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 Supreme Court vide order dated 07.12.10 in SLP No. 16308/2007, Ankur Gutkha Vs Indian Asthma Care Society & Ors., directed the Central Government '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

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:

(1) Dr. K. Srinath Reddy, MBBS, MD(AIIMS), DM(AIIMS), Fellow, NAMS

(2) Dr. P.C. Gupta, Director, Healis -Sekhsaria Institute of Public Health

(3) Dr. Kishore Chaudhry, M.B.B.S., M.D., Scientist - 'F'

(4) Dr. Pankaj Chaturvedi, MBBS,MS,FAIS, FICS

(5) Dr. Naseem Shah, Chief of CDER, AIIMS,

(6) Dr. Sanjay Chaturvedi, MBBS, FAMS

(7) Dr. Deoki Nandan, MD, FAMS, FIPHA, FIAPSM, FISCD,

The details of the core group alongwith support staff is 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.

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 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. *Gutkh*a 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.

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 prevalence 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 cell cancer by 3-4 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 all-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.