.96 ± 3.62 mg/g ($p = 0.0017$); NNN, 7.74 ± 1.70 μg/g versus 4.17 ± 1.35 μg/g ($p < 0.0001$); NNK, 1.23 ± 0.68 μg/g versus 0.61 ± 0.41 μg/g ($p = 0.012$); and total TSNA (including NNN, NNK, NAB and NAT), 14.3 ± 3.82 μg/g versus 6.3 ± 2.56 μg/g ($p < 0.001$). In another study, moist snuff with a high pH and high unprotonated nicotine content, purchased in 2000, contained 15.4 μg/g dry wt NNN and 2.5 μg/g dry wt NNK (Brunnemann *et al.*, 2002). The brand Conwood's Grizzly contained 70.8 μg/g NNN and 10.1 μg/g NNK (Brunnemann *et al.*, 2004).

Table 11 shows an international comparison of the concentrations of two carcinogenic TSNA, NNN and NNK, as well as of tobacco pH (as determined in an aqueous tobacco suspension). The ranges for all three measures are wide and are product-specific and country-specific. The highest values of pH were measured in *naswar* from Uzbekistan (Brunnemann *et al.*, 1985), *toombak* from Sudan (Idris *et al.*, 1998a) and new moist snuff brands recently introduced in South Africa (Ayo-Yusuf *et al.*, 2004). The highest concentrations of NNN and NNK were measured in some moist snuff brands in the USA (135 and 17.8 μg/g tobacco, respectively). However, values as high as 3085 and 7870 μg/g dry wt tobacco, respectively, have been measured in home-made *toombak*.

Although there has been a decline in the concentrations of nitrosamines in some smokeless tobacco products in Sweden and the USA since the 1980s (Djordjevic *et al.*, 1993b; Brunnemann *et al.*, 2004; Österdahl *et al.*, 2004), the trend may not apply to other

Table 10. Levels of tobacco-specific *N*-nitrosamines and *N*-nitrosamino acids in the five leading brands sold in the USA, 1994

Constituents (μg/g dry wt)	Skoal Bandits Straight	Hawken Wintergreen	Skoal Original Fine Cut Wintergreen	Copenhagen Snuff	Kodiak
Tobacco-specific N-nitrosamines (TSNA)					
NNN	5.09 ± 1.03	3.07 ± 0.3	8.18 ± 1.33	8.73 ± 1.44	6.3 ± 1.06
NNK	0.92 ± 0.26	0.23 ± 0.04	1.25 ± 0.13	1.89 ± 0.62	0.55 ± 0.15
Total TSNA	8.19 ± 1.72	4.08 ± 0.44	14.9 ± 2.5	17.24 ± 2.97	10.96 ± 2.44
Nitrite nitrogen	1.3 ± 0.4	1.4 ± 0.8	64.5 ± 41.9	672.0 ± 296.8	2.77 ± 1.13
N-Nitrosamino acids (NNAC)					
NSAR	0.02 ± 0.01	0.07 ± 0.01	0.04 ± 0.0	0.06 ± 0.01	0.04 ± 0.01
MNPA	10.96 ± 1.80	5.62 ± 0.71	2.39 ± 0.34	2.62 ± 0.62	2.23 ± 0.32
MNBA	0.1 ± 0.08	0.33 ± 0.06	0.23 ± 0.06	0.34 ± 0.1	0.19 ± 0.04
NPRO	1.9 ± 0.42	4.89 ± 0.52	4.6 ± 0.8	5.67 ± 1.29	2.39 ± 0.63
Iso-NNAC	0.07 ± 0.02	0.14 ± 0.03	0.13 ± 0.07	0.31 ± 0.12	0.14 ± 0.02
Total NNAC	13.45 ± 2.07	11.56 ± 1.28	8.15 ± 1.3	10.47 ± 2.7	5.7 ± 1.07

From Hoffmann *et al.* (1995)

MNBA, 4-(*N*-methylnitrosamino)butyric acids; MNPA, 3-(*N*-methylnitrosamino)propionic acids; NNK, 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N'*-nitrosonornicotine; NPRO, *N*-nitrosoproline; NSAR, *N*-nitrososarcosine

products and countries. For example, the concentrations of NNN and NNK in the two leading snuff brands in the USA were reduced significantly by 70–90% from 1980 to 1992, based on dry weight (Djordjevic *et al.*, 1993b). However, samples of a new brand of moist snuff introduced on the US market in the 1990s contained very high amounts of NNN and NNK (up to 57.1 and 16.4 μg/g dry wt, respectively) (Hoffmann *et al.*, 1991). Moreover, the commercial brand Conwood's Grizzly, purchased in the USA in 2003, contained 70.8 μg/g dry wt NNN and 10.1 μg/g dry wt NNK (Brunnemann *et al.*, 2004). In Sweden, the concentrations of NNN and NNK in moist snuff decreased, respectively, from 3.8 and 0.8 μg/g in 1983 to 0.49 μg/g and 0.19 μg/g wet wt in 2002 (87% and 76% decrease, respectively; Österdahl *et al.*, 2004). Values for NNN and NNK of up to 3085 and 7870 μg/g, respectively, were reported in *toombak* (Idris *et al.*, 1991, 1998a). The latest report by Stepanov *et al.* (2006) shows the wide range of TSNA concentrations in 19 brands of new and conventional smokeless tobacco products purchased in retail stores in the USA or online from Snus Worldwide, Sweden. Levels of NNN ranged from 0.019 μg/g wet wt in Ariva® hard snuff to 4.5 μg/g in Skoal Long Cut; those of NNK ranged from 0.032 μg/g in Revel to 1.6 μg/g in Copenhagen Long Cut; and those of NAT ranged from 0.12 μg/g in Ariva® to 4.1 μg in Skoal Long Cut Straight. Stepanov *et al.* (2005) also reported a wide range of TSNA concentrations in smokeless tobacco products from India: NNN concentrations ranged from not detected in *supari* and a sample of a

Table 11. International comparison of the pH and concentration ranges of *N*-nitrosonornicotine (NNN) and 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in smokeless tobacco products (μg/g tobacco)

Country	Type of product	pH	Concentration (μg/g tobacco)			References
			Reported as[a]	NNN	NNK	
Belgium	Chewing tobacco		Dry	7.38	0.13	Ohshima *et al.* (1985)
Canada	Moist snuff	7.5–8.23	Dry	50.4–79.1	3.2–5.8	Brunnemann *et al.* (1985)
	Chewing tobacco	5.28	Dry	2.09	0.24	
Denmark	Chewing tobacco		Wet	0.08–1.6	0.02–1.9	Österdahl *et al.* (2004)
Germany	Chewing tobacco	5.01–5.05	Dry	1.4–2.3	0.03–0.30	Brunnemann *et al.* (1985); Tricker *et al.* (1988)
	Dry snuff		Dry	2.4–18.8	0.58–6.4	
			Wet	0.68	0.10	Tricker & Preussmann (1991); Österdahl *et al.* (2004)
India	Moist snuff		Wet	0.56	0.24	Stepanov *et al.* (2005)
	Chewing tobacco	4.36–6.42	Dry	0.47–0.85	0.13–0.60	Brunnemann *et al.* (1985); Tricker *et al.* (1988)
			Wet	15.3–24.4	2.7–6.5	Nair *et al.* (1989)
	Dry snuff		Wet	137–1 356	110–245	Nair *et al.* (1989)
	Khaini		Dry	25.8–40.0	0.11–5.3	Stich *et al.* (1992)
			Wet	39.4–76.9	2.3–28.4	Stepanov *et al.* (2005)
	Khiwam		Dry	2.5–8.95	0.1–1.03	Tricker & Preussmann (1989)
	Gutka		Wet	0.09–1.1	0.04–0.43	Stepanov *et al.* (2005)
			NR	1.9–5.7	10.7–11.5	Gupta (2004)
	Mishri		Dry	0.3–7.0	0.29–1.1	Nair, U.J. *et al.* (1987); Tricker *et al.* (1988)
			Wet	4.21	0.87	Stepanov *et al.* (2005)
			NR	4.02–4.47		Gupta (2004)

Table 11 (contd)

Country	Type of product	pH	Concentration (μg/g tobacco)			References
			Reported as[a]	NNN	NNK	
India (contd)	*Supari*		Wet	ND	ND	Stepanov *et al.* (2005)
			NR	1.9–2.5	4.9–11.6	Gupta (2004)
	Creamy snuff/ toothpaste		Wet	2.5–48.7	1.3–12.5	Nair *et al.* (1989); Stepanov *et al.* (2005)
					4.4–4.9	Gupta (2004)
	Tooth powder		Wet	ND–0.04	ND	Stepanov *et al.* (2005)
	Tuibur		NR	19.7–20.1		Gupta (2004)
	Zarda		Dry	0.4–79	0.22–24.1	Tricker & Preussmann (1988); Tricker *et al.* (1988)
			Wet	4.8–19.9	1.1–3.1	Stepanov *et al.* (2005)
			NR	6.6–7.4		Gupta (2004)
	Other		Wet	1.74–19.2	0.08–2.6	Stepanov *et al.* (2005)
Norway	Moist snuff		Wet	21	3.3	Österdahl *et al.* (2004)
Uzbekistan	*Nass*	11.0–11.8	Dry	0.12–0.52	0.02–0.13	Brunnemann *et al.* (1985)
South Africa	Low-TSNA moist snuff	7.1–10.1	Dry	1.05–2.07	0.27–0.29	Ayo-Yusuf *et al.* (2004); Brunnemann *et al.* (2004)
Sudan	*Toombak*	8.0–11	Dry	141–3 085	188–7 870	Idris *et al.* (1991); Prokopczyk *et al.* (1995)
Sweden	Moist snuff	7.3–8.68	Dry	1.12–154[b]	0.19–2.95	Brunnemann *et al.* (1985); Ohshima *et al.* (1985); Tricker *et al.* (1988); Hoffmann *et al.* (1991); Tricker & Preussmann (1991); Brunnemann & Hoffmann (1992); Djordjevic *et al.* (1993b); Connolly (2001)
			Wet	0.49–4.4	0.19–1.3	Österdahl & Slorach (1988); Österdahl *et al.* (2004)

Table 11 (contd)

Country	Type of product	pH	Concentration (μg/g tobacco)			References
			Reported as[a]	NNN	NNK	
Sweden (contd)	Low-TSNA moist snuff		Wet	0.15–2.3	0.03–0.36	Österdahl *et al.* (2004); Stepanov *et al.* (2006)
	Chewing tobacco		Wet	0.7–1.7	0.01–0.46	Österdahl *et al.* (2004)
Thailand	Chewing tobacco		Dry	0.5	0.1	Tricker *et al.* (1988)
United Kingdom	Moist snuff		Dry	1.1–52.0	0.4–13.0	Hoffmann *et al.* (1988); Brunnemann & Hoffmann (1992)
	Chewing tobacco		Dry	0.9	0.3	Tricker *et al.* (1988)
	Dry snuff		Dry	2.4–16.0	0.58–4.3	Tricker & Preussmann (1991); Brunnemann & Hoffmann (1992)
			Wet	1.8	0.26	Österdahl *et al.* (2004)
USA	Moist snuff	5.2–8.88	Dry	ND–147	ND–17.8	Brunneman *et al.* (1985); Ohshima *et al.* (1985); Hoffmann *et al.* (1986); Adams *et al.* (1987); Brunnemann *et al.* (1987a,b); Chamberlain *et al.* (1988); Hoffmann *et al.* (1988); Tricker *et al.* (1988); Andersen *et al.* (1989); Djordejvic *et al.* (1989a); Hoffmann *et al.* (1991); Brunnemann & Hoffmann (1992); Prokopczyk *et al.* (1992a); Djordjevic *et al.* (1993b); Hoffmann *et al.* (1995); Prokopczyk *et al.* (1995); Connolly (2001); Brunnemann *et al.* (2002, 2004); Österdahl *et al.* (2004); Stepanov *et al.* (2006)
			Wet	0.71–63	0.06–13	
	Low-TSNA moist snuff		Wet	0.62–0.64	0.032–0.033	Stepanov *et al.* (2006)

Table 11 (contd)

Country	Type of product	pH	Concentration (μg/g tobacco)			References
			Reported as[a]	NNN	NNK	
USA (contd)	Chewing tobacco	0.6–6.37	Dry	0.67–6.5	ND–1.05	Brunnemann *et al.* (1985); Chamberlain *et al.* (1988); Andersen *et al.* (1989); Djordjevic *et al.* (1989a); Brunnemann & Hoffmann (1992)
			Wet	0.25–1.1	0.08–0.11	Österdahl *et al.* (2004)
	Dry snuff	5.8–6.3	Dry	9.4–116.1	0.88–84.4	Adams *et al.* (1987); Brunnemann *et al.* (1987a); Andersen *et al.* (1989); Djordjevic *et al.* (1989a)
	Hard snuff/ lozenges		NR	0.02–0.06	0.037–0.043	Stepanov *et al.* (2006)

ND, not detected; NR, not reported; TSNA, tobacco-specific *N*-nitrosamines

[a] Reported as ng/g of dry wt (Dry) or wet wt (Wet) of tobacco

[b] The Working Group was doubtful about the validity of this value; the next highest value was 20 900 ng/g (Ohshima *et al.*, 1985).

tooth powder to 76.9 µg/g wet wt in *khaini*; those of NNK ranged from not detected to 28.4 µg/g in *khaini*.

In recent years, the Swedish Match Company has developed a new method for manufacturing oral snuff that uses select blends of tobacco as well as a new processing method. Instead of the dark fire-cured tobacco commonly used in US snuff, Swedish Match uses tobacco with a low nitrate content, which itself reduces TSNA levels. In addition, the tobacco is processed in a heated closed system that resembles pasteurization of milk, which eliminates bacteria that may be indirectly responsible for the formation of the nitrosamines (Parsons *et al.*, 1986; Gothia, 2004). The company also encourages retailers to refrigerate packages to prevent the formation of TSNA during storage (see below).

In 2001, the MDPH initiated a study aimed at comparing traditional snuff brands with PREPs (Stratton *et al.*, 2001). The study found that the levels of NNN, NNK, NAT and NAB in moist snuff produced by the new manufacturing process (Swedish Match brand Ettan) were up to 45 times lower than those in leading products manufactured under standard processes in the USA (Table 12).

Table 12. Levels of tobacco-specific *N*-nitrosamines (TSNA) in the five leading brands in the USA versus PREP

Company	Brand[a]	NNN (µg/g)	NNK (µg/g)	Total TSNA[b] (µg/g)
Conwood Company	Kodiak	7.4	0.97	16.6
Swedish Match North America	Timber Wolf	3.0	0.95	7.5
Swisher International	Silver Creek	41.4	17.8	127.9
US Tobacco	Copenhagen	14.3	3.4	41.1
	Skoal	20.8	14.3	64.0
Swedish Match	Ettan (PREP)	1.12	0.53	2.8

From Connolly (2001)
NNK, 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine; PREP, potential reduced exposure product
[a] Snuff manufactured in the USA was purchased in the Commonwealth of Massachusetts; Ettan was purchased in Sweden.
[b] Total TSNA includes NNN, NNK, *N*-nitrosoanatabine and *N*-nitrosoanabasine.

In Sweden, all moist snuff brands on the market in 2002 contained low amounts of TNSA: NNN, 0.15–0.61 µg/g wet wt; and NNK, 0.03–0.36 µg/g wet wt. NNN concentrations in moist snuff decreased consistently from 1983 to 2002 from 3.8 to 0.49 µg/g wet wt and those of NNK from 0.80 to 0.19 µg/g wet wt (Österdahl *et al.*, 2004).

Levels of TSNA in new oral snuff brands do not always parallel nicotine content (see Table 7 for the nicotine content and Table 12). For example, Taxi, a very high nicotine-delivery product manufactured by Swedish Match for the South African market, contains low

levels of TNSA: NNN, 2.07 μg/g dry wt; and NNK, 0.29 μg/g dry wt (Brunnemann *et al.*, 2004).

(*c*) 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 nitrosamino acids in smokeless tobacco products. Levels of *N*-nitrosoamino acids in smokeless tobacco products worldwide are presented in Table 13. To date, 11 *N*-nitrosamino acids have been identified in smokeless tobacco: NSAR, *N*-nitrosoazetidine-4-carboxylic acid (NAzCA), MNPA, 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; Djordjevic *et al.*, 1989b; Tricker & Preussmann, 1989, 1991; Hoffmann *et al.*, 1995). Of these, the following have been established as carcinogens in experimental animals: NSAR, MNPA, MNBA and NAzCA. The concentration of the nitrosamino acids depends on the nitrate or nitrite content of the tobacco; in addition, they are formed during prolonged storage, particularly under adverse conditions of temperature and relative humidity (Djordjevic *et al.*, 1993a).

The highest concentrations of *N*-nitrosamino acids in moist snuff purchased in the USA were found in Skoal Bandits Straight and Hawken Wintergren (13.45 and 11.56 μg/g, respectively) and the lowest in Kodiak (5.7 μg/g), which is opposite to the trend observed for TNSA (Hoffmann *et al.*, 1995).

(*d*) *Volatile* N-*nitrosamines*

Volatile *N*-nitrosamines are formed from volatile amines and nitrosating agents. The levels of volatile *N*-nitrosamines in smokeless tobacco products worldwide are presented in Table 14. 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; see also Table 3). The presence of NMOR (see IARC, 1987) indicates contamination with morpholine either from additives or from diffusion of containers coated with morpholine-containing wax (Brunnemann *et al.*, 1985; Brunnemann & Hoffmann, 1991).

(*e*) *Other carcinogenic compounds*

In smokeless tobacco products from the USA, the levels of benzo[*a*]pyrene ranged from < 0.1 to 63 ng/g in moist snuff (Hoffmann *et al.*, 1986) and up to 90.5 ng/g in dry snuff (Brunemann & Hoffmann, 1992; Table 3). Bhide *et al.* (1984a) reported on the whole range of PAHs in Indian smokeless tobacco products such as *mishri* and snuff: benzo[*a*]pyrene, 7.6–66 ng/g; benzofluoranthenes (*b* + *j* + *k*), 35–231 ng/g; indeno[1,2,3-*cd*]pyrene, 4.3–24 ng/g; benz[*a*]anthracene, 19–79 ng/g; chrysene and triphenylene, 37–

Table 14. Comparison of the major carcinogenic volatile *N*-nitrosamines in smokeless tobacco (ng/g dry wt) across countries

Country	Type of product	NDMA	NPYR	NMOR	Reference
Canada	Moist snuff	23–72.8	321–337	21.9–32.8	Brunnemann *et al.* (1985)
	Chewing tobacco	ND	ND	ND	
Denmark	Chewing tobacco	5.5	16	ND	
Germany	Nasal snuff	2.0–82	1.5–75	ND	Brunnemann *et al.* (1985); Tricker & Preussmann (1991); Brunnemann & Hoffmann (1992)
	Chewing tobacco	ND	ND	ND	
India	*Zarda*	2.0–31	6.0–69	ND	Brunnemann *et al.* (1985); Nair, U.J. *et al.* (1987); Tricker & Preussmann (1988, 1989, 1991)
	Khiwam	1.5–28	11–250	NE	
	Chewing tobacco	ND–0.56	1.55–4.48	ND	
	Mishri	12–80	21–99	NE	
Norway	Moist snuff	130	8.9	32.0	Brunnemann & Hoffmann (1992)
Sweden	Moist snuff	ND–63	ND–155	ND–44	Brunnemann *et al.* (1985); Hoffmann *et al.* (1991); Tricker & Preussmann (1991); Brunnemann & Hoffmann (1992); Djordjevic *et al.* (1993a)
	Chewing tobacco	0.2	0.8	0.4	
United Kingdom	Moist snuff	6.0–212	64–860	ND–1.5	Hoffmann & Brunnemann (1988); Tricker & Preussmann (1991); Brunnemann & Hoffmann (1992)
	Nasal snuff	4.5–82	1.5–130	ND	
USA	Moist snuff	ND–265	ND–575	ND–690	Brunnemann *et al.* (1985); Hoffmann *et al.* (1986, 1987); Hoffmann & Brunnemann (1988); Brunnemann & Hoffmann (1991); Hoffmann *et al.* (1991); Brunnemann & Hoffmann (1992)
	Chewing tobacco	4.12–64	ND–0.8	ND–0.6	
	Dry snuff	ND–19	72–148	ND–39	
Former USSR (Central Asian Republics)	*Nass*	ND	1.74–8.82	ND	Brunnemann *et al.* (1985)

ND, not detected; NDMA, *N*-nitrosodimethylamine; NE, not evaluated; NMOR, *N*-nitrosomorpholine; NPYR, *N*-nitrosopyrrolidine

192 ng/g; benzo[*e*]pyrene, 10–110 ng/g; pyrene, 60–169 ng/g; fluoranthene, 55–218 ng/g; and benzo[*ghi*]perylene, 5.6–17 ng/g.

Hoffmann *et al.* (1987) reported the levels of select volatile aldehydes in smokeless tobacco products: formaldehyde, 3.9–6.8 µg/g in moist snuff and 1.6–7.4 µg/g in dry snuff; acetaldehyde, 2.4–7.4 µg/g in moist snuff and 1.4–3.9 µg/g in dry snuff; and crotonaldehyde, 1.0–2.4 µg/g in moist snuff and 0.2–0.6 µg/g in dry snuff.

Uranium was reported in five samples of Indian snuff at a concentration of about 3 pCi/g tobacco (Sharma *et al.*, 1985). Hoffmann *et al.* (1987) reported 0.16–1.22 pCi/g polonium-210 in commercial moist snuff and 0.23–0.39 pCi/g in commercial dry snuff in the USA.

(*f*) *Effect of storage conditions on the levels of* N*-nitrosamines*

The effect of storage conditions on the formation of TSNA in smokeless tobacco was studied in moist and dry snuff and in chewing tobacco.

In a study of the effects of ageing and storage on the levels of TSNA, *N*-nitrosamino acids and volatile *N*-nitrosamines in commercial moist snuff from the USA, it was found that during storage at 4 °C none of these compounds increased significantly (Djordjevic *et al.*, 1993a). However, at higher temperatures, the levels of *N*-nitrosamines and nitrite in the moist snuff increased significantly over time. After 8 weeks of storage at 37 °C, the levels of NNN and NNK had risen threefold (from 6.24 to 18.7 µg/g), those of the *N*-nitrosamino acids MNPA and MNBA had risen 5.2-fold (from 3.13 to 16.3 ppm) and those of volatile *N*-nitrosamines had risen 10-fold (from 0.02 to 0.2 µg/g); moist snuff stored for 8 weeks at 37 °C contained 0.0386 µg/g NDMA, 0.0714 µg/g NPYR and 0.0176 µg/g NMOR. The concentration of 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of NNK, doubled during storage at 37 °C from 0.29 to 0.65 µg/g. In a study conducted by the MDPH (Connolly, 2001), the effect of ageing of snuff was examined over 2, 4 and 6 months. Levels of total TSNA, including NNN, NNK, NAT and NAB, in the leading US brand Copenhagen increased 137%. No significant changes were observed in TSNA levels in Ettan, the Swedish Match moist snuff brand, when subjected to storage under adverse conditions. An earlier study revealed that levels of both NNN and NNK in moist snuff increased 21 and 12-fold, respectively, within the first 24 weeks of storage; in contrast, levels of nicotine decreased 1.3-fold during the same period. Concentrations of NNN and NNK in chewing tobacco and dry snuff during 24 weeks of storage increased 1.5- and 1.8-fold, respectively (Andersen *et al.*, 1989).

1.3.4 *Kentucky (KY) reference smokeless tobacco products*

For research purposes, a series of reference smokeless tobacco products was developed and manufactured by the Tobacco and Health Research Institute (1987) at the University of Kentucky, Lexington, KY (USA) in the late 1980s. Each reference product, i.e. moist snuff, dry snuff and loose-leaf chewing tobacco, was custom made to mimic the chemical composition of commercial products in the respective category. However, speci-

fic flavourings and additives, including those used by manufacturers to influence levels of unprotonated nicotine, were not included in KY reference products. KY reference smokeless tobacco products contain the following ingredients:

Loose-leaf chewing tobacco (1S1): Wisconsin air-cured tobacco, 17.4%; Pennsylvania air-cured tobacco, 15.47%; crushed Burley tobacco stems, 5.8%; glycerin, 3.75%; sucrose, 23.01%; dextrose, 1.7%; maltose, 1.3%; other corn syrup solids, 6.21%; salt, 1.6%; sodium propionate, 0.28%; water, 23.48%.

Dry snuff (1S2): dark-fired tobacco, 22.75%; fire-cured Virginia tobacco, 19.66%; air-cured stems, 33.03%; fire-cured stems, 15.2%; salt, 0.36%; water, 9.0%.

Moist snuff (1S3): dark-fired tobacco, 25.73%; air-cured tobacco, 7.83%; Burley stems, 3.73%; sodium carbonate, 0.51%; sodium chloride, 7.4%; water, 54.80%.

As the blending recipe for KY reference products shows, loose-leaf chewing tobacco and moist snuff contain about 30% of tobacco by weight whereas dry snuff contains 75% of tobacco. The chemical composition of these reference products is shown in Table 15. In addition to data on nicotine, total nitrogen, nitrate nitrogen, total sugars, reducing sugars, moisture, pH, ash, potassium, sodium and calcium (Tobacco and Health Research Institute, 1987), the levels of selected TSNA and *N*-nitrosamino acids are also presented (Djordjevic *et al.*, 1989b; Brunnemann *et al.*, 2002).

1.3.5 *Pesticide residues*

Maximum allowable limits for pesticides on tobacco (e.g. maleic hydrazide, chlordane, dichlorodiphenyltrichloroethane, dichlorodiphenyldichloroethylene, dieldrin, endrine, heptachlor) in Germany, Italy, Spain and the USA are summarized by Sheets (1990).

1.4 Production, consumption and prevalence of use of smokeless tobacco products

This section presents data on sales, consumption and prevalence of use of smokeless tobacco products. Where possible, data are presented separately for each product type. In some countries and surveys, consumption was not measured or reported separately and thus overall consumption or prevalence of use of smokeless tobacco is reported. In most countries, surveys do not specify which type of snuff is used, but the overwhelming majority of snuff is of the moist variety and is taken orally.

Data on prevalence of smokeless tobacco use among youths in South America (Section 1.4.2(*c*)), South Asia (Section 1.4.3) and Africa (Section 1.4.4) rely primarily on the Global Youth Tobacco Survey (GYTS). The GYTS project was developed by WHO and the CDC in the USA. It is an international surveillance project designed to enhance the capacity of countries to monitor tobacco use among youths, and to guide the implementation and evaluation of tobacco prevention and control programmes. The GYTS has been completed in 120 countries. It uses a two-stage cluster sample survey design that produces representative samples of students in grades associated with the ages of 13–15 years.

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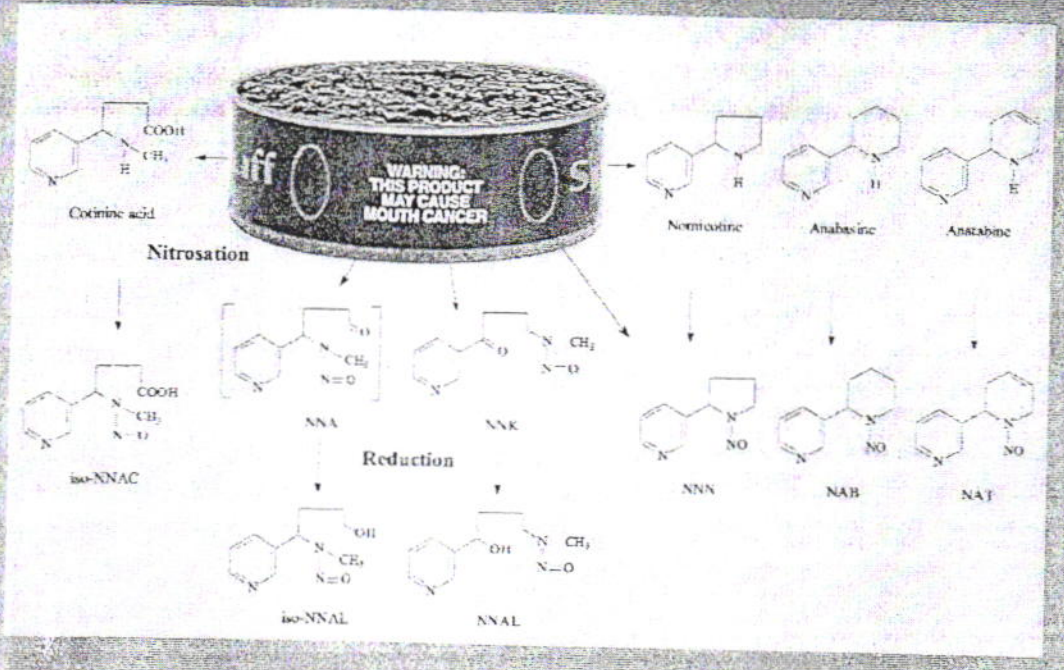
Smokeless Tobacco and Some Tobacco-specific *N*-Nitrosamines



LYON, FRANCE
2007

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Table 35. Type of tobacco product used among tobacco users in Bangladesh, 2003

Type of tobacco product	Individual[a]	Family[a]
Cigarette	382 (49.2%)	391 (39.5%)
Bidi	207 (26.4%)	225 (22.7%)
Hookah	6 (0.7%)	6 (0.6%)
Treated tobacco leaf[b]	326 (41.9%)	363 (36.7%)
Raw dried tobacco leaf[b]	135 (17.4%)	186 (18.8%)
Powdered tobacco leaf	30 (3.9%)	46 (4.6%)
Total	777 (100%)	990 (100%)

From WHO SEARO (2003)
[a] The modalities of tobacco use were documented by the subjects about themselves (individual) or by them about their family members (family).
[b] As constituents of betel quid

(*c*) *India*

India is one of the major producers of chewing tobacco in Asia. A specific feature of tobacco production in India is the variety in the types of tobacco produced. The presence of a strong domestic demand for tobacco product for chewing and application to a relatively large extent influences the cultivation of tobacco for these uses. Tobacco used for chewing and application is grown in Tamil Nadu, Uttar Pradesh, Bihar, West Bengal and Orissa (Reddy & Gupta, 2004).

In 2002, 40.6% of the tobacco production was used in cigarettes, 33.3% in *bidi* production and 12.4% was used for smokeless forms of chewing, snuffing and applied tobacco (Table 36; Reddy & Gupta, 2004). Between 1976 and 1994, chewing tobacco

Table 36. Tobacco production by type of tobacco in India, 2002

Type	Quantity (million kg)	%
Cigarettes	244	40.6
Bidi	200	33.3
Cigar	22	3.7
Hookah	60	10.0
Chewing tobacco	65	10.8
Snuff	10	1.6
Total	601	100

From Reddy & Gupta (2004)

production represented between 11% and 19% of total tobacco production, but production has increased substantially since 1995 (Table 37). In 2002, 65 million kg of chewing tobacco and 10 million kg of snuff tobacco were produced in India (Table 36). This increase was accompanied by a huge growth in the export of both chewing tobacco (9-fold increase between 1995 and 2005) and snuff tobacco (18-fold increase during the same period) (Table 38; Reddy & Gupta, 2004; Tobacco Board, 2006).

Table 37. Production of smokeless tobacco (in millions of kg) in India (derived estimates[a]) and percentage of total tobacco production

Years	Chewing		Snuff	
	Production	%	Production	%
1976–77	80.1	19.1	5	1.2
1977–78	70.8	14.3	6	1.6
1978–79	70	15.4	6	1.3
1979–80	72	16.4	7.6	1.7
1980–81	85.3	17.7	7.5	1.6
1981–82	77	14.8	7.6	1.5
1982–83	76.2	13.1	8.9	1.5
1983–84	78.7	16.0	9.2	1.9
1984–85	89	18.3	6.5	1.3
1985–86	75	17.0	7.9	1.8
1986–87	78	16.9	7.5	1.6
1990–91	78.8	14.2	11.8	2.1
1991–92	79.0	13.5	14.4	2.5
1992–93	71.2	11.9	13.3	2.2
1993–94	65.7	11.7	11.8	2.1
1994–95	138.3	24.4	11.7	2.1
1995–96	118.8	22.2	11.0	2.0
1996–97	156.6	26.1	10.0	1.7
1997–98[b]	108.5	18.9	11.0	1.9

[a] Calculated by the Working Group based on data from Directorate of Tobacco Development (1976–98)
[b] Provisional

Large variations in the prevalences and patterns of smokeless tobacco use occur across the country. Apart from regional preferences due to different socio-cultural norms, the preference for smokeless rather than smoked tobacco is inversely related to education and income (Gupta, 1996). Per-capita consumption of smokeless tobacco has increased among the lower socioeconomic classes between 1961 and 2000 in both rural and urban areas (data from the National Sample Survey Organization, cited in Gupta & Ray, 2003).

Table 38. Exports of tobacco from India by product (in tonnes)

Tobacco product	1995–96	1998–99	2001–2002	2004–2005
Cigarettes	884	1432	2883	7 190
Bidi	676	998	961	1062
Hookah/tobacco paste	9376	12 811	8910	10 600
Chewing tobacco/*zarda*	424	1191	2640	3778
Cut tobacco	512	2506	683	2034
Snuff	6	19	19	110
Total	11 883	18 957	16 076	24 774

From Tobacco Board (2006)

Six sets of data may allow an estimation of the prevalence of smokeless tobacco use in India: (*a*) large sub-national cross-sectional and cohort studies, (*b*) the National Family Health Survey, (*c*) the WHO sub-national study, (*d*) the National Sample survey on household consumer expenditure, (*e*) the Global Youth Tobacco Survey and (*f*) the Sample Registration system (unpublished). The last set of data is not discussed here.

(i) *Sub-national cross-sectional and cohort studies*

It has been estimated that approximately one-third of women and two-thirds of men in India use tobacco in one form or another (WHO, 1997). In prevalence surveys in 10 rural areas in eight states of India, smokeless tobacco was used by 3–53% of men and 3–49% of women (Table 39). In these areas, 2–26% of men and 0–4% of women also reported both smoking and smokeless tobacco use (Gupta & Ray, 2003). In a cross-sectional and cohort study in Mumbai, the prevalence of smokeless tobacco use in 1992–94 was 57.1% among women and 45.7% among men (Gupta, 1996). In another cross-sectional survey in a suburb of Trivandrum, Kerala, where residents were mostly of lower socioeconomic status, chewing practices were reported by 26.8% of men (n = 25 453) and 26.4% of women (n = 34 441), mainly in the form of betel quid with tobacco (Sankaranarayanan *et al.*, 2000).

(ii) *National Family Health Survey*

In the National Family Health Survey-2 conducted in 1998–99, 315 597 individuals aged 15 years or older from 91 196 households were sampled (Rani *et al.*, 2003). Among the study population, 20% (28.1% of men and 12.0% of women) reported chewing tobacco/*pan masala*; however, the prevalence may be underestimated by almost 11% for men and 1.5% for women because of the use of household informants. The prevalence of chewing tobacco/*pan masala* varied significantly (7–60%) between states (Table 40). Chewing of tobacco/*pan masala* was relatively more common (> 16%) in the central, eastern, western (except Goa) and northeastern states (except Tripura) compared with the northern and southern states. The prevalence of chewing tobacco/*pan masala* was significantly higher in rural, poorer and less educated populations compared with urban, wealthier

Table 39. Prevalence (%) of use of various types of tobacco in 10 areas in eight states of India

Area	Chewed[a] or applied	Smoked	Mixed	Total users	Reference
Men					
Bhavnagar, Gujarat	9	56	6	71	Mehta *et al.* (1969)
Darbhanga, Bihar	28	24	26	78	Mehta *et al.* (1969)
Ernakulam, Kerala	14	45	22	81	Mehta *et al.* (1969)
Goa	3	61	5	69	Bhonsle *et al.* (1976)
Mainpuri, Uttar Pradesh	21	41	20	82	Wahi (1968)
Mumbai (urban), Maharashtra	46	14	10	69	Gupta (1996)
Pune, Maharashtra	53	6	2	62	Mehta *et al.* (1972)
Singbhum, Jharkhand	17	50	14	81	Mehta *et al.* (1969)
Srikakulam, Andhra Pradesh	4	70	7	81	Mehta *et al.* (1969)
Trivandrum (urban), Kerala	27	56	NR	83	Sankaranarayanan *et al.* (2000)
Women					
Bhavnagar, Gujarat	15	–[b]	–	15	Mehta *et al.* (1969)
Darbhanga, Bihar	7	41	4	51	Mehta *et al.* (1969)
Ernakulam, Kerala	38	1	1	39	Mehta *et al.* (1969)
Goa	23	24	2	49	Bhonsle *et al.* (1976)
Mainpuri, Uttar Pradesh	9	11	1	21	Wahi (1968)
Mumbai (urban), Maharashtra	57	–	–	57.5	Gupta (1996)
Pune, Maharashtra	49	–	–	49	Mehta *et al.* (1972)
Singbhum, Jharkhand	26	5	2	33	Mehta *et al.* (1969)
Srikakulam, Andhra Pradesh	3	64	–	67	Mehta *et al.* (1969)
Trivandrum (urban), Kerala	26	2	NR	28	Sankaranarayanan *et al.* (2000)

Adapted from Gupta & Ray (2003)
NR, not reported
[a] Including betel quid with tobacco
[b] –, prevalence < 0.5%

and more educated populations in both men and women. The socioeconomic gradients (household wealth, education) had more impact for women than for men. The prevalence of chewing tobacco/*pan masala* was higher among tribal populations than among other communities (Table 41). In a multivariate analysis, the older population (≥ 25 years) had a greater likelihood of chewing tobacco compared with the younger population (15–24 years). Muslim women were more likely to chew tobacco than Hindu women, and the Sikh religion emerged as one of the strongest predictors among women for not chewing tobacco. The differentials by state of residence also persisted in the multivariate analysis. No significant association was observed between urban or rural residence and chewing of tobacco/*pan masala* among men after controlling for other characteristics. However, rural women were less likely to chew tobacco than urban women (Rani *et al.*, 2003).

Table 40. Prevalence of chewing[a] in India by state and by sex (National Family Health Survey, 1998–99)

Region/State	Men	Women
	% (95% CI)	% (95% CI)
North		
Haryana	8.1 (6.7–9.8)	0.9 (0.6–1.3)
Himachal Pradesh	7.8 (6.7–9.1)	0.5 (0.3–0.8)
Jammu & Kashmir	7.3 (5.8–9.1)	0.9 (0.6–1.3)
New Delhi	13.1 (11.5–14.9)	2.5 (1.9–3.2)
Punjab	9.3 (8.0–10.8)	0.2 (0.1–0.4)
Rajasthan	19.0 (17.7–20.4)	3.8 (2.9–4.9)
Central		
Madhya Pradesh	40.3 (38.7–42.0)	14.4 (12.7–16.2)
Uttar Pradesh	36.3 (34.6–38.0)	10.9 (10.1–11.8)
East		
Bihar	51.8 (50.1–53.5)	6.7 (6.0–7.6)
Orissa	49.0 (46.7–51.4)	34.3 (31.9–36.9)
West Bengal	23.2 (20.9–25.6)	15.1 (13.5–17.0)
Northeast		
Arunachal Pradesh	51.6 (47.9–55.3)	33.1 (29.6–36.7)
Assam	47.8 (44.7–51.0)	24.3 (22.1–26.6)
Manipur	34.1 (31.1–37.3)	19.2 (15.5–23.5)
Meghalaya	16.9 (13.8–20.5)	27.6 (23.8–31.7)
Mizoram	60.2 (56.5–63.8)	60.7 (57.2–64.0)
Nagaland	45.0 (41.3–48.8)	16.5 (13.7–19.7)
Sikkim	39.5 (36.5–42.7)	18.6 (16.2–21.2)
Tripura	10.8 (8.9–13.1)	5.2 (3.3–8.1)
West		
Goa	7.7 (6.0–9.9)	8.0 (6.3–10.2)
Gujarat	24.6 (22.8–26.4)	8.0 (7.0–9.2)
Maharashtra	34.1 (32.3–36.0)	18.0 (16.1–20.0)
South		
Andhra Pradesh	10.7 (9.4–12.0)	9.9 (8.4–11.7)
Karnataka	13.8 (12.1–15.6)	14.1 (12.7–15.7)
Kerala	9.4 (8.3–10.7)	10.1 (9.1–11.2)
Tamil Nadu	12.9 (11.5–14.5)	10.7 (9.3–12.2)

From Rani *et al* (2003)
CI, confidence interval
[a] Tobacco or *pan masala*

Table 41. Prevalence (%) of chewing of tobacco/*pan masala* in India (National Family Health Survey, 1998–99)

Variable	Prevalence in % (95% CI)	
	Men	Women
Age (years)		
15–24	4.4 (4.2–4.6)	14.3 (13.8–14.9)
25–39	17.2 (16.8–17.6)	31.6 (30.9–32.3)
40–59	25.7 (25.2–26.2)	35.3 (34.5–36.1)
≥ 60	22.4 (21.7–23.0)	37.4 (36.3–38.5)
Residence		
Urban	20.7 (19.7–21.7)	8.6 (7.9–9.3)
Rural	31.1 (30.4–31.8)	13.3 (12.8–13.8)
Economic status		
Richest 20%	16.4 (15.6–17.2)	4.8 (4.5–5.2)
Second richest	22.8 (22.0–23.7)	9.3 (8.7–9.8)
Middle	28.1 (27.3–28.9)	12.6 (12.0–13.2)
Second poorest	34.4 (33.4–35.4)	15.6 (14.4–15.9)
Poorest 20%	41.9 (40.7–43.2)	19.6 (18.7–20.6)
Years of schooling		
≥ 11	16.9 (16.2–17.7)	1.6 (1.3–1.9)
6–10	23.7 (23.1–24.3)	4.3 (4.0–4.6)
1–5	33.0 (32.1–33.9)	11.5 (10.8–12.1)
No education	38.6 (37.6–39.6)	17.2 (16.6–17.8)
Caste		
Forward caste	24.2 (23.4–25.1)	9.5 (8.9–10.1)
Scheduled caste	30.4 (29.1–31.8)	14.6 (13.7–15.5)
Scheduled tribe	41.1 (39.1–43.1)	20.8 (19.2–22.4)
Other backward castes	28.3 (27.2 –29.4)	10.8 (10.1–11.4)
Religion		
Hindu	29.1 (28.6–29.7)	12.0 (11.5–12.5)
Muslim	25.5 (24.0–27.1)	13.0 (12.1–14.0)
Christian	9.3 (8.0–10.8)	0.1 (0.04–0.3)
Sikh	19.1 (17.0–21.4)	11.5 (10.1–13.2)
Other	31.5 (27.6–35.7)	18.4 (15.3–21.9)

From Rani *et al.* (2003)
CI, confidence interval

(iii) *WHO Sub-national Study*

In a WHO study (Chaudhry, 2001), 35 288 respondents in Karnataka and 29 931 respondents in Uttar Pradesh (aged ≥ 10 years) were surveyed. Tobacco was predominantly used in smokeless form among women of all ages and among men under 30 years of age, both in urban and rural areas. The overall prevalence of current use of smokeless tobacco was 13.9% in Karnataka (13.4% among men, 14.4% among women) (Table 42) and 17.5% in Uttar Pradesh (24.3% among men, 6.6% among women) (Table 43). In Karnataka, the

Table 42. Prevalence by rural/urban area, age and sex of current use of smokeless tobacco in Karnataka, India (WHO Sub-national Study, 2001)

Age group (years)	Urban						Rural					
	Men		Women		Total		Men		Women		Total	
	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)
10–14	281	1.8	224	0.4	505	1.2	925	1.0	818	0.0	1743	0.5
15–19	419	10.3	397	1.0	816	5.8	1700	8.6	1488	0.4	3188	4.8
20–24	432	15.7	403	1.7	835	9.0	1653	16.3	1627	2.8	3280	9.6
25–29	366	18.9	414	2.4	780	10.1	1652	16.9	1634	5.8	3286	11.4
30–34	278	18.0	333	4.8	611	10.8	1394	12.3	1296	11.7	2690	12.0
35–39	313	11.8	381	7.9	694	9.7	1396	13.8	1470	14.1	2866	14.0
40–44	325	16.9	285	12.6	610	14.9	1262	12.3	1208	23.9	2470	18.0
45–49	305	13.4	216	17.1	521	15.0	1187	14.2	964	26.7	2151	19.8
50–54	233	8.2	163	19.0	396	12.6	985	16.1	927	32.8	1912	24.2
55–59	113	8.0	79	12.7	192	9.9	582	17.7	452	39.8	1034	27.4
60–64	108	9.3	146	22.6	254	16.9	792	13.9	660	39.8	1452	25.7
65–69	57	10.5	45	37.8	102	22.5	341	19.6	266	40.6	607	28.8
≥ 70	98	8.2	64	29.7	162	16.7	576	21.7	478	43.5	1054	31.6
All ages	3328	12.6	3150	8.0	6478	10.4	14 445	13.5	13 288	15.9	27 733	14.7

From Chaudhry (2001)

Table 43. Prevalence by rural/urban area, age and sex of current use of smokeless tobacco in Uttar Pradesh, India (WHO Sub-national Study, 2001)

Age group (years)	Urban						Rural					
	Men		Women		Total		Men		Women		Total	
	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)	Sample (no.)	Prevalence (%)
10–14	279	3.2	118	0.8	397	2.5	1641	2.3	681	0.3	2322	1.7
15–19	381	13.9	181	0.6	562	9.6	1937	17.9	792	1.0	2729	13.0
20–24	411	23.6	247	2.4	658	15.7	1905	27.6	1332	2.3	3237	17.1
25–29	351	30.5	256	3.5	607	19.1	1812	30.0	1299	3.5	3111	18.9
30–34	282	25.2	220	6.8	502	17.1	1473	30.8	1203	4.2	2676	8.9
35–39	265	26.8	233	9.9	498	18.9	1406	27.5	1006	6.4	2412	18.7
40–44	269	28.3	187	7.5	456	19.7	1235	27.0	812	9.0	2047	19.8
45–49	231	21.6	141	11.3	372	17.7	1014	27.1	700	12.4	1714	21.1
50–54	173	25.4	89	11.2	262	20.6	885	28.0	466	13.5	1351	23.0
55–59	104	23.1	73	13.7	177	19.2	541	26.6	395	14.7	936	21.6
60–64	109	22.9	57	26.3	166	24.1	647	31.4	328	18.6	975	27.1
65–69	70	27.1	38	23.7	108	25.9	348	30.2	245	12.7	593	22.9
≥ 70	89	36.0	31	19.4	120	31.7	652	32.5	230	16.1	882	28.2
All ages	3014	22.5	1871	7.2	4885	16.6	15 496	24.6	9489	6.4	24 985	17.7

From Chaudhry (2001)

prevalence of use of smokeless tobacco was higher among women compared with men in the age groups above 40 years. In Uttar Pradesh, the proportion of men who used smokeless tobacco was higher than that of women in all age groups. In both regions, prevalence of smokeless tobacco use by women increased with age; for men, prevalence was highest in the age groups 25–29 years and above 70 years. Trends were similar in urban and rural areas. The prevalence of smokeless tobacco use was generally lower among educated women, especially in Karnataka. Clear-cut trends in reduced prevalence with increasing education were not observed in all age groups among men. Muslim men in Karnataka showed a higher oyerall prevalence compared with Hindus, while in Uttar Pradesh, a higher proportion of Hindu men compared with Muslims used smokeless tobacco. The reverse trend was observed among women in the two states [data for other religions were based on too few numbers to be reliable]. Variations in prevalence according to family income did not follow any specific trend, but the prevalence was comparatively lower in both states among women with higher family income (Chaudhry, 2001).

(iv) *National Sample Survey Organisation*

The National Sample Survey Organisation conducted its fifth quinquennial nationwide survey of household consumer expenditure in India during 1993–94. Interviews were conducted in 115 354 households in 6951 villages and in 4650 urban blocks. Prevalence of use of chewing tobacco was 11.2% and 6.3% among men in rural and urban areas, respectively, and 3.9% and 2.0%, respectively, for women (Table 44) (National Sample Survey Organisation, 1998). The prevalence of tobacco use was underestimated because only one household respondant answered for all inhabitants of the household.

Table 44. Prevalence (%) by rural/urban area and sex of use of tobacco in various forms in India (National Sample Survey Organisation)

Form of tobacco consumption	Use	1987–88				1993–94			
		Rural		Urban		Rural		Urban	
		Men	Women	Men	Women	Men	Women	Men	Women
Chewing tobacco[a]	Regular	11.7	5.0	6.3	2.9	11.2	3.9	6.3	2.0
	Casual	1.3	0.6	1.0	0.4	1.4	0.5	0.9	0.3
Snuff	Regular	0.7	0.8	0.4	0.5	0.5	0.6	0.3	0.3
	Casual	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0
Burnt tobacco powder/paste	Regular	2.7	3.1	1.4	1.6	2.7	2.5	1.2	1.0
	Casual	0.3	0.2	0.2	0.1	0.3	0.1	0.1	0.1
Tobacco in any form	Regular	38.7	10.3	23.9	5.3	31.9	8.1	21.6	3.7
	Casual	1.6	0.8	1.8	0.6	1.7	0.7	1.6	0.3

From National Sample Survey Organisation (1998)
[a] Including betel quid with tobacco

Comparison of the data from 1987–88 and 1993–94 (National Sample Survey Organisation, 1998; Gupta & Sankar, 2004) revealed no significant change in overall use of smokeless tobacco during this period (Table 44). Other reports suggest that there has been a shift towards use by younger people and at a very early age. For example, the prevalence of *mawa* use rose from 4.7% in 1969, mainly among older women, to 19% in 1993–94, mainly among younger generations (Gupta, 2000); in a survey conducted among rural children in three states, snuff was ever used by 38% of boys and 12% of girls aged 10–20 years (Krishnamurthy *et al.*, 1997); a comparative study of the prevalence of tobacco use in a rural area in Bihar showed that the prevalence of total tobacco use remained the same between 1967 and 2000, but that there had been a remarkable shift towards the use of smokeless tobacco (Sinha *et al.*, 2003a).

(v) *Global Youth Tobacco Survey (GYTS) and Global School Personnel Survey (GSPS)*

The Global School Personnel Survey (developed by WHO/CDC) is a cross-sectional survey that employs a cluster sample design to produce a representative sample of school personnel drawn from the same schools that were selected for GYTS. All school personnel (including non-teaching staff) in the selected schools were eligible to participate (Sinha *et al.*, 2002).

In the eight northeastern states of India, daily use of smokeless tobacco among school personnel varied from 8.9 (Sikkim) to 49.4% (Mizoram) among men and from 1.6 (Manipur) to 80.3% (Mizoram) among women (Table 45) (Sinha *et al.*, 2003b). In five of the eight states, the prevalence of daily use of smokeless tobacco among men and women was similar. In the eastern region, daily use of smokeless tobacco among school personnel varied from 7.8 (West Bengal) to 58.7% (Bihar) in men and from 1.0 (West Bengal) to 53.4% (Bihar) in women (Sinha *et al.*, 2002, 2003b; Sinha & Gupta, 2004a; Sinha & Roychoudhury, 2004). The prevalence of use of each type of products is detailed in Table 46.

Smokeless tobacco use among students varied between states from 2.8 (Goa) to 55.6% (Bihar) (Table 47). Among boys, it varied from 2.7 (Delhi) to 57.6% (Bihar) and, among girls, from 2.1 (Goa) to 49.2% (Bihar). In 11 of 13 states, prevalences of smokeless tobacco use among boys and girls were similar; boys in Meghalaya and Uttaranchal reported significantly more smokeless tobacco use than girls (Arora *et al.*, 2001; Sinha & Gupta, 2002a,b; Sinha *et al.*, 2003c; Pednekar & Gupta, 2004; Sinha & Gupta, 2004b; Sinha *et al.*, 2004a).

The use of tobacco products as dentrifice among students aged 13–15 years varied widely between states (Table 48). The prevalence among boys compared with that among girls was notably higher in Orissa and Uttaranchal, marginally higher in nine states and marginally lower in three states. Of the specific products, tobacco toothpaste (creamy snuff) and tooth powder (*lal dant manjan*) were common in all 14 states; the prevalence of use ranged from 2 to 32% and from 2 to 29%, respectively. *Gul* was used in eight states and the prevalence of its use ranged from 2 to 6%. Other dentifrice products containing tobacco were: *mishri* and *bajjar* in Goa and Maharashtra; *gudhaku* in Bihar, Orissa, Uttar

Table 45. Prevalence (%) by state of current use of smokeless tobacco[a] among school personnel in the northeastern and eastern regions of India (Global School Personnel Survey, 2001)

Region	Sample size	Prevalence (± 95% CI)					
		Men		Women		Total	
		Daily	Occasional	Daily	Occasional	Daily	Occasional
Northeastern region							
Arunachal Pradesh	533	28.9 (± 8.8)	19.0 (± 11.9)	25.1 (± 20.0)	23.9 (± 13.0)	28.2 (± 5.3)	19.9 (± 8.7)
Assam	782	10.1 (± 3.2)	34.3 (± 6.6)	13.5 (± 9.4)	37.0 (± 14.2)	10.7 (± 3.7)	34.7 (± 5.9)
Manipur	395	21.8 (± 9.5)	53.2 (± 14.1)	1.6 (± 2.7)	74.2 (± 9.9)	14.2 (± 5.9)	61.1 (± 9.2)
Meghalaya	447	30.8 (± 10.5)	20.5 (± 6.4)	17.4 (± 14.0)	39.2 (± 13.4)	24.9 (± 8.7)	28.8 (± 4.7)
Mizoram	307	49.4 (± 10.5)	29.8 (± 12.0)	80.3 (± 13.8)	6.9 (± 6.2)	57.8 (± 8.8)	23.7 (± 8.0)
Nagaland	426	18.5 (± 6.5)	31.3 (± 10.2)	18.1 (± 20.2)	14.4 (± 6.6)	18.3 (± 10.2)	25.4 (± 8.5)
Sikkim	342	8.9 (± 4.3)	45.3 (± 14.3)	51.9 (± 12.0)	21.7 (± 11.3)	17.6 (± 6.7)	40.6 (± 10.6)
Tripura	562	38.3 (± 11.5)	17.2 (± 6.8)	6.8 (± 2.0)	17.7 (± 10.4)	31.2 (± 9.2)	17.5 (± 5.7)
Eastern region							
Bihar	637	58.7 (± 6.3)		53.4 (± 16.1)		57.3 (± 7.5)	
Orissa	517	28.1 (± 13.3)	16.9 (± 9.0)	5.0 (± 5.2)	3.4 (± 3.6)	24.2 (± 11.3)	14.6 (± 8.1)
West Bengal	663	7.8		1.0		5.8	

From Sinha *et al.* (2002; 2003b); Sinha & Gupta (2004a); Sinha & Roychoudhury (2004)
CI, confidence interval
[a] Including betel quid with tobacco

Table 46. Prevalence (%) by type of tobacco product of smokeless tobacco use by school personnel in the north-eastern states of India (Global School Personnel Survey, 2001)

	Prevalence (± 95% CI)							
	Arunachal Pradesh	Assam	Manipur	Meghalaya	Mizoram	Nagaland	Sikkim	Tripur
Betel quid	70.8 (± 9.6)	69.5 (± 6.4)	54.7 (± 9.6)	55.4 (± 4.4)	20.2 (± 3.7)	69.3 (± 5.5)	15.7 (± 7.6)	54.9 (± 8.5)
Gutka	4.1 (± 1.7)	8.6 (± 2.9)	17.9 (± 12.0)	5.1 (± 1.7)	24.8 (± 3.2)	8.3 (± 3.5)	34.4 (± 4.5)	21.0 (± 6.8)
Smokeless tobacco without areca nut	24.3	15.6	27.3	39.4	54.3	20.3	49.9	22.5
Khaini	17.3 (± 8.8)	7.0 (± 1.8)	14.7 (± 2.6)	9.1 (± 2.4)	22.3 (± 2.2)	15.9 (± 5.2)	18.9 (± 5.9)	10.7 (± 2.8)
Gul	0.4 (± 0.4)	2.2 (± 2.0)	3.3 (± 2.9)	12.0 (± 6.5)	16.4 (± 3.2)	2.6 (± 1.5)	15.0 (± 3.8)	1.1 (± 1.0)
Snuff	1.9 (± 1.8)	–	–	–	9.3 (± 1.7)	–	3.0 (± 2.2)	1.2 (± 1.0)
Tuibur	4.1 (± 1.5)	6.1 (± 2.3)	8.4 (± 2.9)	13.1 (± 4.4)	5.6 (± 1.9)	0.6 (± 0.5)	12.4 (± 1.8)	1.1 (± 0.6)
Others	0.6 (± 0.6)	0.3 (± 0.3)	0.9 (± 0.7)	5.2 (± 1.9)	0.7 (± 0.7)	1.2 (± 0.9)	0.6 (± 0.5)	8.4 (± 4.0)
Multiple use	0.8 (± 0.8)	6.3 (± 6.0)	–	–	0.6 (± 0.6)	2.0 (± 2.0)	–	1.7 (± 0.9)
Total (no.)	253	327	243	219	227	180	222	211

From Sinha *et al.* (2003b)
CI, confidence interval

Table 47. Prevalence (%) by state of current use of smokeless tobacco among students in India (Global Youth Tobacco Survey)

Category	Sample size	Prevalence (± 95% CI)		
		Boys	Girls	Total
Arunachal Pradesh	2314	35.0 (± 10.4)	40.2 (± 8.0)	37.2 (± 5.9)
Assam	2177	29.3 (± 5.7)	20.4 (± 5.5)	25.3 (± 5.2)
Bihar	2636	57.6 (± 8.6)	49.2 (± 11.5)	55.6 (± 7.5)
Delhi	1731	2.7 (± 1.2)	2.5 (± 1.7)	2.8 (± 1.2)
Goa	2256	3.3 (± 1.6)	2.1 (± 1.4)	2.8 (± 1.2)
Manipur	1743	51.5 (± 11.4)	40.1 (± 14.5)	46.1 (± 10.2)
Meghalaya	2080	43.0 (± 7.0)	26.8 (± 7.2)	35.3 (± 7.4)
Mizoram	2295	45.7 (± 5.1)	40.1 (± 6.0)	42.9 (± 4.4)
Nagaland	2221	52.5 (± 7.5)	47.2 (± 6.3)	49.9 (± 4.9)
Sikkim	2236	42.5 (± 7.0)	31.8 (± 4.6)	37.7 (± 3.7)
Tripura	1866	39.7 (± 10.4)	29.4 (± 11.2)	35.1 (± 8.7)
Uttaranchal	2641	20.8 (± 11.4)	11.5 (± 6.7)	17.6 (± 9.2)
Uttar Pradesh	4542	21.6 (± 7.1)	14.5 (± 8.3)	19.7 (± 6.3)

From Arora *et al.* (2001); Pednekar & Gupta (2004); Sinha *et al.* (2003c); Sinha & Gupta (2002a,b); Sinha & Gupta (2004b); Sinha *et al.* (2004a)
CI, confidence interval

Table 48. Prevalence (%) of application of tobacco products as dentifrice in 14 states in India (Global Youth Tobacco Survey, 2000–2002)

State	Prevalence (95% CI)			
	Toothpaste	*Gul*	Tooth powder	Others
Arunachal Pradesh	23 (18–27)	2 (1–3)	4 (2–5)	–
Assam	11 (9–14)	3 (1–5)	4 (3–6)	–
Bihar	10 (7–12)	6 (4–7)	49 (43–54)	4 (3–6)
Goa	2 (1–2)	–	2 (1–2)	3 (2–4)
Maharashtra	2 (1–3)	–	2 (1–3)	9 (7–12)
Manipur	25 (22–28)	–	2 (0–3)	5 (1–9)
Meghalaya	18 (12–25)	1 (0–1)	4 (2–5)	–
Mizoram	12 (9–15)	–	9 (6–12)	4 (2–7)
Nagaland	32 (23–40)	3 (2–4)	5 (4–7)	–
Orissa	10 (8–12)	1 (1–2)	25 (23–28)	4 (2–6)
Sikkim	8 (5–11)	–	2 (1–3)	1 (1–1)
Tripura	25 (19–31)	–	3 (1–4)	1 (1–2)
Uttar Pradesh	10 (8–12)	2 (1–3)	29 (24–33)	16 (9–22)
Uttaranchal	18 (14–21)	2 (1–3)	29 (26–32)	11 (5–16)

From Sinha *et al.* (2004b)
CI, confidence interval

Pradesh and Uttaranchal; and tobacco water (*tuibur*) in Manipur, Mizoram, Sikkim and Tripura (Sinha *et al.*, 2004b).

The current use of smokeless tobacco among the participants of the GSPS (Sinha *et al.*, 2003b) and GYTS (Sinha *et al.*, 2003c) surveys in eight of the states is detailed below.

Arunachal Pradesh

In Arunachal Pradesh, betel quid was the most popular form of smokeless tobacco among men (73.6%) and women (51.4%). *Khaini* was used exclusively by men (19.8%), while *tuibur* (32.6%) and snuff (15.2%) were used exclusively by women (Sinha *et al.*, 2003b).

Current use of smokeless tobacco was reported by 37.2% of students (35.0% of boys, 40.2% of girls), whereas smoking was reported by 22.8% (31.8% of boys, 8.3% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 55.2% and use exclusively in the form of application was reported by 28.8%. The remainder used several forms of smokeless tobacco. Among chewers, *gutka* was the most popular product (49.8%), followed by *tamol* and a tobacco mixture (31%). Among appliers, 79.7% applied tobacco toothpaste, 12.3% applied red tooth powder and 8% applied *gul* (Sinha *et al.*, 2003c).

Assam

In Assam, the most popular form of smokeless tobacco use among men was betel quid (75.5%), followed by *khaini* (7.9%) and *gutka* (7.8%). Among women, betel quid (36.3%) was commonest, followed by *tuibur* (35.7%), *gul* (13.5%) and *gutka* (13.4%). *Gul* and *tuibur* were used primarily by women (Sinha *et al.*, 2003b).

Current use of smokeless tobacco was reported by 25.3% of students (29.3% of boys, 20.4% of girls). Current smoking was reported by 19.7% of students (28.6% of boys, 8.9% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 48.5% and that exclusively in the form of application by 18.8%. The remainder used several forms of smokeless tobacco. Among chewers, *gutka* was the most popular product (54.4%), followed by *tamol* and a tobacco mixture (28.9%). Among appliers, 58.5% applied tobacco toothpaste, 25% applied red tooth powder and 16.3% applied *gul* (Sinha *et al.*, 2003c).

Manipur

In Manipur, betel quid (54.7%) was the most popular form of smokeless tobacco among both men and women. The prevalence of *gutka* use among men was higher (24.1%) than that among women (2.6%), while the prevalence of *khaini* use among women was higher (29.1%) than that in men (8.9%). *Tuibur* was used predominantly by women (27.5%) (Sinha *et al.*, 2003b).

Current smokeless tobacco use was reported by 46.1% (51.5% of boys, 40.1% of girls), whereas smoking was reported by 26.8% (40.8% of boys, 10.7% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 53.2% and that exclu-

sively in the form of application by 31.9%. The remainder used several forms of smokeless tobacco. Among chewers, *gutka* (23.7%) was the most popular product (17.9% of boys, 30.2% of girls), followed by *tamol* and a tobacco mixture (18.1% overall, 28.0% of boys, 6.8% of girls). Among appliers, 18.3% of boys and 32.6% of girls applied tobacco toothpaste (Sinha *et al.*, 2003c).

Meghalaya

In Meghalaya, betel quid (55.4%) was the most popular form of smokeless tobacco, followed by *tuibur* (13.1%), *gul* (12.0%) and *khaini* (9.1%). *Gul* and *tuibur* were used primarily by women (Sinha *et al.*, 2003b).

Current smokeless tobacco use was reported by 35.3% (43.0% of boys, 26.8% of girls), whereas smoking was reported by 21.4% (32.1% of boys, 9.9% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 55.2% (62.1% of boys, 47.7% of girls) and that exclusively in the form of application by 22.9% (28% of boys, 17.6% of girls). The remainder used several forms of smokeless tobacco. Chewing was mainly in the form of *gutka* (19.4%), *tamol* with tobacco (9.2%, > 80% of boys) and *tamol* without tobacco (21%). Tobacco was applied by 18.2% as tobacco toothpaste and by 3.9% as red tooth powder (Sinha *et al.*, 2003c).

Mizoram

In Mizoram, among smokeless tobacco users, 24.8% used *gutka*, 22.3% used *khaini*, 20.2% used betel quid, 16.4% used *gul* and 9.3% used snuff. The use of *gutka* and snuff was reported slightly more frequently among women while that of betel quid and *gul* was more frequent among men (Sinha *et al.*, 2003b).

Current smokeless tobacco use was reported by 42.9% (45.7% of boys, 40.1% of girls), whereas current smoking was reported by 34.5% (40.7% of boys, 28.2% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 60.7% and that exclusively in the form of application by 25.0%. The remainder used several forms of smokeless tobacco. Among chewers, use of *gutka* (20%) was reported to be the most popular, followed by *pan* with tobacco (12.9%). Among appliers, the majority preferred tobacco toothpaste (11.8%) (Sinha *et al.*, 2003c).

Nagaland

In Nagaland, betel quid (69.3%), *khaini* (15.9%) and *gutka* (8.3%) were the most prevalent forms of smokeless tobacco used. Betel quid was more common among women, whereas *khaini* was used almost exclusively by men (Sinha *et al.*, 2003b).

Current smokeless tobacco use was reported by 49.9% (52.5% of boys, 47.2% of girls), whereas smoking was reported by 29.6% (38.7% of boys, 19.7% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 62.4% and that exclusively in the form of application by 40%. The remainder used several forms of smokeless tobacco. Among chewers, 28.1% reported chewing *gutka* and 8% reported use

of *pan* with tobacco. Among appliers, the predominant form was tobacco toothpaste (31.7%) (Sinha *et al.*, 2003c).

Sikkim

In Sikkim, *gutka* was the preferred (34.4%) form of smokeless tobacco, followed by *khaini* (18.9%), betel quid (15.7%), *gul* (15.0%) and *tuibur* (12.4%). *Gutka*, *khaini* and *tuibur* were used mainly by men while betel quid and *gul* were used primarily by women (Sinha *et al.*, 2003b).

Current smokeless tobacco use was reported by 37.7% (42.5% of boys, 31.8% of girls), whereas smoking was reported by 23.6% (32.9% of boys, 12.1% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 48.3% and that exclusively in the form of application by 11.3%. Among chewers, *tamol* and tobacco mixture were reported to be the most popular (52.3%), followed by *gutka* (33.5%). Among appliers, 69.2% applied tobacco toothpaste, 21.4% applied red tooth powder and 9.4% applied *tuibur* (Sinha *et al.*, 2003c).

Tripura

In Tripura, betel quid was the most popular (54.9%) form of smokeless tobacco, followed by *gutka* (21.0%) and *khaini* (10.7%). Betel quid was more popular among men while *khaini* was more popular among women (Sinha *et al.*, 2003b).

Current smokeless tobacco use was reported by 35.1% (39.7% of boys, 29.4% of girls), whereas smoking was reported by 21.2% (28.6% of boys, 12.4% of girls). Smokeless tobacco use exclusively in the form of chewing was reported by 57.5% and that exclusively in the form of application by 28.8%. Among chewers, *gutka* was the most popular (21.3%), followed by *tamol* with tobacco (10.5%; 17.0% of boys, 2.6% of girls) and *tamol* without tobacco (23.0%; 23.7% of boys, 22.1% of girls). Thus, boys equally used *tamol* with tobacco or without tobacco, whereas girls preferred *tamol* without tobacco. Among appliers, the majority preferred tobacco toothpaste (25%) (Sinha *et al.*, 2003c).

(vi) *Type of tobacco used by sex and region*

Bhonsle *et al.* (1992) reviewed available data from the 1970s on the prevalence of smokeless tobacco use by type of tobacco. *Khaini* use among men ranged from < 0.5% (Andhra Pradesh) to 44% (Bihar); that among women ranged from < 0.5 (Gujarat, Kerala) to 10% (Jharkhand). Chewing tobacco leaf varied among men from < 0.5 (Bihar, Goa, Gujarat, Jharkhand) to 9% (Andhra Pradesh) and among women from < 0.5 (Gujarat, Jharkhand) to 2% (Andhra Pradesh, Kerala). Applied tobacco (*bajjar* and *gudhaku*) was used by 1% of men and by 14–16% of women in Gujarat and Jharkhand (Tables 49 and 50; Bhonsle *et al.*, 1992).

Among 6271 school children in Goa (western India), 731 were tobacco users. Of these, 56% of boys and 66% of girls used *mishri* and almost half in both groups used creamy snuff (Table 51) (Vaidya *et al.*, 1992). Among 9097 adults (≥ 15 years) in a rural site in Bihar (eastern India), one third (32.7%) used smokeless tobacco, of whom 11.4%

Table 49. Prevalence of use of smokeless tobacco and other chewing products among men in selected states in India

	Gujarat		Kerala		Andhra Pradesh		Jharkhand		Bihar		Goa	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Pan with tobacco	101	2	1640	33	245	4	84	2	301	6	144	6
Pan without tobacco	242	5	15	< 0.5	134	3	–	–	–	–	48	2
Khaini	300	6	–	–	2	< 0.5	1308	27	2149	44	–	–
Tobacco leaf	30	< 0.5	104	2	484	9	9	< 0.5	6	< 0.5	12	< 0.5
Bajjar	52	1	–	–	–	–	–	–	–	–	–	–
Gudhaku	–	–	–	–	–	–	54	1	–	–	–	–
Areca nut	68	1	–	–	–	–	3	< 0.5	184	4	–	–
Multiple products	7	< 0.5	–	–	3	< 0.5	35	< 0.5	24	< 0.5	–	–
No chewing practice	4427	85	3152	64	4481	84	3307	69	2192	45	2311	92
Total	5227		4911		5349		4800		4856		2515	

From Bhonsle *et al.* (1992)

Table 50. Prevalence of use of smokeless tobacco and other chewing products among women in selected states in India

	Gujarat		Kerala		Andhra Pradesh		Jharkand		Bihar		Goa	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Pan with tobacco	1	< 0.5	1881	35	135	3	71	1	96	2	780	27
Pan without tobacco	6	< 0.5	41	< 0.5	25	< 0.5	–	–	–		131	4
Khaini	5	< 0.5	3	< 0.5	–	–	512	10	371	7	–	–
Tobacco leaf	5	< 0.5	118	2	116	2	7	< 0.5	–		18	1
Bajjar	666	14	–	–	–	–	–	–	–		–	–
Gudhaku	–	–	–	–	–	–	833	16	–		–	–
Areca nut	12	< 0.5	2	< 0.5	–	–	1	< 0.5	68	1	–	–
Multiple products	–	–	–	–	2	< 0.5	23	< 0.5	–		–	–
No chewing practice	4149	86	3331	62	4542	94	3801	72	4946	90	2005	68
Total	4844		5376		4820		5248		5481		2934	

From Bhonsle *et al.* (1992)

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used *khaini* and 18.9% used tooth powder that contained tobacco (Table 52) (Sinha *et al.*, 2003a).

Table 51. Prevalence of use of different types of tobacco among schoolchildren in Goa, India

Tobacco product	Boys		Girls	
	No.	%	No.	%
Smoking	13	3	5	2
Mishri	256	56	177	66
Creamy snuff	212	46	128	47
Chewing	66	14	36	13
Single	388	84	219	81
Multiple	73	16	51	19
Total	461	100	270	100

From Vaidya *et al.* (1992)

Table 52. Prevalence of use (%) of different types of tobacco among adults (≥ 15 years) in Bihar, India

Tobacco type	Women	Men	Total
Non-user	55.0	25.9	39.6
Smoked tobacco	23.4	31.6	27.7
Bidi	84.1	82.0	82.9
Others	15.9	18.0	17.1
Smokeless tobacco	21.7	42.6	32.7
Tobacco tooth powder	41.3	8.8	18.9
Khaini	20.0	7.5	11.4
Pan masala	12.1	57.1	43.1
Others	26.6	26.6	26.6
Total (no.)	2586	2910	5496

From Sinha *et al.* (2003a)

A population-based cross-sectional survey was conducted in the city of Mumbai among 99 598 individuals aged 35 years and older during 1992–94 (Gupta, 1996). A high percentage of women used tobacco (57.5%), almost solely in the smokeless form. About one fifth (20%) of the population (26.5% of women; 10.3% of men) used *mishri* alone and 3.7% (1.1% of women; 7.5% of men) used tobacco leaf and lime (Table 53).

Table 53. Prevalence of use of smokeless tobacco and other chewing products in Mumbai, India

	Women		Men		Total	
	No.	%	No.	%	No.	%
Multiple tobacco practices	2013	3.3	2993	7.4	5006	5.0
Mishri	15 740	26.5	140	10.3	19 880	20.0
Mishri + betel quid with tobacco	10 687	18.0	4976	12.4	15 663	15.7
Betel quid with tobacco	3527	5.9	5871	14.7	9398	9.4
Khaini	640	1.1	2997	7.5	3637	3.7
Others with tobacco	1200	2.0	1144	2.9	2344	2.4
Areca nut without tobacco[a]	306	0.5	176	0.4	482	0.5
No chewing practice	25 414	42.7	17 774	44.4	43 188	43.4
Total	59 527	100	40 071	100	99 598	100

From Gupta (1996)

[a] Most frequently as betel quid without tobacco

Among 539 patients who entered hospital in Kerala and were recruited as controls for a case–control study, seven reported use of nasal snuff (Sankaranarayanan *et al.*, 1989a).

(*d*) *Indonesia*

In Indonesia, smokeless tobacco is used mainly as part of a betel quid and mostly in rural areas. Betel quid with tobacco and chewing tobacco were identified as smokeless tobacco products used by a small number of respondents both in Jakarta and Sukabumi. Of 5899 tobacco users, less than 0.5% (22 persons) had used chewing tobacco (Sinha, 2004).

(*e*) *Malaysia*

A cross-sectional survey was conducted to document the use of smokeless tobacco among Kadazan women in a rural area in the state of Sabah, East Malaysia (Gan, 1995). Of the 472 women interviewed, 328 chewed; 60% of all women included tobacco as an ingredient in their chew, while 10% did not. Tobacco with lime was used by 2.3% of women and tobacco only by 1.1%. Women with a low education were more likely to be chewers. The chewing practice was usually acquired during the teenage years and was perceived mainly as a cultural norm. The majority of tobacco chewers (46.3%) used three or four fresh preparations per day. Tobacco use increased with increase in age (Table 54).

In a similar survey among the indigenous people of Sabah State, 845 Bajaus (414 men, 431 women) were interviewed (Gan, 1998). Of these, 74.4% of men smoked compared with 3.3% of women and 77% of women used smokeless tobacco compared with 4.3% of men. Tobacco was commonly used in the form of a betel quid. Among chewers,

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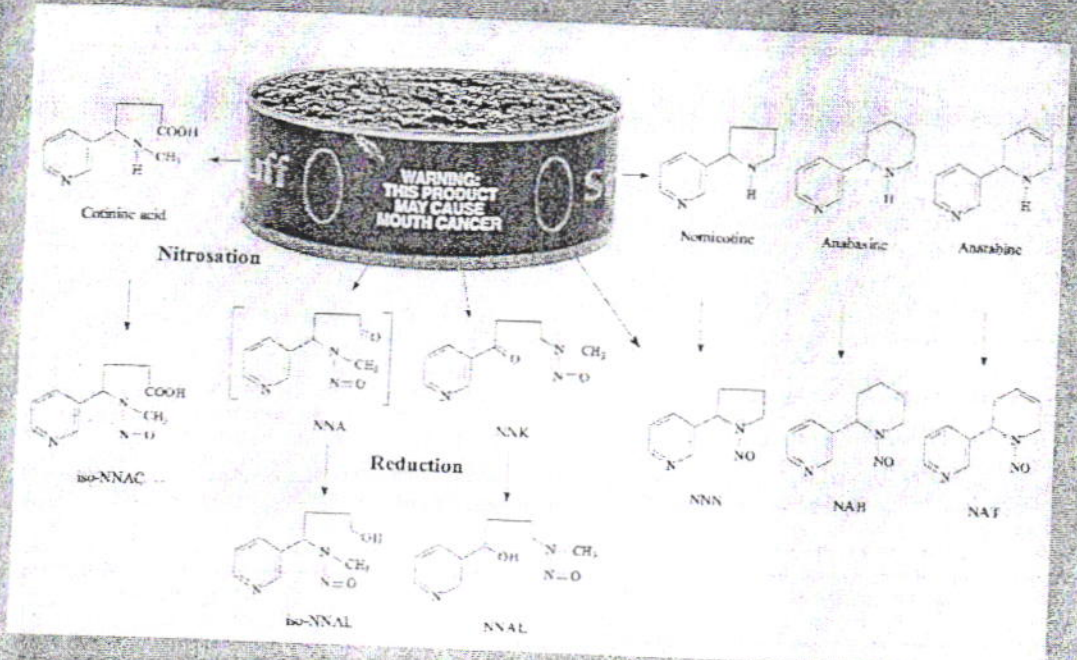

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2007

(c) Other provisions

Other provisions that are not regulated in a majority of countries in Africa include sale by minors in 32 countries (70%), sales of tobacco to minors in 29 countries (63%) (verification of age at the point of sale is not enforced in any African country), free products in 31 countries (67.3%), brand-stretching in 27 countries (58.7%), misleading information on packaging in 32 countries (70%), place of sale in 31 countries (67%), health warnings and messages in 25 countries (54.3%) and the indication of the amount of contents or constituents other than tar and nicotine on packaging in 32 countries (69%) (Shafey *et al.*, 2003).

In Uganda, excise tax on tobacco use was increased by 45% in 1993 (WHO, 1997).

None of the African countries is known to have constituted a National Tobacco Control Committee, none requires constituent disclosures for public or confidential use and none has provisions to enable litigation or measures to reduce the smuggling of tobacco.

2. Studies of Cancer in Humans

2.1 Introduction

Studies that have investigated the association between the use of smokeless tobacco and cancer have often faced a problem of small numbers of cases, which has often precluded an analysis of specific and relevant subgroups; alternatively, when such analyses were carried out, they resulted in imprecise relative risk estimates. This is of particular concern in relation to specific cancer sites, and also to an analysis of categories of smokeless tobacco use as well as to stratification for cigarette smoking and alcoholic beverage consumption. As an example, associations with smokeless tobacco use should preferably have been analysed in never smokers. In making its evaluation, the Working Group gave greatest weight to studies that adequately addressed potential confounding by smoking. In addition, of the studies that were reviewed previously (IARC, 1985), only those that addressed such potential confounding have been included and re-evaluated in this monograph.

The Working Group also considered the possibility of confounding by human papillomavirus (HPV), since there is sufficient evidence in humans that HPV 16 causes cancer of the oral cavity and oropharynx (IARC, 2007). In a systematic review of the detection of HPV DNA in squamous-cell carcinoma of the head and neck, the prevalence of HPV was only 24% in oral and 36% in oropharyngeal cancer (Kreimer *et al.*, 2005), which limits the proportion of cases that can be attributed to this virus. Moreover, negative associations between HPV DNA, tobacco smoking and alcoholic beverage consumption (Gillison *et al.*, 2000) and between HPV, tobacco smoking and *pan* chewing (Herrero *et al.*, 2003) have been observed. Therefore, the Working Group concluded that positive confounding by HPV is unlikely to account for a strong association of these cancers with tobacco chewing.

In this section, case series studies are generally included only if no analytical studies were available from that region or when cancer at the site where the smokeless tobacco was placed was considered.

2.2 Oral use

2.2.1 *Cancer of the oral cavity and pharynx*

The characteristics of cohort studies are summarized in Table 69 and results from these studies on oral and pharyngeal cancer are presented in Table 70.

The design and results of case–control studies on use of smokeless tobacco and cancer of the oral cavity and pharynx are summarized in Table 71.

(*a*) *North and South America*

(i) *Cohort studies*

The US Veterans cohort comprised 293 958 veterans who served in the US Armed Forces during 1917–40, were aged 31–84 years in 1953 and held US government life insurance policies in 1953 (Zahm *et al.*, 1992). Most policy holders were men (99.5%) and nearly all were white. The results on smokeless tobacco were based on 248 046 (84%) veterans who responded to the questionnaire mailed in 1954 or the questionnaire mailed in 1957 to 1954 non-respondents. The cohort was followed up for vital status from 1954 (or 1957) through to 1980, and follow-up was 96% complete; death certificates were available for 97% of the deceased cohort members and identified 129 deaths from oral cancer. The relative risk for oral cancer (ICD-7 140-144) was 3.0 (95% CI, 2.0–4.5) for users of chewing tobacco or snuff and those for infrequent use and frequent use were 1.9 (95% CI, 1.0–3.5) and 3.4 (95% CI, 2.1–5.6), respectively. The corresponding relative risks for the pharynx were 8.7 (95% CI, 4.1–8.3), 4.5 (95% CI, 1.7–11.7) and 11.2 (95% CI, 5.0–25.0), respectively. For early age at first use (≤ 14 years of age), the relative risk was 20.7 (95% CI, 8.0–53.7). [The Working Group noted that the results were not adjusted for tobacco smoking or alcoholic beverage consumption.]

NHANES I was a national probability sample survey of the non-institutionalized US population that oversampled the elderly, poor and women of childbearing age (Accortt *et al.*, 2002). A total of 14 407 adults, aged 25–74 years, underwent health examinations between 1971 and 1975. Of the participants, 13 861 persons (96%) were successfully traced in at least one of the NHANES I Epidemiological Follow-up Studies (NHEFS) in 1982–84, 1986, 1987 or 1992. Death certificates were available for 98% of the decedents. A random sample of 3847 of the cohort was asked about smokeless tobacco use at baseline. In the 1982–84 follow-up, information on smokeless tobacco use was obtained to infer baseline behaviour for study participants who were not part of the original random sample. Participants were considered to be users of smokeless tobacco if they currently used smokeless tobacco at baseline or had ever used it according to the 1982–84 questionnaire. The analysis was restricted to the 6805 black and white subjects, aged 45 years and

Table 69. Descriptions of cohort studies of smokeless tobacco use

Location Reference, name of cohort	Cohort description	Assessment of smokeless tobacco use	Follow-up and outcome	Neoplasms reported (no.)
North America				
Hsing *et al.* (1990), Kneller *et al.* (1991), Zheng *et al.* (1993), Lutheran Brotherhood cohort	26 030 white men aged ≥ 35 years who purchased life insurance from Lutheran Brotherhood Insurance Society, mostly from California, upper Midwest and northeastern USA	17 818 (68.5%) responded to mailed questionnaire; few differences among responders and non-responders in demographic characteristics	Vital status follow-up, 1966–86, 4027 (23%) lost to follow-up, death certificates coded to ICD-9	Pancreas (54) (after exclusion of 3 deaths) Stomach (75) Prostate (149)
Hsing *et al.* (1991), Zahm *et al.* (1992), Heineman *et al.* (1995), US Veterans' cohort	283 958 veterans who served in US Armed Forces during 1917–40 and who were aged 31–84 years in 1953 and held US government life insurance policies, 99.5% of policy holders were men, nearly all were white.	248 046 (84%) responded to the 1954 mailed questionnaire or the 1957 questionnaire mailed to 1954 non-respondents on use of chewing tobacco or snuff; 48 304 used smokeless tobacco, 2308 used smokeless tobacco only	Follow-up 1954–80 (96% complete), death certificates coded according to ICD-7 (97% complete)	Oral cavity and pharynx (129 exposed) Colorectum (838) Prostate (1123) Soft-tissue sarcoma (119)
Putnam *et al.* (2000), Iowa cohort	1601 controls from a case–control study of cancer in Iowa, ascertained from 1986–89 via RDD and HCFA, resident in Iowa, aged 40–86 years, with no prior cancer; exclusion of 24 subjects with proxy respondents (n = 1577)	Mailed questionnaire supplemented by telephone interviews	Vital status follow-up through to 1995 (3 subjects lost); follow-up for prostate cancer incidence through state cancer registry	Prostate (101), after exclusion of the cases diagnosed prior to return of questionnaire
Accort *et al.* (2002), NHANES I Follow-up cohort	Survey of the non-institutionalized US population who underwent a physical health examination in 1971–75; oversampling of the elderly, poor and women of childbearing age, aged 25–74 years (n = 14 407); analysis restricted to white and black subjects, aged 45–75 years at baseline (n = 6805)	In-person interviews of a random sample (n = 3847) on smokeless tobacco use at baseline or in first NHANES I epidemiological follow-up study (NHEFS)	13 861 persons (96%) successfully traced in at least one follow-up survey of the NHEFS in 1982–84, 1986, 1987 and 1992; death certificates available for 98% of the decedents; coded according to ICD-9	Oral cavity (19) Digestive system (NA) Lung (NA)

Table 69 (contd)

Location Reference, name of cohort	Cohort description	Assessment of smokeless tobacco use	Follow-up and outcome	Neoplasms reported (no.)
Chao *et al.* (2002), Henley *et al.* (2005), CPS-II	508 351 men and 676 306 women, aged ≥ 30 years, residing in a US household in which at least one member was 35 years or older (45 years or older for Chao *et al.*, 2002); analysis restricted to men without prior cancer (except non-melanoma skin cancer) at enrolment and with information on tobacco (n = 467 788) (Chao *et al.*, 2002) or restricted to men who never used any other tobacco (Henley *et al.*, 2005)	Questionnaire at enrolment; only men were asked about smokeless tobacco.	Vital status follow-up, 1982–2000 (1996 for Chao *et al.*, 2002); 0.2% lost to follow-up; death certificates coded to ICD-9 (98.9% complete)	Oral cavity and pharynx (46) Digestive system (1999) Stomach (996) Lung (418)
Henley *et al.* (2005), CPS-I and CPS-II	456 487 men and 594 544 women (CPS-I), aged ≥ 30 years, residing in a household in which at least one member was ≥ 35 years old; analysis restricted to men without prior cancer (except non-melanoma skin cancer) at enrolment and who never used any other tobacco.	Questionnaire at enrolment	Vital status follow-up, 1959–72; 6.7% lost to follow-up and 4.9% with follow-up truncated for logistic reasons in 1965; death certificates coded to ICD-7 (97% complete)	Oral cavity and pharynx (13) Digestive system (913) Lung (134)
Europe				
Heuch *et al.* (1983), Boffetta *et al.* (2005), Norwegian cohort	Probability sample of general adult population of Norway from 1960 census and relatives of migrants to the USA, alive on 1 January 1966 (n = 12 431)	Mailed questionnaires on lifestyle habits in 1964 and 1967; information on smokeless tobacco available for 10 136 men	Follow-up for cancer incidence via cancer registries, 1966–2001 (99.85% complete)	Oral cavity and pharynx (34) Oesophagus (27) Stomach (217) Pancreas (105) Lung (343) Kidney (88) Bladder (238)

CPS, Cancer Prevention Study; HCFA, Health Care Financing Administration; NA, not available; NHANES, National Health and Nutrition Examination Survey; RDD, random-digit dialling

Table 70. Results of cohort studies on use of smokeless tobacco and cancer of the oral cavity and pharynx

Location Reference, name of cohort	Use of smokeless tobacco	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders; comments
North and South America				
Zahm *et al.* (1992), US Veterans cohort			Oral cavity (ICD-7 140–144)	
	Never used any tobacco products		1.0	
	Used chewing tobacco or snuff	74	3.0 (2.0–4.5)	
	Infrequent use		1.9 (1.0–3.5)	
	Frequent use		3.4 (2.1–5.6)	
			Pharynx	
	Never used any tobacco products		1.0	
	Used chewing tobacco or snuff	55	8.7 (4.1–18.3)	
	Infrequent use		4.5 (1.7–11.7)	
	Frequent use		11.2 (5.0–25.0)	
	Age at first use ≤ 14 years		20.7 (8.0–53.7)	
Accort *et al.* (2002), NHANES I Follow-up cohort			**SMR**	
	Ever smokeless tobacco use	2	107 (10–308)	
	Exclusive smokeless tobacco use	0	0 (0–580)	0.8 expected
Henley *et al.* (2005), CPS-I and CPS-II			Oral cavity and pharynx (ICD-7 140–148)	Multivariate, adjusted results for men who never used other tobacco products
		CPS-I		
	Never used smokeless tobacco	9	1.0	
	Current use of smokeless tobacco	4	2.0 (0.5–7.7)	
			Oral cavity and pharynx (ICD-9 140–148)	
		CPS-II		
	Never used smokeless tobacco	45	1.0	
	Current use of smokeless tobacco	1	0.9 (0.1–6.7)	
	Former use of smokeless tobacco	0		
Europe				
Boffetta *et al.* (2005), Norwegian cohort			Oral cavity and pharynx (ICD-7 141–148)	
	Never user	25	1.0	
	Ever used smokeless tobacco	9	1.1 (0.5–2.4)	Adjusted for age and smoking
	Current use of smokeless tobacco	6	1.1 (0.5–2.8)	
	Former use of smokeless tobacco	3	1.0 (0.3–3.5)	

CI, confidence interval; CPS, Cancer Prevention Study; NHANES, National Health and Nutrition Examination Survey; SMR, standardized mortality ratio

Table 71. Case–control studies on use of smokeless tobacco and cancer of the oral cavity and pharynx

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North and South America									
Williams & Horm (1977), USA, 1969–71		Cancer of the oral cavity from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Personal interview	Smokeless tobacco Moderate use Heavy use	*Men* 8 3	*Cancer of gum and mouth* 3.9 ($p < 0.01$) 6.7	Age, race, smoking	
					Moderate use Heavy use	1 2	*Cancer of lip and tongue* 0.4 1.9		
					Moderate use Heavy use	2 –	*Cancer of the pharynx* 0.5 –		
Winn *et al.* (1981a,b, 1984); Blot *et al.* (1983); Winn (1986), North Carolina, USA, 1975–78	ICD-8 141, 143–146, 148	Oral and pharyngeal cancer from hospitals discharge diagnoses (156 women) or death certificates (99 women); response rate, 91%	410 (2 per case) matched by age, race, residence, source (hospital or death certificate); excluding mental disorders, cancer of the oesophagus or larynx and other oral or pharyngeal diseases; response rate, 82%	Self- and next-of-kin interviews	Snuff user, nonsmoker	*White women* 79 *Black women* 12	4.2 (2.6–6.7) 1.5 (0.5–4.8)	Poor dentition (Winn *et al.*, 1981b), use of mouthwashes (Blot *et al.*, 1983), fruit and vegetables (Winn *et al.*, 1984), type of respondent (Winn, 1986)	
					Years of snuff use in non-smokers 0 1–24 25–49 ≥ 50	 2 3 10 15	*Cancer of gum and buccal mucosa* 1.0 13.8 (1.9–98.0) 12.6 (2.7–58.3) 47.5 (9.1–249.5)		
					0 1–24 25–49 ≥ 50	*Cancer of other mouth and pharynx* 22 3 14 8	1.0 1.7 (0.4–7.2) 3.8 (1.5–9.6) 1.3 (0.5–3.2)		

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stockwell & Lyman (1986), Florida, USA, 1982	ICD-O 140–149	1920 incident cancers of the lip, tongue, salivary glands, gum, floor of mouth, other parts of mouth, oropharynx, hypopharynx, pharynx (unspec.), nasopharynx, from population-based Florida cancer registry; overall response rate in case group, 82%	6457 cancers of the colon or rectum, cutaneous melanoma, endocrine neoplasias from same source during same time period; response rate, 78%	Information on tobacco use was obtained by chart and histopathology review at reporting institutions; only primary type of tobacco used was recorded	Unspecified		*Lip and tongue* 2.3 (0.2–12.9) *Salivary gland* 5.3 (1.2–23.4) *Mouth and gum* 11.2 (4.1–30.7) *Pharynx* 4.1 (0.9–18.0) *Nasopharynx* 5.3 (0.7–41.6)	Age, sex, race, tobacco use	
Blot *et al* (1988), New Jersey, Atlanta metropolitan area, Santa Clara and San Mateo counties, Los Angeles, USA, 1984–85	ICD 141–149, excluding 142 and 147	1114 incident, pathologically confirmed from population-based cancer registries; all black and white cases, aged 18–79 years; response rate, 75%	1268, RDD for controls aged 64 and younger, HCFA for controls aged 65 and older; frequency-matched on age, sex, race; response rate, 76%	Structured questionnaire interview in home by trained interviewers; next of kin for 22% of cases and 2% of controls	Use of smokeless tobacco	*Men* 46 *Women* 11 *Nonsmoking women* 6	[0.85] [3.4] 6.2 (1.9–19.8)	Age, race, study location, respondent status	Nearly all male tobacco chewers were smokers. Female nonsmokers primarily used snuff rather than chewing tobacco. All six cases had oral cavity cancer
Spitz *et al* (1988), Houston, TX, USA, 1985–87		185 patients (131 men, 54 women), 19–95 years old, at MD Anderson Hospital, histologically confirmed squamous-cell carcinoma of the tongue (25), floor of mouth (14), other parts of the oral cavity (27), orohypopharynx (15), larynx (50); white US residents; response rate not stated	185 patients at MD Anderson Hospital during the same period, randomly selected, frequency-matched on age (± 5 years) and sex, excluding patients with squamous-cell carcinoma of any site; response rate not stated	Self-administered questionnaire as part of the registration procedure	Chewing tobacco Snuff use	23 9	[1.0] 3.4 (1.0–10.9)		All nine snuff dipping cases drank alcohol, seven also chewed tobacco, eight smoked cigarettes and one smoked cigars and pipes; three of four snuff dipping controls also smoked cigarettes

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Franco *et al* (1989), São Paulo, Curitiba and Goiânia, Brazil, 1986–88	ICD-9 141, 143–145	232 histologically confirmed, invasive carcinomas of the tongue, gum, floor of mouth and other parts of the oral cavity, from 3 hospitals in São Paulo, Curitiba and Goiânia, response rate, 98.3%	464 (2 per case) from same or neighbouring general hospitals; individually matched on sex, 5-year age group and trimester of hospital admission, excluding diagnoses of neoplasms or mental disorder	Cases interviewed using structured questionnaire in hospital, controls privately; no proxy respondents	Unspecified	9	[1.4]		Relative risk independent of tobacco smoking and alcohol drinking (data not shown)
Maden *et al* (1992), Washington State, USA, 1985–89	ICD-O 141, 143–146	131 in-situ and invasive squamous-cell cancers of the lip (10), tongue (46), gum, floor of mouth (20), unspecified mouth and oropharynx (33), men aged 18–65 years; response rate, 54.4%	136 identified by RDD, frequency-matched on gender, year of diagnosis and age (5-year groups), response rate, 63%	In-person questionnaire interview at home or elsewhere	Unspecified	19	4.5 (1.5–14.3)	Age	
Marshall *et al* (1992), New York counties, USA, 1975–83		290 histologically confirmed oral and pharyngeal cancer (tongue, 28%; floor of mouth, 14%, oropharynx, 22%, hypopharynx, 13%), excluding black race from 20 hospitals in three New York counties, 513 contacted, 290 (56%) participated	290 individually matched on age (± 5 years), sex and neighbourhood, response rate, 41%	Interview	Snuff and chewing tobacco		'Increased risk (statistically non-significant)'	Matching variables	Data not shown

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mashberg *et al.* (1993), New Jersey, USA, 1972–83		359 male black or white in-situ or invasive squamous-cell carcinoma of the oral cavity and oropharynx (histologically diagnosed) admitted to Veterans hospital in New Jersey; 94% of study subjects enroled between 1977 and 1982; response rate not stated	2280 from same series of patients with biopsied oral lesions without cancer or dysplasia of the oesophagus, pharynx, larynx, lung; response rate not stated	In-hospital questionnaire interview	Smokeless tobacco Chewing tobacco ever Snuff use ever	52	1.0 (0.7–1.4) 0.8 (0.4–1.9)	Age, race, tobacco smoking, alcohol, further adjustments for religion, occupation, origin and interviewer did not 'modify materially' the odds ratio	No dose-response by duration of use (data not shown)
Spitz *et al.* (1993), Houston, TX, USA, 1987–91		108 white patients from MD Anderson Hospital with histologically confirmed cancers of the oral cavity (44), pharynx (31) and larynx (33), response rate not stated	108 blood and platelet donors, frequency-matched by age (± 5 years), sex, race and with no history of cancer; response rate not stated	Self-administered questionnaire in hospital	Chewing tobacco		1.2 'not statistically significant'		Data not shown
Kabat *et al.* (1994), USA, 1977–90		1560 cases from 28 hospitals in eight cities with incident, histologically confirmed cancers of the tongue, floor of mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil, other pharynx, response rate not stated	2948 individually matched on hospital, admission within 2 months after case, age, sex, race, with diseases not thought to be associated with tobacco or alcohol and no prior history of tobacco-related cancers; 50% cancers, 7% benign neoplasms, 43% non-neoplastic conditions; response rate not stated	In-hospital questionnaire interview	Chewing tobacco Snuff use	*Men* 4 *Women* 4	2.3 (0.7–7.3) 34.5 (8.5–140.1)	Among never smokers Among never smokers	Less than 2% of women chewed Among never-smoking women, there were no tobacco chewers, less than 2% of men and women used snuff. Among never-smoking men, 0 of 82 cases and 0.9% of 444 controls used snuff.

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Muscat *et al* (1996), Illinois, Michigan, New York, Philadelphia, USA, 1981–90	ICD-9 141, 143–146, 148, 149	1009 (687 men, 322 women) hospital patients with incident, histologically confirmed cancers of oral cavity and pharynx; aged 21–80 years; response rate, 91%	923 (619 men, 304 women) hospital patients with conditions unrelated to tobacco use, matched by sex, age (± 5 years), race, date of admission (± 3 months); response rate, 97%	In-hospital questionnaire interview	Chewing tobacco: at least once a week for 1 year or more	*Men* 38 *Women* 0	[1.04]		
					Snuff use: at least once a week for 1 or more years	*Men* 9 *Women* 2	[0.81] [1.9]		
Schwartz *et al* (1998), Seattle area counties, WA, USA, 1990–95		284 (165 men, 119 women) from population-based cancer registry with histologically confirmed incident in-situ or invasive (92%) squamous-cell cancers of the tongue, gum, floor of mouth, unspecified mouth, tonsils, oropharynx; aged 18–65 years; response rate, 63.3%	477 (302 men, 175 women) from random digit dialling, frequency matched on sex and age; 3:2 ratio controls to cases; response rate, 60.9%	In-person questionnaire interview	Unspecified	*Men* 11	1.0 (0.4–2.3)		Only one female control used smokeless tobacco
Europe									
Wynder & Wright (1957), Stockholm, Sweden, 1952–55		477 (265 men, 212 women) patients with squamous-cell cancer of lip (15), gingiva (36), tongue (70), buccal mucosa (18), maxillary sinus (45), nasopharynx (40), hypopharynx (116), oesophagus (74), larynx (63)	333 patients from same hospital with other cancers	Interview	Duration of snuff use		Gingiva, buccal mucosa, –2* (non-significant) Other upper aerodigestive tract, 'no association'	Tobacco smoking similar to that in controls Tobacco smoking higher than in controls	*Ridit analysis Cancers often where quid was placed

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Blomqvist *et al.* (1991), Sweden		61 (57 men, four women) patients with squamous-cell cancer of the lower lip from one surgery department	61 age- and sex-matched hospital patients without prior diagnosis of cancer	Interview	Use of snuff	2*			*2 cases and 2 controls used snuff only. No details on mixed tobacco users provided
Lewin *et al.* (1998), Stockholm and southern Sweden, 1988–91		605 men from hospitals and cancer registries with head and neck cancer, oral cavity (128), pharynx (138), larynx (157), oesophagus (123), 40–79 years old, response rate, 90%	756 controls from the population registry, stratified by region and age, response rate, 85%	Personal interviews conducted by two specially trained nurses			*Head and neck* 1.0 (0.6–1.6) 1.2 (0.7–1.9) 1.6 (0.9–2.6) 3.3 (0.8–12.0) 10.5 (1.4–117.8) *Oral cavity* 1.0 (0.5–2.2) 1.8 (0.9–3.7) 1.7 (0.8–3.9) *Pharynx* 0.7 (0.3–1.5) 0.8 (0.3–1.9)	Age, region, smoking, alcoholic beverage consumption	
					Current snuff use Former snuff use > 50 g/week *Never smokers* Current snuff use Former snuff use	43 40 38 9			
					Current snuff use Former snuff use > 50 g/week	10 15			
					Current snuff use Former snuff use	8 7			
Schildt *et al.* (1998), northern Sweden, 1980–89	ICD-7 140, 141, 143–145	418 (175 alive, 235 deceased with relatives) reported to cancer registries with squamous-cell cancer. 354 matched pairs (237 men, 117 women) analysed	From population registry; matched by age, sex, county, vital status and year of death for deceased cases	Postal questionnaire			*Oral cancer* 0.8 (0.5–1.3) 0.7 (0.4–1.1) 1.5 (0.8–2.9) 0.7 (0.4–1.2) 1.8 (0.9–3.5) *Lip cancer* 'Close to unity' 1.8 (0.9–3.7)	Matching variables	'Ever use' also adjusted for smoking and alcoholic beverage consumption
					Ever use of snuff Current snuff use Former snuff use *Never smokers* Current snuff use Former snuff use	39 28 19 9			
					Current snuff use Former snuff use				

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Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
India and Pakistan									
Chandra (1962), India, 1955–59		450 cancers of the buccal mucosa registered in a hospital in Calcutta	500 friends or relatives who came to hospital with the patients, approximately age-matched	[Not reported]	Tobacco chewing	*Men*			Not specified if tobacco product chewed was tobacco only or tobacco with lime
					No		1		
					Yes	18	[2.7]		
						Women			
					No		1		
					Yes	5	[2.5]		
Wahi *et al* (1968), India, 1964–66		346 oral and oro-pharyngeal cancers reported to temporary cancer registry in Uttar Pradesh	10% cluster sample of the district population	Interview			**Period prevalence rate**		*Sun-cured tobacco leaf used with or without lime
					Non-chewers of tobacco		0.36/1000		
					*Patiwala** chewer	84	1.17/1000		
Jafarey *et al* (1977), Pakistan, 1967–72		1192 histologically diagnosed cancers of oral cavity or oropharynx	3562 controls matched for age, sex, place of birth	[Not reported]	Tobacco chewing	*Men*			
					No		1		
					Yes	27	[10.4]		
						Women			
					No		1		
					Yes	39	13.7		
Goud *et al* (1990), India, 1972–75		102 oral cancers from one hospital in Varanesi	102 age- and sex-matched patients from surgical and general wards of same hospital	Questionnaire	**Chewing tobacco**				Not clear whether *khaini* and *zarda* were chewed with or without betel quid
					Khaini	35	[2.1]		
					Zarda	36	[3.7]		
					Khaini and *zarda*	8	[2.8]		
Wasnik *et al* (1998), India [years of study not reported]		123 (73 men, 50 women) histologically confirmed 'oro-pharyngeal' cancers from three hospitals in Nagpur	246 pair-matched controls; 123 non-cancer patients and 123 patients with cancer at other sites, matched for age, sex	[Not reported]	Tobacco chewing	24	11.4 (4.4–29.6)		Results refer to control group 1; in multivariate analysis, all types of tobacco chewing were combined
					Use of tobacco-containing material for cleaning teeth	33	4.1 (2.0–8.7)		

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Merchant *et al.* (2000), Pakistan, 1996–98		79 (54 men and 25 women) histologically confirmed oral squamous-cell cancers (buccal, gingiva, floor of mouth, tongue, palate, fauces and others) from three hospitals	149 (94 men, 55 women) from ortho-paedic and general surgical wards, with no past or present malignancy; individually matched on age, sex, hospital	Structured questionnaire, trained interviewer	Ever use of *naswar*	13	9.5 (1.7–53.5)	Cigarette smoking, alcoholic beverage consumption	
Africa									
Idris *et al.* (1995b), Sudan, 1976–85	ICD-0 141.5, 143.8, 144.9, 145.0, 141.9, 145.5	(1) 375 squamous-cell cancer of the lip, buccal cavity, floor of mouth (sites of preference for placement of quid), (2) 271 squamous-cell cancer of the tongue, palate, maxillary sinus (sites with little or no contact with quid), both groups admitted to the Radiation and Isotope Center, Khartoum, Sudan	(1) 204 non-squamous-cell oral cancer and cancer of non-oral sites unrelated to tobacco, admitted to the same hospital during the same period, (2) 2820 volunteers attending oral health education programmes in various regions of Sudan	Questionnaire at registration in hospital; similar questionnaire administered by trained interviewers to volunteers	*Toombak* Never User < 10 years > 11 years Never User < 10 years > 11 years	 157 218 10 120 	Hospital controls 1.0 7.3 (4.3–12.4) 0.7 (0.3–1.8) 11.0 (4.8–25.1) Population controls 1.0 3.9 (2.9–5.3) 0.2 (0.1–0.4) 4.3 (2.9–6.3)	Age, sex, tribe, residence	

CI, confidence interval; HCFA, Health Care Financing Administration; RDD, random-digit dialling

above for whom data on tobacco were available. Two oral cancers were observed in ever users of smokeless tobacco and 1.9 was expected based on US rates. No oral cancers were observed among exclusive users of smokeless tobacco, but only 0.8 were expected. [The Working Group noted that this study had limited power to examine use of smokeless tobacco and the risk for oral cancer.]

The cohorts of the American Cancer Society comprised volunteers, aged 30 years or above, who responded to a mailed questionnaire and resided in a household in which at least one member was aged 35 years or more (Chao *et al.*, 2002; Henley *et al.*, 2005). The CPS-I cohort included 456 487 men and 594 544 women, and the CPS-II cohort included 508 351 men and 676 306 women. At enrolment in 1959 (CPS-I) or 1982 (CPS-II), cohort members were questioned on use of smokeless tobacco. For CPS-I, vital status was followed-up through to 1972; 6.7% were lost to follow-up and follow-up was truncated for logistic reasons in 1965 for another 4.9%. Death certificates were 97% complete and were coded to ICD-7. For CPS-II, vital status was followed-up through to 1996 (Chao *et al.*, 2002) or 2000 (Henley *et al.*, 2005). Death certificates were 99.8% complete and were coded to ICD-9. Analyses were restricted to men who had had no previous cancer (except for non-melanoma skin cancer) at enrolment. Chao *et al.* (2002) further restricted the analysis to men for whom information on tobacco was available (n = 467 788) and Henley *et al.* (2005) restricted the analysis to men who had never used any other tobacco. In the CPS-I cohort, the hazard ratio for oral and pharyngeal cancers (ICD-7 140-148) for current users of smokeless tobacco was 2.02 (four deaths; 95% CI, 0.53–7.74), adjusted for potential confounders such as alcoholic beverage consumption and dietary intake. In the CPS-II cohort, the multivariate-adjusted hazard ratio for oral and pharyngeal cancers (ICD-9 140-148) was 0.9 (one death; 95% CI, 0.12–6.71) for current users of smokeless tobacco. No deaths occurred among former users of smokeless tobacco.

(ii) *Case–control studies*

A hospital-based case–control study in Atlanta, GA, USA (Vogler *et al.*, 1962), included four groups who were enroled over a 19-month period (1956–57): 333 white patients (235 men, 98 women) who had cancers of the oral cavity, pharynx or larynx, 214 patients who had other diseases of the mouth including leukoplakia, 584 patients who had other cancers and 787 patients who had no cancer and whose mouths were not examined. Use of smokeless tobacco was assessed by interview or questionnaire. Among 642 urban women, 40% of the 38 who had oral cavity cancers, but only 2%, 3% and 1% of the 57 who had other mouth diseases, 170 who had other cancers and 377 non-cancer controls, respectively, had used snuff. Similar findings were observed for the 371 rural women: 75% of the 55 cases of oral cavity cancer had used snuff orally in contrast to 11% of 37 who had other mouth diseases, 20% of 129 who had other cancers, and 11% of 150 non-cancer patients. Only 7% of female rural cases smoked. About 30–40% of urban women smoked cigarettes, but smoking habits were similar in each study group. The differences in snuff use between cases and controls were statistically significant for most of the age strata studied. In contrast to 53 (74%) women who had oral cavity cancer, one

of three female lip cancer patients and two (11%) women who had pharyngeal or laryngeal cancer had used snuff. [The Working Group noted that the reportedly similar proportions of smoking habits among urban women and the low proportion of smokers in the rural women indicate that the association between the use of snuff and cancer of the oral cavity was not confounded by smoking. Confounding by smoking could not be ruled out in men and results are not reported here.]

Williams and Horm (1977) conducted a population-based case–control study of the etiology of cancer at many different sites based on the interview responses of randomly selected incident cases of invasive cancer ($n = 7518$; 57% of those selected) from the Third National Cancer Survey (1969–71). Controls for smoking-related cancer case groups comprised men and women who had cancers that were unrelated to smoking. Among men, use of chewing tobacco and snuff was strongly associated with cancer of the gum or mouth, but not with cancer of the lip and tongue or pharynx; after controlling for age, race and smoking habits, relative risks were 3.9 (eight cases; $p < 0.01$) for moderate and 6.7 (three cases; non-significant) for heavy use of chewing tobacco or snuff. Among women, the relative risk for use of chewing tobacco or snuff for cancer of the gum or mouth was 4.9 (two cases; non-significant).

Winn *et al.* (1981a) conducted a case–control study of cancers of the oral cavity and pharynx among women in North Carolina, USA in 1975–78 to examine reasons for the exceptionally high rates of mortality from these cancers among white women throughout the southeastern USA. A total of 232 women (91% of eligible cases) who had been hospitalized with or who had died from cancers of the tongue (ICD-8 141), gum (ICD-8 143), floor of mouth (ICD-8 144), other mouth (ICD-8 145), oropharynx (ICD-8 146), hypopharynx (ICD-8 148) and pharynx unspecified (ICD-8 149) were included in the case group. Two age-, race- and region of residence-matched controls were obtained for each case; an interview was completed for 410 of the 502 eligible controls, excluding subjects with mental disorders or cancer of the oesophagus, larynx or other oral or pharyngeal diseases. Subjects or their next of kin were interviewed in their homes. Tobacco-related risks were estimated by using a common reference group: women who did not use tobacco. The relative risk for white women who used only oral snuff was 4.2 (79 cases; 95% CI, 2.6–6.7), while the relative risk associated with cigarette smoking among non-users of snuff was 2.9 (70 cases; 95% CI, 1.8–4.7). Among white women, the relative risk for those who both used oral snuff and smoked was 3.3 (11 cases; 95% CI, 1.4–7.8); these women had smoked fewer cigarettes and used snuff for fewer years than women who only smoked or used snuff. Risks for black women were somewhat lower, but they had used snuff for fewer years and had used fewer tins per week. Although 37 women had chewed tobacco, all but three were also oral snuff users. One-third of all oral snuff users had started the practice by the age of 10 years, and the average duration of use among white women was 48 years. For cancers of the gum and buccal mucosa, oral snuff use among nonsmokers was related to years of use, with relative risks of 13.8 (three cases; 95% CI, 1.9–98.0) for 1–24 years, 12.6 (10 cases; 95% CI, 2.7–58.3) for 25–49 years and 47.5 (15 cases; 95% CI, 9.1–249.5) for 50 or more years of use. For cancer at other sites

of the mouse and of the pharynx, the corresponding relative risks were 1.7, 3.8 and 1.3. The findings relating to oral snuff use could not be explained by poor dentition (Winn *et al.*, 1981b) or by use of mouthwashes (Blot *et al.*, 1983). The consumption of fruit and vegetables was associated with a reduction in risk in the study population, and was primarily evident in cigarette smokers but not among oral snuff users (Winn *et al.*, 1984). A subsequent additional analysis compared the findings on snuff use and oral and pharyngeal cancer among study subjects who responded for themselves and those for whom next of kin responded to the questions on tobacco use (Winn 1986). Odds ratios by cancer site and race tended to be higher for self-interview versus next-of-kin data. Among non-smokers and non-alcoholic beverage drinkers, the odds ratio for oral and pharyngeal cancer was 3.8 (81 cases; 95% CI, 2.3–6.3) for snuff use.

Stockwell and Lyman (1986) ascertained cases and controls from the population-based cancer registry in the state of Florida, USA, over a 1-year period in 1982. Cases were persons who had incident cancers of the lip, tongue, salivary glands, gum, floor of mouth, other parts of mouth, oropharynx, hypopharynx, pharynx (unspecified) and nasopharynx (ICD-O 140-149). All cases of cancer of the colon and rectum, cutaneous melanoma and endocrine neoplasia from the same source during same period formed the control group. Data on tobacco use were obtained from clinical and registry records, and were available for 79% of the 2351 study subjects data (82% of cases, 78% of controls). Odds ratios, adjusted for age, sex, race and tobacco use by anatomical site were: tongue, 2.3 (95% CI, 0.2–12.9); salivary gland, 5.3 (95% CI, 1.2–23.4); mouth and gum, 11.2 (95% CI, 4.1–30.7); pharynx, 4.1 (95% CI, 0.9–18.0); and nasopharynx, 5.3 (95% CI, 0.7–41.6). [A limitation of this study is that information on tobacco use was obtained from medical records. It seems improbable that all hospitals in Florida captured this information uniformly and it is possible that clinicians may have been more careful in obtaining medical record information from persons who had these head and neck cancers compared with patients who had other forms of cancer.]

In a case–control study in the USA, 623 patients with head and neck cancer were recruited. Cancers of the oral cavity, the oropharynx and the hypopharynx were used as cases and controls were patients with cancer of the salivary gland, nasopharynx and paranasal sinuses. Among men, 3.5% had ever used snuff or chewed tobacco regularly. The authors reported that "there were no statistically significant differences between cancer site groups on these users of tobacco" (Young *et al.*, 1986) [data not shown].

The population-based case–control study of Blot *et al.* (1988) enroled subjects from cancer registries in New Jersey, Atlanta metropolitan area, Santa Clara and San Mateo counties, and Los Angeles, USA. Cases included all black and white persons aged 18–79 years with incident, pathologically confirmed cancer (coded ICD-9 141–149), excluding cancer of the salivary gland (ICD-9 142) and cancer of the nasopharynx (ICD-9 147) from 1 January 1984 through to 31 March 1985. Random-digit dialling was used to ascertain controls aged 64 years or younger and Health Care Financing Administration (HCFA) was used for controls aged 65 years and older; controls were frequency-matched on age, sex and race to the cases. Structured questionnaires were administered by trained

interviewers in homes and next of kin responded for 22% of cases and 2% of controls. The response rate was 75 and 76% for cases and controls, respectively, and a total of 1114 cases and 1268 controls were included in the analysis. Among men, 6% of 762 cases and 7% of 837 controls used smokeless tobacco, mostly chewing tobacco. Nearly all tobacco chewers were smokers. Among women, 3% of 352 cases and 1% of 431 controls used snuff [odds ratio, 3.44]. Among nonsmoking women, the odds ratio for snuff was 6.2 (95% CI, 1.9–19.8), based on six cases and four controls who used snuff. Nonsmoking women primarily used snuff rather than chewing tobacco. All six cases had oral cavity cancer.

Spitz *et al.* (1988) identified cases who had histologically confirmed squamous-cell carcinoma of the tongue, floor of the mouth, oral cavity, orohypopharynx and larynx in white US residents, at the MD Anderson Hospital, Houston, TX, USA, from January 1985 through to February 1987. Laryngeal cancer accounted for 38% of the 131 male cases. Controls were patients at MD Anderson Hospital during the same period, were randomly selected and were frequency-matched on age (± 5 years) and sex; patients who had squamous-cell carcinoma of any site were excluded. The study included 185 cases (131 men and 54 women) and 185 controls aged 29–95 years. Self-administered questionnaires were part of the registration procedure. The authors reported that there was 'no difference in distribution of sites of malignancy for snuff users compared to all other cases'. Among men, the crude odds ratio for chewing tobacco was [1.0]. For women, the odds ratio for snuff use was 3.4 (95% CI, 1.0–10.9). There was no adjustment for smoking. All nine snuff dipping cases drank alcoholic beverages, seven also chewed tobacco, eight smoked cigarettes and one smoked cigars and pipes. Three of four snuff dipping controls also smoked cigarettes.

Newly diagnosed cases were identified from three hospitals in São Paolo, Curitiba and Goiânia, Brazil, and comprised carcinomas of the tongue, gum, floor of the mouth and other oral cavity (ICD-9 141, 143-145) diagnosed from 1 February 1986 to 30 June 1988 (Franco *et al.*, 1989). Two controls per case were identified from same or neighbouring general hospitals, were individually matched on sex, 5-year age group and trimester of hospital admission and excluded diagnoses of neoplasms or mental disorder. Cases were interviewed using a structured questionnaire in hospital and controls were interviewed privately. Four per cent of 232 cases and 3% of 464 controls used smokeless tobacco. The authors reported that use of smokeless tobacco and oral cancer were 'not associated'. The crude odds ratio was [1.4]. They noted that the relative risk estimates were independent of tobacco smoking or alcoholic beverage drinking, sex or anatomical site. [The Working Group noted that data on the manner in which adjustment was carried out for these factors were not shown and that confidence intervals or statistical significance were not reported.]

A population-based case–control study by Maden *et al.* (1992) enroled subjects from three urban counties of western Washington State, USA. Cases were men aged 18–65 years with in-situ and invasive squamous-cell cancers of the lip, tongue, gum, floor of the mouth, unspecified mouth and oropharynx diagnosed during 1985–89. Controls ascertained by random-digit dialling were frequency-matched to cases on age (5-year groups),

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sex and year of diagnosis; 131 cases (54.4%) and 136 controls (63%) completed in-person questionnaire interviews at home or elsewhere. Of 131 cases, 15% used smokeless tobacco in contrast to 4% of 136 controls, which yielded an age-adjusted odds ratio of 4.5 (95% CI, 1.5–14.3). [The Working Group noted that smoking was not controlled for.]

Histologically confirmed oral and pharyngeal cancers (including cancers of the tongue, floor of the mouth, oropharynx and hypopharynx) were identified in one study (Marshall *et al.*, 1992) from 20 hospitals in three New York counties, USA, during the period 1975–83. Cases of black ethnicity were excluded. Cases were individually matched on neighbourhood, age (± 5 years) and sex. Of 513 cases contacted, 290 (56%) participated and 290 controls were included. The authors noted that "there was a risk associated with chewing tobacco, but it was insignificant, with very few people exposed". [The data to support this statement were not shown.]

Mashberg *et al.* (1993) identified 359 cases among black or white men who had in-situ or invasive squamous-cell carcinoma of the oral cavity or oropharynx in a Veterans hospital in New Jersey, USA, during 1972–83. A total of 2280 patients from the same series of clinical examinations who had no cancer or dysplasia of the pharynx, larynx, lung or oesophagus were recruited and interviewed in hospital between 1977 and 1982 and served as controls; 94% of study subjects participated. Only 52 cases and 255 controls had ever used smokeless tobacco. Chewing tobacco (odds ratio, 1.0; 95% CI, 0.7–1.4) and snuff (odds ratio, 0.8; 95% CI, 0.4–1.9) were not associated with oral cancer. No trend by duration of tobacco chewing was observed [data not shown].

Spitz *et al.* (1993) identified 108 white cases who had histologically confirmed cancers of the oral cavity (44), pharynx (31) and larynx (33) at MD Anderson Hospital, Houston, TX, USA, from June 1987 to June 1991. Controls who had no history of cancer were ascertained from blood and platelet donors and were frequency-matched to cases by age (± 5 years), race and sex. Patients completed a self-administered questionnaire in the hospital. The odds ratio for chewing tobacco was 1.2. Smoking was not controlled for.

Kabat *et al.* (1994) ascertained cases from 28 hospitals in eight cities in the USA. Cases had histologically confirmed cancers of the tongue, floor of the mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil and other pharynx during 1977–90. Controls were individually matched to cases on hospital, admission within 2 months after the case, age, sex and race, and excluded persons with diseases thought to be associated with tobacco or alcoholic beverages or prior history of tobacco-related cancers. The conditions among the controls were: 50% cancers (also including cancer of the stomach, endometrium and leukaemia), 7% benign neoplasms and 43% other diseases. A total of 1560 cases and 2948 controls were included. In-hospital questionnaire interviews were conducted with the study subjects. Among men, 6.1% of 1097 cases and 5.1% of 2075 controls chewed tobacco. Among women, less than 2% of 1336 subjects chewed tobacco. Among never-smoking men, 4.9% of 82 cases were regular chewers as were 2.2% of 448 controls, yielding an odds ratio of 2.3 (95% CI, 0.7–7.3). Among never-smoking women, there were no tobacco chewers. Among never-smoking women, 3.5% of 113 used snuff in contrast to 0% of 470 controls (odds ratio, 34.5; 95% CI, 8.5–140.1). Among never-

smoking men, 0% of 82 cases and 0.9% of 444 controls were snuff users. [The estimate of the odds ratio of 34.5 used 0.5 snuff-using controls.]

Patients aged 21–80 years diagnosed with histologically confirmed cancer of oral cavity and pharynx (ICD-9 141, 143–146, 148, 149) were recruited between 1981 and 1990 from hospitals in Illinois, Michigan, New York and Philadelphia, USA (Muscat *et al.*, 1996). Hospital patients with conditions unrelated to tobacco use were matched to cases by sex, age (± 5 years), race and date of admission (± 3 months). Response rates were 91% for cases and 97% for controls to yield 1009 cases (687 men, 322 women) and 923 controls (619 men, 304 women). A questionnaire interview was conducted with cases and controls. Among men, 5.5% of 687 cases used chewing tobacco at least once a week for 1 year or more as did 5.3% of 619 controls [crude odds ratio, 1.04]. No women used chewing tobacco. Among men, 1.3% of cases and 1.6% of controls used snuff at least once a week for 1 or more years [crude odds ratio, 0.81]. For women, the crude odds ratio for snuff use was [1.9].

Muscat *et al.* (1998) reported a hospital-based case–control study on salivary gland cancer. One hundred and twenty-eight patients with newly diagnosed histologically confirmed salivary gland cancer and 114 age- and gender-matched controls were interviewed. One case reported using snuff, and three cases and three controls were tobacco chewers.

A population-based case–control study was conducted by Schwartz *et al.* (1998) of in-situ and invasive (92%) squamous-cell cancers of the tongue, gum, floor of mouth, unspecified mouth, tonsils and oropharynx in persons aged 18–65 years during 1990–95 in counties of Seattle area, WA, USA. Controls were ascertained by random-digit dialling and were frequency-matched to the cases on sex and age in a 3:2 ratio of controls to cases; 284 cases (165 men, 119 women) and 477 controls (302 men, 175 women) completed an in-person questionnaire interview; response rates among cases and controls were 63.3% and 60.9%, respectively. Among men, 6.7% of 165 cases and 5.6% of 302 controls used smokeless tobacco (odds ratio, 1.0; 95% CI, 0.4–2.3). Only one female control used smokeless tobacco. [The Working Group noted that smoking was not controlled for.]

(iii) *Cross-sectional study*

A cross-sectional study (Sterling *et al.*, 1992) used two nationally representative surveys to examine the relationship between smokeless tobacco use and cancer of the oral cavity and digestive organs: the 1986 National Mortality Follow-back Survey and the 1987 NHIS. The 1986 National Mortality Follow-back Survey was based on a stratified probability sample of 18 733 decedents in 1986 who were 25 years or older at time of death. A questionnaire sent to their next of kin also included questions on use of smokeless tobacco. Information was obtained for 16 598 decedents. The NHIS annually surveys samples of the non-institutionalized civilian population using a multistage, probability sampling design. Interviewers administered a questionnaire to sample persons in the household. The 1987 NHIS obtained data on the use of smokeless tobacco. Using a reference category of less than 100 times lifetime use of smokeless tobacco, the relative risks for cancers of the oral cavity and pharynx (ICD-9 140–149) for 100–9999 and 10 000 or

more lifetime use were 0.9 (95% CI, 0.3–3.4) and 1.2 (95% CI, 0.3–4.6), respectively, adjusted for sex, race, smoking, alcoholic beverage consumption and occupational group. [The Working Group noted concerns due to uncertainty of the comparability of the two surveys.]

(iv) *Characteristics of oral cancer in smokeless tobacco users*

Link *et al.* (1992) studied a series of 874 squamous-cell carcinomas and 129 verrucous carcinomas. Compared with the squamous-cell carcinomas in non-users of smokeless tobacco, those in the 12 users of smokeless tobacco developed later (mean age, 72.6 versus 61.5 years) and occurred in the buccal mucosa vestibule (33.3% versus 7.7%). Compared with the verrucous carcinomas in non-users of smokeless tobacco, those in the 10 users of smokeless tobacco developed later (mean age, 70.5 versus 64.2 years) and were more likely to occur in the buccal mucosa vestibule (80.0% versus 31.2%).

The Tumor Registry of Wake Forest University Medical Center, Winston-Salem, NC, USA, was used to identify all patients with oral cancer seen at this institution between 1977 and 1991 (Wray & McGuirt, 1993). Of 160 cases who used smokeless tobacco (primarily snuff), 128 (119 women, nine men; mean age, 73.3 years) used only snuff. Only 1.6% had used smokeless tobacco for less than 20 years and 78% had used smokeless tobacco for more than 40 years; 80% of the tumours were located where the smokeless tobacco was customarily held — between the cheek and the gum. Only one non-squamous-cell cancer was observed.

(*b*) *Europe*

(i) *Cohort study*

A Norwegian cohort was comprised of two samples; one was a probability sample of the general adult population of Norway identified from the 1960 census and the other consisted of relatives of Norwegian migrants to the USA. Information on snuff use and smoking was collected through mailed questionnaires in 1964 and 1967; response rates were 79% of the probability sample in 1964 and between 88 and 93% in 1997. Of the cohort, 12 431 men were alive on 1 January 1966 and information on snuff use was available for 10 136. Cohort members were followed until December 2001 for cancer incidence using national cancer registries, date of emigration or date of death. The follow-up was 99.9% complete. Cancer incidence was coded according to ICD-7 (see Table 69). After adjustment for age and smoking, the relative risk associated with ever using snuff was 1.10 (nine cases; 95% CI, 0.5–2.4) for oral and pharyngeal cancer (ICD-7 141–148) (see Table 70). The relative risks for former and current users were of the same order of magnitude but were based on smaller numbers (Heuch *et al.*, 1983; Boffetta *et al.*, 2005).

(ii) *Case–control studies*

In a study from Sweden, 477 patients with cancers of the lip, oral cavity, maxillary sinus, nasopharynx, hypopharynx, oesophagus and larynx were compared with 333 patients with other malignancies seen in a hospital in Stockholm, during 1952–55 (Wynder &

Wright, 1957). Cases and controls were interviewed and their medical records were reviewed. More of the patients who had buccal and gum cancer used snuff than controls. There was suggestive evidence by ridit analyses that snuff use was related to buccal mucosal cancer in men; nearly half of the patients were habitual users of snuff and the majority had tumours in the area of the mouth where the quid was held. Tobacco smoking among the cancer cases was similar to that in controls. Other upper aerodigestive tract cancers were not associated with snuff use. [The response rate and the number of snuff users were not reported.]

Blomqvist *et al.* (1991) investigated the role of different risk factors for squamous-cell carcinoma of the lower lip. Fifty-seven men and four women, all treated at the department of plastic surgery at a hospital in Sweden, were interviewed. Age- and sex-matched controls were selected among non-tumour patients without a prior diagnosis of cancer [no further details on the selection of controls were reported]. Two of the cases and two of the controls reported using snuff only [in all further analyses, all types of tobacco consumption were combined into one exposure factor].

In a population-based case–control study of 161 cases who had intra-oral squamous-cell carcinoma and 400 controls drawn from the Danish Central Population Register, matched on age and sex, eight patients and 14 controls were using or had used chewing tobacco (Bundgaard *et al.*, 1995). [No risk estimate reported.]

Lewin *et al.* (1998) studied squamous-cell carcinoma of the head and neck in Stockholm and the southern regions of Sweden. Cases included cancer of the oral cavity, pharynx, larynx and oesophagus and were identified through the hospital departments that treated the majority of these cases and the regional cancer registries in 1988–91. Controls were selected as a stratified random sample from the population registries that covered the source population. The number of cases identified was 605 and the number of controls selected was 756; the participation rates were 90 and 85%, respectively. Of the 605 cases, 128 were cancers of the oral cavity and 138 were cancers of the pharynx. Exposure data, including snuff use, were collected by personal interviews conducted by two specially trained nurses. The relative risk for the whole case group was 1.0 (43 cases; 95% CI, 0.6–1.6) for current snuff use, 1.2 (40 cases; 95% CI, 0.7–1.9) for former snuff use and 1.6 (38 cases; 95% CI, 0.9–2.6) for use of > 50 g/week, after adjustment for smoking and alcoholic beverage consumption. In the subgroup of never smokers, the relative risk in the whole case group for ever users of smokeless tobacco was 4.7 (nine cases; 95% CI, 1.6–13.8); the relative risk for current use was 3.3 (95% CI, 0.8–12.0) and that for former use was 10.5 (95% CI, 1.4–117.8). When the analysis was restricted to cancer of the oral cavity, the relative risk was 1.0 (10 cases; 95% CI, 0.5–2.2) among current users, 1.8 (15 cases; 95% CI, 0.9–3.7) among former users and 1.7 (95% CI, 0.8–3.9) among users of more than 50 g/week. For cancer of the pharynx, the relative risks for current and former snuff use were 0.7 (eight cases; 95% CI, 0.3–1.5) and 0.8 (seven cases; 95% CI, 0.3–1.9), respectively.

A study in the northern region of Sweden comprised cases of oral cancer (ICD-7 140, 141, 143, 143–145) diagnosed in 1980–89 (Schildt *et al.*, 1998) and identified through

cancer registries. Of the 418 cases, 175 were alive at the time of the study and 235 deceased had relatives. Controls were matched on age, sex, county and vital status. For each living case, one control was selected from the population registry; for each deceased case with relatives, one deceased control was selected from the Cause of Death Registry. Controls were further matched on age, sex, county and, for deceased cases, on year of death. Exposure, including use of snuff, was assessed based on a postal questionnaire sent to the living subjects and to the next of kin for the deceased; 354 matched pairs were analysed. The relative risk was estimated to be 0.7 (39 cases; 95% CI, 0.4–1.1) for current snuff users and 1.5 (28 cases; 95% CI, 0.8–2.9) for former snuff users. After restriction to never-smokers, the corresponding relative risks were 0.7 (19 cases; 95% CI, 0.4–1.2) and 1.8 (nine cases; 95% CI, 0.9–3.5), respectively. For lip cancer, the relative risk was 1.8 (95% CI, 0.9–3.7) for former snuff users and 'close to unity' for current snuff users. [The Working Group noted that the odds ratio in former snuff users increased from 1.5 (95% CI, 0.8–2.9) to 3.0 (95% CI, 0.9–9.4) in an analysis restricted to live subjects. Further, there was only a relative weak effect of smoking (relative risk, 1.1; 95% CI, 0.7–1.6) in an analysis with simultaneous adjustment for snuff and alcoholic beverage use.]

(c) *India and Pakistan*

Many studies from South-East Asia combined all smokeless tobacco use into one category, which was frequently termed tobacco chewing. In these studies, tobacco chewing often includes chewing of betel quid with tobacco. All such studies have been included in the monograph on betel-quid and areca-nut chewing (IARC, 2004a) and are not included here. Studies that have reported separate results for tobacco chewing without betel quid are reviewed here.

Chandra (1962) selected 450 cases of cancer of the buccal mucosa registered in a hospital in Calcutta, India, during 1955–59, and used 500 of the friends or relatives who came to the hospital with the patients as controls. Cases and controls were approximately age matched. Tobacco chewing was reported by 6.3% of 287 cases and 4.2% of 410 controls among men and 3.1% of 163 cases and 2.2% of 90 controls among women. Relative risks for tobacco chewing compared with no chewing or smoking were [2.7] for men and [2.5] for women. [The author did not clarify whether the chewing habit was tobacco only or tobacco plus lime.]

A population-based prospective study was reported by Wahi *et al.* (1968) from a temporary cancer registration system established in Uttar Pradesh (Mainpuri district). Over a period of 30 months (1964–66), a total of 346 oral- and oropharyngeal cancer cases were detected and confirmed. Exposure data were obtained by questionnaire, and a house-to-house interview survey was conducted on a 10% cluster sample of the district population. The numbers in various exposure categories were then extrapolated to the population as a whole and used as denominators to calculate oral cancer 'period prevalence rates' for different types of tobacco chewing. Prevalence rates among non-chewers of tobacco and chewers of *Pattiwala* (sun-cured tobacco leaf with or without lime) were 0.36/1000 and 1.17/1000 (based on 84 exposed cases), respectively. [The Working Group noted that

differences in age between cancer patients and the population sample do not seem to have been taken into account; and it is possible that the prevalence of chewing within the population was age-dependent.]

Jafarey *et al.* (1977) reported a hospital-based case–control study in Pakistan. The cases were 1192 histologically diagnosed oral cavity and oropharyngeal cancers. The 3562 controls were matched for age, sex and place of birth. Among men, 4% of 683 cases and 3% of 1978 controls and, among women, 7.7% of 509 cases and 3% of 1584 controls chewed tobacco, yielding relative risks of 10.4 and 13.7, respectively, compared with those who neither chewed nor smoked. [The Working Group considered that, although the chewing in this study is reported as 'tobacco' chewing, in view of other publications by the same authors, it was probably chewing of tobacco and lime.] Eighty-four patients and 114 controls used *naswar* (tobacco, slaked lime and indigo) and 88 patients and 1690 controls did not chew. The relative risk associated with *naswar* use was 14.2. [The Working Group noted that potential confounding due to other tobacco-related practices was not adjusted for.]

Goud *et al.* (1990) reported a case–control study of 102 oral cancer cases from a hospital in Varanesi, India, and an equal number of age- and sex-matched controls selected from general and surgical wards. The odds ratios were [2.1] for *khaini* use, 3.7 for *zarda* use and 2.8 for *khaini* plus *zarda*. [It was not clear whether *khaini* and *zarda* were chewed by themselves or in some cases as an ingredient of betel quid. There was no mention of control for smoking.]

Wasnik *et al.* (1998) reported a matched case–control study of 123 cases of histologically confirmed 'oropharyngeal' cancers [ICD codes not specified — probably included oral and pharyngeal cancers] selected from three hospitals in Nagpur, India. Two control groups were used: one of 123 non-cancer patients and another of 123 patients with cancer at other sites [not specified]. Controls were matched for age and sex. Of the cases, 24 were tobacco chewers (excluding those who chewed betel quid) and 33 reported using tobacco-containing material for cleaning teeth [these may include betel-quid chewers]. Unadjusted odds ratios for the two control groups were 11.4 (24 cases; 95% CI, 4.4–29.6) and 23.7 (95% CI, 7.7–72.4) for chewing tobacco without betel quid and 4.1 (33 cases; 95% CI, 2.0–8.7) and 8.7 (95% CI, 3.3–22.9) for using tobacco-containing material for cleaning teeth. In a multivariate analysis, tobacco chewing (19.5% of cases) was combined with betel-quid chewing (63.4% of cases) and the odds ratio was 8.0 (95% CI, 4.9–14.8) when smoking, alcoholic beverage consumption, occupation and the use of tobacco-containing cleaning material were included in an unconditional logistic regression model. In the same model, the odds ratio for using tobacco-containing material for teeth cleaning was 5.2 (95% CI, 2.5–11.8).

Merchant *et al.* (2000) conducted a case–control study of 79 histologically confirmed primary oral squamous-cell carcinomas from three hospitals in Karachi, Pakistan. The 149 controls were selected from orthopaedic and general surgical wards, had no history of malignancy and were individually matched on hospital, sex and age (± 5 years). Ever use of *naswar* was reported by 13 cases and 10 controls to yield an odds ratio (adjusted for

cigarette smoking and alcoholic beverage consumption) of 9.5 (13 cases; 95% CI, 1.7–52.5).

(*d*) *Other parts of Asia*

One case of oral cancer was reported among 289 *naswar* users in the Kazakh SSR who underwent oral examination; no oral cancer was seen in 243 smokers or in 1480 persons who neither smoked nor used *naswar* (Aleksandrova, 1970).

Nugmanov and Baimakanov (1970) carried out a study in the Kazakh SSR in which the practices of oral cancer patients were compared with those of controls in relation to use of *naswar*. Of 93 oral cancer patients, 30.1% used *naswar* compared with only 6.7% of 247 controls. Further comparisons that involved 28 *naswar* users with oral cancer and 19 *naswar*-using controls revealed that patients with oral cancer used *naswar* more frequently and kept it in the mouth longer than controls. [The Working Group noted that the sources of cases and controls were not reported; confounding due to other tobacco-related practices was not adjusted for; and no adequate statistical analysis was performed.]

In a study from Saudi Arabia (Amer *et al.*, 1985), 49% of 68 patients with oral cancer reported using *shammah*. [The Working Group noted that the actual percentage may be higher, since *shammah* is illegal in Saudi Arabia and there may be some reluctance to admit to its use.]

Ibrahim *et al.* (1986) reported on the association between use of smokeless tobacco products and the risk for squamous-cell carcinoma of the head and neck. Between December 1981 and December 1983, 38 patients who had oral cancer and 26 patients who had pharyngeal or laryngeal cancer were seen at the King Faisal Hospital, Saudi Arabia. Based on information from the patients' files and further questioning during follow-up, all the 38 patients with oral cancer either used *al-shammah* alone (16) or used both *al-shammah* and *alquat* (22). Fourteen of the 26 patients with pharyngeal and laryngeal cancer used *al-shammah* alone.

From February 1982 to December 1989, a total of 65 patients who had squamous-cell carcinoma of head and neck (21 cancers of the oral cavity, 35 cancers of the pharynx including 28 cancers of the nasopharynx and nine cancers of the larynx) were seen at the King Faisal Hospital (Al-Idrissi, 1990); 17 of the 65 cases (26.2%) had chewed a mixture of tobacco, pepper and oil (*al-shammah*) for an average of about 10 years. [The Working Group noted that this case series probably overlapped with that reported by Ibrahim *et al.* (1986).]

The records from the Tumour Registry of the King Faisal Specialist Hospital and Research Center, Saudi Arabia, from 1976 to 1995 were reviewed (Allard *et al.*, 1999). Among a total of 26 510 cancer patients, the frequency of oral cancer was investigated, specifically for those primary sites located near the habitual placement of *shammah* (mucosa of the lower lip, lower gum, tongue, floor of the mouth, cheek mucosa, vestibule of mouth and retromolar area). Of the 794 such oral cancers, 35.4% were referred from the province of Jizan. The percentage of such oral cancer cases from this province was substantially higher than that of other oral cancers (6.2%), total malignant cases referred

to the hospital from that province (5.6%) and the population of that province (6.0%) when compared with the whole of Saudi Arabia. [The Working Group noted that no information about the frequency of smokeless tobacco use in the province of Jizan was provided.]

(*e*) *Africa*

Elbeshir *et al.* (1989) interviewed 62 of 78 consecutive cases of oral cancer seen at the Department of Oral Surgery, Dental School, Khartoum, Sudan. Fifty (81%) patients (30 men, 20 women) who used oral snuff (*saffa*), five smoked cigarettes and a pipe, four only smoked cigarettes and eight patients reported no use of tobacco in any form. The mean duration of *saffa* use was 30 years (range, 10–45 years); 82% of the cases had used *saffa* for 20 years or more and one patient (aged 17 years) started using *saffa* at the age of 7 years.

During the period 1970–85, 850 cases of oral cancer (ICD 140–145), including 646 squamous-cell carcinomas and 204 tumours of other histology, were referred to the Radiation and Isotope Centre Khartoum, the only centre in Sudan that offered radiotherapy and chemotherapy to cancer patients (Idris *et al.*, 1995a). The squamous cell-carcinomas were classified into sites that had direct contact with the *toombak* quid (lip, buccal mucosa, floor of the mouth) (n = 375) and sites with less or no contact (tongue, palate, maxillary sinus) (n = 271). Information on *toombak* use or cigarette smoking, age, sex, area of residence and tribal origin was obtained from the cases and controls through questionnaires routinely administered to all patients admitted to the Centre. Among the three groups who had squamous-cell carcinomas with direct contact, with less or no contact and tumours of other histologies, 218 (58%), 52 (19%) and 23 (11%) used *toombak*, respectively. The corresponding numbers for cigarette smokers were 46 (12%), 29 (11%) and 21 (10%).

Using the same data, Idris *et al.* (1995b) investigated the association between use of *toombak* and carcinoma of the oral cavity in a case–control study. Squamous-cell carcinomas at sites with direct contact or with less or no contact were defined as case group 1 or case group 2, respectively, and the non-squamous-cell cancers served as control group 1. In addition, a second control group of 2820 volunteers who attended oral health education programmes in various regions of Sudan was recruited. For the first case group compared with never users of *toombak*, the odds ratios adjusted for age, sex, tribe and area of residence for *toombak* use were 7.3 (218 cases; 95% CI, 4.3–12.4) and 3.9 (95% CI, 2.9–5.3) for hospital and volunteer controls, respectively. Among users of *toombak* for > 11 years, the corresponding odds ratios were 11.0 (120 cases; 95% CI, 4.8–25.1) and 4.3 (95% CI, 2.9–6.3), respectively. Corresponding odds ratios for the second case group were moderately and statistically non-significantly increased compared with hospital controls and not increased compared with the control group of volunteers.

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2.2.2 *Precancerous lesions*

Studies on the natural history of oral cancer suggest that several potentially malignant lesions and conditions precede the development of cancer of the oral cavity. Oral precancerous lesions of relevance are leukoplakia and erythroplakia (Pindborg *et al.*, 1996).

(*a*) *North America*

(i) *Cross-sectional studies*

A number of cross-sectional studies or case series in the USA have reported prevalences of oral soft-tissue lesions among smokeless tobacco users (Greer & Poulson, 1983; Wolfe & Carlos, 1987; Creath *et al.*, 1988; Cummings *et al.*, 1989; Ernster *et al.*, 1990; Grady *et al.*, 1990; Creath *et al.*, 1991; Greene *et al.*, 1992; Kaugars *et al.*, 1992; Little *et al.*, 1992; Sinusas *et al.*, 1992; Grasser & Childers, 1997; Tomar *et al.*, 1997; Martin *et al.*, 1999) (Table 72).

All studies showed higher prevalences of oral soft-tissue lesions in smokeless tobacco users compared with tobacco non-users; in those studies that distinguished between chewing tobacco and snuff (Ernster *et al.*, 1990; Grady *et al.*, 1990; Greene *et al.*, 1992; Sinusas *et al.*, 1992; Tomar *et al.*, 1997), a higher prevalence was observed both with chewing tobacco and with snuff.

In those studies that controlled for smoking, the relative risks for oral leukoplakia in smokeless tobacco users exceeded those of non-users for smokeless tobacco overall (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999), for snuff (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999) and for chewing tobacco (Ernster *et al.*, 1990; Tomar *et al.*, 1997).

Strong dose–response relationships were observed between intensity and duration of use of smokeless tobacco, snuff or chewing tobacco. Increasing use of smokeless tobacco was associated with increasing prevalences of mucosal lesions whether measured by hours per day with tobacco in the mouth (Ernster *et al.*, 1990; Greene *et al.*, 1992; Tomar *et al.*, 1997), amounts used (Creath *et al.*, 1988; Ernster *et al.*, 1990; Greene *et al.*, 1992; Martin *et al.*, 1999), shorter time since last used (Ernster *et al.*, 1990; Greene *et al.*, 1992), duration of use in months or years (Creath *et al.*, 1988; Ernster *et al.*, 1990; Greene *et al.*, 1992; Tomar *et al.*, 1997; Martin *et al.*, 1999) or frequency of use in days per month (Tomar *et al.*, 1997). Dose–response relationships were reported separately for chewing tobacco (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999) and for snuff (Ernster *et al.*, 1990; Tomar *et al.*, 1997).

Prevalences or prevalence odds ratios for oral lesions were higher in current than in former users, and former users had higher prevalences or prevalence odds ratios than never users (Ernster *et al.*, 1990; Grady *et al.*, 1990; Creath *et al.*, 1991; Greene *et al.*, 1992; Sinusas *et al.*, 1992; Tomar *et al.*, 1997).

Overall prevalence of lesions was higher among snuff users compared with tobacco chewers (Ernster *et al.*, 1990; Grady *et al.*, 1990; Greene *et al.*, 1992; Kaugars *et al.*, 1992; Sinusas *et al.*, 1992; Grasser & Childers, 1997; Tomar *et al.*, 1997; Martin *et al.*,

Table 72. Use of smokeless tobacco and prevalence of precancerous lesions in cross-sectional studies in the USA

Reference, study location, period	Study population	Prevalence of use, type of tobacco product	Type of lesions[a]	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or p value)	Adjustment for potential confounders; comments
Greer & Poulson (1983)[a], Denver, CO	1119 adolescents in grades 9–12	10.4% [current] users of smokeless tobacco	Mucosal alterations according to own classification (degree 1–3)	Non-user	0		
				User	42.7		
				Severity of lesions			Distribution of lesions among users with lesions (n = 50)
				Degree 1	50		
				Degree 2	36		
				Degree 3	14		
Wolfe & Carlos (1987), New Mexico [not reported]	226 Navajo American adolescents, aged 14–19 years	Use within last 7 months, 64.2%, of which 58.6% used snuff, 4.8% chewing tobacco, 36.6% both	Leukoplakia according to Greer & Poulson (1983) (degree 1–3)	Non-user	3.7	1.0	34/37 lesions coincided with the reported site of habitual quid placement
				User	25.5	8.9 (p = 0.001)	
				Degree 2 lesion	4.1		
				Degree 3 lesion	8.3		
				Duration (years)			
				≤ 1	13.3	3.6	
				2	15	4.1	
				3	38.5	10.4	
				4	62.5	16.9	
				≥ 5	21.1	5.7	
				Frequency of use			
				≤ 1 day/week	11.9		
				1–2 days/week	33.3		
				3–4 days/week	42.9		
				≥ 5 days/week	40.0		
Cummings *et al.* (1989), Buffalo, NY, 1985	25 professional baseball players, aged 22–44 years, participation rate, 93%	76% ever use, chewing or dipping tobacco	Soft-tissue lesion diagnosed by dental oncologist	Non-user	0		In 4/5 subjects, lesion occurred at the location where tobacco was held
				Ever user	26.3		

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use, type of tobacco product	Type of lesions[a]	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or *p* value)	Adjustment for potential confounders; comments
Ernster *et al.* (1990), Grady *et al.* (1990), Countrywide, 1988	1109 professional baseball players, participation rate, 85%	42% current, 4% occasional, 13% former, among current users, 75% used snuff, 21% chewed tobacco	Oral leukoplakia /erythroplakia, diagnosed by specially trained dentist, graded 1-4 (categories similar to those of Greer & Poulson, 1983)	Non-user	1.4	1.0	Adjustment for age, race, cigarette smoking, alcoholic beverage consumption and dental hygiene did not change results significantly; no chewing tobacco user had a degree 3 or 4 lesion, histology of lesions described in Daniels *et al.* (1992); 94% of lesions located in the mandibular area, including 42% in the anterior area
				Former user	1.4	1.0 (0.2–5.0)	
				Occasional	2.5	1.8 (0.2–14.5)	
				Current	46.3	60.0 (27.8–129.5)	
				Chewing	17.2	14.5 (5.7–36.7)	
				Snuff	55.6	86.9 (39.9–189.5)	
				Amount used			
				Snuff (can week)			
				< 1	36.4	39.8 (17.3–91.7)	
				2–3	69.2	156.2 (66.5–367.1)	
				> 4	83.6	354.1 (129.2–970.2)	
				Chew (pouches/week)			
				< 1	12.5	8.5 (3.0–32.9)	
				2–3	16.7	12.3 (3.8–51.3)	
				> 3	33.3	30.8 (9.4–128.3)	
				Duration of use (years)			
				≤ 3	32.4	33.2 (14.2–77.9)	
				4–6	52.0	75.1 (33.4–169)	
				7–9	52.7	77.4 (32.3–185)	
				≥ 10	50.0	69.4 (29.4–164)	
				Hours in mouth/day			
				0–0.5	24.5	22.6 (9.5–53.7)	
				> 0.5–1.0	42.8	52.1 (22.2–122)	
				> 1.0–1.5	53.6	80.1 (32.2–199)	
				> 1.5–2.0	67.5	144 (53–391)	
				> 2.0–4.0	62.5	115 (46.0–291)	
				> 4.0	83.8	361 (107–1215)	
				Time since last use (hours)			
				> 24	18.6	15.9 (5.9–42.9)	
				> 12–24	22.7	20.4 (8.4–49.3)	
				> 1–12	55.1	85.2 (37.1–195)	
				≤ 1	74.3	201 (84.9–475)	
				Type of snuff			
				Copenhagen	61.3	111 (50.1–246)	
				Skoal	54.0	81 (33–199)	
				Hawken	5.3	3.9 (0.5–33.0)	

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use, type of tobacco product	Type of lesions[a]	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or *p* value)	Adjustment for potential confounders; comments
Creath *et al.* (1988, 1991), Alabama [not reported]	1116 adolescent football players, aged 10–19 years	4.8% current, 30.2% former, among current users, 35 used snuff, 7 used chew and 12 used both	Oral leukoplakia diagnosed by dentist, according to Axell *et al.* (1984)	Non-user Ever user Skoal Copenhagen Former user Current user	0.5 3.0 1.2 13	1.0 6.3 ($p < 0.005$) 21.1 ($p < 0.01$) 5.8 ($p < 0.001$)	Current user = having used for at least 6 months and still using it; former user = stopped at least 1 month before study; 13/15 lesions in the mandibular vestibule retromolar areas
Greene *et al.* (1992), Countrywide, 1989–90	894 professional baseball players recruited in 1989–90	37% current users (within week of interview)	Oral leukoplakia/ erythroplakia, diagnosed by specially trained dentist, graded 1–4 (categories similar to those of Greer & Poulson, 1983)	Non-user Former Current Seasonal use Year-round use Snuff Copenhagen Skoal Hawken Chewing tobacco	2.9 3.5 51.7 32.1 66.7 61.2 72.3 42.6 11.1 14.8	1.0 36.0	Extension of studies by Ernster *et al.* (1990) and Grady *et al.* (1990); degree 3–4 lesions found only in current users; prevalence available by seasonality of use for numerous variables
Kaugars *et al.* (1992), Virginia [not reported]	347 users of smokeless tobacco recruited by advertisement; all white men aged 14–77 years	Use for at least 6 months	Epithelial dysplasia, graded 1–4 (focally mild-mild-moderate-severe)	All users Degree 3–4 lesions Snuff Chewing tobacco	[13] [0.9] [14.4] [8.3]		All lesions at the site of placement of the tobacco in the mouth

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use, type of tobacco product	Type of lesions*	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or *p* value)	Adjustment for potential confounders, comments
Little *et al* (1992), Oregon, Washington	245 out-patients drawn from Kaiser Permanente Dental Care Program who used smokeless tobacco	100% user (use during the previous week)	Soft-tissue lesions diagnosed by dental hygienist according to Greer & Poulson (1983)	Overall	79		85% of lesions at the placement of tobacco
				Severity of lesions			*Read from graph
				Grade I	28		
				Grade II	27		
				Grade III	23		
				Grade III lesions			
				Frequency of use			
				≤ 2 days/week	7		
				3–6 days/week	7*		
				Daily	33		
				Times/day			
				< 2 (n = 24)	0		*Read from graph
				2–5	18		
				≥ 6 (n = 59)	37		
				Duration (years)			
				≤ 2	13		
				2–5	18*		
				6–10	18*		
				≥ 11	47		
Sinusas *et al* (1992), 1990	2006 professional baseball players of major and minor leagues	42.7% current use, 16.5% former use, moist snuff, chewing tobacco, plug tobacco, exclusively or in combination	Leukoplakia diagnosed by specially trained doctor, according to modification of the classification system by Greer & Poulson (1983) (degree 1–3)	Never user	6		One degree 3 lesion present in a year-round user of chewing tobacco
				Former user	6		
				Seasonal user	8		
				Year-round user	37	9.35 (3.46–26.21)	
				Type of tobacco			
				Moist snuff	34.2		
				Chew or plug	16.7		
Grasser & Childers (1997), North Carolina, 1995	214 soldiers aged 18–47 years	7% current, 7% former, smokeless tobacco undefined	Oral leukoplakia, diagnosed by board-certified oral pathologist	Non-user	1 lesion		
				Chew	0 lesion		
				Snuff	4 lesions		

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use, type of tobacco product	Type of lesions[a]	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or *p* value)	Adjustment for potential confounders, comments
Tomar *et al* (1997), Countrywide excluding Alaska, 1986–87	17 027 school children aged 12–17 years; response rate, 78%	3.1% smokeless tobacco (2.0% snuff, 1.5% chewing tobacco)	'Smokeless tobacco lesions' according to Greer & Poulson (1983) criteria, diagnosed by trained dental examiners	All subjects	1.5		Adjusted for age, cigarette smoking (current, former, never) and alcoholic beverage consumption (current, former, never); data on prevalence of lesions of different degrees (1–3) by duration of use, frequency of use and exposure time, for snuff and for chewing tobacco separately; 65% of lesions located in mandibular buccal vestibules, of which 24% in anterior labial vestibule or labial mucosa
					Snuff	*Chewing tobacco*	
				Current	18.4 (8.5–39.8)	2.5 (1.3–5.0)	
				Former	2.4 (1.0–6.1)	1.3 (0.7–2.2)	
				Duration (months)			
				< 1	1.0	1.0	
				1–12	8.1 (3.8–17.4)	2.0 (0.6–6.1)	
				13–24	23.3 (10.5–51.4)	6.6 (1.7–25.2)	
				> 24	58.9 (21.3–162)	13.4 (6.1–29.5)	
				Frequency (days/month)			
				0	1.0	1.0	
				1–14	4.2 (1.6–11.4)	2.9 (1.1–7.9)	
				15–29	7.9 (2.9–21.7)	4.8 (1.3–18.2)	
				30–31	51.4 (19.7–134)	12.1 (5.5–26.5)	
				Min/day in the mouth			
				< 1	1.0	1.0	
				1–30	9.5 (4.3–20.7)	2.8 (1.1–7.1)	
				31–105	14.6 (5.5–39.0)	6.3 (2.7–14.5)	
				> 105	26.7 (9.8–72.9)	11.1 (4.3–29.1)	
Martin *et al* (1999), Texas, 1996	3051 male US Air Force trainees; participation rate, 99.97%	9.9% current users, of whom 93.4% used snuff, 6.6% chewed	Oral leukoplakia	*Duration of use (months)*			Percentage of severe lesions according to duration of use and amount used per day available; 97% of lesions found in the mandibular buccal or labial sulcus
				1–12	14.8	11.2 (5.5–22.6)	
				13–24	30.9	28.8 (15.1–54.1)	
				25–48	48.1	59.9 (34.0–105)	
				> 49	70.8	156 (81.0–303)	
				Cans snuff /day			
				< 1/2	29.6	24.0 (14.6–39.2)	
				1/2–1	44.8	46.0 (25.4–83.6)	
				> 1	63.0	108.2 (59.8–196.9)	
				Chewing tobacco	5.0	3.4 (0.08–22.3)	
				Type of snuff			
				Copenhagen	54.7	77.7 (43.4–139.6)	
				Skoal	38.3	40.0 (24.4–65.7)	
				Kodiak	36.2	36.5 (17.8–74.9)	

CI, confidence interval

[a] Greer and Poulson (1983) established a classification into three degrees of severity (instead of four degrees used previously) to be applied to persons who have used smokeless tobacco four years or less

amount used per day. In a logistic regression analysis, length of use was the only predictor of the severity of the lesions (odds ratio, 1.14; 95% CI, 1.01–1.29). The only lesion seen in a tobacco chewer was level I.

(iii) *Reversal of lesions*

Grady *et al.* (1991) examined 1031 male professional baseball players for oral lesions. Of these, 389 were current smokeless tobacco users and 185 had oral lesions. Those with leukoplakia were asked to return for biopsies 1–21 days after the initial examination, and 131 players complied. In the time between examinations, 15% of the lesions resolved and 18% improved by one degree. The lesions most likely to have resolved were smaller lesions in players 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. Duration of smokeless tobacco use and the number of days between the initial examination and follow-up examination were not associated with the disappearance or regression of lesions.

In a study at a US Air Force camp, male basic trainees were examined upon entry to camp, between 2 and 6 days after they had last used smokeless tobacco (Martin *et al.*, 1999). Of the 302 smokeless tobacco users, 119 had oral leukoplakia. At the end of the 6 weeks of cessation of tobacco use during training, 109 of the 119 were re-examined and 97% of the lesions had completely resolved.

(iv) *Progression of lesions*

Between 1988 and 1991, 70 patients with advanced oral leukoplakia were enroled in an intervention study to assess the efficacy of various chemopreventive treatments (all patients were treated). The relative risk for developing oral cancer in the one patient who chewed tobacco compared with the 21 who did not chew tobacco was 0.6 (95% CI, 0.2–1.6) (Lee *et al.*, 2000). [No information was given on the assessment of tobacco use or on the etiology of oral leukoplakia.]

(*b*) *Europe*

(i) *Prevalence of precancerous lesions*

A study of five coal mines in South Lancashire, United Kingdom (Tyldesley, 1971), revealed that, among 1490 miners, 1.7% of surface workers and 34.3% of underground workers chewed tobacco. Of these, 91.2% also smoked cigarettes. In a subanalysis of 280 chewers and 122 non-chewers, none of the non-users had leukoplakia compared with 3.6% of the chewers. In all cases, leukoplakia was observed at multiple sites. All patients with lesions were also smokers.

A randomly selected sample of 918 adults living in a Swedish county was examined for the presence of oral mucosal lesions. None of the women and 79 (17.6%) of the men dipped snuff. Among them, 58 used snuff only, 16 used snuff and smoked cigarettes and five used snuff and smoked a pipe. The prevalence of oral leukoplakia was 2.8% among

men and 1.1% among women; none of the lesions occurred among snuff users (Salonen *et al.*, 1990).

(ii) *Malignant transformation*

Among 450 patients with leukoplakia recorded between 1956 and 1970 at the University Hospital of Copenhagen, Denmark, 32 were snuff users. A 1-year follow-up was conducted for 394 patients. Among them, two of the snuff-induced lesions became malignant or dysplastic, which corresponded to a transformation rate of 6.2%. In contrast, 19.5% of the other leukoplakia patients developed carcinoma or showed dysplasia (Roed-Petersen & Pindborg, 1973).

(*c*) *India*

Because of the high prevalence of chewing betel quid with or without tobacco in South-East Asia, and particularly in India, many studies that investigated the prevalence of smokeless tobacco use did not dissociate the use of mixtures that included tobacco from those that did not. For this reason, it is difficult to assess precancerous lesions associated with smokeless tobacco only.

A case–control study design was applied to the baseline data of a cross-sectional study in Kerala, India, of a population screened by oral visual inspections that included 927 cases of oral leukoplakia (411 women, 516 men) and 47 773 population-based controls with no oral disease (29 876 women, 17 897 men). Interviews were conducted with structured questionnaires by health workers. Clinical diagnosis of oral precancers was confirmed by dentists and oncologists. For men and women who consumed only chewing tobacco combined, the odds ratio for leukoplakia adjusted for age, sex, education, body mass index, pack–years of smoking and years of alcoholic beverage drinking was 30.9 (eight cases; 95% CI, 13.7–69.7). For both sexes combined in an analysis restricted to nonsmokers and non-drinkers who consumed only chewing tobacco, the odds ratio for leukoplakia adjusted for age, sex, education and body mass index was 263.0 (three cases; 95% CI, 68.5–∞) (Jacob *et al.*, 2004). One tobacco-only chewer had multiple premalignant lesions (Thomas *et al.*, 2003).

(*d*) *Other parts of Asia*

A cross-sectional study on the prevalence of oral cancer and precancerous lesions among 674 consecutive dental patients carried out in Riyadh, Saudi Arabia, described 13 patients with oral leukoplakia, three of whom used *shammah*. The other lesions occurred among cigarette and *shisha* smokers (Mani, 1985).

A study conducted in Gizan province, Saudi Arabia, included 661 Saudi citizens aged ≥ 15 years. *Shammah* was used by 28% of the study population. Of the surveyed population, 129 (19.5%) had lesions of the oral mucosa diagnosed clinically as leukoplakia. All affected subjects reported the use of *shammah* for more than 5 years (Salem *et al.*, 1984). The lesions were almost always at the site where *shammah* was habitually held.

Male residents of nine villages in one local authority district in the Samarkand Oblast of Uzbekistan were invited to attend a medical examination, which included an interview concerning *naswar* use, smoking and alcoholic beverage consumption (Zaridze *et al.*, 1986). A total of 1569 residents were interviewed and had oral examination, of whom 42% reported using *naswar*. Oral leukoplakia was diagnosed in 127 (8%) individuals, with a total of 144 lesions. The most frequent sites of these lesions were the floor of the mouth, the lower surface of the tongue and the tip of the tongue (38%). [*Naswar* is usually placed under the tongue.] The prevalence of leukoplakia was highest among individuals who both smoked and used *naswar* (21%). Among nonsmokers, the prevalence of leukoplakia was 2.2% among *naswar* non-users, 11.5% among former users and 12% among current users.

A built-in case–control study was carried out to investigate the possible relationship between *naswar* use and practices and the risk for leukoplakia. A total of 191 cases were defined as having oral leukoplakia, while 466 controls were free of leukoplakia. Use of *naswar* was significantly associated with the risk for oral leukoplakia in ever users (3.8; 95% CI, 2.6–5.6), in former users (3.0; 95% CI, 1.1–8.3) and in current users (3.9; 95% CI, 2.6–5.5), adjusted for smoking, alcoholic beverage consumption and age. A significant dose–response relationship was observed with earlier age at start of *naswar* use ($p = 0.027$), duration of use ($p < 0.001$), daily frequency of use ($p < 0.001$) and lifetime intake of *naswar*, calculated as reported daily frequency at the time of interview multiplied by years of use ($p < 0.001$) (Evstifeeva & Zaridze, 1992).

(*e*) *Africa*

Idris *et al.* (1996) reported on 281 Sudanese subjects (229 men, 50 women and two sex not recorded) with distinctive *toombak*-associated oral lesions that were detected from a random population sample of 5500 persons during a house-to-house survey in northern Sudan. Subjects were interviewed regarding their tobacco habits. *Toombak*-related mucosal lesions were recorded according to a four-point scale proposed by Axéll *et al.* (1984). The majority of the cases had lesions in the anterior lower labial sulcus, the predominant site for snuff dipping among Sudanese. A strong association between the severity of the mucosal lesions and longer lifetime duration (> 10 years) of *toombak* use was found. None of the most severe lesions (degree 4) occurred among subjects with less than 10 years of use.

Ahmed *et al.* (2003) applied exfoliative cytology to 300 volunteers (100 exclusive *toombak* users, 100 exclusive cigarette smokers and 100 non-users of any form of tobacco) to assess the presence and severity of epithelial atypia. Cytological smears were obtained for all subjects from the buccal or labial mucosa, the sites where *toombak* quids are placed. Moderate and severe epithelial atypia was detected in seven of 300 study subjects, in five of 100 *toombak* dippers, in two of 100 cigarettes smokers and in none of the non-users of any form of tobacco.

2.2.3 *Cancer of the oesophagus*

Table 73 summarizes the case–control studies of smokeless tobacco and cancer of the oesophagus.

(*a*) *America*

The population-based case–control study by Williams and Horm (1977), described in Section 2.2.1, also reported on oesophageal cancer. Among men, the relative risk for moderate use of chewing tobacco or snuff based on two exposed cases was 0.9, adjusting for age, race and smoking.

Cases of oesophageal cancer, primarily (85%) squamous-cell carcinomas, ascertained in 1982–84 in selected hospitals in South Carolina, USA, were matched with two hospital controls per case by hospital, race and age (± 5 years). In addition, oesophageal cancer deaths among men who were residents of eight coastal counties of South Carolina were identified in 1977–81 and matched by race, age, county of residence and year of death to decedents who died from other causes. Controls with a diagnosis at admission or cause of death related to alcoholic beverages or diet were excluded. A total of 207 cases and 422 controls were included in the study. Users of smokeless tobacco were defined as those who had used at least one pouch or plug of chewing tobacco or a small can of snuff per week for at least 1 year. Relative to non-users of tobacco, the odds ratio for users of smokeless tobacco only was 1.7, and 1.2 (95% CI, 0.1–13.3) when adjusted for study series and alcoholic beverages (Brown *et al.*, 1988).

(*b*) *Europe*

(i) *Cohort study*

In the Norwegian cohort study (Boffetta *et al.*, 2005) described in Section 2.2.1, the relative risk for oesophageal cancer was 1.4 (nine cases; 95% CI, 0.6–3.2) for ever use compared with never use of snuff and adjusted for age and smoking (Table 74).

(ii) *Case–control studies*

The case–control study by Lewin *et al.* (1998) (see Section 2.2.1) reported results separately for oesophageal cancer. The relative risks for current and former versus never use of snuff were 1.1 (10 cases; 95% CI, 0.5–2.4) and 1.3 (nine cases; 95% CI, 0.6–3.1), respectively, after adjustment for age, smoking and alcoholic beverage intake. The relative risk for users of ≥ 50 g/week was 1.9 (95% CI, 0.8–3.9).

All patients with a new diagnosis of adenocarcinoma of the oesophagus or gastric cardia and half of the patients with oesophageal squamous-cell carcinoma were included in a population-based study that comprised the whole population of Sweden (< 80 years) during 1995 through to 1997 (Lagergren *et al.*, 2000). Cases were identified from all clinical departments in Sweden that were involved in the treatment of these diagnoses as well as from local tumour registries. Controls were randomly selected from the study population and frequency-matched for age and sex to the oesophageal adenocarcinoma

Table 73. Case–control studies of smokeless tobacco use and cancer of the oesophagus

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North America							
Williams & Horm (1977), USA, 1969–71	Cancer of the oesophagus from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Moderate use Heavy use	2	0.9 –	Age, race, smoking	No exposed cases among women
Brown *et al.* (1988), USA, 1982–84 (cancer cases) 1977–81 (cancer deaths)	207 from selected hospitals in South Carolina; deaths in 8 coastal counties; 74 incident male oesophageal cancer cases (85% squamous-cell carcinoma), ≤ 143 male oesophageal cancer deaths, aged ≤ 79 years; response rate, 85% (incident cases), 94% (deceased cases and controls)	422; 157 hospital patients matched on hospital, race, age ± 5 years; ≤ 285 deaths, matched on race, age, county of residence, year of death; controls with diagnosis at admission or cause of death related to alcoholic beverages or diet excluded, response rate, 95% (hospital controls)	Non-user of tobacco Smokeless tobacco only		1.0 1.2 (0.1–13.3)	Study series and alcoholic beverages	Use defined as at least one pouch or plug of chewing tobacco or a small can of snuff per week for ≥ 1 year
Europe							
Lewin *et al.* (1998), Stockholm and southern Sweden, 1988–91	605 including 123 cancers of the oesophagus from hospitals and cancer registries, 40–79 years old; overall response rate, 90%	756 from the population registry, stratified by region and age; response rate, 85%	Current snuff use Former snuff use > 50 g/week	10 9	1.1 (0.5–2.4) 1.3 (0.6–3.1) 1.9 (0.8–3.9)	Age, region, smoking, alcoholic beverages	

Table 73 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Lagergren *et al.* (2000), Sweden, 1995–97	Incident adeno-carcinomas of the oesophagus (189), 87% men; gastric cardia cancers (262), 85% men; squamous-cell cancers of the oesophagus (167), 72% men; < 80 years old; response rates, 87%, 83%, 73%, respectively	820 frequency-matched to adenocarcinoma of the oesophagus by age, sex; response rate, 73%	*Oesophagus (squamous-cell carcinoma)*			Age, sex, tobacco smoking, alcoholic beverages	Additional results by intensity of snuff use reported in text
			Never use of snuff	134	1.0		
			Ever use of snuff	33	1.4 (0.9–2.3)		
			> 25 years of use	14	2.0 (0.9–4.1)		
			Oesophagus (adeno-carcinoma)				
			Never use of snuff	154	1.0		
			Ever use of snuff	35	1.2 (0.7–2.0)		
			> 25 years of use	15	1.9 (0.9–4.0)		
			Gastric cardia (adenocarcinoma)				
			Never use of snuff	209	1.0		
			Ever use of snuff	53	1.2 (0.8–1.8)		
			> 25 years of use	15	1.1 (0.6–2.2)		
Asia							
Phukan *et al.* (2001), India, 1997–98	502 (358 men, 144 women) histologically confirmed cancers of the oesophagus (predominantly squamous-cell cancer) from one hospital, response rate, 94%	Two visitors matched for age, sex	*Men*			Alcoholic beverage drinking	*Dried tobacco chewed alone
			Non-chewer/nonsmoker		1.0		
			**Chadha* chewer	20	3.2 (1.6–9.5)		
			Women				
			Non-chewer/nonsmoker		1.0		
			**Chadha* chewer	8	6.2 (2.4–12.1)		
			Men			Smoking	
			Non-chewer/non-alcoholic beverage drinker		1.0		
			**Chadha* chewer	16	3.8 (1.9–8.5)		
			Women				
			Non-chewer/non-alcoholic beverage drinker		1.0		
			**Chadha* chewer	7	5.8 (2.1–12.4)		

CI, confidence interval

Table 74. Results of cohort studies on use of smokeless tobacco and cancer of the oesophagus and pancreas

Reference, name of study	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Oesophagus				
Boffetta *et al.* (2005), Norwegian Cohort Study	Never user	18	1.0	Adjusted for age, smoking
	Ever user	9	1.40 (0.61–3.24)	
	Current user	4	1.06 (0.35–3.23)	
	Former user	5	1.90 (0.69–5.27)	
Pancreas				
Zheng *et al.* (1993), Lutheran Brotherhood Study	Ever users of ST	16	1.7 (0.9–3.1)	Adjusted for age, alcoholic beverages, smoking
Boffetta *et al.* (2005), Norwegian Cohort Study	Never user	60	1.0	Adjusted for age, smoking
	Ever user	45	1.67 (1.12–2.50)	
	Current user	27	1.60 (1.00–2.55)	
	Former user	18	1.80 (1.04–3.09)	

cases. Exposure data were collected through face-to-face interviews by professional interviewers. For oesophageal adenocarcinoma, the participation rate was 87% and the number of cases was 189; for gastric cardia cancer, the rate was 83% and the number of cases was 262; for squamous-cell carcinoma of the oesophagus, the participation rate was 73% and the number of participating cases was 167; 87%, 85% and 72% of the cases were men, respectively. The participation rate among the 820 controls who participated in the study was 73%. For gastric cardia adenocarcinoma, the odds ratio among ever users of snuff was 1.2 (53 cases; 95% CI, 0.8–1.8). For oesophageal adenocarcinoma, snuff users had a relative risk of 1.2 (35 cases; 95% CI, 0.7–2.0) compared with never users. Patients with more than 25 years of use had an adjusted relative risk of 1.9 (15 cases; 95% CI, 0.9–4.0) and those who used 15–35 quids per week had a relative risk of 2.0 (17 cases; 95% CI, 1.0–4.3). For the category of highest use (> 35 quids per week), no excess risk was seen. For oesophageal squamous-cell carcinoma, the relative risk was 1.4 (33 cases; 95% CI, 0.9–2.3) when ever users were compared with never users. Similarly to adenocarcinoma, for those with more than 25 years of use, the relative risk was 2.0 (14 cases; 95% CI, 0.9–4.1); those who used 15–35 quids per week had a relative risk of 2.1 (15 cases; 95% CI, 1.0–4.4) and those with highest intensity of use had no excess risk.

(*c*) *India*

Many studies from South-East Asia combined all smokeless tobacco use into one category, which was often termed tobacco chewing. In these studies, tobacco chewing

often included chewing of betel quid with tobacco. All such studies have been reviewed in the monograph on betel-quid and areca-nut chewing (IARC, 2004a) and are not included here. Only studies that reported separate results for tobacco chewing without betel quid are reviewed here.

A hospital-based case–control study was carried out in Assam, India, from 1997 to 1998, and recruited 502 (358 men, 144 women) histologically confirmed cases of oesophageal cancer (predominantly squamous-cell carcinomas), and two visitor controls per case group-matched for age and sex. Among nonsmokers compared with non-chewers (after adjusting for alcoholic beverage consumption), the odds ratio for developing oesophagal cancer associated with the use of dried tobacco leaf alone (locally known as *chada*) was 3.2 (20 cases; 95% CI, 1.6–9.5) and 6.2 (8 cases; 95% CI, 2.4–12.1) for men and women, respectively. Similarly, the risk for oesophageal cancer among non-alcoholic beverage drinkers for *chada* users compared with non-chewers (after adjusting for smoking) was 3.8 (16 cases; 95% CI, 1.9–8.5) among men and 5.8 (seven cases; 95% CI, 2.1–12.4) among women (Phukan *et al.*, 2001).

(*d*) *Africa*

Babekir *et al.* (1989) described the age, sex and geographical distribution of oesophageal cancers seen at the University Hospital of Khartoum, Sudan, in 1979–86. The annual crude incidence rates were 1.19/100 000 in the northern region and 0.17/100 000 or below in any of the other seven regions. Placing tobacco under the tongue or in the labiodental groove was discussed as a potential risk factor. No significant difference in the incidence was observed for the different tribes (Arab and Nuba) of the northern region. Alcoholic beverage drinking was excluded as a potential confounder since a similar difference in incidence rates was observed among women who rarely drink alcoholic beverages.

2.2.4 *Cancer of the pancreas*

Results of the cohort studies are presented in Table 74 and the case–control studies are summarized in Table 75.

(*a*) *North America*

(i) *Cohort study*

The Lutheran Brotherhood Insurance Society cohort comprised 17 818 (68.5%) of 26 030 white male policy holders, who responded to a mailed questionnaire in 1966 (Zheng *et al.*, 1993) (see Table 69). Cohort members were 30 years of age or older and lived in California, upper midwest or northeastern USA. After 20 years of follow-up for vital status in 1986, 4027 (23%) persons were lost to follow-up. At 11.5 years of follow-up, respondents, non-respondents and respondents lost to follow-up did not differ significantly with respect to demographic variables. Fifty-seven deaths from pancreatic cancer occurred during the 20-year follow-up period. For dietary reasons, 1656 respondents (including three pancreatic cancer deaths) were excluded from the analysis. The relative

Table 75. Case–control studies of smokeless tobacco use and cancer of the pancreas

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North America							
Williams & Horm (1977), USA, 1969–71	Cancer of the pancreas from 7518 (57% of randomly selected) incident invasive cancers who participated in the population based Third National Cancer Survey	Cancer at sites unrelated to tobacco	*Smokeless tobacco* Moderate use Heavy use	 2 1	 0.3 0.3	Age, race, smoking	No exposed cases among women
Farrow & Davis (1990), Washington, USA, 1982–86	148 married men from population-based cancer registry, aged 20–74 years; 46% histologically confirmed; interview with wife of patient	188 married men from same counties; frequency-matched on age (5-year categories); selected by RDD	Ever chewed tobacco	Prevalence among cases and controls, 6.9%	0.8 (non-significant)	Race, education	Further adjustment for age and dietary factors did not affect the odds ratio
Muscat *et al.* (1997), New York, Pennsylvania, Michigan, Illinois, USA, 1985–93	484 incident histologically confirmed from daily hospital admission logs, aged 21–80 years; response rate, 51%	954 individually matched 2:1 on hospital, sex, age (± 5 years), race, year of diagnosis; patients without tobacco-related diseases; response rate, 63%	Never smoker and long-term (≥ 20 years) quitter Tobacco chewer ≥ 1 year and not current cigarette smoker Use of snuff ≥ 1 year	 6 2	1.0 3.6 (1.0–12.8) [Not reported]		Analysis restricted to men as no woman chewed tobacco or used snuff

Table 75 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Alguacil & Silverman (2004), Atlanta, GA, Detroit, MI, New Jersey (USA), 1986–89	154 carcinoma of exocrine pancreas from population-based cancer registries, aged 30–79 years, lifelong non-smokers of cigarettes, of 1153 identified, 46.5% interviewed	844; RDD for cases ≤ 64 years; HCFA for cases aged ≥ 65 years; frequency-matched on age, race, sex, study site; lifelong non-smokers of cigarettes; 78% interviewed	Non-user of tobacco		1.0		
			Chewing tobacco and/or snuff				
			Ever used	7	1.4 (0.5–3.6)	Race, sex, geographic site, cigar smoking, age	
			Only used	5	1.1 (0.4–3.1)		
			Tobacco type				
			Chewing tobacco		1.7 (0.6–4.5)		Tobacco chewers used more per week (7.2 oz.) than users of snuff (2.4 oz.). 1 can snuff = 1.2 oz., 1 unit chewing tobacco = 3-oz pouches or 2.33-oz plugs.
			Snuff		1.1 (0.4–3.5)		
			Ounces/week				
			≤ 2.5		0.3 (0.04–2.5)		
			> 2.5		3.5 (1.1–10.6)		
					p for trend = 0.04		
			Duration of use				
			≤ 20 years		1.1 (0.1–11.0)		
			> 20 years		1.5 (0.6–4.0)		
					p for trend = 0.42		

CI, confidence interval; HCFA, Health Care Financing Administration; RDD, random-digit dialling

risk for ever users of smokeless tobacco was 1.7 (16 deaths; 95% CI, 0.9–3.1), adjusted for age, alcoholic beverages and smoking.

(ii) *Case–control studies*

The population-based case–control study by Williams and Horm (1977) reported in Section 2.2.1 also reported on pancreatic cancer. Among men, the relative risks for cancer of the pancreas and for moderate or heavy use of chewing tobacco or snuff were 0.3 (two cases) and 0.3 (one case), respectively, adjusted for age, race and smoking. There were no exposed cases among women.

A population-based study included married men newly diagnosed with pancreatic cancer in the Seattle (USA) area and population-based controls frequency-matched on age (Farrow & Davis, 1990). A telephone interview with the wives was conducted between 2 and 4.5 years after diagnosis. Complete information was available for 148 cases and 188 controls. The odds ratio for chewing tobacco was 0.8 (overall prevalence, 6.9%) with a confidence interval that included 1.0 [smoking was not controlled for].

Muscat *et al.* (1997) conducted a hospital-based study in New York, Pennsylvania, Michigan and Illinois, USA. Of the 949 cases aged 20–81 years ascertained between 1985 and 1993 and the 1526 eligible controls, 484 cases and 949 controls were interviewed in the hospital. The controls did not have tobacco-related diseases, and were individually matched to cases on hospital, sex, age, race and year of diagnosis. The major reasons for non-interviews were that the patient was too ill or unable to communicate. Relative to never smokers and long-term quitters (≥ 20 years), the odds ratio for tobacco chewers who were not current cigarette smokers was 3.6 (95% CI, 1.0–12.8).

In a large population-based case–control study of incident cases of carcinoma of the exocrine pancreas in the Atlanta area, Detroit and New Jersey, USA, lifelong nonsmokers of cigarettes were examined (Alguacil & Silverman, 2004). Forty-one per cent of the cases died before interview, but response rates for the surviving cases and controls were 75% or better. Controls enroled by random-digit dialling (for cases ≤ 64 years) and HCFA (for cases ≥ 65 years) were frequency-matched to the cases on age, race, sex and study site. Persons were considered to be snuff users if they ever used snuff, whereas tobacco chewers were defined as those who used one pouch or plug per week for at least 6 months. Relative to non-users of tobacco, the odds ratio for ever having used smokeless tobacco was 1.4 (95% CI, 0.5–3.6) and that for having used smokeless tobacco only was 1.1 (95% CI, 0.4–3.1), adjusted for race, sex, geographic site, cigar smoking and age. In a statistical model with cigar smoking, chewing tobacco and snuff and pancreatic cancer as the outcome, the odds ratios were 1.7 (95% CI, 0.6–4.5) for chewing tobacco and 1.1 (95% CI, 0.4–3.5) for using snuff. Dose–response relationships were evaluated and adjusted for age, sex, race, cigar smoking and geographical region. Users of 2.5 oz or less of smokeless tobacco per week had an odds ratio of 0.3 (95% CI, 0.04–2.5) whereas users of more than 2.5 oz had an odds ratio of 3.5 (95% CI, 1.1–10.6; p for trend = 0.04). For 20 years or less of smokeless tobacco use, the odds ratio was 1.1 (95% CI, 0.1–11.0) and that for more than

20 years was 1.5 (95% CI, 0.6–4.0; p trend = 0.42). Tobacco chewers used more ounces of tobacco per week than users of snuff (7.2 versus 2.4 oz).

(*b*) *Europe*

In the Norwegian Cohort Study (Heuch *et al.*, 1983; Boffetta *et al.*, 2005), the relative risk for pancreatic cancer for ever use of smokeless tobacco was 1.7 (45 cases; 95% CI, 1.1–2.5); similar results were obtained for former and current users. After stratification on smoking status, the relative risks were 1.9 (28 cases, 95% CI, 1.1–3.1) among current smokers and 0.9 (three cases; 95% CI, 0.2–3.7) among never smokers. The results in current smokers were adjusted for amount of smoking. [The Working Group noted that never smokers were too few to give meaningful results and that the absence of an effect for lung cancer speaks against confounding by cigarette smoking.]

2.2.5 *Cancers at other sites*

The characteristics of cohort studies are presented in Table 69 and their results are summarized in Table 76. Case–control studies are summarized in Table 77.

(*a*) *Cancer of the stomach*

(i) *Cohort studies*

In the Lutheran Brotherhood cohort, white men aged 35 years and above were followed for vital status for 20 years (Kneller *et al.*, 1991). Relative to men who had never used tobacco, the relative risk for smokeless tobacco users was 2.3 (18 deaths; 95% CI, 0.98–5.2). Stratification by pack–years of smoking reduced this relative risk to 1.6 (95% CI, 0.6–4.5). Among nonsmokers who used smokeless tobacco, the relative risk was 3.8 (three deaths; 95% CI, 1.0–14.3).

Among men in the CPS-II cohort, and relative to having never used any type of tobacco, the relative risk for stomach cancer among current users of smokeless tobacco only was 1.6 (8 deaths; 95% CI, 0.8–3.3) adjusted for age, race, education, family history of stomach cancer, consumption of high-fiber grain foods, vegetables, citrus fruits or juices, use of vitamin C, multivitamins and aspirin. For former users of smokeless tobacco only, the relative risk was 1.1 (95% CI, 0.3–4.5) (Chao *et al.*, 2002).

In the cohort study from Norway, the relative risk for stomach cancer and for ever use of snuff was 1.1 (74 cases; 95% CI, 0.8–1.5) compared with never users. Results were similar for current and former users (Boffetta *et al.*, 2005).

(ii) *Case–control studies*

The case–control study by Williams and Horm (1977) described in Section 2.2.1 also reported on stomach cancer. Among men, the relative risks for stomach cancer and for moderate or heavy use of chewing tobacco or snuff were 1.0 (6 cases) and 1.7 (6 cases), respectively, adjusted for age, race and smoking.

Table 76. Results of cohort studies on use of smokeless tobacco and cancer at other sites

Reference, name of study	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Stomach				
Kneller *et al.* (1991), Lutheran Brotherhood Study	Never used any tobacco		1.0	
	Smokeless tobacco users	18	2.3 (0.98–5.2)	
	Smokeless tobacco users (adjusted*)	18	1.6 (0.6–4.5)	*Stratified by pack–years of smoking
	Smokeless tobacco only users	3	3.8 (1.0–14.3)	
Chao *et al.* (2002), CPS-II	Never used any tobacco	169	1.0	Adjusted for age, race, education, family history of stomach cancer, aspirin use, dietary factors
	Current smokeless tobacco only	8	1.58 (0.76–3.28)	
	Former smokeless tobacco only	2	1.11 (0.27–4.50)	
Boffetta *et al.* (2005), Norwegian Cohort Study	Never user	143	1.0	Adjusted for age, smoking
	Ever user	74	1.11 (0.83–1.48)	
	Current user	42	1.00 (0.71–1.42)	
	Former user	32	1.29 (0.87–1.91)	
Colon and rectum				
Heineman *et al.* (1995), US Veterans Study	Never used any tobacco	782	1.0	Relative risks for smokeless tobacco users who never smoked cigarettes, pipes or cigars
	Smokeless tobacco user			
	Colon	39	1.2 (0.9–1.7	
	Rectum	17	1.9 (1.2–3.1)	
Digestive tract				
Accort *et al.* (2002), NHANES I Follow-up	No tobacco use		1.0	Adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, dietary fat intake
	Men			
	Ever smokeless tobacco user/never smoker		0.9 (0.3–2.3)	
	Ever smokeless tobacco user/ever smoker		0.7 (0.3–1.8)	
	Women			
	Ever smokeless tobacco user/never smoker		0.8 (0.3–2.7)	
	Ever smokeless tobacco user/ever smoker		0.2 (0.1–1.1)	

Table 76 (contd)

Reference, name of study	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Henley *et al.* (2005), CPS-I and CPS-II	*CPS-I*			Restricted to men who never used other tobacco products; adjusted for age, race, education, body mass index, exercise, aspirin use, alcoholic beverages, dietary factors; CPS-II also adjusted for status, type of employment
	Never use of smokeless tobacco	760	1.0	
	Current use of smokeless tobacco	153	1.26 (1.05–1.52)	
	CPS-II			
	Never use of smokeless tobacco	1932	1.0	
	Current use of smokeless tobacco	48	1.04 (0.77–1.38)	
	Former use of smokeless tobacco	19	0.99 (0.63–1.57)	
Lung				
Accort *et al.* (2002), NHANES I Follow-up	No tobacco use		1.0	Adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise, fruit/vegetable intake
	Men			
	Ever smokeless tobacco user/never smoker		–	
	Ever smokeless tobacco user/ever smoker		22.6 (6.4–80.3)	
	Women			
	Ever smokeless tobacco user/never smoker		9.1 (1.1–75.4)	
	Ever smokeless tobacco user/ever smoker		1.2 (0.2–8.9)	
Boffetta *et al.* (2005), Norwegian Cohort Study	Never user	39	1.0	Adjusted for age, smoking
	Ever user	72	0.80 (0.61–1.05)	
	Current user	44	0.80 (0.58–1.11)	
	Former user	28	0.80 (0.54–1.19)	
Henley *et al.* (2005), CPS-I and CPS-II	*CPS-I*			Restricted to men who never used other tobacco products; adjusted for age, race, education, body mass index, exercise, aspirin use, alcoholic beverages, dietary factors; CPS-II also adjusted for status, type of employment
	Never use of smokeless tobacco	116	1.0	
	Current use of smokeless tobacco	18	1.08 (0.64–1.83)	
	CPS-II			
	Never use of smokeless tobacco	378	1.0	
	Current use of smokeless tobacco	18	2.00 (1.23–3.24)	
	Former use of smokeless tobacco	4	1.17 (0.43–3.14)	

Table 76 (contd)

Reference, name of study	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Soft-tissue sarcoma				
Zahm *et al* (1992), US Veterans Study	Never used any tobacco	20	1.0	No smokeless tobacco only users with soft-tissue sarcoma
	Used smokeless tobacco and other tobacco products	20	1.4 (0.8–2.6)	
Prostate				
Hsing *et al* (1990), Lutheran Brotherhood Study	Never used any tobacco	19	1.0	Adjusted for cigarette smoking; similar results for 58 subjects for whom prostate cancer was not the underlying cause of death
	Ever used smokeless tobacco	42	2.1 (1.1–4.1)	
	Occasional	5	1.4 (0.5–3.9)	
	Former user	13	1.8 (0.8–3.9)	
	Regular	24	2.4 (1.3–4.9)	
	Smokeless tobacco only	10	4.5 (2.1–9.7)	
Hsing *et al* (1991), US Veterans Study	Never used any tobacco	1075	1.0	
	Smokeless tobacco only	48	1.2 (0.9–1.6)	

CI, confidence interval, CPS, Cancer Prevention Study; NHANES, National Health and Nutrition Examination Survey

Table 77. Case–control studies of smokeless tobacco use and cancer at other sites

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stomach							
Williams & Horm (1977), USA, 1969–71	Cancer of the stomach from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Smokeless tobacco Moderate use Heavy use	*Men* 6 6	 1.0 1.7	Age, race, smoking	Personal interview
Hansson *et al* (1994), Sweden, 1989–92	338 incident from population-based national cancer registry, aged 40–79 years, histologically confirmed, response rate, 74%	679, randomly selected from population registries, stratified by age and sex, response rate, 77%	Snuff dipping		0.7 (0.47–1.06)	Age, sex, socio-economic status, vegetable intake	All subjects are also included in Ye *et al.* (1999).
Ye *et al* (1999), Sweden, 1989–95	561 incident from population-based national cancer registry, aged 40–79 years; histologically confirmed; response rate, 62%	1164, randomly selected from population registries, stratified by age and sex; response rate, 75.9%	Snuff dipping *Stomach cancer* Ever user among never smokers *Cardia* Current Former *Distal intestinal* Current Former *Distal diffuse* Current Former	 11 9 6 26 18 11 8	 0.5 (0.2–1.2) 0.5 (0.2–1.1) 0.8 (0.3–1.9) 0.8 (0.5–1.3) 0.9 (0.5–1.6) 0.6 (0.3–1.2) 0.7 (0.3–1.6)	Age, residence area, body-mass index, socio-economic status, smoking	Data available on age at start, duration and intensity of snuff dipping

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Extra-hepatic bile duct							
Chow *et al* (1994), Los Angeles county, USA, 1985–89	64 incident cancers of the extrahepatic bile duct (ICD-O 156.1), 41 of the ampulla of Vater (ICD-O 156.2), aged 30–84 years, histologically confirmed, white race, response rate, 76%; for the 58% of deceased cases, information obtained from next-of-kin	255; RDD for cases ≤ 64 years; HCFA for cases ≥ 65 years; matched on age (5-year age groups), sex; no history of cholecystectomy; response rate, 84% (RDD), 87% (HCFA)	Chewing tobacco [current]	Ampulla of Vater 3	18 (1.4–227.7)		Exposed cases also smoked cigarettes and 2 also used cigar/pipes
Nasal cavities							
Brinton *et al* (1984), USA, 1970–80	193 from four hospitals in North Carolina and Virginia, cancers of the nasal cavities and sinuses ICD-8 160.0, 160.2–160.5, 160.8–160.9 (86 squamous-cell carcinomas, 24 adenocarcinomas or adenoid cystic carcinomas, 36 other carcinomas, 14 other histologies), aged ≥ 18 years, response rate, 82.9%	*Live cases*: two hospital patients per case matched on hospital, year of admission, age, sex, race, excluding controls with admission diagnosis of other cancers or other diseases of the upper aero-digestive tract *Deceased cases*: one per case with similar criteria as above; one deceased identified from state vital statistics offices; response rate, 78.0%	Use of chewing tobacco Use of snuff	15 23	1.0 (ref.) 0.7 (0.4–1.5) 1.0 (ref.) 1.5 (0.8–2.8)	Sex	Similar results for matched analyses [data not shown]
Stockwell & Lyman (1986), Florida, USA, 1982	92 incident cancers of the nasal cavities and accessory sinuses from population-based Florida cancer registry; overall response rate, 82%	6457; all cancers of the colon or rectum, cutaneous melanoma, endocrine neoplasias from same source during same time period; response rate, 78%	Unspecified	1	3.3 (0.4–25.9)	Age, sex, race, tobacco use	Only primary type of tobacco used was obtained from chart and histopathology reviews

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Laryngeal cancer							
Stockwell & Lyman (1986), Florida, USA, 1982	797 incident cancers of the larynx from population-based Florida cancer registry; overall response rate, 82%	6457, all cancers of the colon or rectum, cutaneous mealnoma, endocrine neoplasias from same source during same time period; response rate, 78%	Unspecified	5	7.3 (2.9–18.3)	Age, sex, race, tobacco use	Only primary type of tobacco used was obtained by chart and histopathology reviews
Lewin *et al* (1998), Stockholm and southern Sweden, 1988–91	605, including 157 cases of cancer of larynx, from hospitals and cancer registries, 40–79 years old; overall response rate, 90%	756 from the population registry, stratified by region, age; response rate, 85%	Current snuff use Former snuff use	15 9	1.0 (0.5–1.9) 0.8 (0.4–1.7)	Age, region, smoking, alcoholic beverages	
Lung							
Williams & Horm (1977), USA, 1969–71	Cancer of the lung from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Smokeless tobacco Moderate use Heavy use	*Men* 26 10	 0.7 0.8	Age, race, smoking	Personal interview
Sarcoma							
Zahm *et al* (1989), Kansas, USA, 1976–82	133 incident soft-tissue sarcomas from population-based registry considered 90% complete, histologically confirmed, white men, aged ≥ 21 years; 50% of interviews with next-of-kin; response rate for cases and controls, 93%	948; for living cases: white men selected through RDD and HCFA, frequency-matched by age (± 2 years); for deceased cases: decedents from Kansas, frequency-matched on age (± 2 years) and year of death, excluding lymphomas, sarcomas, ill-defined malignancies and homicide or suicide; 49% of interviews with next-of-kin	Ever use of smokeless tobacco *Location of tumour* Upper gastrointestinal Lung, pleura, thorax Head, neck, face Others *Cell type* Fibromatous Adipose Myomatous Others	28 4 5 3 16 7 3 7 11	1.8 (1.1–2.9) 3.3 (0.8–12.6) 3.1 (0.9–10.5) 2.4 (0.5–10.2) 1.4 (0.7–2.5) 1.8 (0.7–4.7) 1.1 (0.2–4.2) 2.1 (0.8–5.3) 1.9 (0.9–3.9)		

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Breast							
Spangler *et al.* (2001b), Spangler (2002), North Carolina, USA, 1990–91	Eight Cherokee women with prevalent breast cancer (ascertained by personal history) from population-based survey in Cherokee tribal lands; age at diagnosis: three, < 55 years; five, ≥ 55 years; response rate, 81% (cases and controls combined)	962 other survey respondents	Ever use of smokeless tobacco Diagnosed at age < 55 years ≥ 55 years	 1 2	 1.3 (0.12–13.9) 1.2 (0.14–9.52)		Unknown whether smokeless tobacco use preceeded cancer diagnosis
Prostate							
Hayes *et al.* (1994), Georgia, Michigan, New Jersey, USA, 1986–89	981 men with incident pathologically confirmed prostate cancer from a population-based registry, aged 40–79 years; response rate, 76%	1315; RDD for cases ≤ 64 years, HCFA for cases ≥ 65 years; frequency-matched on age, sex, race; response rate, 74%	Never used tobacco *Tobacco chewing* Former Current *Snuff* Former Current	 56 14 10 10	1.0 1.0 (0.6–1.5) 0.5 (0.2–1.0) 0.6 (0.3–1.4) 5.5 (1.2–26.2)	Age, race, study site	
Urinary bladder							
Howe *et al.* (1980), Canada, 1974–76	632 (480 men, 152 women) newly diagnosed bladder cancers identified in three provinces	632 neighbours, individually matched by age (± 5 years), sex	Ever use of chewing tobacco, relative to never use	NR	0.9 (0.5–1.6)	Controlling for cigarette smoking did not affect the risk estimates.	61 discordant pairs

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hartge *et al.* (1985), 10 areas in USA, 1977–78	2982 from population-based cancer registries, aged 21–84 years; response rate, 75%	2469 RDD and 3313 HCFA, frequency-matched by age, sex, geographic distribution of the cases; response rate, 82% (HCFA), 84% (RDD)	Snuff Chewing tobacco	11 40	0.8 (0.4–1.6) 1.02 (0.7–1.5)	Race, age, residence, pipe, cigars, chewing tobacco/snuff	Analysis restricted to men who never smoked cigarettes.
Slattery *et al.* (1988), Utah, USA, 1977–83	332 histologically confirmed from population-based Utah cancer registry; white men aged 21–84 years; response rate, 76.3%	686; RDD for cases ≤ 64 years, HCFA for cases ≥ 65 years, matched 2:1 on age, sex, response rate, 81.5%	Snuff Chewing tobacco *Snuff* Never smoker Smoker *Chewing tobacco* Never smoker Smoker	16 21	1.0 (0.5–1.9) 1.1 (0.6–1.9) 2.7 (0.5–15.6) 0.7 (0.4–1.4) 2.8 (0.4–20.2) 1.2 (0.7–2.2)	Crude, unmatched	
Burch *et al.* (1989), Alberta, Ontario, Canada, 1979–82	826 histologically confirmed population-based through cancer institute, tumour registry and hospitals, aged 35–79 years; response rate, 67%	792; randomly selected from province-wide annually updated listings, matched 1:1 on age (± 4 years), sex, area of residence; response rate, 53%	Ever snuff use Ever chewing tobacco	9 26	0.6 (0.3–1.1) 0.5 (0.2–1.1)	Age, lifetime cigarette consumption	Analysis restricted to 627 men

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Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Kidney							
Goodman *et al.* (1986), USA, 1977–83	267 incident primary adenocarcinomas of kidney, aged 20–80 years, from 18 hospitals in six US cities; response rate, 89%	267, individually matched on hospital, sex, race, age (± 5 years), time of admission; non-tobacco-, non-obesity related disease; response rate, 88%	Ever use* of chewing tobacco	13	4.0 (1.1–14.2)	Matched analysis	*At least once a day for 1 year or more
			Ever versus never use of chewing tobacco, among never users of cigarettes		0.9 (0.2–5.1)	Queteletet index, decaffeinated coffee, pack-years, chewing tobacco (ever, never), pack-years × chewing tobacco.	Analysis restricted to 189 men
			Joint effect for smoking of 30 pack–years of cigarettes and tobacco chewing versus never use of any tobacco		26.00 (4.41–153.00)		
Asal *et al.* (1988), Oklahoma, USA, 1981–84	315 incident renal cell carcinomas from 29 hospitals; ascertained by tissue diagnosis (95%) or radiological examination (5%); response rate, 91%	313 hospital patients, individually matched by age (± 5 years), sex, race, hospital, time of interview; patients with kidney disease or pyshiatric diagnosis excluded; 336 RDD, frequency-matched by age (± 10 years), sex	Use of snuff		3.6 (1.2–13.3)		Among 209 men in matched-pair analysis with hospital controls

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McLaughlin *et al.* (1995), Australia, Denmark, Germany, Sweden, USA, 1989–92	1732 population-based (hospital-based in Germany) renal-cell adenocarcinomas, aged 20–79 years; histologically or cytologically confirmed; response rate, 72.3%	2309 from population registers, electoral rolls, residential lists, HCFA, RDD; response rate, 74.7%	Smokeless tobacco	11	1.3 (0.6–3.1)	Age, sex, centre, body mass index	Analysis restricted to men because no women used smokeless tobacco.
Muscat *et al.* (1995), Illinois, Michigan, New York, Pennsylvania, USA, 1977–93	788 renal-cell carcinomas, excluding renal pelvis; histologically confirmed from selected hospitals	779 patients with diseases unrelated to tobacco use, from daily admission lists, frequency-matched on age (± 5 years), sex, race, year of diagnosis	Ever chewing tobacco relative to non-users of smoklesss tobacco *Chews/week* ≤ 10 chews > 10 chews	2.6%	3.2 (1.1–8.7) 2.5 (1.0–6.1) 6.0 (1.9–18.7) *p* for trend < 0.05		Analysis restricted to men because no women used chewing tobacco. [Snuff was included in questionnaire but not mentioned in results]. Chewing tobacco defined as ever used regularly for at least 1 year
Brain							
Zheng *et al.* (2001), Iowa, USA, [not reported]	375 incident gliomas from population-based registry, 40–85 years of age; histologically confirmed; response rate, 91%	2434; drivers' licence records for cases aged ≤ 64 years, HCFA for cases ≥ 65 years; frequency-matched by age (5-year groups), sex; 6.5:1 ratio controls:cases; those with history of cancer excluded; response rate, 82% (licence), 80% (HCFA)	Chewing tobacco or use of snuff	Not reported	"Use of snuff or chewing tobacco was not associated with a significantly increased risk of brain cancer for either men or women."		

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Non-Hodgkin lymphoma							
Brown *et al.* (1992a), Iowa, Minnesota, USA, 1981–84	622 white men with incident histologically confirmed non-Hodgkin lymphoma, aged ≥ 30 years; population-based, outside of metropolitan areas; 89% interviewed	820 living; RDD for cases ≤ 64 years, HCFA for cases ≥ 65 years, frequency-matched on site, age (± 5 years); response rate, 77% (RDD), 79% (HCFA)	All lymphoma Follicular Diffuse Small lymphocytic	19 7 5 4	1.3 (0.7–2.5) 1.7 (0.7–4.3) 0.8 (0.3–2.3) 1.7 (0.5–5.4)	Age, state	Same subjects as study by Schroeder *et al.* (2002)
Schroeder *et al.* (2002), Iowa, Minnesota, 1980–82 (Minnesota), 1981–83 (Iowa)	622; 40% had archival tissue available	1245 controls; 820 living controls and 425 deceased, from state death certificate files; interviews with next-of-kin of deceased subjects	*All cases* Chewing tobacco Snuff *t(14;18)-positive* Chewing Snuff *Age started chewing* > 18 years ≤ 18 years *t(14;18)-negative* Chewing Snuff *Age started chewing* > 18 years ≤ 18 years	11% 10% 10 7 59 13 9 12 8 16	1.3 (0.9–1.8) 1.0 (0.7–1.4) 1.7 (0.9–3.1) 1.0 (0.5–2.0) 1.3 (0.6–2.9) 2.5 (1.0–6.0) 1.0 (0.6–1.8) 0.9 (0.6–1.6) 1.2 (0.6–2.2) 1.0 (0.3–3.0)	Age, state, vital status	Same subjects as in study by Brown *et al.* (1992a). Ever used if used daily for at least 3 months

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Leukaemia							
Brown *et al.* (1992b), Iowa, Minnesota, USA, 1981–84	578 incident leukaemias, white men aged ≥ 30 years, from cancer registry in Iowa or 'special surveillance network of hospitals in Minnesota', histologically confirmed, response rate, 86%, interviews with close relatives for deceased or too ill subjects	820 living; RDD for cases ≤ 64 years; HCFA for cases ≥ 65 years; frequency-matched on age (5-year groups), state, response rate, 77% (RDD), 79% (HCFA)	Non-user of tobacco		1.0	Age, state, alcoholic beverage use	
			Chewing tobacco/snuff only	24	*All* 1.8 (0.9–3.3)		
				3	*Acute non-lymphocytic* 0.9 (0.2–3.1)		
				2	*Chronic myelogenous* 2.1 (0.4–10.7)		
				10	*Chronic lymphocytic* 1.9 (0.8–4.3)		
				4	*Myelodysplasia* 2.7 (0.8–9.4)		
				5	*Other* 3.0 (0.9–9.2)		

CI, confidence interval; HCFA, Health Care Financing Administration; NR, not reported; RDD, random-digit dialling

Two case–control studies on stomach cancer were conducted in selected counties in central and northern Sweden with different rates of stomach cancer incidence (Hansson *et al.*, 1994; Ye *et al.*, 1999) (Table 77). Eligible cases were all patients with newly diagnosed and histologically confirmed stomach cancers between 1989 and 1992 or 1995, and were ascertained via personal contacts at all departments of surgery and pathology, supplemented by record linkages to the regional and national cancer registries. In the early study (Hansson *et al.*, 1994), the odds ratio for snuff dipping adjusted for age, sex, socioeconomic status and vegetable intake was 0.7 (95% CI, 0.5–1.1). In the later study (Ye *et al.*, 1999), the stomach cancers were classified as cancer of the cardia or of the distal stomach. About two controls per case were selected from the continuously updated population registry with stratification for age and sex. Face-to-face interviews were performed by specially trained personnel. The participation rates were 62% and 76% for cases and controls, respectively; the majority of the non-participants among the cases had died before the interview. For cardia cancer, the relative risk for current snuff use was 0.5 (95% CI, 0.2–1.1) and that for former users was 0.8 (95% CI, 0.3–1.9). For distal stomach cancer, the relative risks for current use were 0.8 (95% CI, 0.5–1.3) for the intestinal type and 0.6 (95% CI, 0.3–1.2) for the diffuse type. After restriction to never smokers and after combining all sites, the relative risk for ever using snuff was 0.5 (95% CI, 0.2–1.2). [The limitation is small numbers in the subgroups, which precludes e.g. site-specific analysis in never-smokers with various categories of snuff use.]

(*b*) *Cancer of the colon and rectum*

Risk for colorectal cancer was examined in relationship to smokeless tobacco use among members of the US Veterans' cohort (Heineman *et al.*, 1995). Relative to those who had never used tobacco, smokeless tobacco users who had never smoked cigarettes, pipes or cigars had a relative risk of 1.2 (39 deaths; 95% CI, 0.9–1.7) for cancer of the colon and 1.9 (17 deaths; 95% CI, 1.2–3.1) for cancer of the rectum.

(*c*) *Cancer of the extra-hepatic bile duct*

A population-based case–control study in Los Angeles County, USA, included 64 cases of cancer of extra-hepatic bile duct, 41 cases of cancer of ampulla of Vater, and 255 controls (Chow *et al.*, 1994). In-person questionnaire interviews were conducted with the cases or their next-of-kin. Results obtained for the entire group of cases (personal and surrogate interviews) and for the subgroup with personal interviews only were consistent. An odds ratio of 18 (95% CI, 1.4–227.7) for chewing tobacco was observed for cancers of ampulla of Vater. [All cases of cancer of the ampulla of Vater who chewed tobacco also smoked.]

(*d*) *Cancer of the digestive system (combined)*

The case–control study by Sterling *et al.* (1992), described in Section 2.2.1, also reported results for cancers of the digestive organs (ICD-9 150–159). Using a reference

category of less than 100 lifetime uses of smokeless tobacco, the relative risks for 100–9999 and 10 000 or more lifetime uses were 0.2 (95% CI, 0.04–0.5) and 0.61 (95% CI, 0.3–1.1), respectively.

Gastrointestinal cancer deaths (ICD-9 150–159) were examined in the NHANES I follow-up study. Relative to non-users of tobacco, the hazard ratios for users of smokeless tobacco only for men and women were 0.9 (95% CI, 0.3–2.3) and 0.8 (95% CI, 0.3–2.7), respectively, adjusted for age, race, poverty index ratio, alcoholic beverage and dietary fat intake (Accortt *et al.*, 2002).

In the CPS-I cohort, men who reported current use of smokeless tobacco and never used other tobacco products had statistically significantly higher death rates than never users (153 deaths; hazard ratio, 1.3; 95% CI, 1.1–1.5) after adjustment for age, race, educational level, body mass index, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use. In the CPS-II cohort, compared with never users, the hazard ratio for men who reported current use of smokeless tobacco but never used any other tobacco products was 1.04 (48 deaths; 95% CI, 0.8–1.4) adjusted for the same variables and status and type of employment (Henley *et al.*, 2005).

(e) *Cancers of the respiratory tract*

(i) *Nasal cavities*

Brinton *et al.* (1984) performed a case–control study of risk factors for cancers of the nasal cavities and sinuses (ICD 8 160.0, 160.2–160.5, 160.8–160.9). Cases were selected from four hospitals in North Carolina and Virginia, USA, between 1 January 1970 and 31 December 1980. Cases were aged 18 years or older and were residents of the state in which the admitting hospital was located. For each case alive at the time of the interview, two hospital controls were selected and matched to the case on hospital, year of admission, age, sex, race and other factors. Controls with a primary diagnosis at admission of other cancers or other diseases of the upper aerodigestive tract were excluded. For deceased controls, two different controls were selected: a hospital control derived in the same manner as above and a deceased control identified through state vital statistics offices. A total of 193 cases, 232 hospital controls and 140 death certificate controls were identified and telephone interviews with study subjects or their next of kin were successfully conducted for 160 of the cases (82.9%) and 290 controls (78.0%). The cancers were 86 squamous-cell carcinomas, 24 adenocarcinomas or adenoid cystic carcinomas, 36 other carcinomas and 14 other histological types. Unmatched stratified analyses and logistic regression analyses for matched data were performed. Since the results were similar for the two analytical approaches [data not shown], only results that ignored the individual matching were presented. Sex-adjusted odds ratios for tobacco chewers or snuff users were 0.7 (15 cases; 95% CI, 0.4–1.5) and 1.5 (23 cases; 95% CI, 0.8–2.8), respectively. The odds ratio for snuff use and squamous-cell tumours was 1.9.

A case–control study in Florida assessed the association with use of smokeless tobacco among 92 cases of cancer of the nasal cavities and 6457 controls (Stockwell &

Lyman, 1986). Tobacco use was determined from medical and cancer registry records and was available for 79% of subjects. The odds ratio for smokeless tobacco was 3.3 (95% CI, 0.4–25.9), adjusted for age, race, sex and tobacco use. [The limitations of this study are presented in Section 2.2.1.]

(ii) *Larynx*

A case–control study in Florida assessed the association with use of smokeless tobacco among 797 cases of cancer of the larynx and 6457 controls (Stockwell & Lyman, 1986). Tobacco use was determined from medical and cancer registry records and was available for 79% of subjects. The odds ratio for smokeless tobacco was 7.3 (95% CI, 2.9–18.3), adjusted for age, race, sex and tobacco use. [The limitations of this study are presented in Section 2.2.1.]

The case–control study by Lewin *et al.* (1998, see Section 2.2.1) reported results separately for cancer of the larynx. Relative risks for curent and former use of snuff were 1.0 (95% CI, 0.5–1.9) and 0.8 (95% CI, 0.4–1.7), respectively, after adjustment for age, smoking and alcoholic beverages.

(iii) *Lung*

Lung cancer deaths were examined in the NHANES I follow-up study (Accortt *et al.*, 2002). In the multivariate analysis and relative to non-users of tobacco, the hazard ratio for women who used only smokeless tobacco was 9.1 (95% CI, 1.1–75.4), adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise and fruit/vegetable intake. No deaths from lung cancer occurred among men who used smokeless tobacco only.

In the CPS-I cohort, the hazard ratio for lung cancer for current smokeless tobacco users who never used other tobacco products was 1.1 (18 deaths; 95% CI, 0.6–1.8) after adjustment for age, race, level of education, body mass index, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use (Henley *et al.*, 2005). In the CPS-II cohort, the hazard ratio for men who reported current use of smokeless tobacco but never used any other tobacco products compared with never users was 2.0 (18 deaths; 95% CI, 1.2–3.2) adjusted for the same variables and status and type of employment. The hazard ratios were similar for those who chewed but never used snuff and for those who used snuff but never chewed.

In the Norwegian cohort study, the relative risk for lung cancer was 0.8 (72 cases; 95% CI, 0.6–1.1) in a comparison of ever users of smokeless tobacco with never users and adjusting for age and smoking. Results were similar for ever or current users of smokeless tobacco and when stratified by smoking status (Boffetta *et al.*, 2005).

The case–control study by Williams and Horm (1977) described in Section 2.2.1 also reported on lung cancer. Among men, the relative risks for lung cancer and for moderate or heavy use of chewing tobacco or snuff were 0.7 (26 cases) and 0.8 (10 cases), respectively, adjusted for age, race and smoking.

(*f*) *Sarcoma*

In the US Veterans' cohort, the relative risk for soft-tissue sarcomas associated with smokeless tobacco use relative to persons who never used tobacco products was 1.5 (95% CI, 0.8–2.7). None of the users of smokeless tobacco who never used other tobacco products developed a soft-tissue sarcoma (Zahm *et al.*, 1992).

A population-based registry in Kansas, USA, provided information on white men aged 21 years or older in 1976–82 who had soft-tissue sarcomas (Zahm *et al.*, 1989). Controls were recruited through RDD and HCFA and were frequency-matched to cases on age (± 2 years). In addition, decedents from Kansas during the same period were selected for deceased cases. Controls with lymphomas, sarcomas or ill-defined malignancies, or who were homicides or suicides were excluded. Telephone interviews were conducted with 133 cases and 948 controls. The odds ratio for ever use of smokeless tobacco was 1.8 (95% CI, 1.1–2.9). Odds ratios for smokeless tobacco use by anatomic site of the soft-tissue sarcoma were: upper gastrointestinal, 3.3 (95% CI, 0.8–12.6); lung, pleura and thorax, 3.1 (95% CI, 0.9–10.5); head, neck and face, 2.4 (95% CI, 0.5–10.2); and others, 1.4 (95% CI, 0.7–2.5). The odds ratios by cell type were: fibromatous, 1.8 (95% CI, 0.7–4.7); adipose, 1.1 (95% CI, 0.2–4.2), myomatous, 2.1 (95% CI, 0.8–5.3), and others, 1.9 (95% CI, 0.9–3.9). The relative risk was highest for those diagnosed at age 80 years or above (relative risk, 3.2; 95% CI, 1.0–10.1).

(*g*) *Breast*

In a study by Spangler *et al.* (2001b) and Spangler (2002), Cherokee Indian women were investigated over a 2-year period, and prevalent breast cancer cases were identified through medical histories from the women themselves, and other female survey respondents formed the control group; the women were interviewed in their homes. The odds ratio for use of smokeless tobacco in the women diagnosed at less than 55 years of age was 1.3 (one case; 95% CI, 0.1–13.9) and that in women diagnosed at more than 55 years was 1.2 (two cases; 95% CI, 0.1–9.5). [There are major limitations to this study. There was no medical verification of breast cancer and the time relationship between use of smokeless tobacco and breast cancer diagnosis was not reported.]

(*h*) *Cervix uteri*

The population-based case–control study of randomly selected patients from the Third National Cancer Survey (1969–71) also reported results on cervical cancer (Williams & Horm, 1977). Controls for the cervical cancer case group comprised patients with other cancers that were unrelated to smoking. The relative risks controlled for smoking, age and race were 4.7 (six cases: $p < 0.05$) for moderate and 3.6 (four cases; non-significant) for heavy use of chewing tobacco or snuff. [The Working Group noted that multiple comparisons were made of many risk factors and many cancer sites in this study and, therefore, that some positive findings may have been due to chance alone.]

(*i*) *Prostate*

The 1601 controls from a case–control study of cancer were used to form a historical cohort in Iowa, USA; they were ascertained in 1986–89 via RDD and US HCFA, had Iowa residency, were aged 40–86 years and had no prior cancer. Twenty-four subjects who required proxy respondents were excluded, which left 1577 in the cohort who answered a mailed questionnaire that was supplemented by telephone interviews. The cohort was followed for vital status, and three persons were lost to follow-up; 103 cases of prostate cancer were identified through the state cancer registry. Two cases were subsequently excluded due to diagnosis before the questionnaire was returned. The authors reported that 'no association was seen for [....] snuff and chewing tobacco' (Putnam *et al.*, 2000). [The Working Group noted that data were not presented to support this statement.]

The Lutheran Brotherhood cohort was examined for deaths from prostate cancer (Hsing *et al.*, 1990). Relative to never use of tobacco, the relative risk for users of smokeless tobacco only was 4.5 (10 deaths; 95% CI, 2.1–9.7) adjusted for age. Ever use of smokeless tobacco compared with never use of tobacco yielded a relative risk of 2.1 (42 deaths; 95% CI, 1.1–4.1), adjusted for age and cigarette smoking. Other relative risks were 1.8 (13 deaths; 95% CI, 0.8–3.9) for former users of smokeless tobacco, 1.4 (5 deaths; 95% CI, 0.5–3.9) for occasional users and 2.4 (24 deaths; 95% CI, 1.3–4.9) for regular users, adjusted for age and cigarette smoking. The relative risk for death from prostate cancer listed on the death certificate, but not as the underlying cause, was 2.3 (14 deaths; 95% CI, 1.0–5.2) for regular users of smokeless tobacco and 2.5 (eight deaths; 95% CI, 1.0–6.5) for smokeless tobacco only users.

In the US Veterans' cohort, the relative risk for prostate cancer of smokeless tobacco only users compared with those who never used any tobacco was 1.2 (48 deaths; 95% CI, 0.9–1.6) (Hsing *et al.*, 1991).

In-home interviews were conducted with population-based cases of prostate cancer and RDD and HCFA controls in the Atlanta metropolitan area, in Detroit and in 10 New Jersey counties, USA (Hayes *et al.*, 1994). Controls were frequency-matched on age and race. Interviews were completed for 981 cases and 1315 controls. Relative to those who had never used tobacco, the odds ratios for chewing tobacco were 1.0 (95% CI, 0.6–1.5) for former users and 0.5 (95% CI, 0.2–1.0) for current users. For snuff, the odds ratios were 0.6 (95% CI, 0.3–1.4) for former and 5.5 (95% CI, 1.2–26.2) for current users.

(*j*) *Penis*

In a case–control study in Chennai, India, in which 505 cases of squamous-cell carcinoma of the penis were identified over a period of 30 years (Harish & Ravi, 1995), the relative risk for snuff users was 4.2 (95% CI, 1.6–11.3) after adjustment for smoking, tobacco chewing and phimosis. [It was not clear whether snuff was used orally or nasally.]

(k) *Urinary bladder*

A population-based case–control study was conducted in three provinces of Canada (Howe *et al.*, 1980). Eligible cases were all patients who had recently been diagnosed with urinary bladder cancer; controls were matched individually for sex, age and neighbourhood. The study included 480 men and 152 women (cases), and the same number of controls. In a matched pair analysis, no association between chewing tobacco and bladder cancer was observed; the estimated relative risk was 0.9, based on 61 discordant pairs, and remained unchanged after controlling for smoking.

The study by Hartge *et al.* (1985) included 2982 patients with urinary bladder cancer who were identified from records of 10 large population-based cancer registries throughout the USA (1977–78) and who were interviewed to obtain information on tobacco use and other factors. A total of 5782 population-based controls were included: controls aged under 65 years were chosen by a RDD and those aged 65 years and older were selected from the HCFA. The analysis was restricted to men. Among men who never smoked cigarettes, the relative risk for bladder cancer was 1.0 for chewing tobacco and 0.8 for use of snuff, after controlling for age, race, residence and other non-cigarette tobacco practices.

In a population-based case–control study, urinary bladder cancer cases were identified from the Utah Cancer Registry between 1970 and 1983 in individuals aged 21–84 years (Slattery *et al.*, 1988). RDD and HCFA controls were frequency-matched to cases on age and sex. After exclusion of women and non-white subjects, 332 cases and 686 controls for whom information on tobacco was obtained through an interview at the participants' homes were analysed. The crude odds ratios for urinary bladder cancer were 1.03 for use of snuff and 0.96 for chewing tobacco. When never smokers and smokers were examined separately, the odds ratios for snuff use were 2.7 (95% CI, 0.5–15.6) among never smokers and 0.8 (95% CI, 0.4–1.4) among smokers. Corresponding estimates for tobacco chewing were 2.8 (95% CI, 0.4–20.2) and 1.2 (95% CI, 0.7–2.2).

A population-based case–control study of urinary bladder cancer was conducted in the Alberta and Ontario populations of Canada (Burch *et al.*, 1989). Province-wide annually updated listings were used to identify randomly selected controls who were matched to cases on age, sex and area of residence, and all participants completed a questionnaire. Response rates were 67% for cases and 53% for controls. The odds ratio for urinary bladder cancer was 0.6 (95% CI, 0.3–1.1) for ever versus never use of snuff, and 0.5 (95% CI, 0.2–1.1) for ever versus never chewing tobacco, adjusted for lifetime cigarette consumption. Analyses that were restricted to subjects who had never smoked cigarettes gave similar results [data not shown].

(l) *Kidney*

A hospital-based case–control study identified cases of renal cancer aged 20–80 years in 18 hospitals in six US cities in 1977–83 (Goodman *et al.*, 1986). A total of 267 controls were identified by RDD and were individually matched 1:1 on hospital, sex, race, age, time of admission and non-tobacco- and non-obesity-related diseases. The matched odds

ratio for chewing tobacco among men was 4.0 (95% CI, 1.1–14.2) compared with never users. The final logistic model included Quetelet index, consumption of decaffeinated coffee, pack–years of cigarette smoking and chewing tobacco (ever, never and an interaction term of pack–years × chewing tobacco). Based on this model, the odds ratio for chewing tobacco among never users of cigarettes was 0.9 (95% CI, 0.2–5.1).

In a case–control study in 29 hospitals in Oklahoma, USA (Asal *et al.*, 1988), 315 cases and 313 controls were individually matched on age, sex, race, hospital and time of interview. Controls with kidney disease or psychiatric diagnoses were excluded and interviews were conducted during hospitalization. Among men, snuff use was associated with a risk for renal-cell carcinoma to yield an odds ratio of 3.6 (95% CI, 1.2–13.3). [Smoking was not controlled for.]

A case–control study (McLaughlin *et al.*, 1995) that used cases from several countries was carried out in Europe, Australia and the USA. The main source of cases was population-based cancer registries, except in Germany, where cases were identified through hospital networks. Controls were selected from various sources, and interviews were completed for 1732 cases and 2309 controls. The odds ratio for use of smokeless tobacco only versus no use of tobacco was 1.3 (95% CI, 0.6–3.1), adjusted for age, sex, centre and body mass index.

In a case–control study in the USA, cases were ascertained from selected hospitals in the states of New York, Pennsylvania, Illinois and Michigan during 1977–93 (Muscat *et al.*, 1995). Controls who had conditions that were unrelated to tobacco use were selected from the same hospitals and were frequency-matched on age, sex, race, hospital and year of diagnosis. Questionnaires were administered by interviewers in the hospitals. A total of 788 cases and 779 controls were included in the analyses. Relative to men who had never chewed tobacco, the odds ratio for ever use of smokeless tobacco regularly for at least 1 year was 3.2 (95% CI, 1.1–8.7). A dose–response relationship was observed and yielded an odds ratio of 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. [Smoking was not controlled for.]

(*m*) *Brain*

In a population-based case–control study in Iowa, USA, data from 375 brain cancer cases and 2434 controls from drivers licence records and HCFA were analysed (Zheng *et al.*, 2001). Cases were 40–85 years of age and controls were selected at a ratio to cases of 6.5:1. Information on tobacco use was obtained through a mailed questionnaire. Next of kin were used as respondents when the cases were deceased. Response rates were above 80% for both cases and controls. The authors reported that "use of [...] snuff or chewing tobacco was also not associated with a significantly increased risk of brain cancer for either men or women". [Data to support this statement were not presented.]

(*n*) *Non-Hodgkin lymphoma*

Iowa and non-metropolitan areas in Minnesota, USA, were the sites of two population-based studies of non-Hodgkin lymphoma in men (Brown *et al.*, 1992a; Schroeder *et al.*,

2002). White male cases aged 30 years and older were identified in 1980–82. Living cases were matched to RDD and HCFA controls; state vital status lists provided controls for deceased cases. Controls were frequency-matched to cases on age, state of residence and vital status. In-person interviews were conducted for 622 cases and 1245 controls or their next of kin. Persons were considered to be smokeless tobacco users if they had used it daily for at least 3 months. In an analysis by lymphoma subtypes using cases and living controls only, odds ratios adjusted for age and state for users of smokeless tobacco only compared with never users of tobacco were: all lymphomas, 1.3 (95% CI, 0.7–2.5); follicular, 1.7 (95% CI, 0.7–4.3); diffuse, 0.8 (95% CI, 0.3–2.3); small lymphocytic, 1.7 (95% CI, 0.5–5.4); high-grade, 1.3 (95% CI, 0.1–10.8); and unclassified, 1.5 (95% CI, 0.3–7.4). For multiple myeloma, the odds ratio was 1.9 (95% CI, 0.5–6.6), adjusted for age. In a further analysis of lymphoma subtypes by t(14;18) positivity (Schroeder *et al.*, 2002), no consistent pattern emerged.

(*o*) *Leukaemia*

Brown *et al.* (1992b) conducted a case–control study of tobacco use and risk for leukaemia. Personal interviews were conducted with subjects or with close relatives for those who were deceased or too ill. Odds ratios adjusted for age, state and use of alcoholic beverages for users of smokeless tobacco only compared with non-users of tobacco were: all leukemias, 1.8 (95% CI, 0.9–3.3); acute non-lymphocytic, 0.9 (95% CI, 0.2–3.1); chronic myelogenous, 2.1 (95% CI, 0.4–10.7); chronic lymphocytic, 1.9 (95% CI, 0.8–4.3); myelodysplasia, 2.7 (95% CI, 0.8–9.4); other, 3.0 (95% CI, 0.9–9.2).

2.3 Nasal use

2.3.1 *Cancer of the oral cavity*

Three case–control studies from Kerala, India (Sankaranarayanan *et al.*, 1989a,b, 1990a) investigated the association between nasal snuff use and cancer of oral subsites among men (Table 78).

The first part of the study (Sankaranarayanan *et al.*, 1989b) focused on cancer of the anterior two-thirds of tongue and floor of the mouth and comprised 158 cases and 314 controls who were selected from a pool of 546 hospital controls with non-malignant conditions at sites other than the head and neck and were matched for age and religion. For cancer of the tongue and floor of the mouth, the age-adjusted odds ratio was 3.0 (95% CI, 0.9–9.6) for regular snuff users and 4.3 (95% CI, 1.2–14.7) for occasional snuff users. The odds ratio for < 100 unit years was 10.0 (95% CI, 1.2–86.1) and that for ≥ 100 unit years was 1.1 (95% CI, 0.2–6.2).

The second part of the study on cancer of the gingiva (Sankaranarayanan *et al.*, 1989a), comprised 109 cases, and the third part on cancer of buccal and labial mucosa comprised 250 cases (Sankaranarayanan *et al.*, 1990a). All 546 controls from the same pool as that in the first study were used for both the second and third studies. For gingival

Table 78. Case–control studies of nasal use of smokeless tobacco and oral cancer

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders
Sankaranarayanan *et al.* (1989b), India, 1983–84	Tongue (ICD-9 141.1, 141.2, 141.3, 141.4), floor of mouth (ICD-9, 144)	158 men; biopsy-proved cases of cancer from one hospital	314 male patients with non-malignant conditions at sites other than head and neck; matched by age, religion	*Snuff inhalation* No Yes	142 8	1.0 3.0 (0.9–9.6)	Age
				Snuff inhalation Never < 100 unit years ≥ 100 unit years	142 6 2	1.0 10.0 (1.2–86.1) 1.1 (0.2–6.2)	
Sankaranarayanan *et al.* (1989a), India, 1983–84	Gingiva (ICD-9, 143.0, 143.1)	109 men from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	*Snuff inhalation* No Yes	100 4	1.0 3.0 (0.7–12.6)	*Bidis*, alcoholic beverages, betel quid
Sankaranarayanan *et al.* (1990a), India, 1983–84	Buccal mucosa (ICD-9, 145.0, 145.1, 145.6), labial mucosa (ICD-9, 140.3, 140.4)	250 men from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	*Snuff inhalation* No Yes	232 12	1.0 2.9 (0.98–8.8)	*Bidis*, alcoholic beverages, betel quid
				Snuff inhalation Never < 100 unit years ≥ 100 unit years	232 7 5	1.0 15.7 (2.0–125.3) 2.0 (0.6–6.6)	Age

cancer, the age-adjusted odds ratio for daily snuff use was 3.9 (95% CI, 1.2–12.7) and that for occasional use was 3.8 (95% CI, 1.1–13.5). The odds ratio for regular snuff use was 3.0 (95% CI, 0.7–12.7) after adjustment for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use. For cancer of the buccal and labial mucosa, the age-adjusted odds ratio was 4.0 (95% CI, 1.5–10.3) for regular snuff users and 2.3 (95% CI, 0.8–7.0) for occasional snuff users. After adjusting for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use, the odds ratio was 2.9 (95% CI, 0.98–8.8). The odds ratio for users of < 100 unit years was 15.7 (95% CI, 2.0–125.3) and that for users of ≥ 100 unit years was 2.0 (95% CI, 0.6–6.6).

2.3.2 *Cancer of the oesophagus*

The series of case–control studies from Kerala, India, also reported on 267 male patients with cancer of the oesophagus and the same 546 controls (Sankaranarayanan *et al.*, 1991). The age-adjusted odds ratio for daily snuff use was 2.4 (95% CI, 0.8–7.0) and that for occasional use was 3.6 (95% CI, 1.2–10.7) (Table 79). [The Working Group noted that effect estimates were not adjusted for smoking or betel quid chewing.]

2.3.3 *Cancer of the paranasal sinus*

Shapiro *et al.* (1955) studied 37 Bantu cases of cancer of the paranasal sinus from radiation therapy department records from 1949–51 of a group of hospitals in Johannesburg, South Africa. Cancer of the paranasal sinuses (22 men, five women) accounted for a high proportion of respiratory tract cancer (71% of men, 83% of women) in Bantu Africans. This was in sharp contrast to European cases seen in the Transvaal, where only seven (5%) of the respiratory tract cancers occurred in the nasal sinuses. Most of the cancers were in the maxillary antrum (28/34 studied) and were described typically as well-differentiated 'squamous epitheliomata'. The authors noted that 80% of the 28 antral cancer cases reported 'prolonged and heavy' use of snuff in contrast to only 34% of Bantu men with cancer at other sites. According to Keen *et al.* (1955), 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. The authors stated that 'there was no obvious correlation' between cancer of the maxillary antrum and cigarette, pipe or *dagga* [marijuana] smoking. [The Working Group noted that the source and nature of the control group was not described.]

2.3.4 *Cancer of the larynx*

The series of case–control studies from Kerala, India, also reported on 191 male patients with biopsy-proved cancer of the larynx and used the same 546 controls (Sankaranarayanan *et al.*, 1990b). The age-adjusted odds ratio for daily snuff use was 1.2 (95% CI, 0.3–4.9) and that for occasional use was 2.8 (95% CI, 0.9–8.7) (Table 79). [The Working Group noted that effect estimates were not adjusted for smoking.]

Table 79. Case–control studies of nasal use of smokeless tobacco and cancer at other sites

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders
Oesophagus						
Sankaranarayanan *et al.* (1991), India, 1983–84	207 men from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	Snuff inhalation No Yes	 192 7	 1.0 2.4 (0.8–7.0)	Age
Larynx						
Sankaranarayanan *et al.* (1990b), India, 1983–84	191 men biopsy-proved from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	Snuff inhalation No Yes	 182 3	 1.0 1.2 (0.3–4.9)	Age
Lung						
Hsairi *et al.* (1993), Tunisia, 1988–89	110 (107 men, 3 women) from one hospital in Tunis; 77 histologically confirmed	110 men individually matched on age, sex, cigarettes/day (± 5)	Use of smokeless tobacco	20	2.2 (0.9–5.6)	Age, sex, number of cigarettes/day, water pipe, cannabis

2.3.5 *Cancer of the lung*

A case–control study was conducted by Hsairi *et al.* (1993) on 110 (107 men, three women) bronchial cancer patients and 110 controls individually matched for age, sex and number of cigarettes (± 5) smoked per day (Table 79). Cases were recruited from December 1988 to May 1989 in the Ariana Hospital that covered Tunis City and the suburban area; controls were chosen among residents of the same area. Twenty cases (18.2%) and eight controls (7.3%) had ever inhaled snuff, which yielded a crude odds ratio of 2.8 (95% CI, 1.2–6.8). The Cochrane Mantel-Haenzel method was used to adjust the association for age, sex, cigarette use (0, 1–10, 11–20, ≥ 20 per day), and water pipe and cannabis use. The adjusted odds ratio obtained was 2.2 (95% CI, 0.9–5.6). The authors indicated that no quantitative analyses were appropriated as the amounts used were 'relatively weak'. [The paper was written in French and the expression 'tabac à priser' was used for smokeless tobacco. The Working Group deduced that this represented nasal use of snuff according to the popular meaning of this expression. Nine interviewers were involved in the data collection. The control recruitment was not reported in detail.]

3. Studies of Cancer in Experimental Animals

The Working Group that evaluated smokeless tobacco previously noted that the majority of the early studies evaluated at that time (IARC, 1985) had various deficiencies, such as lack of quantitative and qualitative information on the nature of tobacco extracts and the degree of extraction, insufficient length of treatment, small group sizes and, in some cases, lack of appropriate controls. Since that time, new studies have been published and are included in this section. The cumulative published evidence for carcinogenicity of smokeless tobacco in experimental animals is summarized below and has also been reviewed recently (Hoffmann & Djordjevic, 1997; Grasso & Mann, 1998).

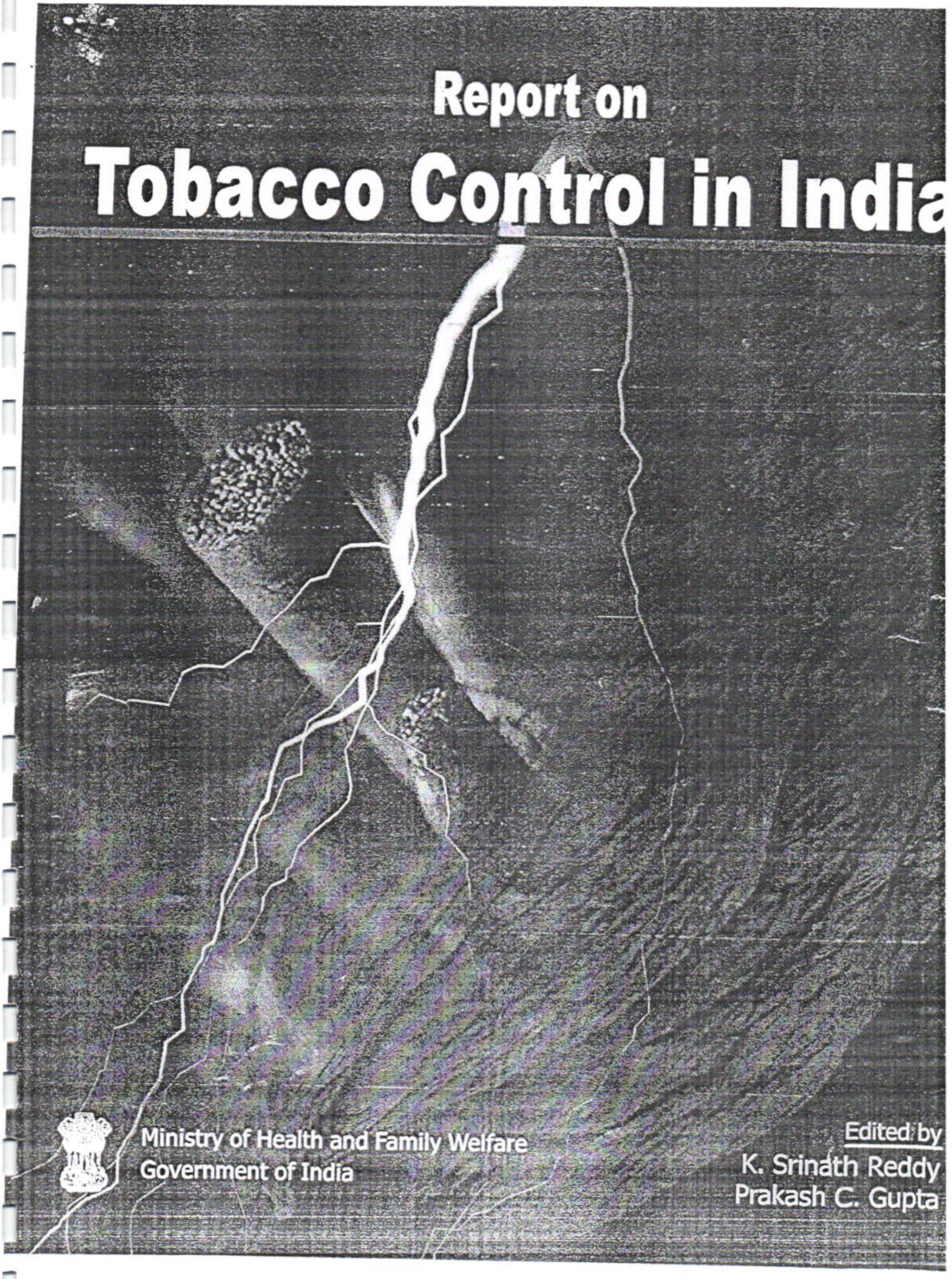
3.1 Tobacco

3.1.1 *Oral administration*

(*a*) *Mouse*

Groups [numbers unspecified] of male Swiss mice, 6–8 weeks of age, were administered a tobacco extract (ethanol extract from 50 g tobacco diluted in 10 mL distilled water) from a commercially available Indian chewing tobacco at a dilution of 1:25 or 1:50 [actual dose unspecified] by oral intubation for 15–20 months. A further group of mice was fed a diet that contained an extract of 10 g tobacco per 5 kg diet for up to 25 months. A group of 20 mice received distilled water only by intubation and served as controls. Administration of the 1:25 dilution was terminated at 18 weeks because of high mortality. Tumour incidences at 15–20 months were 0/4, 8/15 and 4/10 in the control, 1:50 dilution

Report on
Tobacco Control in India



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Hooklis

Hooklis are clay pipes commonly used in western India. Once the pipe is lit, it is smoked intermittently. On an average, 15 g of tobacco is smoked daily. *Hookli* smoking was practised by 11% of the 5227 men studied in the Bhavnagar district of Gujarat.[5]

Chillum

Chillum smoking is an exclusively male practice; it is limited to the northern states of India, predominantly in rural areas. The *chillum* is a straight, conical pipe made of clay, 10–14 cm long, held vertically. In a survey of 35,000 individuals in the Mainpuri district of Uttar Pradesh, 28% of the villagers were found to be *chillum* smokers. *Chillum* smoking requires a deep pulmonary effort. Often, one *chillum* is shared by a group. They are made locally, are inexpensive and easily available. *Chillum* probably predates the introduction of tobacco to India and was used for smoking opium and other narcotics.[6]

Hookah

The *hookah* is an Indian water pipe in which the tobacco smoke passes through water before inhalation.

In a random sample of 4859 men and 5481 women from the Darbhanga district of Bihar, 2% and 28%, respectively, reported smoking the *hookah*.[5] The reason given for this female predominance is that it is inconvenient for men to carry a *hookah*, whereas women remain at home most of the time. There has been a considerable fall in the reported consumption of *hookah* tobacco. *Hookah* smoking thus appears to be on the decline in India.[1]

Non-tobacco smoking products

Non-tobacco smoking products are also available. An herbal cigarette (brand name *Nirdosh*) has been available for a long time. Recently a herbal *beedi* (brand name *Vardaan*) has been launched. Ostensibly, these products are marketed as aids to smoking cessation. No scientific evaluations have been carried out and little is known about their efficacy.

Smokeless forms of tobacco

The term 'smokeless tobacco' is used to describe tobacco that is consumed without heating or burning at the time of use. Smokeless tobacco can be used orally or nasally. For nasal use, a small quantity of very fine tobacco powder mixed with aromatic substances called dry snuff is inhaled. This form of smokeless tobacco use, although still practised, is not very common in India. No scientific report is available in the literature and therefore nasal inhalation of snuff will not be further dealt with in this chapter.

The oral use of smokeless tobacco is widely prevalent in India; the different methods of consumption include chewing, sucking and applying tobacco preparations to the teeth and gums. Smokeless tobacco products are often made at home but are also manufactured. Recently, a variety of smokeless tobacco products have been produced industrially on a large scale, commercially marketed and are available in small plastic and aluminium foil packets.

Paan (betel quid) with tobacco

Paan chewing, or betel quid chewing, is often erroneously referred to as 'betel nut chewing'. *Paan* consists of four main ingredients—betel leaf (*Piper betle*), areca nut (*Areca catechu*), slaked lime [$Ca(OH_2)$] and catechu (*Acacia catechu*). Betel leaves contain volatile oils such as eugenol and terpenes, nitrates and small quantities of sugar, starch, tannin and several other substances.[7] Condiments and sweetening agents may be added as per regional practices and individual preferences. Some time after its introduction, tobacco became an important constituent of *paan*, and currently most habitual *paan* chewers include tobacco.

Tobacco is the most important ingredient of *paan* for regular users. It is used in the raw state (as in Kerala) as well as after processing. Processing, additives and names differ from place to place. Tobacco is referred to as *kaddipudi* and *hogesoppu* in Karnataka, *kadapan* in Orissa and West Bengal, and *pattiwala* in Uttar Pradesh. *Zarda* and *kiwam* are commercially manufactured varieties often used as ingredients in *paan*.

Paan masala

Paan masala is a commercial preparation containing areca nut, slaked lime, catechu and condiments, with or without powdered tobacco. *Paan masala* contains almost all the ingredients that go into the making of a *paan*, but are dehydrated so that the final product is not perishable. It comes in attractive sachets and tins, which can be stored and carried conveniently. *Paan masala* is very popular in urban areas and is fast becoming popular in rural areas. Although the actual prevalence of this practice is not known, its popularity can be gauged by the production figures: according to commercial estimates, the Indian market for *paan masala* is now worth several hundred million US dollars.

Tobacco, areca nut and slaked lime preparations

Combinations of tobacco, areca nut and slaked lime are chewed in several regions of north India, where they are known by different names.

Mainpuri tobacco

In the Mainpuri district of Uttar Pradesh and nearby areas, this preparation is very popular. It contains mainly tobacco with slaked lime, finely cut areca nut, camphor and cloves. In a study of 35,000 individuals in Mainpuri, 7% of the villagers used this product.[6]

Mawa

This preparation contains thin shavings of areca nut with the addition of some tobacco and slaked lime. Its use is becoming popular in Gujarat, especially among the youth. *Mawa* use is also prevalent in other regions of the country. The prevalence of *mawa* chewing has increased tremendously in recent years. Its magnitude can be assessed from the fact that the Bhavnagar city administration appealed to the people not to litter the streets with the cellophane wrappers of *mawa*, as they clogged the city drains!

Tobacco and slaked lime (*khaini*)

Use of a mixture of sun-dried tobacco and slaked lime, known in some areas as *khaini*, is widespread in Maharashtra and several states of north India. A regular *khaini* user may carry a double-ended metal container, one side of which is filled with tobacco and the other with slightly moistened slaked lime. A small quantity of tobacco is taken in the palm and a little slaked lime is added. The ingredients are then mixed vigorously with the thumb and placed in the mouth. In Maharashtra and Gujarat, *khaini* is placed in the premolar region of the mandibular groove, whereas in Bihar and Uttar Pradesh, it is generally held in the lower labial groove. In the Singhbhum district of Bihar, this product is often kept on the dorsum of the tongue. In a study of over 100,000 villagers in Pune, Maharashtra, 28% used tobacco–slaked lime; the practice was more common among men (52%) than women (10%). In the Singhbhum and Darbhanga districts of Bihar, 27% and 44% of the 4800 and 4856 men, respectively, used *khaini* and of the 5248 and 5481 women, 10% and 7%, respectively, used *khaini*.[8]

Chewing tobacco

Small pieces of raw or commercially available finely cut tobacco are used for this purpose. Chewing of tobacco alone, however, does not appear to be very common in India. Among the 10,000 dental outpatients in Lucknow, Uttar Pradesh, and 57,000 industrial workers in Ahmedabad, Gujarat, 2.1% and 2.6% chewed tobacco alone, respectively.[9,10]

Snus

Swedish snuff called *snus* is available in teabag-like pouches. The pouch can be kept in the buccal or labial groove and sucked. It is marketed in India by the Swedish Match Company under the brand name Click.

Tobacco products for application

Several smokeless tobacco preparations such as *mishri*, *gudhaku*, *bajjar* and creamy snuff, are intended primarily for cleaning the teeth. Such use, however, soon becomes an addiction. In India, there is a widespread misconception that tobacco is good for the teeth. Many companies take advantage of this misconception by packaging and positioning their products as dental care products without explicitly stating so. The reason is that by law, oral care products cannot contain tobacco. The law is not strictly enforced and some oral care products may still contain tobacco.

Mishri

Mishri is a roasted, powdered preparation made by baking tobacco on a hot metal plate until it is uniformly black. Women, who use it to clean their teeth initially, soon apply *mishri* several times a day. This practice is common in Maharashtra. In a survey of 100,000 individuals in a rural area, 22% were *mishri* users; the prevalence was 39% among women and 0.8% among men.[8] *Mishri* use is also prevalent in Goa.

Gul

Gul is a pyrolysed tobacco product. It is marketed under different brand names in small tin cans and used as a dentifrice in the eastern part of India. In the Global Youth Tobacco Survey (GYTS), *gul* use was reported by 6% in Bihar, 3% each in Arunachal Pradesh and Nagaland, 2% each in Assam, UP and Uttaranchal.[2,5] In similar surveys of school personnel in several northeastern states of India, female school personnel reported significantly higher *gul* use than males; Assam (13.5% vs 0.1%), Meghalaya (25% vs 1.9%), Nagaland (6.2% vs 1.4%) and Sikkim (46.5% vs 3.9%).[11,12]

Bajjar

Bajjar is dry snuff (also known as *tapkeer)* applied commonly by women in Gujarat on the teeth and gums. In a survey of 4844 women in Bhavnagar district, 14% reported using *bajjar*.[4]

Lal dantmanjan

Lal dantmanjan is a dentifrice; a red-coloured tooth powder. Traditionally, it contained tobacco but after the passage of a law banning the use of tobacco in dental care products, the listing of tobacco as an ingredient was stopped. A laboratory test of five samples of red tooth powder that did not declare tobacco as an ingredient found a tobacco content of 9.3–248 mg per gram of tooth powder.[12] The GYTS, which focuses on school students in the age group of 13–15 years, found the prevalence of its use to be 49% in Bihar, 29% each in UP and Uttaranchal, 25% in Orissa, 9% in Mizoram, 5% in Nagaland, 4% each in Arunachal, Assam and Meghalaya, 3% in Tripura, and 2% each in Goa, Maharashtra, Manipur and Sikkim.[12]

Gudhaku

Gudhaku is a paste made of tobacco and molasses. It is available commercially and is carried in a metal container but can be made by the users themselves. It is commonly used in Bihar, Orissa, Uttar Pradesh and Uttaranchal. *Gudhaku* is applied to the teeth and gums, predominantly by women. In the GYTS, the prevalence in these states ranged from 4% to 16%.[10,11] In a survey in the Singhbhum district of Bihar, 1% of men and 16% of women used *gudhaku*.[5]

Creamy snuff

Commercial preparations of tobacco paste are marketed in toothpaste-like tubes. They are advertised as possessing anti-bacterial activity and being good for the gums and teeth. These products are thus used like regular toothpaste,

but users soon become addicted. This practice seems popular with children in Goa.[13]

Tobacco water

Tobacco water (known as *tuibur* in Mizoram and *hidakphu* in Manipur) is manufactured by passing tobacco smoke through water. Its use was reported by 872 persons (7.2%) among the 12,185 adults surveyed in the Aizawl district of Mizoram and 139 persons (6.5%) among the 2137 adults surveyed in the Churchandpur district of Manipur; use was similar among males and females. The frequency of tobacco water use varied from 1 to 30 times/day; in Aizawl and Churchandpur districts, 36.7% and 92.1% reported being frequent tobacco water users (more than five times a day), respectively.[14]

Nicotine chewing gum

Nicotine chewing gum containing 2% nicotine (brand name *good-kha*) has been launched as a help for tobacco cessation. For chewers, it is available in *gutka* flavour and for smokers, in mint flavour.

Areca nut preparations

Some areca nut preparations are chewed without the inclusion of tobacco, but this practice may be present concurrently with the use of smokeless tobacco or tobacco smoking. Alkaloids present in areca nut are known to give rise to carcinogenic nitrosamines and areca nut has recently been evaluated as a human carcinogen by the World Health Organization (WHO).[15] The use of areca nut by itself appears to be mildly addictive but when used with tobacco, the effect multiplies manifold. Chewing of areca nut products is very common in India; therefore, a brief resume of these products is included here.

Areca nut

In addition to being an ingredient of *paan*, occasional chewing of areca nut (usually processed) alone is quite common in India, but habitual chewing is comparatively rare. Exclusive areca nut chewing was observed in 2% of 100,000 villagers in Maharashtra.[8] In other rural areas of India also, areca nut chewing was reported to a limited extent. In Assam, a fermented form of areca nut, known as *tamol* or *bura tamol*, is chewed extensively. This is prepared by preserving raw areca nuts together with areca leaves in an underground pit with an inner lining of straw for four months. *Bura tamol* is often infected with fungus. This product contains high levels of arecoline.

Supari

Areca nut is known as *supari* in several parts of north India. Some commercial *supari* preparations are made by cutting dried areca nuts into bits and roasting them in fat to which flavouring, sweetening agents and condiments are added. *Supari* is marketed in attractive aluminium foil packs, in tins and in simple paper packets. Offering *supari* to guests, especially after meals, is a prevalent and well-accepted social custom.

Meetha mawa

Meetha (sweet) *mawa* consists of thin shavings of areca nut, grated coconut, dried fruits and other sweetening agents. It is used commonly in Gujarat and similar preparations with different names are used widely in other regions.

Paan without tobacco

Occasional *paan* chewers generally prefer *paan* without tobacco. Chewing *paan* without tobacco, known as *tambula* in Sanskrit, is an ancient practice in India. Areca nut is an indispensable ingredient of *paan*. In addition, a wide range of chewing products including a chewing gum that may not contain either areca nut or tobacco but contains strong betel quid flavours is available in the market.

3.1 TOBACCO USE PRACTICES

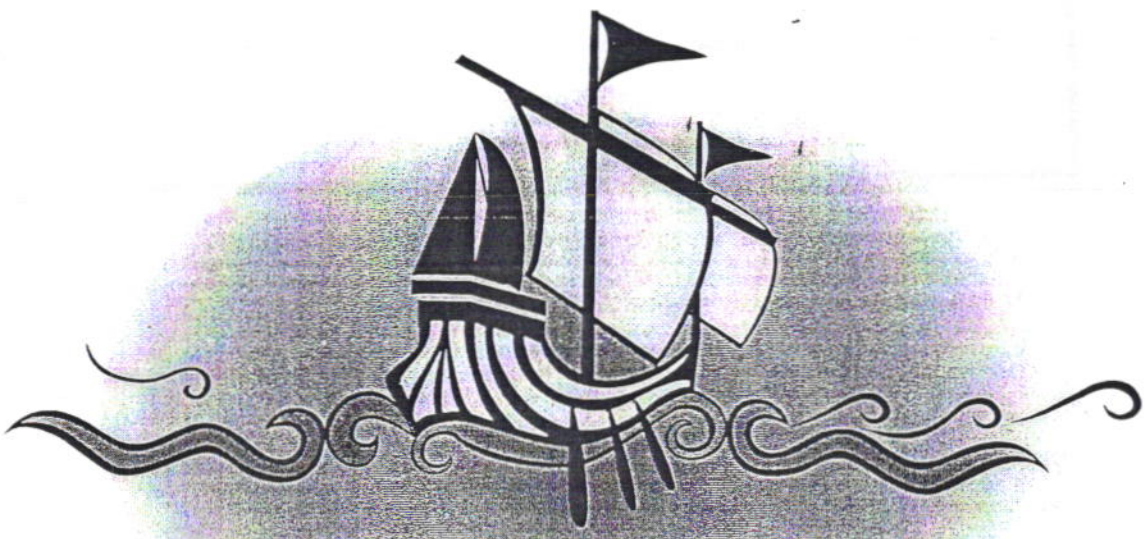
KEY MESSAGES

- In India, *beedi* smoking is the most popular form of tobacco smoking.
- Cigarette smoking is the second most popular form of tobacco smoking.
- *Paan* with tobacco is the major chewing form of tobacco.
- Dry tobacco–areca nut preparations such as *paan masala*, *gutka* and *mawa* are also popular and highly addictive.
- Tobacco dentifrice is popular, especially in some areas, and children also use it.

135

ANNEXURE - 3

Smokeless Tobacco Fact Sheets



September 22-25, 2002

3rd International Conference on Smokeless Tobacco

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Smokeless Tobacco Fact Sheets

Introduction

Smokeless tobacco products have been in existence for thousands of years among populations in South America and Southeast Asia. Over time, these products have gained popularity in the throughout the world. Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Oral smokeless tobacco products are placed in the mouth, cheek or lip and sucked (dipped) or chewed. Tobacco pastes or powders are used in a similar manner and placed on the gums or teeth. Fine tobacco powder mixtures are usually inhaled and absorbed in the nasal passages.

There is sufficient evidence that the use of smokeless tobacco causes cancer in humans. Smokeless tobacco contains carcinogens, which contribute to cancers of the oral cavity and the risk of other head and neck cancers. Smokeless tobacco use also causes a number of noncancerous oral conditions and can lead to nicotine addiction similar to that produced by cigarette smoking.

This compendium of **fact sheets** on smokeless tobacco products includes information about the brand and common names of the products, their geographic location of use, their constituents (ingredients), how the products are used, who primarily uses the products, and the processes for manufacturing the products. This information has been organized by geographic region of the world – the Americas, Europe, Asia, Africa and the Middle East.

These fact sheets were prepared by NCI and CDC specifically for the participants of the "3rd International Conference on Smokeless Tobacco, Advancing Science & Protecting Public Health," September 22-25, 2002, Stockholm, Sweden. They are works in progress and should be considered drafts. Any additional information on smokeless tobacco products would be greatly appreciated for the development of future editions.

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Chimó

BRAND NAMES: San Carleño, El Tovareño, El Tigrito, El Sabroso, El Gran Búfalo, El Dragón, El Morichal

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: Venezuela

PRODUCT CONSTITUENTS: Tobacco leaf, sodium bicarbonate, brown sugar, ashes from the Mamón tree (Meliccoca bijuga), and vanilla and anisette flavoring. The ingredients vary according to the region within Venezuela.

HOW USED: A small amount of Chimó is placed between the lip or cheek and the gum and left there for some time, usually 30 minutes. The mixture of Chimó and saliva is spit out.

WHO USES: Children, teenagers, unskilled workers in rural and urban areas. Chimó use has become fashionable in the last 5 years among urban teenagers, regardless of social and economic status.

PROCESSING / MANUFACTURING: Tobacco leaves are crushed and boiled for several hours, starch and fiber are discharged. The remaining portion becomes a concentrated product, 10 kilos of tobacco becomes one kilo of "Pasta". For maturation it is then placed in natural containers, or "taparas"(the dried fruit from Tapara tree), or wrapped in banana leavès. The matured paste is "seasoned" with other ingredients, listed above. Finally packaged in small tins or candy-like wrapped cylinders. Most factories are small.

Bhonsle RB, Murti PR, Gupta PC. Tobacco habits in India. In: Gupta PC, Hamner JE, Murti PR, editors. Control of Tobacco-Related Cancers and Other Diseases. Proceedings of an International Symposium; 1990 Jan 15-19; TIFR, Bombay, India. Oxford University Press 1992. p. 25-46.

Novoa D, Maudell W, Ross A, Torres R, Escaffi P. Chimó a risk factor for chronic cardiopathy in rural chagasic and non-chagasic Venezuelan adults. Presentation at the XI Congreso Latinoamericano de Parasitologia. Lima, Perú; 1993.

Persson PG, Carlsson S, Svanstrom L, Ostenson CG, Efendic S, Grill V. Cigarette smoking, oral moist snuff use and glucose intolerance. J Intern Med. 2000 Aug;248 (2):103-10.

Seelkopf C, Rojas A. Estudio sobre el Chimó. Universidad de Los Andes, Venezuela.

Wilbert J. The cultural significance of tobacco use in South America. In: Seaman G, Day JS, editors. Ancient Traditions: Shamanism in Central Asia and the Americas. Denver: University Press of Colorado & Denver Museum of Natural History; 1994. p. 47-76.

Nicotine Lozenge

BRAND NAMES: Ariva

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: United States

PRODUCT CONSTITUENTS: tobacco, mint, eucalyptus

HOW USED: Held in mouth and sucked until dissolved.

WHO USES: Not yet determined.

PROCESSING / MANUFACTURING: Commercially manufactured by Star Scientific.

Loose Leaf Chew

BRAND NAMES: Red Man, Red Man Golden Blend, Red Man Select, Granger, Work Horse (Swedish Match products), Scotten, Dillon, Levi Garrett, HB Scott, Taylors Pride, Red Fox (Conwood products), Beech-Nut Regular, Beech-Nut Wintergreen, Beech-Nut Spearmint (National products), Chattanooga Chew (Swisher product)

COMMON NAMES: chewing tobacco, spit tobacco

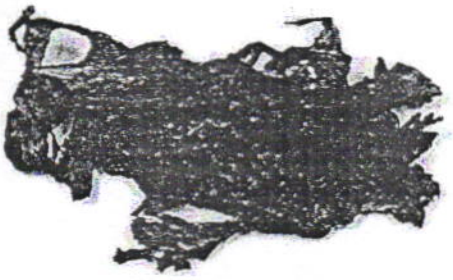
GEOGRAPHIC LOCATION OF USE: United States

PRODUCT CONSTITUENTS: leaf tobacco, sweetener, and/or licorice

HOW USED: A piece of tobacco 0.75 to 1 inch in diameter is placed between the cheek and lower lip, typically toward the back of the mouth. It is either chewed or held in place.[1] Saliva is spit or swallowed.

WHO USES: In 2000, U.S. prevalence of current (used within the past 30 days) smokeless tobacco use (includes both snuff and chewing tobacco) for those 12 years old and over was 3.4%: 6.5% of males and 0.5% of females.[2]

PROCESSING / MANUFACTURING: Commercially manufactured. Loose **cigar tobacco leaves** are air-cured, then stemmed, cut or granulated and loosely packed to form small strips of shredded tobacco. Most brands are sweetened and flavored with **licorice.** Typically sold in pouches weighing about 3 ounces.[1] Loose-leaf tobacco has a high average sugar content (approximately 35%).[3]



1 Asma, S. (1998). Definitions of tobacco products. Unpublished Work

2 Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, 2001.

3 Severson HH. The S.T.O.P Guide: Smokeless Tobacco Outreach & Prevention. 1 ed. Point Richmond (CA): Applied Behavior Science Press; 1997.

Moist Plug

BRAND NAMES: Red Man Moist Plug, Totems, RJ Gold (Swedish Match products), Levi Garrett Plus, Taylors Pride (Conwood products)

COMMON NAMES: chewing tobacco, spit tobacco

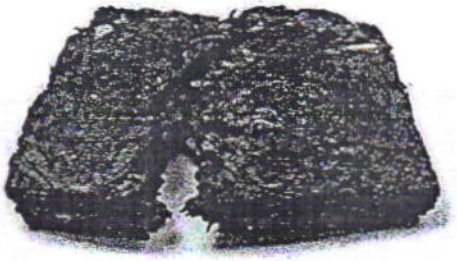
GEOGRAPHIC LOCATION OF USE: United States

PRODUCT CONSTITUENTS: enriched tobacco leaves, fine tobacco, sweetener, and/or licorice

HOW USED: Chewed or held between the cheek and lower lip.[1] Saliva is spit or swallowed.

WHO USES: In 2000, U.S. prevalence of current (used within the past 30 days) smokeless tobacco use (includes both snuff and chewing tobacco) for those 12 years old and over was 3.4%: 6.5% of males and 0.5% of females.[2]

PROCESSING / MANUFACTURING: Commercially manufactured. **Enriched tobacco leaves** (Burley and bright tobacco or cigar tobacco) or fragments are wrapped in **fine tobacco** and pressed into bricks. Moist plug tobacco has at least 15% moisture. Most plug tobacco is flavored and sweetened with **licorice**. Plus tobacco is packaged as a compressed brick or flat block wrapped inside natural tobacco leaves. Typically weighs 7 to 13 ounces.[1] Sugar content is approximately 24%.[3]



1 Asma, S. (1998). Definitions of tobacco products. Unpublished Work.

2 Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, 2001.

3 Severson HH. The S.T.O.P Guide: Smokeless Tobacco Outreach & Prevention. 1st ed. Point Richmond (CA): Applied Behavior Science Press; 1997.

Plug (chew)

BRAND NAMES: Days Work (Swedish Match product), Conwood (Conwood product), Brown & Williamson (Brown & Williamson product)

COMMON NAMES: chewing tobacco, spit tobacco

GEOGRAPHIC LOCATION OF USE: United States

PRODUCT CONSTITUENTS: enriched tobacco leaves, fine tobacco, sweetener and/or licorice

HOW USED: Chewed or held between the cheek and lower lip.[1] Saliva is spit or swallowed.

WHO USES: In 2000, U.S. prevalence of current (used within the past 30 days) smokeless tobacco use (includes both snuff and chewing tobacco) for those 12 years old and over was 3.4%: 6.5% of males and 0.5% of females.[2]

PROCESSING / MANUFACTURING: **Enriched tobacco leaves** (Burley and bright tobacco and cigar tobacco) or fragments are wrapped in **fine tobacco** and pressed into bricks. Plus or "firm plug" tobacco has less than 15% moisture. Most plug tobacco is flavored and sweetened with **licorice**. Plus tobacco is packaged as a compressed brick or flat block wrapped inside natural tobacco leaves. Package typically weighs 7 to 13 ounces.[1]

1 Asma, S. (1998). Definitions of tobacco products. Unpublished Work

2 Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, 2001.

Twist Roll (chew)

BRAND NAMES: Conwood (Conwood product), R.C. Owen (R.C. Owen product), R.J. Reynolds (R.J. Reynolds product)

COMMON NAMES: chewing tobacco, spit tobacco

GEOGRAPHIC LOCATION OF USE: United States

PRODUCT CONSTITUENTS: tobacco, tobacco leaf extract

HOW USED: Chewed or held between the cheek and lower lip.[1] Saliva is spit or swallowed.

WHO USES: In 2000, U.S. prevalence of current (used within the past 30 days) smokeless tobacco use (includes both snuff and chewing tobacco) for those 12 years old and over was 3.4%: 6.5% of males and 0.5% of females.[2]

PROCESSING / MANUFACTURING: Handmade by commercial manufacturers. Dark, air-cured leaf **tobacco** is treated with a tar-like **tobacco leaf extract** and twisted into rope-like strands that are dried. Typically, no flavoring or sweetener is added. The final product is a pliable, but dry, rope. The product is sold by the piece in small (1 to 2 ounce) or larger sizes based on the number of leaves in the twist.[1]

1 Asma, S. (1998). Definitions of tobacco products. Unpublished Work.

2 Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, 2001.

Gul

BRAND NAMES: None

COMMON NAMES: Gadakhu

GEOGRAPHIC LOCATION OF USE: Central and Eastern India[1]

PRODUCT CONSTITUENTS: tobacco powder, molasses, other ingredients

HOW USED: Often used for cleaning teeth.[1]

WHO USES: Primarily women.[2]

PROCESSING / MANUFACTURING: Commercially manufactured. Since 1986, gul has been machine produced and sold in toothpaste-like tubes.[3]

Photo not available

1 Puttaiah R., Carley K., Holavanahalli R. Tobacco, betel-quid chewing and oral health. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995. p.1-9.

2 Gupta, P. (2001). Regional Summary for Southeast Asia World Health Organization.

3 Trends in tobacco use (2001c). [On-line]. Available: http://www.doctoronnet.com/addictions/2trends.php3

Gutkha

BRAND NAMES: Manikchand, Moolchand, Tulsi, Shimla, Sikandar, Pan Parag

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: India, Southeast Asia, United Kingdom[1]

PRODUCT CONSTITUENTS: betel nut, catachu, tobacco, lime, saffron, flavoring

HOW USED: Held in the mouth and chewed. Saliva is generally spit out, but sometimes swallowed.[1]

WHO USES: Very popular among boys and young men due to targeted advertising and marketing.

PROCESSING / MANUFACTURING: Commercially manufactured. **Tobacco**, **betel nut** and **catechu** are mixed together with several other ingredients, flavored, and sweetened. Product is sold in small brightly-colored packets, which appeal to children.[1,2]

1 Gangwal, K. (2001). What is gutkha? [On-line]. Available:http://www.antigutkha.com/what_is_gutkha.html

2 Gupta PC. Gutka: a major new tobacco hazard in India. Tob Control 1999;8:132.

Iq'mik

BRAND NAMES: None

COMMON NAMES: None

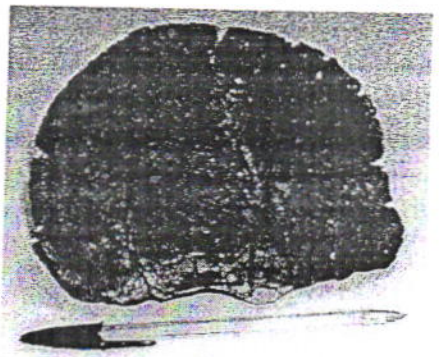
GEOGRAPHIC LOCATION OF USE: Alaska (United States)

PRODUCT CONSTITUENTS: tobacco, punk ash[1]

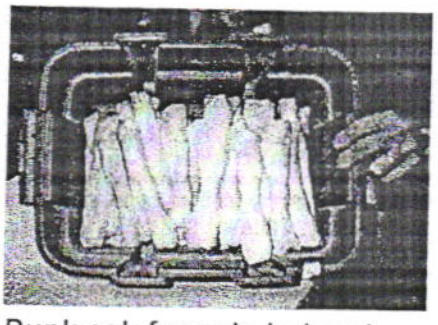
HOW USED: Users pinch off a small piece and chew the iq'mik. The user may pre-chew the iq'mik and place it in a small box for later use by others, including children and sometimes teething babies.[2]

WHO USES: Alaska Natives (men, women and children).[1] One study found that 52% of Yukon-Kuskokwim Delta Alaska Natives used iq'mik.[2]

PROCESSING / MANUFACTURING: Fire-cured **tobacco** leaves are mixed with **punk ash** (ash generated by burning a woody fungus that grows on the bark of birch trees). The ingredients are available at grocery stores and retail outlets, but are generally combined by the user before use.[1] It is believed that the punk ash in the mixture raises the pH level in the mouth, increasing the dose and enhancing the delivery of nicotine to the brain.[2]



Punk, whole fungus



Punk ash for sale in local grocery store

Fire cured tobacco leaves for sale

1 J. Kaur & F.E. Jackson (personal communication, March 27, 2001).

2 Gerjevic S. Iq'mik use a 'pediatric epidemic' in Y-K Delta. Fairbanks Daily News-Miner 2002 Jan 6.

Khaini

BRAND NAMES: Raja, Kuber

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: Bihar (India), Western and central states of India,[1] Maharashtra (India)[2]

PRODUCT CONSTITUENTS: tobacco, slaked lime paste,[3] sometimes areca nut

HOW USED: Held in the mouth, in a similar manner to moist snuff.[4] The product is kept in the mouth for 10 to 15 minutes[5] and sucked from time to time.[2]

WHO USES: Most common among men but used by women as well.

PROCESSING / MANUFACTURING: **Powdered tobacco** and **slaked lime paste** are combined by the user in his/her palm and formed into a ball.[6] **Areca nut** is sometimes added.[1] Usually prepared by a user from basic ingredients at the time of use.

1 Puttaiah R., Carley K., Holavanahalli R. Tobacco, betel-quid chewing and oral health. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995. p.1-9.

2 Murti P, Gupta P, Bhonsle R. Betel quid and other smokeless tobacco habits in India: oral health consequences. Dent J Malaysia 1997;18:16-22.

3 US Department of Health and Human Services. Health consequences of using smokeless tobacco: a report of the Advisory Committee to the Surgeon General. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, 1986.

4 World Health Organization. Tobacco or health: a global status report. Geneva: World Health Organization, 1997.

5 William S. Betel-quid chewing: a community perspective. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995.

6 Trends in tobacco use (2001c). [On-line]. Available: http://www.doctoronnet.com/addictions/2trends.php3

Qiwam (kimam)

BRAND NAMES: None

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: India

PRODUCT CONSTITUENTS: tobacco, spices (cardamom, saffron and/or aniseed), additives such as musk[1]

HOW USED: Paste is placed in the mouth and chewed.[2] Also used in betel quid.

WHO USES: Upper socio-economic groups.

PROCESSING / MANUFACTURING: **Tobacco** leaves are processed by removing their stalks and stems, then boiled and soaked in water flavored with **spices** and **additives**. The resulting pulp is mashed, strained, and dried into a paste.[1,2]

1 Puttaiah R., Carley K., Holavanahalli R. Tobacco, betel-quid chewing and oral health. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995. p.1-9.

2 Trends in tobacco use (2001c). [On-line]. Available: http://www.doctoronnet.com/addictions/2trends.php3

Mawa

BRAND NAMES: None

COMMON NAMES: None

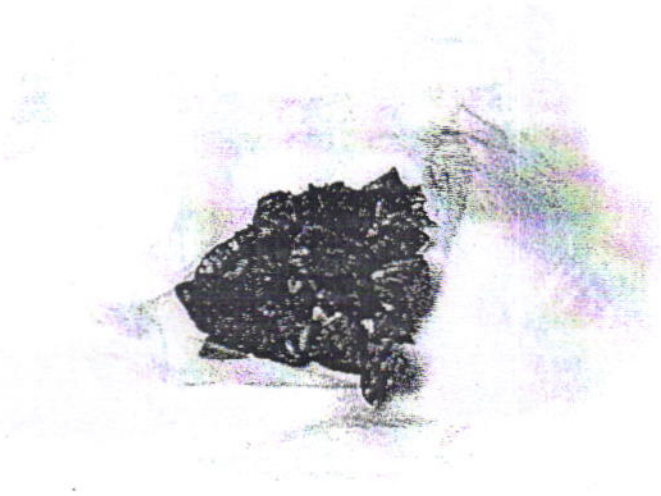
GEOGRAPHIC LOCATION OF USE: Bhavnagar (India), Gujarat[1]

PRODUCT CONSTITUENTS: tobacco, slaked lime, areca nut

HOW USED: Placed in the mouth and chewed for 10 to 20 minutes.

WHO USES: Young men.

PROCESSING / MANUFACTURING: Small pieces of sun-cured **areca nut** are mixed with **tobacco flakes** and **slaked lime** (liquid calcium hydroxide). The mixture is rubbed together to combine. The resulting mixture is about 95% areca nut.



1 Murti P, Gupta P, Bhonsle R. Betel quid and other smokeless tobacco habits in India: oral health consequences. Dent J Malaysia 1997;18:16-22.

Mishri (masheri, misheri)

BRAND NAMES: None

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: Maharashtra (India)

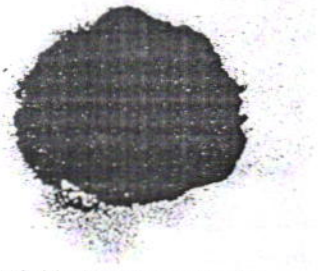
PRODUCT CONSTITUENTS: tobacco

HOW USED: Applied to the teeth and gums,[1] often for the purpose of cleaning the teeth.[2] Users then tend to hold it in their mouths (due to the nicotine addiction).[3]

WHO USES: Predominantly women. More common in lower socio-economic groups.

PROCESSING / MANUFACTURING: **Tobacco** is baked on a hot metal plate until toasted or partially burnt,[4] then powdered.

Woman applying Mishri to gums and teeth



1 Murti P, Gupta P, Bhonsle R. Betel quid and other smokeless tobacco habits in India: oral health consequences. Dent J Malaysia 1997;18:16-22.

2 World Health Organization. Tobacco or health: a global status report. Geneva: World Health Organization, 1997.

3 Puttaiah R., Carley K., Holavanahalli R. Tobacco, betel-quid chewing and oral health. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995. p.1-9.

4 US Department of Health and Human Services. Health consequences of using smokeless tobacco: a report of the Advisory Committee to the Surgeon General. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, 1986.

Nass (naswar, niswar)

BRAND NAMES: None

COMMON NAMES: naswar, niswar

GEOGRAPHIC LOCATION OF USE: Central Asia, Iran, Afghanistan, Pakistan, Baluchistan (India)[4]

PRODUCT CONSTITUENTS: *Nass*: tobacco, ash, cotton or sesame oil,[1] water, and sometimes gum.[2] *Naswar, niswar*: tobacco, slaked lime, indigo, cardamom, oil, menthol, water.

HOW USED: Held in the mouth for 10 to 15 minutes. Naswar is sometimes chewed slowly.[3]

WHO USES: Information not available.

PROCESSING / MANUFACTURING: Sun- and heat-dried **tobacco** leaves, **slaked lime, ash** from tree bark, and **flavoring** and **coloring agents** are mixed together. **Water** is added and the mixture is rolled into balls.[5]

Photo not available

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1 US Department of Health and Human Services. Health consequences of using smokeless tobacco: a report of the Advisory Committee to the Surgeon General. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, 1986.

2 Doshi, S. (2001). Tobacco. [On-line]. Available: http://www.doctorsaab.com/asppages/tobacco.asp

3 World Health Organization. Tobacco or health: a global status report. Geneva: World Health Organization, 1997.

4 Maher R. Chewing of various types of quids in Pakistani population and their associated lesions. Dent J Malaysia 1997;18:12-15.

5 Trends in tobacco use (2001c). [On-line]. Available: http://www.doctoronnet.com/addictions/2trends.php3

Pan Masala (betel quid)

BRAND NAMES: Manikchand, Mahak, Pan Parag #1, Vimal, Crane, Rajdarbar, Kuber, Yamu, Badshah, Tulsi, Rahat, Pan King, Jubilee, Kanchan[1]

COMMON NAMES: betel quid

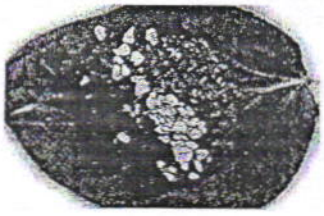
GEOGRAPHIC LOCATION OF USE: India, Sri Lanka, Pakistan, Bangladesh, Myanmar, Thailand, Cambodia, Malaysia, Singapore, Indonesia, Philippines, New Guinea, Taiwan, China[3]

PRODUCT CONSTITUENTS: Tobacco, areca nuts, slaked lime, betel leaf.[2] "Chewing tobacco" is sometimes used, and flavoring agents such as menthol, camphor, sugar, rosewater, aniseed, mint, or other spices are sometimes added in different regions. [3,4]

HOW USED: A *quid* is placed in the mouth (usually between the gum and cheek) and gently sucked and chewed.[4] Pan masala is sometimes served in restaurants after the meal.[4]

WHO USES: Most common among women, but used by men as well.

PROCESSING / MANUFACTURING: Commercially prepared, vendor prepared or assembled at home.[5] **Areca nut** is boiled, roasted, or sun-dried.[3] **Tobacco** may be used raw, sun-dried, and roasted, then finely chopped, powdered and scented. Alternatively, the tobacco may be boiled, made into a paste and scented with **rosewater** or **perfume**. To assemble, **slaked lime** and **catechu** are smeared on a **betel leaf**. The betel leaf is folded into a funnel shape and tobacco, areca nut and any other ingredients are added. The top of the funnel is folded over, resulting in a *quid*, which is placed in the mouth for use.[4]



Handmade

Manufactured

1 Halarnkar S. A New Way to Die? India Today 1997 Aug 11; p. 72-73.

2 World Health Organization. Tobacco or health: a global status report. Geneva: World Health Organization, 1997.

3 Puttaiah R., Carley K., Holavanahalli R. Tobacco, betel-quid chewing and oral health. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health: 1995. p.1-9.

4 William S. Betel-quid chewing: a community perspective. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995.

5 Gupta, P. (2001). Regional Summary for Southeast Asia World Health Organization.

Creamy Snuff

BRAND NAMES: Ipco (Asha Industries product)[1], Denobac, Tona, Ganesh

COMMON NAMES: tobacco toothpaste

GEOGRAPHIC LOCATION OF USE: India

PRODUCT CONSTITUENTS: tobacco, clove oil, glycerin, spearmint, menthol, camphor

HOW USED: Often used to clean teeth.[2] The manufacturer recommends letting the paste linger in the mouth before rinsing.[1]

WHO USES: Primarily women.[3]

PROCESSING / MANUFACTURING: Commercially manufactured. Sometimes marketed as a dentifrice.

1 Ipco creamy snuff. (2001). [On-line]. Available: http://www.ipcosnuff.com/creamy.htm

2 World Health Organization. Tobacco or health: a global status report. Geneva: World Health Organization, 1997.

3 Gupta, P. (2001). Regional Summary for Southeast Asia World Health Organization.

Dry Snuff

BRAND NAMES: Al Capone Powder, Conwood (Conwood product), Swisher (Swisher product), US Tobacco (U.S. Tobacco product), Brown & Williamson (Brown & Williamson product)

COMMON NAMES: tapkeer

GEOGRAPHIC LOCATION OF USE: United States, United Kingdom, India

PRODUCT CONSTITUENTS: tobacco

HOW USED: Typically, a pinch is held between the lip and gum or cheek. It may also be inhaled into the nostrils.[1]

WHO USES: In 2000, U.S. prevalence of current (used within the past 30 days) smokeless tobacco use (includes both snuff and chewing tobacco) for those 12 years old and over was 3.4%: 6.5% of males and 0.5% of females.[2]

PROCESSING / MANUFACTURING: Tobacco is fire-cured, then fermented and processed into a dry, powdered form. The moisture content of the finished product is less than 10%. It is packaged and sold in small metal or glass containers.[1]

1 Asma, S. (1998). Definitions of tobacco products. Unpublished Work.

2 Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies. NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, 2001.

Moist Snuff

BRAND NAMES: Copenhagen, Skoal, Skoal Bandits, Happy Days (U.S. Tobacco products), Hawken, Kodiak (Conwood products), Red Wood, Gold River, Silver Creek (Swisher products), Red Man, Timber Wolf, (Swedish Match products)

COMMON NAMES: spit tobacco, dip

GEOGRAPHIC LOCATION OF USE: United States

PRODUCT CONSTITUENTS: tobacco

HOW USED: A pinch (called a *dip*) or a pouch is placed and held between the lip and cheek or gum.[1] Saliva may be swallowed or, more commonly, spit out.

WHO USES: In 2000, U.S. prevalence of current (used within the past 30 days) smokeless tobacco use (includes both snuff and chewing tobacco) for those 12 years old and over was 3.4%: 6.5% of males and 0.5% of females.[2]

PROCESSING / MANUFACTURING: The **tobacco** is either air- or fire-cured, then processed into fine particles ("fine cut") or strips ("long cut"). Tobacco stems and seeds are not removed. Moisture content of the final product is up to 50%. The tobacco is sold either loose (in such products as Skoal, Copenhagen and Kodiak), or packaged in small, ready-to-use pouches called *packets* or *sachets* (in such products as Skoal Bandits). Nicotine is released more rapidly from the fine cut form due to the greater surface area. Moist snuff is the most commonly used form of tobacco in the United States.[1]

1 Asma, S. (1998). Definitions of tobacco products. Unpublished Work.

2 Substance Abuse and Mental Health Services Administration. Summary of Findings from the 2000 National Household Survey on Drug Abuse. Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD, 2001.

Snus (snuff)

BRAND NAMES: Catch, General, Timber Wolf (Swedish match products)

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: Sweden, India [4]

PRODUCT CONSTITUENTS: tobacco, water, sodium carbonate, sodium chloride, moisturizer, flavoring, nicotine[1]

HOW USED: A pinch (called a *dip*) is placed between the gum and upper lip.[2] The average user keeps snus in the mouth for 11 to 14 hours per day. In Sweden, the portions come in two different doses: regular and "mini-portions" (1.0g and 0.5g of tobacco).

WHO USES: Approximately 20% of Swedish men and about 2% of Swedish women use snus daily.[3] The number of women using snus is increasing.[1]

PROCESSING / MANUFACTURING: Finely ground dry **tobacco** is mixed with **aromatic substances**, **salts**, **water**, and **humidifying agents**. The product is kept cold to avoid fermentation. The final product has a moisture content of about 50% and has a damp consistency.[3]

Eucalyptus flavored

1 Bolinder, G. (1997). Long-term use of smokeless tobacco: cardiovascular mortality and risk factors Stockholm: Karolinska Institute.

2 Idris A, Ibrahim S, Vasstrand E, Johannessen A, Lillehaug J, Magnusson B, Wallstrom M, Hirsch J, Nilsen R. Swedish snus and the Sudanese toombak: are they different? *Oral Oncol* 2001; 34: 558-566.

3 Ryden C, Wallskar H. Progress & Challenge: Tobacco Control (Swedish Style). 2000. Stockholm, National Institute of Public Health. Ref Type: Pamphlet

4 Gupta PC. India: Swedish Match steps in. Tob Control 2001 Dec;10(4):304E.

Toombak

BRAND NAMES: None

COMMON NAMES: None

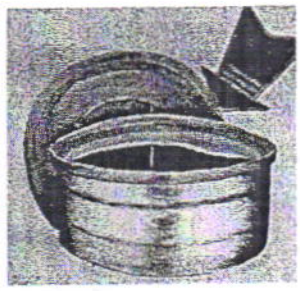
GEOGRAPHIC LOCATION OF USE: Sudan

PRODUCT CONSTITUENTS: tobacco, sodium bicarbonate

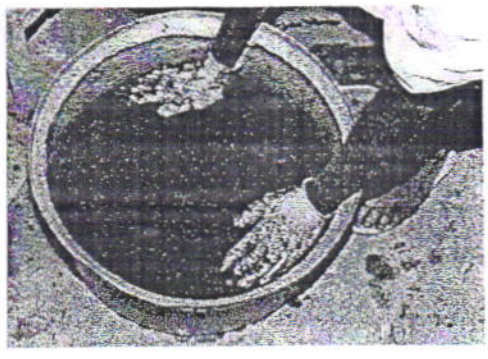
HOW USED: Product is rolled into a ball, weighing about 10g, called a *saffa*. The saffa is held between the gum and the lip or cheek, or under the tongue on the floor of the mouth. It is sucked slowly for 10 to 15 minutes. Male users periodically spit, while female users typically swallow the saliva generated. The user usually rinses his/her mouth with water after the saffa is removed.[1]

WHO USES: About 34% of Sudanese men and 2.5% of women aged 18 years and older.[1]

PROCESSING / MANUFACTURING: **Tobacco** leaves are harvested and left in a field for uniform drying. The leaves are then tied into bundles, sprinkled with water, and stored for a couple of weeks at 30 to 45°C to allow fermentation. The leaves are then ground up and aged for up to a year. After aging, toombak vendors (in toombak shops) place the product in bowls and gradually add **sodium bicarbonate** until the mixture is approximately 4 parts tobacco to 1 part sodium bicarbonate. The mixture is blended by hand and constantly tested with the tips of the fingers until it becomes moist and hardened. The toombak is then placed in an airtight container for about 2 hours prior to sale.[1]



Toombak wholesale advertisement



Toombak processed by hand

1 Idris A, Ibrahim S, Vasstrand E, Johannessen A, Lillehaug J, Magnusson B, Wallstrom M, Hirsch J, Nilsen R. Swedish snus and the Sudanese toombak: are they different? *Oral Oncol* 2001; 34: 558-566.

Red Tooth Powder

BRAND NAMES: Dabur

COMMON NAMES: lal dantmanjan

GEOGRAPHIC LOCATION OF USE: India

PRODUCT CONSTITUENTS: tobacco

HOW USED: Most often used to clean teeth.

WHO USES: More often used by women.

PROCESSING / MANUFACTURING: Unknown

Zarda

BRAND NAMES: Baba, Bharat, Gopal

COMMON NAMES: None

GEOGRAPHIC LOCATION OF USE: India, Arab countries

PRODUCT CONSTITUENTS: tobacco, lime, spices, vegetable dyes, areca nut

HOW USED: Often used as ingredient in betel quid.[1] Chewed.

WHO USES: Men and women in middle to upper socio-economic groups.

PROCESSING / MANUFACTURING: **Tobacco** leaves are broken up and boiled with **lime** and **spices**. The mixture is dried and colored with **vegetable dyes**, then mixed with finely chopped **areca nuts**.[2]

1 World Health Organization. Tobacco or health: a global status report. Geneva: World Health Organization, 1997.

2 Puttaiah R., Carley K., Holavanahalli R. Tobacco, betel-quid chewing and oral health. In: Bedi R, Jones P, editors. Betel-quid chewing and tobacco chewing among the Bangladeshi community in the United Kingdom. London: Centre for Transcultural Oral Health; 1995. p.1-9.

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VOLUME 85

Betel-quid and Areca-nut Chewing and Some Areca-nut-derived Nitrosamines

LYON, FRANCE
2004

BETEL-QUID AND ARECA-NUT CHEWING

1. Exposure Data

1.1 Composition of betel quid

Areca-nut/betel-leaf/tobacco chewing habits are widely prevalent in many parts of Asia and in migrant communities arising therefrom. Many betel-quid products in different parts of the world are not actually chewed; rather, they are placed in the mouth or applied to the oral cavity and remain in contact with the oral mucosa. Nevertheless, it is recommended that they all be considered as part of the betel-quid chewing habit. Given the varied ingredients and combinations used in different parts of the world, an accurate description of terms is essential (see Glossary A for definitions and synonyms).

1.1.1 *Betel quid*

The term 'betel quid' is often used with insufficient attention given to its varied contents and practices in different parts of the world. A 'betel quid' (synonymous with '*pan*' or '*paan*') generally contains betel leaf, areca nut and slaked lime, and may contain tobacco. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners, are added according to local preferences. In addition, some of the main ingredients (tobacco, areca nut) can be used by themselves or in various combinations without the use of betel leaf. Numerous commercially produced mixtures containing some or all of these ingredients are also available in various parts of the world. A consensus workshop held in 1996 (Zain *et al.*, 1999) recommended that the term 'quid' should be defined as 'a substance, or mixture of substances, placed in the mouth [...], usually containing at least one of the two basic ingredients, tobacco or areca nut, in raw or any manufactured or processed form.'

A chewing substance may primarily consist of (Table 1):

- areca nut alone, without any betel leaf, slaked lime or tobacco
- chewing tobacco without any areca nut
- areca nut with components of betel vine and any other ingredients except tobacco (betel quid without tobacco)
- areca nut with components of betel vine and any other ingredients including tobacco (betel quid with tobacco).

Table 1. Composition of the different types of chewing substances

	Areca nut[a]	Betel[b]			Catechu[d]	Tobacco[e]	Slaked lime
		Leaf	Inflo-rescence	Stem[c]			
Areca	X						
Betel quid without tobacco	X	X			(X)[f]		X
Betel quid with tobacco	X	X			(X)[f]	X	X
Gutka	X				X	X	X
Pan masala[g]	X				X		X
Khaini						X	X
Mawa	X					X	X
Mainpuri tobacco	X					X	X
Lao-hwa (Taiwan)	X[g]		X				X
Betel quid (Taiwan)	X[g]	X					X
Stem quid (Taiwan)	X[g]			X			X
Naswar						X	X
Zarda						X	X

[a] May be used unripe, raw or processed by baking, roasting or baking with sweetening, flavouring and decorative agents (see Table 2).
[b] In place of the leaf, the inflorescence or its stem may also be used (see Table 2).
[c] Stem of inflorescence
[d] In powdered or paste form (see Table 2)
[e] In flaked, powdered or paste form, with or without processing, with or without sweetening (see Table 2)
[f] ( ) means optional
[g] Used in unripe form

It is recommended that, when the term 'betel quid' is used, other ingredients used to make up the quid be specified. A betel quid is often formulated to an individual's wishes with selected ingredients. In many countries, ready-made, mass-produced packets of the above products are now available as proprietary mixtures known as *pan masala* or *gutka* (see Section 1.2). The major constituents of a betel quid are listed in Table 2 and are outlined below.

1.1.2 *Areca nut*

Areca nut is the seed of the fruit of the oriental palm *Areca catechu*. It is the basic ingredient of a variety of widely used chewed products. Use of the term 'betel nut' is not botanically correct; it has caused considerable confusion in the scientific literature and should be avoided.

Areca nut is an important agricultural product in many regions of the world. The world's largest producers of areca nut, as estimated by the Food and Agriculture Organiza-

Table 2. Constituents of betel quid

Constituent	Origin/preparation
Areca nut	Unripe/ripe Whole/sliced Raw/roasted/sun dried Boiled/soaked in water Fermented (under mud)
Piper betle L.	Fresh leaf Inflorescence Stem
Slaked lime	From coral From shell fish From quarried lime stone
Tobacco	Sun dried Fermented Boiled with molasses Perfumed Concentrated extract (kiwam)
Catechu (extracted from)	• Heartwood of *Acacia catechu* or *A. suma* • Leaves of *Uncaria gambier* • Bark of *Lithocarpus polystachya* (*nang ko*)
Spices	Cloves Cardamom Aniseed (± sugar coat)
Sweeteners	Coconut Dried dates
Essences	Rose essence Menthol Mint Rose petals

Updated from Gupta & Warnakulasuriya (2002)

tion (FAO), are listed in Table 3. The FAO has estimated that world production of areca nut is increasing (FAO, 2003). In most South Asian countries where information is available, the production of areca nut has increased several fold over the past four decades. In India, production of the nut has risen nearly threefold and may reflect the commercialization of areca products since the early 1980s. Notably, Bangladesh is a significant contributor to the agricultural base of areca-nut production, but its use by the Bangladeshi population is not well documented (see Section 1.3.3).

There are several palms under the genus *Areca* that are native to South and South-East Asia and the Pacific islands. An annotated list of the *Areca* species according to their geo-

Table 3. Production of areca nut by country since 1961 (in millions of tonnes)

Country	1961	1971	1981	1991	2001
Bangladesh	62 995	23 369	25 051	24 120	47 000
India	120 000	141 000	195 900	238 500	330 000
Indonesia	13 000	15 000	18 000	22 812	36 200
Kenya	NA	NA	NA	100	90
Malaysia	6 500	3000	2 500	4000	2500
Maldives	1	1	5	16	37
Myanmar	8000	19 203	25 807	32 270	51 463
Taiwan, China[a]	3718	10 075	24 358	111 090	165 076
Thailand	NA	NA	NA	13 250	20 500
World	428 428	423 296	583 242	892 316	1 305 732

From FAO (2003)
NA, not available
[a] From Council of Agriculture, ROC (2003)

graphical cultivation in South and South-East Asia and in the Pacific basin was given by Furatado (1933). Areca nut for chewing is obtained exclusively from *Areca catechu*, which is believed to be native to Sri Lanka, West Malaysia and Melanesia (IARC, 1985a). This tropical palm tree bears fruit all year, which are ovoid or oblong with a pointed apex, measuring 3–5 cm in length and 2–4 cm in diameter. The outer surface is green when unripe and orange-yellow when ripe. The seed (endosperm) is separated from a fibrous pericarp, is rounded with a truncated base and is opaque and buff-coloured with dark wavy lines. It has a characteristic astringent and slightly bitter taste and is consumed at different stages of maturity according to preference. An individual may consume the whole nut or thin slices of the nut, in its natural state or after processing in many forms.

The nut may be used fresh or it may be dried and cured before use, by sun-drying, baking or roasting (Table 2). Areca fruit may also be boiled and fermented (in eastern parts of India, Sri Lanka) by covering it with mud to soften the nut for consumption. These treatments change the flavour of the nut and its astringency. In Taiwan, China, areca nut is most often used in the unripe stage when it is green, like a small olive.

Areca nut is known colloquially in Hindi and other languages in India as *supari*; it is called *puwak* in Sri Lanka, *gua* in Sylheti (Bangladesh), *mak* in Thailand, *pinang* in Malaysia, *daka* in Papua New Guinea, *pugua* in Guam and *Kun-ywet* in Myanmar (IARC, 1985a).

Chemical constituents

Comprehensive analyses of the chemical composition of areca nut have been reported and reviewed (Raghavan & Baruah, 1958; Shivashankar *et al.*, 1969; Arjungi, 1976; Jayalakshmi & Mathew, 1982). The major constituents of the nut are carbohydrates, fats,