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SUMMARY OF THE EVIDENCE AND FINDINGS
AND CONCLUSIONS CONCERNING THE
ADVERSE HEALTH EFFECTS OF SNUFF

GOVERNMENT DOCUMENTS
COLLECTION

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I. INTRODUCTION/EXECUTIVE SUMMARY

On February 6 and 7, 1985, the Massachusetts Department of Public Health conducted public hearings on proposed regulations declaring snuff, a smokeless tobacco product, to be a hazardous substance and requiring the following health warning label on containers of snuff sold in the Commonwealth:

WARNING: Snuff is addictive and may cause mouth cancer
and other mouth disorders.

The Department is under no legal obligation to prepare a summary of testimony and findings prior to the adoption of regulations. However, given the public interest in this matter, the Department has prepared a brief summary of the evidence and of certain findings and conclusions concerning several issues raised by the testimony received. This summary is not intended to be exhaustive, and the regulations as adopted are not necessarily based solely on these findings alone to the exclusion of other conceivable evidence.

To provide an overview this introduction will consist of a brief outline of each of the topics reviewed in the order in which they appear in the report.

Section II summarizes the Department's authority to promulgate a regulation requiring a health warning label on snuff containers.

Section III contains a discussion of the definition of snuff, and presents information on sales and use including a number of studies on use by ado-

lescent males. The Massachusetts study of 5,000 high school students found that 15 percent tried smokeless tobacco during the last year, and 12 percent of the boys used it very often or several times.

Section IV reviews the testimony and evidence concerning the association between snuff and oral cancer. This section is divided into three parts.

Part A of Section IV deals with the epidemiological evidence. Over 40 case series, case control and cohort studies are presented. The studies showed consistency, specificity and strength for the association between smokeless tobacco use and human oral cancer. Risk for oral cancer was found to increase fourfold for snuff users, and up to fiftyfold for long term users. Opponents to the regulation challenged the association and referenced the Smith study, a ten year follow-up study of 1,751 users that found no oral cancer among the group. However, the Smith study failed to follow-up on 201 of the study participants. Two epidemiologists who testified stated that this methodologic flaw raises serious questions about the value of the study's findings.

Part B reviews the clinical evidence that demonstrates snuff use produces "leukoplakia" or white patches in the mouth of some users at the site the tobacco is held, and that a significant percent of these transform into malignant cancer over time. This position was also challenged. Opponents argued that the causes of leukoplakia are unknown, and snuff-associated leukoplakias have not been scientifically shown to develop into cancer. However, the scientific evidence submitted to the Department demonstrated that snuff is an etiologic agent in the formation of leukoplakia. This

conclusion is in accord with the position of several concerned agencies, such as the World Health Organization (W.H.O.).

Part C examines animal studies which demonstrate that the nitrosamines contained in snuff induce tumor development in animals, including the oral cavity. Opponents of the proposed regulations acknowledged that these compounds produce tumors in animals.

Epidemiologic, animal experimentation and clinical evidence presented in section IV support the conclusion that a strong causal relationship exists between snuff use and oral cancer. Based on this evidence both the National Cancer Advisory Board (NCAB) to the National Cancer Institute and the International Agency for Research on Cancer (IARC) of W.H.O. state unequivocally that snuff is a human carcinogen. In February of 1985, NCAB stated, "there is a cause and effect relationship between smokeless tobacco use and human cancer." In November 1984, IARC concluded, "there is sufficient evidence that oral use of snuffs of the types commonly used in North America and Western Europe is carcinogenic to humans."

Section V of the report presents evidence that use of snuff causes periodontal disease at the site in the mouth where the tobacco is held.

Section VI discusses nicotine's potential to produce addiction. Snuff produces blood nicotine levels equivalent to those produced from smoking. Evidence was submitted which demonstrated that nicotine at these levels produces effects similar to that produced by other drugs of abuse, can be dependence-producing and can result in addictive behavior.

Those opposed to the Department's labeling proposal challenged classification of nicotine as dependence-producing and addictive. They argued that addictive drugs must produce life threatening withdrawal symptoms, result in occupational or social impairment, and that users must require clinical treatment to quit. However, a review of the criteria of the National Institute of Drug Abuse, W.H.O. and the American Psychiatric Association found that these conditions are not accepted criteria for classifying tobacco as a dependence-producing substance.

Section VII reviews the testimony on industry advertising and knowledge of adverse health effects among users. Industry advertising was found to portray "going smokeless" as a safe, healthy habit and to lack any health warnings. A number of young consumers testified that they did not know of health problems associated with snuff. In addition, it was the opinion of several state and national governmental and voluntary agencies that the public is not informed of possible health problems caused by snuff.

Section VIII presents the Department's findings and declarations concerning snuff.

Section IX includes a brief discussion of the changes made in the proposed regulations following the public hearing process and a copy of the final version of the regulations.

A brief summary of the testimony and a list of agency positions are included in the Appendix.

II. Authority

Pursuant to G.L. c.94B, the Commissioner of Public Health may, by reasonable rules and regulations, declare a substance to be hazardous and require special labeling requirements which are found to be necessary for the protection of the public health and safety.

The Smokeless Tobacco Council argued that Massachusetts cannot impose a label requirement on containers of snuff because the area of tobacco regulation has been preempted by the federal government.(1) However, there is no federal statute or regulation which governs the labeling of snuff. Nor has Congress expressed an intent to remove the labeling of snuff from state regulation. In the absence of Congressional action, the fact that Congress could require warning labels on snuff but has not done so does not foreclose the Commonwealth from requiring a label to protect the health and safety of its residents.

Testimony was also received from the Smokeless Tobacco Council, the Byfield Snuff Company and the National Association of Tobacco Distributors (NATD) concerning the burden that a label requirement would impose on the industry and interstate commerce.(2-4) The President of the Byfield Snuff Company, the only Massachusetts manufacturer of snuff, stated that it would not be economically feasible for a small business to compete with larger manufacturers if a label was required. The Smokeless Tobacco Council and NATD claimed that imposition of a labeling requirement on snuff would disrupt interstate tobacco snuff distribution because labeled products would have to be targeted for Massachusetts, thereby increasing costs for manufac-

turers and distributors. However, the industry reported that the share of the market affected by the label would be negligible - one quarter of one percent of the total national sales of snuff.(5) Testimony was also presented concerning the need for a national approach.

It is recognized that the label requirement may force changes in the distribution system for snuff and may cause some additional expense for manufacturers and distributors of the product. However, legal precedent has established that where a state acts to protect the health interests of its citizens, the resulting burden on interstate commerce is not unreasonable or impermissible under the Commerce Clause.

Conclusion

The authority of the Commissioner of the Department of Public Health to require a warning label on snuff is not preempted by federal law or regulation. Based on the evidence summarized in this report, the Commissioner has concluded that the benefits of preventing and reducing disease caused by the use of snuff far outweigh the additional expense to the industry of providing a health warning label to consumers.

III. Description of Snuff and Reports on Use

Snuff is a cured, ground tobacco that is consumed orally or nasally. It is dry or moist and is produced in three forms.(6) Dry snuff is made from fire-cured tobacco that is ground and pulverized to a flour-like consistency to which other ingredients are added, including spices for flavor. In normal consumption the user places a small pinch between gum and cheek where it comes into contact with the oral tissue. The tobacco mixes with saliva and nicotine is absorbed through the oral mucosa into the blood stream.

Moist snuff is finely cut tobacco with a high moisture content. Fine cut tobacco is the third type of snuff which was classified as chewing tobacco until 1980 by the United States Department of Agriculture.

Dry snuff has traditionally been used among female textile workers from the South. Other occupations where use of smokeless tobacco is common include steel, mining, logging and farming. In recent years use has increased among young white males. According to the Tobacco Encyclopedia, "In the 80's (the) market began to gravitate toward the white collar, 18-35 year old age group, of whom college students are an important factor."(7) Recent surveys on use indicate that smokeless tobacco is becoming popular among adolescents.

Snuff is used in Britain through nasal sniffing, and in Scandinavia, the United States and North Africa orally. Prior to the invention of the cigarette, smokeless tobacco was the most popular form of tobacco used in the United States. Estimates for the number of users nationally ranges from seven million to 22 million.(8,9)

Table I presents eight different studies done throughout the United States on use by male high school and college students. The studies indicate that a significant percentage of adolescent males report regular use of smokeless tobacco. A 1984 Massachusetts survey of 5,000 male and female high school students found that 15 percent reported trying smokeless tobacco during the last year. Twenty-eight percent of the boys had tried it at least once and 12 percent reported using it several times or very often.

TABLE I
SURVEYS ON USE OF SMOKELESS TOBACCO
AMONG MALE ADOLESCENTS

<u>Source</u>	<u>State</u>	<u>Age</u>	<u>Percent Users</u>
Greer (1983)	Colorado	14-18	11% (R)
Offenbacher (1983)	Georgia	10-16	20% (U)
Hunter (1983)	Louisiana	8-9	21% (U)
McCarty (1984)	Massachusetts	12-17	12% (R)
Severson (1983)	Oregon	12-16	14% (R)
Glover (1983)	Texas	11-18	9% (R)
Edwards (1984)	Utah	10-18	10% (LW)
Glover (1985)	National	17-21	12% (R)

R = Regular Use

U = Frequency of Use
Unavailable

LW = Use During Last Week

Smokeless tobacco consumption among young males is increasing. The 1975 Hunter study of Louisiana youth found four percent using snuff. A follow-up study of the same age group in 1982 found a 24 percent use rate, a fivefold increase.(10) During the same period Hunter reported a decline in cigarette smoking. Sales figures also indicate an upward trend particularly for moist and fine cut snuff. As shown in Table II, sales for moist snuff have risen substantially from 23.7 million pounds in 1978 to

37.1 million pounds in 1984, a 55 percent increase. During the same period, sales for cigarettes fell, while sales for chewing tobacco rose approximately ten percent.

TABLE II
DOMESTIC SALES OF
CHEWING TOBACCO, MOIST SNUFF AND CIGARETTES

	<u>1978</u>	<u>1980</u>	<u>1982</u>	<u>1984*</u>
Moist Snuff (1)	23.0	27.3	32.7	37.1
Chewing Tobacco (1)	80.7	89.0	88.0	88.9
Dry Snuff (1)	13.0	12.7	11.2	10.1
Cigarettes (2)	615.3	628.2	600.0	593.0

* Projected annual sales based on first nine months.

(1) In Millions of Pounds

(2) In Billions of Cigarettes

Source: United States Department of Agriculture 1984

IV. Oral Cancer

It is well established that epidemiologic evidence can demonstrate causality and criteria have been developed to determine if an association between a particular agent and disease is causal. The criteria include consistency, strength, specificity, temporal relationship, and coherence for the association that exposure to the agent is causally related to the disease.(11) If these criteria are met the clinical and experimental evidence must also support the association.

The age adjusted annual incidence rate for oral cancer is 11 cases per 100,000 persons. This rate has not significantly changed during the last twenty years. Males experience a rate three times greater than females 17.2/100,000 versus 5.6/100,000. There are approximately 27,000 new cases each year in the country and 9000 deaths.(12) In Massachusetts there are an average of 900 new cases and 300 deaths each year. It is the sixth common form of cancer in the state.(13) The most common oral cancer is squamous cell carcinoma. Tobacco smoking has been determined to be a major cause of cancers of the mouth and alcohol use acts synergistically with smoking to increase risk.(14)

There are two types of oral cancer associated with snuff. The first is verrucous cancer which is a locally invasive lesion that does not easily metastasize. The second is squamous cell carcinoma which is an aggressive lesion that readily spreads. Individuals with this lesion have a five year survival rate of less than fifty percent.

Many early studies report that snuff use is associated with induction of verrucous cancers and not squamous cell. However, more recent evidence

shows that squamous cell may be the predominant lesion. McQuirt reports that of 57 patients with oral cancer who used snuff to the exclusion of cigarettes, pipes, and alcohol, the majority of cancers were squamous cell lesions. Of 24 that clinically appeared verrucoid, 24 were found to be well differentiated squamous cell lesions on histological evaluation. (McQuirt reference Appendix B, Table III-VII; Appendix B, Table III-VII references.)

A. Epidemiological Evidence

The earliest report in the medical literature postulating an association between snuff and cancer was made by Dr. John Hill of England in 1761.(15) In the United States, Dr. Warren of Massachusetts reported on tongue cancer in a male tobacco chewer in 1837.(16)

Since then numerous epidemiologic studies have been conducted on the association. Tables III - VIII summarize 43 studies. Table III presents 18 case series studies that show a high proportion of patients with oral cancer had been users of smokeless tobacco. Nine studies reported more than 50 percent of the cases having a history of smokeless tobacco use, and six studies reported from 25 to 49 percent.

Table V presents four case control studies showing that smokeless tobacco users had a significant increase in risk to oral cancer. However, smoking was not controlled for in a majority of them and the type of smokeless tobacco used was not specified. Table VI lists five case control studies in which smoking was controlled for in four and use of snuff was found to significantly increase risk to oral cancer. Table VII presents six follow-

Table III-1

PROPORTIONS OF SMOKELESS TOBACCO USERS IN SERIES OF PATIENTS WITH UPPER DIGESTIVE/RESPIRATORY CANCERS

First Author	Year Publ.	U.S. State or Country	Series Description	Proportion of Smokeless Users
Abbe	1915	New York	100 patients with mouth cancer	138 chewed tobacco
Ahlborn	1937	Sweden	545 male patients with oral cavity, pharynx, larynx, esophagus cancer	708 of 68 gum/cheek cancer patients, 378 of 312 lip cancer patients, 268 of 78 other oral cancer patients, 168 of 87 pharynx/larynx/esophagus cancer patients used smokeless tob.
Ackerman	1946	Missouri	31 patients with verrucous carcinoma of mouth	618 of 18 patients with buccal mucosal cancer were 'Inveterate' tobacco chewers
Wilkins	1957	Georgia	81 patients with gum cancer	508 of 44 women dipped snuff, 328 of 37 men chewed tobacco
Dunn	1962	Florida	112 patients with cancer of oral cavity, larynx, nasopharynx	38 chewed tobacco 58 dipped snuff
Goethals	1963	Minnesota	55 patients with verrucous carcinoma of oral cavity	138 chewed tobacco
Rosenfeld	1963, 69	Tennessee	300 women with gum/cheek cancer 225 women with tongue, floor of mouth cancer	908 dipped snuff 228 dipped snuff

(Testimony of Dr. Deborah Minn 2/85)

Table III-2

Brown	1965	Georgia	275 patients with cancer of buccal mucosa/ gum/multiple primaries 350 patients with cancer of floor or roof of mouth, tongue	350 of women, 200 of men dipped snuff or chewed tobacco 50 of women, 60 of men dipped snuff or chewed tobacco
Coleman	1965	Virginia	23 patients with gum/cheek cancer	100% used snuff or chewing tobacco
Laffall	1965	Washington, D.C.	107 Black patients with oral cancer	570 of 7 patients with buccal mucosa cancer chewed tobacco
Kreus	1966	Missouri	77 patients with verrucous carcinoma of oral cavity	470 chewed tobacco, 40 dipped snuff
Dunn	1967	Florida	427 patients with oral cavity, pharynx, larynx cancers	90 of 45 floor of mouth ca. pts., 110 of 10 palate/alveolar ridge ca. pts., 420 of 26 of buccal mucosa ca. pts., 80 of 40 tonsillar cancer pts., 00 pts. with other cancers used smokeless tobacco
Ischo	1967, 68	Denmark	535 patients with stomach cancer and medical record notation on tobacco use	250 of 385 men, 00 of 150 women used smokeless tob.
Fonta	1969	Kentucky	10 patients with verrucous head and neck cancer	90% tob. chewers or snuff dippers
Ischo	1975	Denmark	493 patients with stomach cancer and tobacco use data available in records	30-35% of male smokers and non- smokers used smokeless tobacco
Martabelle	1977	Alabama	245 patients with squamous cell carcinoma of oral cavity and tob. use data available in records	510 of 39 patients from path. re- gister dipped snuff, 50 chewed tob. 310 of 206 patients from tumor reg. dipped snuff, 60 chewed tobacco
Asell	1978	Sweden	375 patients with oral cavity cancer in selected anatomic sites	280 of 176 with tob. habits known used snuff
McGuirt	1983	North Carolina	169 women with "buccal head and neck cancer"	330 used snuff or chewing tob.

Table IV

CASE REPORTS ON CASE SERIES OF SMOKELESS TOBACCO USERS WITH CANCER

First Author	Year Publ.	U.S. State or Country	Series Description	Cancer at Site of Tumor Placement
Radmond (Mill)	1970 (1961)	England	2 snuff inhalers with nasal cancer	Yes
Myndar (Warren)	1976 (1937)	Massachusetts	Tongue cancer in a male tobacco chewer	Not mentioned
Friedell	1941	Illinois	8 tobacco chewing males with carcinoma of the mouth, slow growing, well-diff. Chewed 32-65 years. Leukoplakia in 7/8	6/8 Yes
Moertel	1958	Minnesota	Male with 2 squamous cell carcinomas in the buccal mucosa who chewed tobacco.	Yes
Root	1960	Minnesota	Bar cancer in farmer who placed snuff in ear for 42 years	Yes
Borgar	1960	Nova Scotia, Canada	4 males with verrucous carcinoma of buccal mucosa and "long standing" tobacco chewing habits. All over 70 years old. Two with leukoplakia.	Yes, 2/4 same side
Landy	1961	Arkansas	25 patients with bucco-gingival cancer who used snuff. Average age 68. Used snuff 20 or more years. Leukoplakia common.	Most
Stecker	1964	Minnesota	71 year old male with oral cancer and leukoplakia who used snuff 10-12 hours daily for 40 years.	Yes
Gundstrom	1962	Sweden	29 men with cancer in the anterior oral vestibule who used snuff. Multiple primaries, candida, leukoplakia common	Yes, by design
McGuire	1963b	North Carolina	57 persons with oral cavity cancer who used smokeless tobacco, but no smoking or alcohol. Frequent recurrences, new primaries. Many used smokeless tobacco 40 or more years. 61% with leukoplakia	89%

Table V

CASE-CONTROL STUDIES OF SMOKELESS TOBACCO USE (UNSPECIFIED) AND ORAL CAVITY CANCER

Author, Year, & State Where Study Conducted	Cases	Controls	Smokeless Tobacco Findings
Moore et al., 1952, 1954 Minnesota	40 male patients with oral cavity cancer	38 male patients with benign surgical conditions	65% of cases, 32% of controls used smokeless tobacco, $p < 0.01$
Pescock et al., 1960 North Carolina	56 patients with oral cavity cancer	146 patients frequency matched rec'd, sex, economic status; 217 "randomly" sampled outpatients	Significant association for older, low economic inpatients; positive association in older, not younger race-sex groups
Vincent and Marchetta, 1963 New York	106 patients with cancer of the oral cavity, pharynx, larynx	150 successive patients in same sex and age group at gastro- intestinal clinic	16% of 89 male cases, 5% of 100 male controls used smokeless tobacco
Willems and Morn, 1977 Many states in U.S.	84 patients with cancer in gum/ other mouth parts. 106 with lip- tongue cancer	556 patients with cancer in sites unrelated to smoking	Relative risk (RR) for smokeless tobacco, controlling for age, race, smoking. Gum/other mouth cancer in men: RR mod = 3.9, RR heavy=6.7. Tongue/lip cancer in men: Only RR heavy is high, RR=1.9. Only estimate for women: gum/other mouth cancer, RR mod.=4.9

up studies of which four showed an increased risk up to threefold for cancer of the mouth, pharynx, esophagus and other sites.

Dr. James Smith and Dr. Deborah Winn conducted epidemiological studies which have been heavily referenced by experts who have studied this association. (17, 18) The Smith study was frequently referenced by opponents of the regulation as pathological and epidemiological evidence that snuff-induced leukoplakia do not transform into malignant lesions and that large groups of snuff users do not experience higher than expected rates of oral cancer. (19) The Smith study reported on a population of 15,000 snuff users and tobacco chewers. Of these, 1,651 were observed for cytological, histological and clinical evaluation for ten years. Of the original group of 1,751 cases, 1,550 received follow-up examinations and showed no cancer or serious oral mucosal changes after ten years.

According to Dr. William Blot of the National Cancer Institute, Smith did not conduct a careful follow-up study. (20) The failure to account for 201 of the 1,751 cases seriously weakened the results of the study since it is possible that many of the 201 had died and that some had died of oral cancer.

Dr. Kupper, an epidemiologist who testified for the Smokeless Tobacco Council, agreed with this analysis. In evaluating the Smith study, Kupper stated "it is important to point out that only 1,751 of the original snuff users were followed for any appreciable time (between 5½ and 10 years). Of these, a large number (201) were lost. These small numbers, coupled with the rarity of oral cancer and the shortness of the follow up period, make it hard to interpret the findings from (this study)." (21) Consequently,

Table VI

CASE-CONTROL STUDIES OF SNUFF DIPPING AND ORAL CAVITY CANCER

Author, Year & State Where Study Conducted	Cases	Controls	Snuff Findings
Wynder et al., 1957b	472 pts. with cancer of lip, oral cavity, nose, sinus, pharynx, larynx, esophagus	271 patients with other cancers.	Snuff use associated with gum/ buccal mucosal cancer. Cancer often where quid placed.
Vogler et al., 1962	333 Patient with lip, oral cavity pharynx, larynx cancer	3 groups: 214 other mouth disease, 584 other cancer, 787 non-cancer patients.	40% urban female cases, 2%, 3%, 1% controls dipped; 75% female cases, 37%, 20%, 11% controls dipped.
Georgle			
Wynder et al., 1977	873 oral cavity cancer patients	873 age, sex, race, city matched patients without smoking related disease	Among males, 1.7% cases, 2.7% controls dipped, less than 1% of females dipped.
New York			
Weastbrook et al., 1980	35 female patients with buccal mucosa, gum cancer	35 random age stratified sample of female patients	91% of cases, 2% controls dipped
Arkansas			
Winn et al., 1981	232 female patients with oral cavity and pharynx cancer	410 age, race, residence matched controls with other diseases/ causes of death	46% of cases, 30% of controls dipped snuff. Statistically sig. relative risk in white non-smokers, 4.2
North Carolina			

Table VII

FOLLOW-UP STUDIES OF POPULATIONS USING SMOKELESS TOBACCO

First Author	Year Publ.	U.S. State or Country	Cohort Description	Results
Road-Petersen	1973	Denmark	394 pte. with leukoplakia, including 32 snuff dippera	Variable follow-up, 3.16 rate of malignant transformation in dippera (1 case) in contrast to 19.5% in non-users of snuff. Inconclusive, very small sample.
Tyldesley	1971 1976	England	22 coal miners, all but 8 lost to follow-up by Year 5.	1 squamous cell carcinoma at year 4 at site of quid placement. Inconclusive, very small sample.
Smith	1970, 75	Tennessee	1550 snuff dippera with oral lesions (not dyskeratotic or malignant)	10 year follow-up yielded no malignancies. Not clear that follow-up methods would have detected new oral cancer pte. A prevalence of oral cancer of 2/500 also mentioned.
Schuman	1982	U.S.A.	16930 persons followed for 15 years	3 fold increased risk of pancreas cancer for former tob. chewers (stat. sig.). Also 2.5 to 3 fold increased cancer risks for oral cavity, pharynx, and esophagus.
Nauch-Schuman	1983 1982	Norway	11959 males, 2519 females from Norway followed for 12 years	2.9 fold increased risk of pancreas cancer in smokeless users, adj. for cigarettes and alcohol. Also 2.5-3 fold increased risks for oral, pharynx, esophagus cancer.
Winn	-	U.S.A.	230000 U.S. veterans followed for 16 years	Increased risks (1.3-3 fold) for most oral pharynx cancer sites. Also increased risks for esophagus, small intestine, peritoneum

the absence of malignancies in the Smith study does not negate the conclusions reached in numerous other studies that the use of snuff is associated with a significant increased risk to oral cancer.

The Winn study was a case control study of 250 women with oral cancer. It controlled for multiple risk factors such as, age, race, residence, occupation, smoking and alcohol consumption, and found a fourfold increase in risk attributed to snuff alone. The Winn study was criticized by opponents of the regulation for use of proxy respondents in cases where the patient had died.(22) However, when use of proxy respondents was taken into account, the magnitude of the association did not change. Dr. Kupper of the University of North Carolina acknowledged that the Winn study, in conjunction with other evidence, established use of snuff as a risk factor for oral cancer at the site of contact. However, Kupper maintained that the association had been demonstrated for Southern rural women only, and was not causal.(23)

Causal Significance of the Association

1. Consistency of the Association

As referenced earlier, of the 18 cases series studies presented in Table V, 15 reported that 25 percent or more of the patients with cancer used smokeless tobacco. Of the 15 case control and cohort studies, 13 found a positive association between use and cancer. These studies were done in different geographic areas in the United States and Europe, and involved different study groups and study methods. The studies almost uniformly

demonstrate a consistent association between smokeless tobacco use and oral cancer.

2. Strength of the Association

As shown in Tables V, VI and VII, the risk to oral cancer is significantly higher for smokeless tobacco users than nonusers. The four studies that computed relative risk (Winn et al, Schuman, Heuch and Schuman, and Winn) found the increase in risk to be from 1.3 to 4.2. The Winn, et al., and Williams and Horn studies examined dose response relationship. Winn found long term users (50 years or more) to have a risk 50 times greater than nonusers. Williams found heavy smokeless tobacco users to have a risk of 6.7 versus 3.9 for moderate users.

3. Specificity of the Association

Table IV presents ten case histories and case series; nine of these show that the cancer occurred in the mouth at the site the tobacco was held. One interesting case supporting the specificity of the association involves a Minnesota farmer who developed cancer in his ear after placing snuff there for 42 years.

4. Temporal Relationship of the Association

Two cohort studies (Schuman, and Schuman and Heuch) showed occurrence of cancer among a significant number of users over a long (15 years, and 12 years) follow up period. Histologic evidence supports this relationship. As will be discussed in Section IVB, use of snuff produces clinical

leukoplakia, and a significant percent of leukoplakia have been shown to transform into cancer over time further supporting the temporal relationship. (24)

5. Coherence of the Association

Dose Response Relationship

As referenced earlier, a dose response relationship has been established for use of smokeless tobacco and oral cancer and supports the coherence of the association.

Correlation of Sex Differences in Oral Cancer

Oral cancer is predominantly a disease of males. However, females from the Southeast of the United States have rates similar to that of males. In that section of the country, snuff is heavily used by females and is reported to be a factor for this unexpected level of oral cancer.

Correlation of Oral Cancer Incidence Among Populations With Different Smokeless Tobacco Habits

International surveys indicate the United States has about one-third the oral cancer incidence of India, which has the world's highest rate.(24) Although Indians smoke and chew a variety of substances, cancerous and pre-cancerous lesions are found predominately among those who use smokeless tobacco. The high incidence of oral cancer in India is attributed to the widespread use of chewing tobacco (47 to 73 percent of the population)

rather than to a difference in the rate at which tobacco users develop cancerous lesions. Studies of Indian populations indicate that oral cancer risk is greater for smokeless tobacco users than for smokers and increases with duration of smokeless tobacco use.(25, 26,27)

Experimental Studies

There is experimental evidence that show nitrosamines contained in snuff are capable of inducing malignant tumors in the mouths of animals. This evidence is presented in Section IV C.

Conclusion

An evaluation of the epidemiological evidence presented to the Department shows that use of snuff significantly increases oral cancer risk.

IVB. Histopathological Evidence

Leukoplakia is a clinical term that describes a patch or plaque in the mouth that cannot be characterized clinically or pathologically as any other disease.(28) Clinical reports of snuff induced leukoplakia show the tissue to have a white appearance and often to be wrinkled or fissured. Because of the inability to predict cellular changes from clinical observations, microscopic evaluations of biopsies of leukoplakias are necessary to determine the pathologic state of the tissue. On biopsy, 90 percent of leukoplakia show benign changes including hyperkeratosis or thickening of the epithelium, chronic inflammation of the connective tissue, or cellular degeneration. In the remainder premalignant dysplasias or malignant cancer may be present.(29)

TABLE VIII

Case Reports or Case Series of Smokeless Tobacco Users
With Oral Leukoplakia

First Author	Year Published	U.S. State or Country	Description of Population	Findings
Pinborg, J.J.	1962	Denmark	Male patients with snuff use 20 - 30 years, age unknown	Four of seven exhibited cellular changes, thickening of squamous epithelium, mucosa membrane slightly whitish and delicately folded appearance.
Pinborg, J.J.	1963	Denmark	Twelve white males age 39 - 83 with use 20 to 30 years	Oral mucosa exhibited histologically marked hyperplasia of outer epithelial layer - parakeratosis found deeper.
Road-Petersen, B	1973	Denmark	Thirty-two male snuff users of 450 patients mean age of 38.4 years equivalent of 22 years of constant use.	Vacuolated cells in epithelium - streaks of parakeratinized cells, epithelial hyperplasia and hyalinized eosinophilic deposits around salivary glands.
Arell, T.	1976	Sweden	One hundred fourteen male dippers age 20 - 88	Thirteen cases with increased number of eosinophilic granulocytes; nine cases with amorphous, weakly eosinophilic areas in connective tissue papillae. All cases showed increased epithelial thickness.
Pinborg, J.J.	1980	Denmark	Male snuff users with average age 38.6. Daily use.	Twelve biopsy specimens. Oral leukoplakia on lower lip in seven cases, buccal mucosa in three, buccal groove in three, and upper lip in one. Chevron pattern of keratinization in all specimens - hyperplastic epithelium.
Mirsch, J.M.	1982	Sweden	Fifty habitual snuff dippers all males age 13 - 84 years, mean age 41.	Salivary glands and excretory ducts showed degenerative change - more severe than pathologic changes in surface epithelium. Epithelial hyperplasia in deeper layers; hydrophobic unsaturated lipid in surface.
Fritthof, L.	1983	Sweden	Twenty-one male snuff users age 31 - 79 mean age of 53 years	Two cases of gingival retraction. Amyloid structures in subepithelial connective tissue, characteristic lesion. Mild dysplasia five cases.

Table IX

PREVALENCE OF MALIGNANT TRANSFORMATION IN ORAL LEUKOPLAKIA

<u>Study</u>	<u>Country</u>	<u>Year</u>	<u>Size of Study</u>	<u>Period Prevalence of Malignant Transformation</u>	<u>Observation Period</u>
Renstrup	Denmark	1958	80	2.26	
Sugar and Banoczy	Hungary	1959	86	5.8	11 years
Shafer & Waldron	USA	1961	332	8.1	
Pindborg, Renstrup, et al	Denmark	1963	185	3.2	
Mele and Mongini	Italy	1966	141	3.5	3 mos. to 9 years (+)
Einhorn and Warell	Sweden	1967	782		1-44 years ($\bar{x}$ = 11.7 years)
				1.3	1-3 years
				2.4	within 10 years
				4.0	after 20 years
Pindborg, Renstrup, et al	Denmark	1968	248	4.4	9 years
Silverman and Rozen	USA	1968	117	6.0	1-11 years
Road-Petersen	Denmark	1971	331	3.6	median 4.3 years
Banoczy and Sugar	Hungary	1972	520	7.2	25 years
Banoczy	Hungary	1977	670	5.97	5-25 years

An analysis of 3,256 cases of leukoplakia showed 80.1 percent were simple hyperkeratosis (thickened cells with retained nuclei), 12.2 percent mild to moderate dysplasias (cellular conditions that point toward malignant transformation), 4.5 percent carcinoma in situ and 3.1 percent invasive carcinoma.(30) Over time three to six percent of leukoplakia become cancerous.(31)

Snuff as a Cause of Leukoplakia

The World Health Organization's Center for Oral Precancerous Lesions has determined that tobacco is an etiological agent for formation of oral leukoplakia.(32) This is demonstrated by numerous studies that show occurrence of leukoplakia at the site tobacco is held, and remission of the lesion when use is stopped. Clinical severity has been found to be directly proportional to exposure, that is, the longer the use of snuff, the more intense the clinical change.(33)

Table VIII presents ten case series studies that show a high proportion of leukoplakia among snuff users. All of the studies demonstrate significant cellular changes in the oral mucosa of users at the site the snuff was held. Cellular changes that are reported range from simple hyperkeratosis to mild dysplasia.

One English study reported a 7.9 percent incidence of leukoplakia among tobacco chewers and smokers.(34) Five other studies among adults which reported that the use of tobacco was associated with oral leukoplakia are also summarized in Table IX. In addition, Table IX includes three studies done in the United States on adolescents which show over 50 percent of smoke-

less tobacco users with oral leukoplakia at or near the site where the tobacco was held. These studies demonstrate that a significant portion of snuff users develop clinical leukoplakia at the site where the quid of tobacco is placed.

Speakers in opposition to the proposed regulation questioned the significance of the oral changes induced by snuff and challenged the relationship between leukoplakia and snuff use. Dr. Mincer of the University of Tennessee relied on a study by Frithiof(35) for the proposition that lesions caused by snuff "were too superficial and easily reversible to warrant the designation of leukoplakia." (36) However, a review of Frithiof's study shows that his decision not to use the term leukoplakia was based on his opinion that as a clinical term, leukoplakia should not be used in a diagnostic context. Because Frithiof determined the lesions he found to be caused by snuff use, he did not describe the lesions as leukoplakia. In five out of 21 cases where lesions were found, Frithiof reported mild dysplasia which are potentially cancerous lesions. Further, Frithiof concluded that each year in Sweden a number of cases of oral cancer develop among Swedish snuff users where the snuff is held.

Dr. Furst of the University of San Francisco challenged the finding that snuff use causes leukoplakia.(37) He cited Shafer, et al., (38) to support his premise that the etiology of leukoplakia is unknown. The reference given by Dr. Furst for Shafer was not up-to-date.(39) In Shafer's most recent text on oral pathology published in 1983, he states that tobacco is generally accepted as an extrinsic factor that can cause leukoplakia.

Leukoplakia and Oral Cancer

According to the W.H.O.'s 1978 Report, a significant percent of leukoplakia transform into malignant lesions. Malignant transformations are reported among tobacco and non-tobacco induced leukoplakia. A long exposure time is generally required before malignant transformations occur, but some may occur without warning. Oral cancer may also occur in the absence of leukoplakia. Leukoplakias that show cellular dysplasia on biopsy are at a greater risk to malignant transformation than ones that do not.(40)

Table IV includes ten case series studies of smokeless tobacco users with oral cancer. Six of the studies reported that leukoplakia was common in the mouths of cancer patients.

Table IX shows 11 studies that followed patients with oral leukoplakia for a number of years and found malignant transformation rates from 1.3 to 8.7 percent depending on years of exposure.

Frithiof, Hirsch, Pindborg and Roed-Peterson have reported dysplasia in biopsies of snuff induced leukoplakia.(41-44)

Dr. Furst challenged the finding that some leukoplakia transforms into malignancies and referenced studies by Axell, Smith, Banoczy, Einhorn and Silverman as evidence that the relationship has not been proven.(45-49)

A thorough review of these references supports the opposite view, that snuff use causes leukoplakia and a significant number of leukoplakia transform into malignancies over time.

With regard to the Axell study, Dr. Furst stated that Axell found no "cellular or epithelial dysplasia... among 114 men." (50) The Axell study involved biopsy of 114 lesions found in 1,200 snuff dippers. (The clinical diagnosis of snuff dippers' lesions was determined when a lesion on the oral mucosa was found to be at the exact site the snuff was placed.) In all 114 cases Axell found significant histopathological changes. Axell did not find dysplasia or cancer among the 114 persons. This is not surprising given the small number of persons biopsied and long exposure time associated with snuff induced cancer. Dr. Kupper of the University of North Carolina who testified on behalf of the Smokeless Tobacco Council, commented on the Axell study. According to Kupper, "The negative findings from the Axell (1976) study are of interest. However, since the results are based on such a short time period, and since the study takes place in another culture, it cannot be said to provide evidence against the reasonably consistent findings in the United States studies, that Southern rural white women who are long-term snuff users apparently are at increased risk for developing oral cancer." (52) It is important to note that a later 1978 follow-up study by Axell did find a five-sixfold increase in risk to oral cancer among snuff users. (53)

A review of the Banoczy and Sugar 1972 article found the following statement: "Follow-up examinations of 520 patients with oral leukoplakia during a 25-year period showed cancer development in 31 cases, i.e., 5.9 percent." (54) In an subsequent 1977 article, Banoczy reported "examination of 670 patients with oral leukoplakia during a 30-year follow-up showed cancer development in 40 cases, 6 percent. Dysplasia was

observed in 24 percent of the histologically examined leukoplakia; 13 percent of the dysplasia cases subsequently showed development of carcinoma."(55) Dr. Furst references the Einhorn and Wersall study which reported a 2.4 percent cancer development after ten years among patients with leukoplakia and reported a 4 percent prevalence of malignant transformation after 20 years in the same study. He also reported on the Silverman study in which six or .13 percent of 6,718 persons with leukoplakia were found with cancer.(56) Given the fact that the general population rate of oral cancer is 11 cases/100,000 per year, the levels reported in all four studies are significantly higher than would be expected by chance, and strongly support the association between leukoplakia and oral cancer.

The methodological flaws of the Smith study are discussed in Section IVA. Because of these flaws, the validity of Smith findings have been questioned by other scientists.

Some speakers argued that non-snuff induced leukoplakia have a higher malignant transformation rate than snuff induced leukoplakia.(57) This finding does not alter the fact that a significant percentage of tobacco induced leukoplakia do become malignant.

Testimony was also submitted which asserted that other factors such as deficiencies in the immune system, diet, dental hygiene, and genetics play a possible role in formation of leukoplakia and oral cancer, and that consequently, one factor cannot be singled out as a cause.(58, 59) It is recognized that many factors singly or in combination may be associated with leukoplakia. However, it has been well established by scientific evi-

dence that tobacco use alone significantly increases risk to oral leukoplakia and oral cancer.

Conclusion

Expert testimony established that the use of snuff is an etiologic factor in formation of oral leukoplakia, that leukoplakia formed by snuff is a potentially cancerous lesion and that a significant percent of these lesions transform into oral malignancies.

IVC. Experimental Evidence and Mechanism of Carcinogenesis

A number of toxic and tumorigenic substances have been identified in tobacco smoke that may act as tumor initiators and promoters. Since snuff is not combusted, users are not exposed to smoke particulates such as polycyclic aromatic hydrocarbons or tar.(60) However, they are exposed to tobacco specific nitrosamines as well as other N-nitroso compounds, such as nitrosomorpholine. Over 250 nitrosamine compounds have been shown to produce cancer in animals.(61)

Nitrosamines are chemical compounds formed through the nitrosation of amino substances, such as, amines, ureas and amides. The nitrosating agent may include nitrites, nitrogen oxide, organic nitrite or other nitroso compounds. In the case of snuff, they are formed during the processing of the tobacco from the amino substances present in the plant and nitrates delivered through fertilization.(62) N-nitroso compounds can also form endogenously in the mouth of snuff users through reaction between saliva and tobacco products.(63)

Nitrosamines are found in other consumer products such as, cosmetics, beer, cured meats and processed rubber products. Certain occupational settings, including, rubber, steel, and leather processing plants can be a source of exposure. Based on experimental evidence, the Federal Food and Drug Administration and Department of Agriculture have set strict action levels for human exposure to these compounds. The action level for NDMA (dimethylnitrosamine) in beer is 10 parts per billion (ppb), for total volatile nitrosamines in baby bottle nipples 10 ppb, and for cured meats 5 ppb.(64, 65) The total concentration of the four most common nitrosamines found in snuff sold in the United States ranges from 2,000 ppb to 80,000 ppb.(66) (Tolerance limits have not been set for snuff since Congress has restricted the FDA and USDA from regulating tobacco products.) The four most common tobacco specific nitrosamine compounds (TSNA) found in snuff are N-nitrosornicotine (NNN), N-nitrosoanabasine (NAB), N-nitrosoanatabine (NAT), and 4-(methyl N-nitrosamino) 1-(3-pyridyl)-1-butanone (NNK).

Carcinogenicity of Nitrosamines Contained in Snuff

NNK and NMOR have been shown to be potent animal carcinogens. NNN is moderately active; NAB is weak; and NAT has been found to be inactive in one animal study. (68-71) Dr. Stephen Hecht presented evidence on the carcinogenicity of nitrosamines. Table X summarizes the results of thirteen studies done on three different animal species that show production of benign and malignant tumors in seven different organ sites through exposure to tobacco specific nitrosamines. The studies and other evidence show a dose response relationship exists for exposure to nitrosamines and induction of cancer.(72) The more frequent the daily or weekly

dose, the sooner the tumor arises; the higher the concentration of nitrosamine, the greater the incidence of tumor formation. In general tumor onset occurs from two months to a year after initial exposure. With the exception of the A/J mouse, spontaneous tumors do not occur in the target organ of the animals studies. The studies show that the tumors occur almost exclusively in the target tissue of exposed animals and not the controls indicating that the N-nitrosocompound is the carcinogenic agent.

TABLE X

Carcinogenicity of Tobacco-Specific Nitrosamines

Nitros- amine	Species and Strains	Route of Application*	Principal Target Organs	Dose	Reference
NNN	A/J mouse	i.p.	lung	0.12 mmol/mouse	1-3
	F344 rat	s.c.	nasal cavity		4-6
		p.o.	esophagus	0.2-3.4 mmol/rat	
			esophagus	0.1-3.6 mmol/rat	4,7,8
			nasal cavity		
	Sprague-Dawley rat	p.o.	nasal cavity	8.8 mmol/rat	9
	Syrian golden hamster	s.c.	trachea nasal cavity	0.9-2.1 mmol/ hamster	10-12
NNK	A/J mouse	i.p.	lung	0.12 mmol/mouse	2,3
	F344 rat		nasal cavity	0.2-2.8 mmol/rat	5,6
			lung, liver		
	Syrian golden hamster	s.c.	trachea, lung nasal cavity	0.9 mmol/hamster 0.005 mmol/hamster	11
NAT	F344 rat	s.c.	none	0.2-2.8 mmol/rat	6
NAB	F344 rat	p.o.	esophagus	3-12 mmol/rat	6,14
	Syrian golden hamster	s.c.	none	2 mmol/hamster	10
NNA	A/J mouse	i.p.	none	0.12 mmol/mouse	

(Testimony submitted by Dr. Hecht)

- (*) I.P. - Intraperitoneal injection
S.C. - Subcutaneous injection
P.O. - Administered orally

Dr. William Lijinsky of Litton Bionetrics reported formation of oral and liver tumors among female F344 rats after 50 weeks of exposure to a concentration of 0.45ppm of nitrosomorpholine (NMOR). He found that as the concentration of NMOR increased so did tumor incidence.(73)

Dr. Stephen Hecht of the American Health Foundation presented the results of two studies that demonstrated NNK and NNN can produce oral tumors in hamsters and rats.(74) Table XI summarizes the results of the hamster study. In the second study tumors were produced in the tongue of rats though the esophagus was the major target tissue.

TABLE XI
Carcinogenicity of NNK, administered by oral
swabbing in Syrian golden hamsters

<u>Number of Animals With Tumors</u>						
	<u>Number of Animals</u>	<u>Cheek Pouch</u>	<u>Nasal Cavity</u>	<u>Larynx</u>	<u>Trachea</u>	<u>Lung</u>
NNK	23	4a	11b	6a	10c	20d
Control	24	0	0	0	0	0

- a) all in male hamsters
- b) 6 male, 5 female
- c) 7 male, 3 female
- d) 10 male, 10 female

(Testimony submitted by Dr. Hecht)

Both NNN and NNK have been found to be mutagenic in salmonella typhimurium. They also induce unscheduled DNA synthesis in primary cultures of rat hepatocytes. When metabolized these compounds form biologically active intermediates that modify DNA to cause point mutations that can initiate the carcinogenic process.(75-77)

Of particular interest is the formation of the electrophilic intermediate methyldiazohydroxide, upon metabolism of NNK(78). This intermediate is well known in chemical carcinogenesis for its ability to methylate DNA in

vivo. One of the products of DNA methylation of O⁶-methylguanine, which has been unequivocally shown to be capable of inducing miscoding in DNA(79). It has frequently been observed that persistence of O⁶-methylguanine in tissues of animals treated with methylating carcinogens such as N-methyl-N-nitrosourea, dimethylnitrosamine, or 1,2-dimethyl-hydrazine is associated with tumor development in those tissues(80). Thus, the observation that treatment of animals with NNK leads to formation of O⁶-methylguanine in their target tissues is important(81,82). The metabolic processes leading to DNA methylation by NNK also have been shown to occur in human tissues including the buccal mucosa(83). Additional metabolic reactions also occur in animal and human tissues(84). The formation of O⁶-methylguanine in DNA, upon exposure to NNK, provides a mechanistic link between nicotine, the major habituating agent in snuff and source of the methyl group, and initiation of the carcinogenic process.

Human Exposure to Nitrosamines from Snuff

A human who consumes one-third of a can (10 grams) of snuff daily will be exposed to approximately 164 ug of nitrosamines. As shown in Table XII, this level is approximately 10 times greater than that received from smoking and 100 times greater than that from other known environmental sources. Over the course of 30 years, the ten gram user will conceivably receive a dose that has been shown to produce a statistically significant, positive trend in liver cancer for animals exposed to a similar concentration of a comparable nitrosamine, N-nitrosodimethylamine (DMN).(85) Dr. Lijinsky reported that he found tumor production to occur for NMOR at exposure levels experienced by human snuff users.(86)

TABLE XII

Estimated Exposure of U.S. Residents to Nitrosamines(15)

Source of Exposure	Nitrosamines	Primary Exposure Route	Daily Intake ug/Person	
Beer	NDMA	Ingestion	0.34	
Cosmetics	NDELA	Dermal Absorption	0.41	
Cured meat: cooked bacon	NPYR	Ingestion	0.17	
Scotch whiskey	NDMA	Ingestion	0.03	TOTAL
Cigarette smoking	VNA(16)	Inhalation	0.3	16.2
	NDELA	Inhalation	0.5	
	NNN	Inhalation	6.1	
	NNK	Inhalation	2.9	
	NAT+NAB	Inhalation	7.2	

Snuff Dipping(17)	VNA	Ingestion	3.1	
	NDELA	Ingestion	6.6	TOTAL
	NNN	Ingestion	75.0	164.5
	NNK	Ingestion	16.1	
	NAT+NAB	Ingestion	73.4	

The Smokeless Tobacco Council submitted testimony challenging some of these findings. Dr. Grasso of Rubins Institute agreed that N-nitroso compounds are present in snuff and induce cancer in laboratory animals.(87) However, he asserted that animal studies do not show that oral tumors are produced by exposure to nitrosamines and that nitrosamines are site specific and not "contact" carcinogens. As referenced earlier, animal studies were cited which show that nitrosamines induce tumors in the oral cavity of animals. In addition, studies have shown that oral administration of N-nitroso compounds can produce tumors in the esophagus of animals.

Dr. Grasso argued that there is no epidemiologic evidence to show that nitrosamines cause cancer in humans.(88) For ethical reasons such studies may be impossible to conduct. The absence of direct human studies does not diminish the concern that exposure to N-nitroso compounds can increase cancer risk in humans. Scientific opinion supports the concept that animal data on nitrosamines should be viewed as evidence that nitrosamines are capable of producing similar effects in humans. In the absence of human studies, the World Health Organization (W.H.O.) International Agency for Research on Cancer concluded that nitrosamines proven to cause cancer in two species of laboratory animals "should be regarded for practical purposes as if they were carcinogenic to humans."(89)

Hirsch has reported malignant tumor formation in rats that were exposed to snuff alone placed in a surgically created test canal in the mouth of the animal.(90) Hirsch found that after nine months one rat out of 55 developed a squamous cell cancer in the mouth.

Dr. Furst of the University of San Francisco criticized the Hirsch study, claiming that the rat species used is known to develop spontaneous tumors.(91) However, this claim cannot be substantiated. In a communication from Dr. Hirsch to the Department, Hirsch stated "In our preliminary studies, it was possible to induce tumors in the oral cavity in the rats. Tumors appeared only in rats exposed to snuff. Sprague Dawley rats that were used in the experiments are not known to develop spontaneous tumors. We have performed intraoral experiments with potent carcinogens at our laboratory during the last 20 years and not once seen spontaneous tumors in the oral cavity."(92)

Conclusion

The overwhelming majority of testimony on the experimental evidence indicates that the nitrosamines contained in snuff are potent animal carcinogens which significantly increase cancer risk in humans.

Summary Conclusion on Oral Cancer

Based on epidemiological, histopathological and experimental evidence submitted to the Department, it has been shown that snuff is a human carcinogen and that the use of snuff is causally related to oral cancer in humans. This conclusion is consistent with a similar finding of the W.H.O.'s International Agency for Research on Cancer and the National Cancer Institute's National Advisory Board (see Appendix B).

V. PERIODONTAL DISEASE

Snuff is a major risk factor in periodontal disease because it has been shown to produce pathological changes in the soft tissues of the mouth. (Section IVB discusses soft tissue changes that occur in snuff induced oral leukoplakia.) The most common form of periodontal damage is destruction of the gum tissue that is attached to the tooth surface where the snuff is held.

Dr. Christen of the Indiana University School of Dental Medicine and Dr. Mehta of the Tufts Dental School testified that the gingival tissue which is adjacent to the tooth is chronically inflamed by the injurious properties of snuff and recedes from the tooth surface over time.(93,94) Greer and Poulson have defined this type of periodontal problem caused by smokeless tobacco as "site-specific gingival recession with apical migration of the gingiva to or beyond the cemento-enamel junction with or without clinical evidence of inflammation."(95) Tooth loss may result, and the exposed root surface is prone to decay.

A number of case histories and clinical studies were presented showing periodontal problems to occur at the site where smokeless tobacco was held. They include a 1966 study by Van Wyk of South Africa where he reported chronic inflammation of periodontal tissue brought about by the use of snuff.(96) In a Swedish study, long-term snuff users were found to have gingival recession and periodontal destruction around the anterior teeth where the tobacco was held.(97) Four other case reports(98-101) were presented showing periodontal breakdown among smokeless tobacco users.

Three case series reports were presented on young male users all showing high levels of periodontal disease. A Texas study of 14 college students done by Christen found 57 percent of the users to have gingival recession where the snuff was held.(102) A Colorado study of 117 high school student users found that 20 percent had periodontal or mucosal lesions in their mouth.(103) A second Colorado survey of 56 rural teenagers found four percent had periodontal lesions and 23 percent both mucosal lesions and periodontal destruction.(104) In the majority of these studies, use of snuff was implicated as the etiologic agent.

Dr. Weathers of the Emory University Dental School presented the results of his study of 500 Atlanta school children, in which he found no difference in the incidence of gingival recession, mucosal pathology or decay between users and nonusers of smokeless tobacco as long as the mouths of the adolescents were clean and free of gum inflammation.(105) His finding is not in keeping with Greer's conclusion referenced earlier that loss of periodontal attachment occurred without inflammation. Dr. Weathers did not submit a copy of his study for review or a reference for the study.

Conclusion

The use of snuff significantly increases risk of periodontal disease and can cause irreversible loss of gingival tissue attachment adjacent to the site where the snuff is held.

VI. NICOTINE DEPENDENCE/ADDICTION

Snuff is a dependence inducing substance which can lead to addictive behavior. The use of snuff results in elevated nicotine levels in the blood stream of a user similar to that obtained from cigarette smoking. The effect of nicotine levels produced by smoking has been shown through human and experimental studies to satisfy all the criteria for dependence. Commonalities exist between use of snuff and other drugs of abuse that support the finding that snuff is a dependence inducing substance. Clinical criteria have been developed for diagnosis and treatment of tobacco dependence by the American Psychiatric Association.

Snuff as a Source of Nicotine

The mean concentration of nicotine in moist snuff has been found to range from 6.9 mg/g. to 14.4 mg/g.(106) The concentration for cigarettes has been reported to be from 0.06 mg/g. to 2.2 mg/g.(107) Use of snuff has been shown to produce blood nicotine levels equivalent to those produced by smoking.(108)

In a study by Gritz, et al. subjects consumed about one third of a can of moist ground snuff (10.8 gm) in eight dips spaced throughout an eight hour period. In this study, "nicotine absorption was observed and resulted in an increase in mean plasma concentration from 2.9 ng/ml after overnight abstinence to 21.6 ng/ml after 6 to 8 hours of consumption ad libitum was recorded. Plasma cotinine concentrations rose from a morning mean of 137.3 ng/ml to an afternoon mean of 197.2 ng/ml, concentrations that are typical of those reached in regular cigarette smokers."

Nicotine as a Dependence Producing Drug

According to the National Institute of Drug Abuse (NIDA), three criteria define a drug as having the potential for producing dependence. First, the drug is psychoactive. Second, it produces euphoric effects that can be objectively defined and, finally, it is a biologic reinforcer, that is, the chemical activity of the drug is sufficient to establish and maintain compulsive ingestion.(109) Nicotine has been shown to produce these effects in humans and is classified as a dependence producing drug.(110)

A recent article by Pomerleau reviewed a number of studies that demonstrate the psychoactive and euphoric effects of nicotine.(111) Other studies were presented that showed that nicotine produces euphoric effects similar to other drugs of abuse.(112,113) Additional studies showed nicotine to be a reinforcer, and that users developed patterns of self administration because of the reinforcing effects of the drug that lead to compulsive use.(114) Dr. Jack Henningfield of the National Institute of Drug Abuse (NIDA) reported that history and science leave no doubt that tobacco, in a variety of forms, can be an addictive drug, and that the nicotine delivered by tobacco is a dependence producing drug and a prototypic drug of abuse. (Dr. Henningfield explained that the terms "addiction", "dependence" and "abuse" although they may have a different focus, are used interchangeably.)(115)

Commonalities Between Nicotine Use and Other Drugs of Dependence

According to the NIDA drug dependency is a state in which a person's freedom of choice has been compromised by the physical effects of the drug on the brain and nervous system.(116)

Nicotine and other drugs that produce dependence such as alcohol, cocaine and morphine have four common characteristics. First, they are psychoactive, that is they affect the chemistry of the brain and central nervous system. Second, they produce dependence and lead to compulsive use. Third, when one attempts to abruptly stop use, physiological and psychological distress may occur depending on the drug or individual. Finally, there is a tendency of users who have stopped to relapse and go back to use despite their desire to quit. NIDA has concluded that smoking is the most widespread form of drug dependence in the nation and as Henningfield stated, "any form of nicotine should be considered to have the potential to produce dependence until proven otherwise."(117)

Clinical Criteria for Tobacco Dependence

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III)(118) also recognizes the addictive potential of nicotine and states that the essential features for tobacco dependence are continuous use of tobacco for at least one month with either (1) unsuccessful attempts to stop or significantly reduce the amount of tobacco use on a permanent basis, (2) the development of tobacco withdrawal, or (3) the presence of a serious physical disorder (e.g., respiratory or cardiovascular disease) that the individual knows is exacerbated by tobacco use. If the criteria are met, the individual is diagnosed as being dependent.

Five smokeless tobacco users testified, many of whom used the word "hooked" to describe their dependence. All expressed great difficulties in quitting implying that they were dependent. One 18 year old Massachusetts high

school student reported that he started chewing tobacco at thirteen and switched to snuff at fifteen. He reported using two cans of snuff a day last spring and stated, "when I tried to stop dipping, I couldn't do it." (119)

Another high school senior started using snuff when he was 16 years old. He said that when he first tried it, he felt a little bit of dizziness and a little light headedness. "Kids in sports," he said, "do it not as a once-in-awhile, but as an everyday thing." He stated, "I tried to quit and I just couldn't stop." (120)

A 30 year old male stated that he was introduced to snuff as a healthful alternative to smoking over twenty years ago. He said, "I've tried to quit countless times, usually smoking cigarettes to replace my desire to dip snuff." (121)

A Brockton high school student used snuff for two years and reported, "I tried to quit and I just stopped for a day, and then I start getting the . . . well, I start feeling that I wanted another dip. It's addictive." He said that his friends have trouble quitting because "sometimes when you get all nervous, you just feel like a dip or a chew, it just relaxes you and calms you down." He added that he would never think of smoking because, "If you play sports, you just don't smoke." (122)

Dr. Nathaniel Rowe of the University of Michigan testified that of four patients who had oral surgery to remove tumors of the mouth caused by smokeless tobacco, two continued to use smokeless tobacco following surgical treatment despite the life threatening nature of the tumors that were removed. Dr. Rowe described this continued use as addiction. (123)

Several speakers challenged classifying smokeless tobacco as addictive for a number of reasons.

Mr. John Curtin, representing the Smokeless Tobacco Council, stated that in 1964, the Surgeon General's Advisory Committee concluded that tobacco use is not addictive and little has occurred since then to change this.(124) The weight of the evidence does not support this position. Considerable research has been conducted since 1964 that supports the finding that nicotine is addictive and major health agencies have taken positions that nicotine is a dependence producing drug.

Dr. Arthur Furst and Father Joseph Martin, President of Ashley Treatment Center, testified that in order for a drug to be addictive, it must produce life-threatening withdrawal symptoms.(125,126) Dr. Powell, President of Educational Training Programs in Connecticut, stated "dependence (addiction) . . . involves impairment of one's social and/or occupational functioning."(127) However, according to the diagnosis criteria of the American Psychiatric Association, neither life threatening withdrawal symptoms nor social/occupational impairment are criteria for establishing tobacco dependence.(128)

Further, Father Joseph Martin and Dr. David Powell challenged classification of smokeless tobacco as addictive because, in their experience, individuals had not been treated clinically to quit as in the case for alcohol, morphine or cocaine.(129,130)

However, even though treatment is not a criteria for diagnosing dependence, Dr. Glover, of the East Carolina University, reported that he has conducted

two smokeless tobacco clinics and could not get one person to stop using snuff for more than half a day. (131) Further, there are numerous smoking cessation programs throughout the state and nation that assist individuals who wish to quit smoking. Individuals are treated clinically by physicians and many are prescribed nicorette gum (a prescription drug) as part of clinical therapy. Since nicotine can produce dependence regardless of the method of delivery, there is no reason to believe that individuals who use smokeless tobacco would require anything less than what is available to cigarette smokers in order to stop. In addition, as use of smokeless tobacco increases, it is probable that programs similar to the cigarette cessation program will be developed for smokeless tobacco. The National Cancer Institutes will be awarding grants in 1985 to develop and test smokeless tobacco cessation programs. (132)

Conclusions

Testimony supports the view that snuff tobacco delivers nicotine to the blood stream of users in concentrations similar to that of smokers. Nicotine is a prototypic drug of abuse which has been shown to produce dependence and addictive behavior in the user. For this reason, snuff is classified as a potentially addictive substance.

VII. PUBLIC KNOWLEDGE OF THE ADVERSE HEALTH EFFECTS OF SNUFF

Testimony was submitted by several individuals and organizations which related to both consumer knowledge of the adverse health effects of snuff and the industry's promotional activities to increase consumer acceptance of this product.

Several speakers attributed increased use of snuff to television advertisements which use popular sports figures to promote the product. A number of television and print advertisements were reviewed. One witness testified that the ads instructed nonusers on how to use snuff, implied that use was a safe alternative to smoking, and used subliminal messages to imply that use added to athletic prowess and was a clean, healthy, and safe practice.(133) Several speakers criticized these commercials for ignoring known health problems.(134,135) For example, one ad instructs the viewer how to use snuff and states, "at first you could feel a slight irritation on the gum, ...but learning is part of the fun, and these things pass with practice. Two weeks should make you a pro."(136) Although the ad acknowledges gum irritation, it goes on to instruct the user to ignore it.

Representatives of the Smokeless Tobacco Council testified that the industry does not intentionally direct its ads to youth, and that industry adheres to a voluntary code which prohibits advertisements in print or media programs aimed primarily at the youth market. The Council also stated that it supports current legislation to raise the sales age in Massachusetts to 18.(137)

At the hearing, testimony from students, teachers and parents indicated that there was a general lack of knowledge of the potentially harmful effects which may result from the use of snuff.

Dr. Glover of East Carolina University discussed the results of studies he had done on high school students from the Southwest. He found that a majority of students did not think the use of snuff was a health hazard or that the use of snuff was as dangerous as smoking. He attributed this in part to the lack of educational programs at the high school level similar to cigarette smoking prevention programs.(138)

Mrs. Marsee, the mother of a boy from Oklahoma who used snuff heavily until he developed tongue cancer at age 18, stated that her son, Sean, was not aware of any adverse health consequences. She testified that Sean was a track athlete before his death, that he did not smoke cigarettes, and that he considered snuff a safe alternative to smoking based on the promotion of snuff by sports personalities and the lack of a warning label similar to that on cigarettes.(139)

Students from North Easton, Taunton and Brockton high schools testified that they did not know that snuff could cause adverse health effects when they first started. The students from North Easton stated that they would not have started to use snuff if they had known of the potential health problems.(140-143)

The coordinator for health education at Brockton High School testified that many students are unaware of the dangers of smokeless tobacco and that there were no curriculum materials available on the subject.(144) Ms. Anne Hughes of North Easton, Massachusetts, testified that few parents know anything about smokeless tobacco and little information is available on the hazards.(145)

A dental hygienist from Phillips Academy testified that many students at the school are using the product and that they have a complete lack of knowledge of the potential health effects.(146) Two private dentists testified that many adolescent snuff users are not aware of the potential health problems associated with smokeless tobacco.(147,148)

Conclusion

Testimony indicated that adults and adolescents are not knowledgeable about the potential harmful effects of snuff and that promotional campaigns by the industry to encourage use of the product provide no information of potential adverse health consequences.

VIII. SUMMARY OF FINDINGS

Some of the testimony and evidence referred to "smokeless tobacco", and did not specify whether the tobacco was snuff or chewing tobacco. In general, the testimony implicated tobacco as the noxious agent and stated that the form in which it was delivered was incidental to its action. However, the critical experimental, clinical and epidemiologic evidence presented did identify snuff to be a prime offending agent. For this reason, the findings will deal with snuff only. The following findings are made:

1. Snuff contains nitrosamines which have been shown to cause cancer in laboratory animals, and have been classified as potential human carcinogens.
2. The use of snuff has been shown to form oral leukoplakia, which in a significant percentage of cases transform into cancerous lesions.
3. The epidemiological, histopathological and experimental evidence has shown use of snuff to be causally related to oral cancer, and snuff to be a human carcinogen.
4. The nicotine contained in snuff is a prototypic drug of abuse that can lead to dependence (addiction).
5. Based on findings (1) - (3), snuff is toxic under the Massachusetts Hazardous Substance Act, G.L. c.94B, §1 (Hazardous Substance Act) as a substance which has the capacity to produce personal injury or illness to man through ingestion or absorption through body surfaces.
6. Snuff induces localized inflammation of oral tissues on prolonged or repetitive contact, causing in some cases periodontal disease which may result in tooth loss and other gum disorders.

7. Based on finding (6), snuff is an irritant under the Hazardous Substance Act, section one, as a substance not corrosive which on immediate, prolonged or repetitive contact with normal living tissue will induce a local inflammatory reaction.
8. Based on the determination that snuff is toxic and an irritant, it is a hazardous substance within the meaning of the Hazardous Substance Act, section one.
9. Advertisements for the use of snuff provide no information concerning the possible adverse health consequences of snuff use.
10. In general, the public is not knowledgeable concerning the possible adverse health consequences of snuff use.
11. The labeling requirements of section one of the Hazardous Substance Act alone are not adequate for the protection of the public health and safety in view of the special hazard presented by snuff.
12. Requiring a health warning label on snuff is not preempted by federal regulation or statute and does not constitute an impermissible burden on interstate commerce. .

IX. REGULATIONS

Following a review of the testimony and written comments submitted in response to the proposed regulations, the Department has determined that a sufficient basis exists for requiring a warning label on snuff containers sold in Massachusetts.

In response to the testimony and comments to the testimony and comments recieved during the public hearing process, the proposed regulations have been modified in several respects.

First, the definition of snuff has been refined to more accurately describe this particular form of smokeless tobacco and to exclude snuff used in the nasal cavity. (Section 650.005) Second, the label has been changed to warn that snuff "can be" addictive rather than "is" addictive, and "can cause" mouth cancer rather than "may cause" mouth cancer. In addition, the final regulation contains greater specificity concerning the type, location and size of the required label. (Section 650.105) Finally, the regulations contain an effective date of December 1, 1985. (Section 650.105) (Although testimony was requested on label size and placement, as well as effective date, no testimony was submitted on these issues.)

105 CMR: DEPARTMENT OF PUBLIC HEALTH

105 CMR 650.000 is amended in the following manner:

[1] Section 650.005 Supplemental Definitions is amended by adding:

(3) "Snuff," is a form of smokeless tobacco, often referred to as such, which is a finely ground or cut tobacco mixture that is intended to be placed in the oral cavity.

[2] Section 650.015: Listing of Toxic Substances is amended by adding:

(3) Snuff.

[3] Section 650.016: Listing of Irritants is amended by adding:

(3) Snuff.

[4] Section 650.017: Listing of Hazardous Substances is amended by adding:

(3) Snuff.

[5] Adding the following section after 650.100:

650.105: Labeling of Snuff

(1) Any container or package of snuff shall be deemed to be misbranded as of December 1, 1985 unless:

(a) It meets the requirements set forth at 105 CMR 650.004(20)(a) and (b); and

(b) It bears the following label conspicuously placed, either on the top or side of the container or package:

<p>WARNING: Use of snuff can be addictive and can cause mouth cancer and other mouth disorders.</p>
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(2) The label required in subsection (1) shall be white with nine (9) point, bold type black lettering and shall be no smaller than 1/4 inch by 1 1/4 inches.

(3) The label required in subsection (1) may be either printed directly on the container or preprinted provided that any preprinted label is:

- (a) commercially printed; and
- (b) has adherence and/or surface retention such that the surface of the label is destroyed before the label can be removed from the container.

REGULATORY AUTHORITY

105 CMR 650.000: M.G.L. c.94B and M.G.L. c.111, §5.

APPENDIX A

NOTE: These statements are extremely abbreviated and do not reflect the entirety of the various position statements that were received as testimony. Consequently, interested persons are advised to read the oral and written transcript of the hearing for a complete and accurate understanding of the Agency's positions.

Organizations Testifying In Support of Regulation

1. Action for Children's Television
Strongly supports health warning labels for snuff.
2. Association of State and Territorial Dental Directors
Supports warning labels on smokeless tobacco
3. American Cancer Society
Risk of oral cancer is substantially greater among users of smokeless tobacco. Fully supports the health warning labels.
4. American Dental Association
Supports the proposed health warning labels for snuff. Correlation between smokeless tobacco and oral cancer is strong. Potentially precancerous lesions are commonly found in mouths of smokeless tobacco users. Periodontal disease is seen in mouths of smokeless tobacco users.
5. American Heart Association
Nicotine increases risk of heart disease and stroke. Urges labeling of all smokeless tobacco products.
6. American Lung Association
Encourages requiring health warning labels on smokeless tobacco products. Nicotine is an addictive substance.
7. Mayor's Office of Consumers Affairs - City of Boston
Supports regulation for health warning labels.
8. Boston Department of Health and Hospitals - City of Boston
Proposed regulations should be implemented.
9. Coalition on Smoking or Health
Represents nationally American Heart Association, American Lung Association, American Cancer Society and 24 additional agencies. Scientific evidence supports the conclusion the use of tobacco containing nicotine is addictive and the use of snuff is directly linked to oral cancer and other diseases. The Coalition and member agencies endorse the proposed regulation and urge Massachusetts to act now and require health warning labels.
10. Federal Centers for Disease Control
Available evidence indicates chronic use could have serious consequences including oral cancer. Commends Massachusetts for addressing issue.
11. Group Against Smoking Pollution
Massachusetts should require health warning labels on smokeless tobacco products.

12. Massachusetts Society of Dentistry for Children and Massachusetts Academy of Pediatric Dentistry
Scientific research has adequately documented the harmful and carcinogenic effects which tobacco produces in the human oral mucosa.
13. Massachusetts Dental Hygienists' Association, Inc.
Supports the proposed regulation to require warning labels on snuff.
14. Massachusetts Society of Oral Maxillofacial Surgeons
Urges the adoption of the regulation declaring snuff to be a hazardous substance and requiring a health warning label on cans of snuff. Premalignant lesions of the oral cavity, oral cancer, periodontal disease and dental erosions are directly attributable to use of this product.
15. Massachusetts Public Health Association
Nicotine is an addictive drug. Smokeless tobacco has been implicated in the etiology of oral cancer and periodontal disease. Massachusetts should require warning labels on snuff.
16. National Institute on Drug Abuse
National Institutes for Health
Nicotine is a prototypic drug of abuse.
17. National Cancer Advisory Board
National Cancer Institute
National Institutes of Health
There is sufficient evidence of a cause and effect relationship between smokeless tobacco use and human oral cancer. Smokeless tobacco produces leukoplakia and damage to periodontal tissue. Smokeless tobacco contains sufficient nicotine to produce addiction. The Advisory Board supports labeling of smokeless tobacco products.
18. United States Department of Health and Human Services, Office of the Surgeon General
Smokeless tobacco including snuff does indeed pose a cancer threat and is associated as well with certain other pathological oral conditions. Supports the public's right to be aware of the negative health consequences from using snuff and chewing tobacco.
19. Public Citizen Health Research Group
Smokeless tobacco has been shown to be addictive, and has been shown to cause oral cancer. Urges Massachusetts to adopt warning label.
20. World Health Organization
International Agency for Research on Cancer
Snuff of the type sold in the United States is a human carcinogen.

Organizations Testifying in Opposition to Regulation

1. Massachusetts Candy and Tobacco Distributors Association
National Association of Tobacco Distributors
Opposes state by state approach of product labeling.
Supports national approval.
2. Smokeless Tobacco Council, Inc.
Use of smokeless tobacco has not been proven scientifically to
cause any health problems including oral cancer.
Massachusetts Department of Public Health lacks authority to
require a warning label.
Supports raising sales age to 18.
Massachusetts should defer this issue to appropriate federal
agency.

APPENDIX B

References

1. Table I
2. Tables III-VII
3. Table VIII
4. Table IX
5. Tables X-XI
6. General References

NOTE: Where the written statements of the witness is referenced, the name of the presenter is given first, next (w) appears indicating written testimony, and the number of the page of the written statement last. In the case of oral statements, the page of the oral transcript is given. Both the written statements and copy of the oral transcripts are available for review from the Department.

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APPENDIX C

SUMMARY OF TESTIMONY

NOTE: These summaries are extremely abbreviated and do not reflect the entirety of the various statements and written submissions received. Consequently, interested persons are advised to read the transcript of the hearing and the text of the written submissions for a complete and accurate understanding of the testimony. These documents are available at the office of the Department.

1. WINN, Deborah, Ph.D.
Senior Staff Fellow
Epidemiology and Biostatistics Program
National Cancer Institute
verbal/written - 2.6.85

In certain regions of the country many oral cancer deaths are caused by smokeless tobacco.

Oral cancer usually occurs at location in mouth where tobacco is held.

Three case control studies link chewing tobacco habits with oral cancer.

Four case control studies show an association for oral cancer and snuff use only.

Winn study shows use of snuff increases risk to cancer fourfold, and for long-term users fiftyfold. Dose response relationship was found. In the study no other characteristic could eliminate snuff as a risk factor including alcohol, diet and ill-fitting dentures.

Controlling for use of next of kin interviews did not affect the results.

Smith study is inconclusive due to weak follow-up.

Three cohort studies show two to threefold increase in risk to oral cancer from snuff.

2. HECHT, Stephen, Ph.D.
Division Chief of Chemical Carcinogenesis
American Health Foundation
verbal/written - 2.6.85

Snuff contains high levels of nitrosamines which induce cancer in animals. The types are termed NNN, NAT, NAB and NNK.

Concentration of nitrosamines in snuff is 1,000 times greater than that in bacon.

Average daily intake of nitrosamines from beer, meat and cosmetics, range from .2 to .7 micrograms. For a snuff dipper using 10 grams of snuff, the daily level of nitrosamine intake is 330 micrograms. This level has been shown to produce tumors in animals.

NNK and NNN have been shown to produce cancer in the mouths of animals.

3. ROWE, Nathaniel, D.D.S., M.S.D.
Professor of Oral Pathology and Pathology
Schools of Dentistry and Medicine
University of Michigan
verbal - 2.6.85

Out of 33 oral cancer cases reported to University of Michigan biopsy service, four were from smokeless tobacco users. Three used snuff and one "tobacco." Two of the four had no history of smoking or alcohol use.

Two patients couldn't stop using tobacco following extensive mouth surgery. They are addicted.

Use of smokeless tobacco increases risk to oral cancer.

4. CHRISTEN, Arden G., D.D.S.
Chairman and Associate Professor
Department of Preventive Dentistry
Oral Health Research Institute
Indiana University School of Dentistry
verbal/written - 2.6.85

Gingival recession, periodontal breakdown and tooth loss can occur as a result of use of smokeless tobacco.

Use of smokeless tobacco can produce leukoplakia that has the potential to transform into cancer.

Use of smokeless tobacco can cause tooth abrasion.

5. HENNINGFIELD, Jack, Ph.D.
Acting Chief, Human Performance Laboratory
Addiction Research Center
National Institute on Drug Abuse
John Hopkins University School of Medicine
verbal/written - 2.7.85

Nicotine is a prototypic drug of abuse that may lead to compulsive use equivalent to alcohol, cocaine and morphine use. A similar position on nicotine is held by the National Institute on Drug Abuse, World Health Organization and American Psychiatric Association.

Common misconceptions about drug dependence exist that classify it is immoral, elicit behavior or that withdrawal is life threatening.

The terms addiction, dependence and abuse are used somewhat interchangeably but all have a different focus.

Nicotine is contained in all tobacco products. Nicotine is a potent pharmacological agent that affects mood and behaviour.

According to animal and human studies, nicotine is psychoactive. It is an euphoriant and it is a biological reinforcer. In combination these three factors classify nicotine as a prototypic dependency producing drug.

Smokeless tobacco delivers significant quantities of nicotine to the system of the user. Therefore, it has the potential to produce dependence.

There is no technical or scientific difference between the terms addiction and dependency. They both mean compulsive use of a substance in the face of danger.

6. GREENBERG, Allen, Esq.
Staff Attorney
Public Citizen Health Research Group
verbal/written - 2.6.85

Industry advertising fails to convey information that smokeless tobacco is harmful.

Surgeon General's investigation is not needed for Federal Trade Commission or Massachusetts to require warning labels. Sufficient evidence already exists.

Surgeon General Koop has stated smokeless tobacco poses a cancer threat and the World Health Organization recently concluded that snuff is a human carcinogen.

The conclusion of the Smith study is not meaningful because he failed to follow up drop outs.

Warning label should be required.

7. GLOVER, Elbert, Ph.D.
Associate Professor
Department of Community Health
East Carolina University
verbal/written - 2.6.85

Texas Public School Survey found nine percent of the students responding used smokeless tobacco. Many teenagers did not know dangers of use.

An Oklahoma public school survey found a linear relationship between use of smokeless tobacco and age. Twenty-two percent of students in the 11th grade used snuff.

National collegiate survey found 12 percent of those surveyed used smokeless tobacco.

Use is up in the nation and many persons are not aware of the potential health problems.

It is extremely hard to get users to stop once they are "hooked." Use should not be viewed as a passing fad.

8. MARSEE, Betty Anne
Parent
Ada, Oklahoma
verbal - 2.6.85

Sean Marsee, son of testifier, used moist snuff from age 12 to 18. He developed oral cancer of the tongue near where the snuff was held and died from complications of the cancer in February of 1984.

Sean Marsee felt smoking was dangerous and snuff use was not because cigarette packages had warning label on them and snuff packages didn't.

Sean Marsee had no other habits which could result in oral cancer. Cancer developed because of snuff and supports warning labels.

Warning labels should be required.

9. SALMON, Thomas, M.S., M.P.H.
Director
Division of Drug Rehabilitation
Massachusetts Department of Public Health
verbal/written - 2.6.85

Massachusetts survey found 15 percent of Massachusetts high school students used smokeless tobacco during the past year; 6.2 percent used it several times or very often.

Twenty-eight percent of the males surveyed used it during last year.

Warning labels should be required.

10. HUGHES, Paul
High school student
North Easton, MA
verbal/written testimony - 2.6.85

Used chewing tobacco since eighth grade and snuff since sophomore year of high school.

As a result of this, lost appetite and weight.

Tried to stop many times but couldn't.

In spring of last year used two cans of snuff per day and developed white lines in his mouth that would become sore.

Many of his friends dip and are "addicted" to snuff.

People don't realize the health problems. The product should be labeled.

11. LAWRENCE, Alan
High school student
Taunton, MA
verbal - 2.6.85

Started chewing tobacco at age 16 did not consider product harmful.

Stated he is addicted and is unable to quit the habit.

12. HUGHES, Ann
Parent
North Easton, MA
verbal - 2.6.85

Educational information concerning smokeless tobacco is not available to parents.

Her son, Paul Hughes, was unable to stop using snuff.

Warning labels should be required.

13. DOHERTY, Mark, D.M.D.
Dental Director
Dorchester House Health Center
verbal - 2.6.85

When he asked young athletes about snuff none were aware it was harmful.

Students reported their only exposure to snuff was from peer pressure, emulation of pro-athletes and favorable TV advertisement.

Labels should be required so young people can make responsible decisions whether to use snuff or not.

14. MECKLENBURG, Robert, D.D.S., M.P.H.
Chief Dental Office
United States Public Health Service
Office of the Surgeon General
verbal/written - 2.6.85

Supports warning health labels. According to Dr. Mecklenburg industry says nothing should be done because there is as yet no ultimate proof and no direct cause

Dr. Mecklenburg has seen cancer and periodontal disease among smokeless tobacco users.

Use of smokeless tobacco is very heavy among American Indian children.

Industry implies that use is safe alternative to smoking.

The increase in use is attributable to heavy media advertising.

I believe absolutely that adequate evidence of harm already exists. Stronger evidence is coming. Action should be taken now and advising the public of risk is our responsibility.

Surgeon General's position is "Smokeless tobacco, including snuff does indeed pose a cancer threat."

15. MYERS, Matthew L.
Executive Director
Coalition on Smoking or Health
verbal/written - 2.6.85

Supports labeling by the Department of Public Health.

The users of smokeless tobacco are at risk to be addicted to it.

Use has increased substantially among youth in the nation.

Use of snuff is directly linked to oral cancer.

16. CORBIN, Stephen, D.D.S. M.P.H.
Acting Chief of Dental Disease Prevention Activity
Centers for Disease Control
Testifying for J. Michael Lane, M.D.
Director, Center for Preventive Services
verbal/written - 2.6.85

Chronic use of smokeless tobacco is harmful including potentially causing oral cancer.

Commends Massachusetts for taking action.

17. CHARREN, Peggy
President
Action for Children's Television

verbal/written - 2.6.85

Tobacco companies "know how to sell the public a bill of goods".

Children watch 26 hours of TV each week; 80 percent of the time they watch adult TV programming.

Tobacco companies know use of sports figures in short spots have impact on young people; it manipulates attitudes and values.

ACT will petitioning the FTC and FCC to ban advertising of smokeless tobacco products. ACT strongly supports the labeling requirement.

18. LONBORG, James, D.M.D.
Private practice
former professional baseball pitcher
verbal - 2.6.85

Dr. Lonborg is concerned as a dentist and ex-probaseball player. The hazards associated with smokeless tobacco are not well-known to the consuming public.

Dr. Lonborg has treated patients with dental problems caused by smokeless tobacco.

Professional athletes would not appear in ads if they knew dangers.

Warning labels should be required.

19. DEVANEY, Thomas, D.D.S.
Member, Council on Dental Health and Health Planning
American Dental Society
verbal/written - 2.6.85

"The correlation between oral cancer and long-term smokeless tobacco use is too strong to be ignored."

There is damage to oral tissues in long-term snuff users.

ADA and Massachusetts Dental Society support warning labels.

20. CONNOLLY, Gregory N., D.M.D., M.P.H.
Director, Division of Dental Health
Massachusetts Department of Public Health
verbal/written - 2.6.85

The Division of Dental Health is responsible for investigating smokeless tobacco.

Enters scientific studies into the record.

Twenty-six studies from 1915 to present indicate 1,206 cases of oral cancer in long-term snuff users with a 40-50 percent mortality rate.

Scientific evidence clearly shows need for warning labels to read "Warning. Use of Snuff is Addictive, May Cause Mouth Cancer and Other Dental Problems."

21. GUPTA, Prakash C., D.S.
Takemi Research Fellow
School of Public Health
Harvard University
verbal/written - 2.7.85

Oral cancer is the most common form of cancer in India and tobacco chewing is principle cause.

Oral cancer is often preceded by white lesions and a very high correlation has been found between tobacco chewing, white lesions and oral cancer.

There is sufficient evidence that smokeless tobacco used in the United States is carcinogenic and is causally related to oral cancer.

22. LIJINSKY, William, Ph.D.
Litton Bionetics
Under contract to National Cancer Institute
Chief
Laboratory of Chemical and Physical Carcinogenesis
verbal/written - 2.7.85

N-nitrosamines are present in high levels of snuff and have produced cancer in the mouth and other body parts of animals.

An animal study in progress has produced cancer in the mouth at 1 ppm, a NNN level equivalent to that in snuff.

It would be unrealistic to assume man is the only species not affected and exposure to snuff does increase risk to cancer.

23. GUINTA, John, D.M.D., M.S.
Professor of Oral Pathology
Tufts University, School of Dental Medicine
verbal/written - 2.7.85

Oral effects of smokeless tobacco include discolored teeth, bad breath, tooth abrasion, decay, decreased sensory perception, gum disease and leukoplakia.

Smokeless tobacco produces leukoplakia, a clinical term. Upon biopsy, leukoplakia can be a simple callous, epithelial dysplasia or cancer.

24. TSAMPROURIS, Anthi, D.M.D., M.S.
Associate Professor
Tufts University School of Dental Medicine
Representing Massachusetts Academy of Pediatric Dentistry and
Massachusetts Society of Dentistry for Children
verbal/written - 2.7.85

Scientific evidence has documented that smokeless tobacco causes cancer.

Condemns use of smokeless tobacco.

25. MEHTA, Nashir, D.M.D.
Associate Professor
Department of Periodontology
Tufts University School of Dental Medicine
verbal/written - 2.7.85

Long term use of smokeless tobacco is directly linked to oral leukoplakia, gingival recession and gum disease.

Three to six percent of oral leukoplakias become cancerous.

26. KELLY, John, D.M.D., M.D.
Assistant Professor of Oral and Maxillofacial Surgery
Harvard University School of Medicine
Oral and Maxillofacial Department
Massachusetts General Hospital
verbal- 2.7.85

Surgical treatment of oral cancer results in significant disfigurement and disability.

Cost of hospital and surgical care of oral cancer case \$20,000 to \$25,000.

27. SHAFFER, Howard, Ph.D.
Assistant Professor of Psychology
Department of Psychology
Harvard University School of Medicine
Cambridge Hospital
North Charles Institute for the Addiction
verbal - 2.7.85

Supports warning label, recommends that word addictive be changed to chemical dependence and feels that warning labels will have limited impact.

Nicotine produces chemical dependence, withdrawal syndrome and behavioral craving.

Addiction and dependence are not synonymous and should not be interchanged.

28. PALLADINO, George, Lt. Col., Ph.D.
Professor of Chemistry
United States Military Academy
verbal/written - 2.7.85

Nicotine in smokeless tobacco is addictive.

Nitrosamines in snuff have been shown to cause cancer.

Supports health warning label of snuff.

29. FOSTER, Ken
Consumer
verbal - 2.7.85

Used snuff for more than 20 years. It was recommended as safe alternative to smoking.

Did not know snuff could cause cancer.

Tried to quit but couldn't.

Supports warning label.

30. BERNAYS, Edward L.
Public Relations Counsel
Cambridge, MA
verbal - 2.7.85

Tobacco taken by mouth should be labeled.

31. DIETZ, William H., Jr., M.D., Ph.D.
Pediatrician
Tufts University School of Medicine
Member, American Academy of Pediatrics Task Force on
Children's Television
verbal/written - 2.7.85

Ads for smokeless tobacco promote it as an alternative to smoking.

Use of professional athletes in ads are directed to receptive adolescents.

Supports warning labels.

32. AMICK, Carol C., M.P.A.
Senator, Massachusetts State Senate
Former newspaper editor
verbal/written 2.7.85

Ads for snuff aimed at adolescent males. They use subliminal messages to seduce youth and use sports figures in advertisements.

Supports warning labels.

33. BOYD, Gayle, Ph.D.
Division of Cancer Prevention and Control
National Cancer Institute
verbal/written - 2.7.85

The National Cancer Advisory Board has concluded there is sufficient scientific evidence for a cause and effect relationship between snuff and cancer.

Smokeless tobacco contains sufficient nicotine to be addictive.

Public awareness of the health effects of snuff is limited.

Recommends health warning labels.

34. ALLUKIAN, Myron, D.D.S., M.P.H.
Assistant Deputy Commissioner
Director, Bureau of Community Dental Programs
Department of Health and Hospitals
City of Boston
verbal - 2.7.85

Smokeless tobacco may act as a chronic irritant.

State has the responsibility to inform adults and children of potential harm from smokeless tobacco.

35. BERTONAZZI, Louis R.
Senator, Massachusetts State Senate
Vice Chairman, Joint Committee on Health Care
verbal/written - 2.7.85

Evidence is overwhelming showing nicotine addictive.

Evidence is targeted to youth.

Snuff advertising is targeted to youth.

Strongly recommend health warning labels.

36. DAYNARD, Richard, Esq.
Professor
Northeastern University School of Law
President
GASP (Group Against Smoking Pollution) of Massachusetts
Co-Chairman, Tobacco Products Liability Project
verbal/written - 2.7.85

Tobacco Liability Project supports suits against tobacco industry for health problems associated with tobacco use.

37. SMITH, Robert, D.M.D.
President, Massachusetts Society of Oral Maxillofacial Surgeons
verbal/written - 2.7.85
- Use of snuff is directly linked to premalignant lesions of the oral cavity, oral cancer and periodontal disease.
- Supports health warning labels.
38. MODICA, Diane
Commissioner, Mayor's Office of Consumer Affairs and Licensing
Boston
verbal/written - 2.7.85
- Snuff is gaining popularity among young people and no information about health risks is available to them.
- Supports health warning labels.
39. SCHNIPPER, Lowell, M.D.
Beth Israel Hospital
President-Elect
American Cancer Society, Massachusetts Division
verbal/written - 2.7.85
- Use of smokeless tobacco causes oral leukoplakia and three to five percent of these become cancerous.
- Risk of oral cancer is far greater among snuff users than non-users.
- Young people habituated to nicotine from smokeless tobacco may switch to cigarettes later in life.
- Supports warning label.
40. SWEDA, Edward, Esq.
Legislative Secretary, GASP
verbal/written - 2.7.85
- Smokeless tobacco serves as a gateway to smoking.
- Snuff advertising hides the fact the product is harmful.
- Supports warning label.
41. RICCARDI, Vincent
Coordinator of Health Education
Brockton High School
verbal/written - 2.7.85
- Many of the high school students in sports use smokeless tobacco but are not knowledgeable of dangers.
- Supports educational program to curb use of snuff.

42. SCHUBBUCH, Ralph
Student, Brockton High School
verbal/written - 2.7.85

Had no knowledge of health problems associated with snuff when he started using it.

After using it, he developed sores in his mouth.

Started to use snuff because others on sport team did, and athletes used it on television.

He found it hard to stop using snuff.

43. RICCARDI, Mark
Student, Brockton High School
verbal - 2.7.85

Used smokeless tobacco for two years and tried to quit but had trouble because it is addictive.

Athletes at Brockton High School would never consider smoking. Teachers and students alike were unaware of snuff's potential hazards.

44. WALSH, Joan, R.D.H.
Infirmary, Phillips Academy
Andover, MA
verbal - 2.7.85, written - 2.12.85

Students use smokeless tobacco at Phillips Andover but don't know the health effects or dangers.

Supports warning label.

There is a growing trend among teenagers to use snuff nationally.

45. LANIDES, Maria
Concerned Citizen
Albany, New York
verbal - 2.7.85

There is heavy use of snuff by students in New York, because of heavy advertising.

Supports warning label.

46. JOHNSON, Elizabeth
Director, Environmental Program
American Lung Association of Massachusetts
verbal/written - 2.7.85

Massachusetts students have reported switching from cigarettes to smokeless tobacco because they think it is safe.

Supports warning label.

47. SILVESTRI, Ronald, M.D.
Pulmonary Physician
New England Deaconess Hospital
Member, Massachusetts Thoracic Society
verbal - 2.7.85

Concerned over high addictive potential to nicotine from smokeless tobacco.

Supports warning label.

48. CARLSON, Craig D.,
Representing Massachusetts Dental Hygienists' Association,
Inc.
verbal/written - 2.7.85

Supports proposed regulation.

Recommends ban on television advertising.

Recommends listing ingredients of smokeless tobacco (nitrosamines, cyanide, nicotine, insect residues) on package.

49. ROSEN, Robert, M.D.
Physician
Rhode Island
verbal - 2.7.85

Use of smokeless tobacco will increase risk of oral cancer.

50. DUANE, Barney
Director of Public Relations
American Heart Association, Massachusetts Affiliate
Representing W. John Powell, M.D.
President, American Heart Association, Massachusetts Affiliate
verbal/written - 2.7.85

Ingestion of tobacco affects blood pressure, heart rate and blood clotting, thus increasing risk of heart attacks.

Cancer, gum disease and tooth loss are linked to smokeless tobacco use.

Support health warning labels.

51. KOTELCHUCK, Milton, Ph.D., M.P.H.
 President, Massachusetts Public Health Association
 verbal/written - 2.7.85

Use of smokeless tobacco is a threat to health.

Nicotine is an addictive drug.

Supports warning label.

52. PIERSON, Benjamin, Jr.
 President
 Byfield Snuff Company
 Byfield, MA
 verbal/written - 2.7.85

Opposes regulations.

It is economically not feasible for a small business to compete with larger manufacturers if a label is required.

If a label is required, it should be done at federal level.

53. CURTIN, John, Esq.
 Partner
 Bingham, Dana and Gould (law firm)
 Representing Smokeless Tobacco Council, Inc.
 verbal - 2.7.85, written - 2.22.85

The Smokeless Tobacco Industry was not given sufficient time to prepare for the hearing and was not consulted prior to the Department of Public Health's decision to proceed with warning label.

Snuff is not addictive and has not been scientifically established to cause disease.

The Federal government is considering the smokeless tobacco issue and Massachusetts should defer to the federal government.

Massachusetts' Hazardous Substance Labeling Act is based on the federal law and federal law does not encompass tobacco. Therefore, the Commissioner of Public Health does not have the authority over smokeless tobacco.

A warning label requirement in Massachusetts would impose an undue burden on interstate commerce and be in conflict with United States Constitution.

53. KERRIGAN, Michael J.
President, Smokeless Tobacco Council, Inc.
Washington, D.C.
verbal/written - 2.7.85

Smokeless Tobacco Council opposes warning labels.

Use of snuff has declined over the last 50 years and seven million Americans use it today. Massachusetts use is one-fourth of one percent of the total United States usage.

Smokeless tobacco has not been proven scientifically to cause any health problem.

The issue is best left at the federal level where there are proper checks and balances.

Animal studies have not found smokeless tobacco to cause cancer.

Snuff use may become a settled practice, but it is not addictive.

The industry has set up the Smokeless Tobacco Research Council to conduct research on health effects.

Smokeless tobacco advertising is not aimed at youth. The target audience for advertising is males 18-49.

The Smokeless Tobacco Council supports sales restrictions to those under 18.

If smokeless tobacco is required to carry a health warning label, eggs and red meat should also be required to do so.

54. ROMARY, Paul
Legislative Aide
Representing Representative John McNeil
Co-Chairman, Joint Committee on Health Care
verbal/written - 2.7.85

Rep. McNeil applauds the Department of Public Health for bringing the issue to the public's attention.

There is enough scientific evidence available to recognize the potential risk of smokeless tobacco.

In Winthrop, Massachusetts the superintendent of schools adopted a smokeless tobacco ban because of the high use by students in school. In Malden the use is low.

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55.

FURST, Arthur, Ph.D., Sc.D.
Distinguished University Professor Director (Emeritus)
Institute of Chemical Biology
University of San Francisco
President American College of Toxicology

Smokeless tobacco cannot be classified as addictive. Tolerance of a certain level of a substance is produced in an addicted persons and more of that substance is needed. This is not true for smokeless tobacco. Epidemiological or statistical studies do not demonstrate causal relationships. They provide hypothesis which researchers can explore through experimental or clinical studies.

Leukoplakia is a clinical term. Three studies have found no significant cellular changes among the "leukoplakia" of snuff dippers. It is not a premalignant condition. Smokeless tobacco has not been shown to cause leukoplakia. Other factors such as nutrition and poor oral hygiene play an important role in oral leukoplakia.

The Winn study failed to control for "ill fitting dental appliances," poor nutrition or socioeconomic status. He questions the validity of this study's findings.

Animal studies have not produced oral cancer following exposure to snuff except in the Hirsch study. However, only one animal out of 52 exposed to snuff produced a tumor, and the animal used was susceptible to tumors. Hirsch concedes that the tumor may have developed spontaneously.

A few N-nitroso compounds have been found in snuff but none have induced oral cancer in test animals.

Indian studies report oral cancer caused by "quids" that contain tobacco, betel nuts and leaves and lime. It is scientifically unsound to single out tobacco since the same lesions are found in those who don't chew.

The term premalignant is a misnomer.

The Smith study found no oral cancer among 1,550 users followed for ten years. The Axell study found no oral cancer among 114 users with leukoplakia. Based on scientific studies, it is not possible to conclude smokeless tobacco use causes oral cancer.

Scientists do not know how a normal cell becomes malignant.

He cannot make the association that cigarette smoking causes cancer.

56. POWELL, David J., Ph.D.
 President
 Education and Training Programs, Inc.
 Hartford, CT
 verbal - 2.7.85

Dependency (addiction) means loss of control over intake of a substance consumed and the impairment of one's social and occupational functioning.

Smokeless tobacco does not meet the criteria for addiction or dependency. It does not meet the criteria of the American Psychiatric Association or World Health Organization.

Use of the word addictive in relation to smokeless tobacco may mislead youth to believe that truly addictive substances are harmless.

Cigarette smoking does not produce dependency.

57. GIFTOS, Peter
 Vice President
 National Association of Tobacco Distributors
 Past President
 Massachusetts Candy and Tobacco Distributors Association
 verbal/written - 2.7.85

Groups wishing to testify in opposition to the proposed regulations weren't given sufficient time to prepare for hearing.

State by state labeling approach places an unnecessary burden on distributors. He supports a national approach.

Manufacturers probably won't bother putting labels on and the distributors will have to instead and will have to bear the cost of this.

He questions the ability to enforce this regulation.

58. GREENBERG, Allen, Esq.
 Staff Attorney
 Public Citizen Health Research Group
 written 2.19.85

Challenges Dr. Furst's claim that smokeless tobacco does not cause cancer.

A causal relationship exists if there is consistency, strength and specificity of the association, and biologic plausibility. Smokeless tobacco fits the criteria.

World Health Organization's finding that arsenic causes cancer was based solely on epidemiological evidence.

Many of Dr. Furst's statements are misleading or wrong.

59. CARLSON, Robert H., M.D.
Emergency Care Clinic
Birmingham, AL
written - 2.20.85

Have not seen significant problems with users of smokeless tobacco.

Cigarette smoking and alcohol have been shown to produce significant health problems. Smokeless tobacco has not.

Does not support label.

60. HECHT, Stephen, Ph.D.
American Health Foundation
written - 2.19.85

Dr. Furst contradicted himself on cancer causation.

61. GUINTA, John, D.M.D., M.S.
Tufts University School of Dental Medicine
written - 2.19.85

Dr. Furst's statements on leukoplakia came from outdated text books. New versions of Shaffer text states the use of tobacco causes leukoplakia. Leukoplakia on biopsy shows histologic changes.

Dr. Furst's statements on Axell study misleading. Axell reported all biopsies of leukoplakia showed histologic changes.

Dr. Furst does not understand the term "pre-malignant." Epithelial dysplasia (cervical intraepithelial neoplasia) is recognized as a precursor to invasive cervical cancer.

62. GUPTA, Prakash C., D.Sc.
Takemi Research Fellow
Harvard University School of Public Health
written - 2.21.85

Rejects Dr. Furst's statement that "epidemiologic or statistical studies ... do not demonstrate causal relations." Cause-and-effect relationships among humans can only be ascertained through epidemiologic reasoning and epidemiologic studies. Animal studies can be supportive of epidemiologic evidence.

Rejects Dr. Furst's statement that tobacco does not produce leukoplakia. Tobacco use causes oral leukoplakia and risk of oral cancer much greater among persons with leukoplakia.

Rejects Dr. Furst's statement "that the term premalignant is a misnomer." World Health Organization has defined "precancer as the part of the tissue in which oral cancer is more likely to occur than its normal counterpart."

Dr. Furst has misinterpreted results of the six studies he presented. Dr. Gupta personally knows all the authors except two and states they would be surprised by Dr. Furst's interpretation that smokeless tobacco does not cause leukoplakia and increase risk to oral cancer.

Rejects Dr. Furst's statement that nutrition and dental hygiene play a role in development of leukoplakia.

Rejects Dr. Furst's statement the Indian studies showing leukoplakia and oral cancer among tobacco chewers failed to control for non-tobacco ingredients. These ingredients were controlled for and tobacco was found to be the agent.

63. STRAUSS, Peter
Secretary
National Association of Tobacco Distributors
written 2.19.85

Does not support label.

Urges Massachusetts to let federal government deal with labeling.

64. DUFFY, George P.
President
Massachusetts Candy and Tobacco Distributors, Inc.
written 2.22.85

Asks that a hearing be held on economic and social effects of labeling before regulations are issued.

Concerned with criminal sanctions of the law.

65. CURTIN, John J., Jr., Esq.
Dana, Bingham and Gould
written - 2.22.85

Hearings did not prove snuff is addictive nor that it has been scientifically proven to cause human disease.

Proposed label is unfair and inaccurate.

Commissioner lacks statutory authority to require such labeling.

Regulations are constitutionally defective since federal government regulates tobacco.

Regulations are invalid because they impose unreasonable and excessive burden on interstate commerce.

66. BROTMAN, Richard, Ph.D.
Professor of Psychiatry
New York Medical College
written - 2.22.85

Addiction is not a medical term, but a misused popular term.

Using the term "addiction" may have a boomerang effect that will attract people particularly, youngsters to use it.

If a label is required, use technical health terms not an alarming one like "addictive."

67. GRASSO, Paul, M.D.
Professor of Experimental Pathology
Rubens Institute, University of Surrey
written 2.22.85

Reviewed animal studies on nitrosamine compounds, found in snuff. NNN, NNK, NAB, NNA and NAT.

NNN and NNK are moderately active carcinogens that produce esophageal, lung and other tumors in the body of animals. They have not been shown to produce tumors in the oral cavity, and because of their metabolism are site specific, not contact carcinogens.

NAB and NNA are very weak carcinogens and likely to be organ specific, not site specific, and NAT is inactive.

No experimental evidence is available to show that nitrosamines in snuff are oral carcinogens, and no direct human evidence shows that nitrosamines cause cancer in humans.

68. JENNINGS, B. R., Ph.D.
Associate Professor of Pathology
Director Clinical (Immunology)
The Regional Medical Center of Memphis
University of Tennessee Medical Center
written - 2.22.85

Deficiencies in the immune system may influence susceptibility to tumors. Tumors of the head and neck have been shown to be associated with cellular

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deficiencies.

Other factors influence immune response such as heredity, age, sex, race, alcohol use and pappilloma virus.

No studies exist associating smokeless tobacco use and oral cancer that have taken into account all risk factors. Therefore, the proposed label is not scientifically warranted.

69. KUPPER, Lawrence L.
Professor of Biostatistics
University of North Carolina
School of Public Health
written - 2.22.85

Reviewed basic principles of epidemiology, case history, case control and follow-up studies done in the United States and Europe on smokeless tobacco including Winn, Smith and Axell.

Smith study shows no association but it is hard to interpret because of many drop outs and short study period.

Axell study does not provide relevant evidence to United States because it is based on short period of time and takes place in another culture.

Winn study has three weaknesses. Quality of data is weakened by use of proxy respondents for deceased cases. Statistical methods used are not state of the art today. Recommends reanalysis using conditional logistic regression. Interpretation can only be applied to study group, (i.e., rural white Southern women.)

Concludes use of snuff is a risk factor for oral cancer for rural white Southern women only. More research is needed before it can be established as a risk factor for general United States population.

70. LA VIA, Mariano F., M.D.
Professor of Laboratory Medicine
Director, Division of Diagnostic Immunology
University of South Carolina Medical School
written 2.22.85

The causes of oral cancer as well as mechanisms for its occurrence are unknown.

Immune system plays an important role in pathogenesis and evolution of cancerous lesions, and patients with a malfunctioning system develop cancer more frequently.

Dr. LaVia's studies have found vitamin A imbalances in patients with lymphocyte changes and oral lesions. His studies have shown no correlation between smokeless tobacco use and oral lesions.

There may be some statistical relationship between smokeless tobacco and oral cancer, but more experimental studies are needed before conclusions can be made.

71. MARTIN, Joseph C. Reverend
President
Ashley Treatment Center
written 2.22.85

Alcohol addiction is the compulsive use of a sedative drug that results in serious life problems, and cannot be stopped unaided. Physical and mental dependence result from this use.

Smokeless tobacco use doesn't fit the criteria for addiction.

The word addiction should be reserved for alcohol, heroin or cocaine.

Warning label using the word addiction is unwarranted and provides no useful purpose.

72. MINCER, Harry H., D.D.S., M.S., Ph.D.
Professor of Oral Pathology
University of Tennessee
written 2.22.85

Scientific studies have not established that the use of snuff will produce serious changes in oral tissues including oral cancer.

Leukoplakia is a clinical term that shows on biopsy four conditions, hyperplasia (thickening of the tissue), atrophy (thinning of the deeper layers), dysplasia and cancer.

Dr. Mincer's studies on persons who smoke, use snuff, chew tobacco or use no tobacco found no relationship between leukoplakia and histological conditions.

Leukoplakia does not progress in orderly fashion to dysplasia or oral cancer.

Dysplasia may transform into cancer, but at a low rate (10 percent).

The Smith study does not support a statistical association between use of snuff and oral cancer.

Other factors such as heredity, deficiencies with immune system, diet, alcohol, viruses and yeast may play a greater role in formation of oral cancer than tobacco.

There may be a statistical association between snuff use and oral cancer, but the cause is unknown.

73. POWELL, David J., Ph.D.
President
Education and Training Programs, Inc.
written - 2.22.85

Does not support use of term addictive, it is not accurate.

Dependence (addiction) means loss of control over intake of a substance quantity consumed and impairment of one's social and occupational functioning.

Smokeless tobacco does not meet criteria for addiction or dependence. It does not meet criteria of the American Psychiatric Association or World Health Organization.

Use of the word addictive in connection with smokeless tobacco raises major concerns for children reading the label.

74. WEATHERS, Dwight R., D.D.S., M.S.D.
Chairman
Department of Oral Pathology
Emory University School of Dentistry
written - 2.22.85

Oral cancer is a multifactoral disease, the cause of which is unknown.

There appears to be an association between smokeless tobacco and leukoplakia. Leukoplakia is a clinical term and is not a predictor of cancer.

Dr. Weathers' study on 500 schoolchildren found that smokeless tobacco did not change the level of gum disease or tooth decay if the children had clean mouths.