

The Health Consequences of Using Smokeless Tobacco

**A Report of the
Advisory Committee to the Surgeon General**

1986

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Bethesda, Maryland 20892**

**NIH Publication No. 86-2874
April 1986**

CONTENTS

Foreword	v
Preface	vii
Acknowledgments	ix
Introduction, Overview, and Conclusions	xvii
Chapter 1. Prevalence and Trends of Smokeless Tobacco Use in the United States	1
Chapter 2. Carcinogenesis Associated With Smokeless Tobacco Use	29
Chapter 3. Noncancerous and Precancerous Oral Health Effects Associated With Smokeless Tobacco Use	95
Chapter 4. Nicotine Exposure: Pharmacokinetics, Addiction, and Other Physiologic Effects	137
Index	187

FOREWORD

This report on *The Health Consequences of Using Smokeless Tobacco* completes the Public Health Service's initial examination of smokeless tobacco's role in the causation of cancer, noncancerous and precancerous oral diseases or conditions, addiction, and other adverse health effects. Almost 30 years after the Public Health Service's first statement on the health effects of cigarette smoking, it is now possible to issue the first comprehensive, indepth review of the relationship between smokeless tobacco use and health.

Ironically, while cigarette smoking has declined during the past 20 years, the production and apparent consumption of smokeless tobacco products have risen significantly. These increases are in marked contrast to the decline in smokeless tobacco use in the United States during the first half of this century. Indeed, smokeless tobacco products, particularly chewing tobacco and snuff, have recently emerged as popular products for the first time since the turn of the century. National estimates indicate that at least 12 million Americans used some form of smokeless tobacco during 1985 with use increasing especially among male adolescents and young male adults.

The increased use and appeal of this product assume major public health significance because the evidence reveals that smokeless tobacco can cause oral cancer, can lead to the development of oral leukoplakias and other oral conditions, and can cause addiction to nicotine. The strength of the association between these conditions and smokeless tobacco use combined with the upward trend in this behavior incites the same alarm as was true with the knowledge that spitting spread tuberculosis. That concern led to the original public rejection of tobacco chewing and dipping as unsanitary and antisocial. It is critical that our society prevent the use of this health hazard and avoid the tragic mistake of replacing the ashtray with the spittoon.

This report is the work of numerous experts within the Department of Health and Human Services and in the non-Federal scientific community. I express my gratitude for their contributions.

C. Everett Koop, M.D.
U.S. Surgeon General

PREFACE

This report discusses the health consequences of smokeless tobacco use. It constitutes a comprehensive review by an Advisory Committee to the Surgeon General of the available scientific literature to determine whether using smokeless tobacco increases the risk of cancer and non-cancerous oral diseases and effects, leads to addiction and dependence, and contributes to other health consequences.

AFTER A CAREFUL EXAMINATION OF THE RELEVANT EPIDEMIOLOGIC, EXPERIMENTAL, AND CLINICAL DATA, THE COMMITTEE CONCLUDES THAT THE ORAL USE OF SMOKELESS TOBACCO REPRESENTS A SIGNIFICANT HEALTH RISK. IT IS NOT A SAFE SUBSTITUTE FOR SMOKING CIGARETTES. IT CAN CAUSE CANCER AND A NUMBER OF NONCANCEROUS ORAL CONDITIONS AND CAN LEAD TO NICOTINE ADDICTION AND DEPENDENCE.

The major overall conclusions of this report are the following:

1. It is estimated that smokeless tobacco was used by at least 12 million people in the United States in 1985 and that half of these were regular users. The use of smokeless tobacco, particularly moist snuff, is increasing, especially among male adolescents and young male adults.
2. The scientific evidence is strong that the use of snuff can cause cancer in humans. The evidence for causality is strongest for cancer of the oral cavity, wherein cancer may occur several times more frequently in snuff dippers compared to nontobacco users. The excess risk of cancer of the cheek and gum may reach nearly fiftyfold among long-term snuff users.
3. Some investigations suggest that the use of chewing tobacco may also increase the risk of oral cancer, but the evidence is not so strong and the risks have yet to be quantified.
4. Experimental investigations reveal potent carcinogens in smokeless tobacco. These include nitrosamines, polycyclic aromatic hydrocarbons, and radiation-emitting polonium. The tobacco-specific nitrosamines often have been detected at levels 100 or more times higher than Government-regulated levels of other nitrosamines permitted in foods eaten by Americans.

5. Smokeless tobacco use can lead to the development of oral leukoplakias (white patches or plaques of the oral mucosa), particularly at the site of tobacco placement. Based on evidence from several studies, a portion of leukoplakias can undergo transformation to dysplasia and further to cancer.
6. Gingival recession is a commonly reported outcome of smokeless tobacco use.
7. A number of studies have shown that nicotine exposure from smoking cigarettes can cause addiction in humans. In this regard, nicotine is similar to other addictive drugs such as morphine and cocaine. Since nicotine levels in the body resulting from smokeless tobacco use are similar in magnitude to nicotine levels from cigarette smoking, it is concluded that smokeless tobacco use also can be addictive. Besides, recent studies have shown that nicotine administered orally has the potential to produce a physiologic dependence.
8. Some evidence suggests that nicotine may play a contributory or supportive role in the pathogenesis of coronary artery and peripheral vascular disease, hypertension, peptic ulcers, and fetal mortality and morbidity.

ACKNOWLEDGMENTS

This report was prepared by the Department of Health and Human Services under the direction and general editorship of Joseph W. Cullen, Ph.D., Chairman of the Advisory Committee on the Health Consequences of Using Smokeless Tobacco. The following individuals were members of the Advisory Committee:

Catherine S. Bell, M.S., Acting Chief, Prevention Research Branch, Division of Clinical Research, National Institute on Drug Abuse, Rockville, Maryland

William Blot, Ph.D., Chief, Biostatistics Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

James P. Carlos, D.D.S., M.P.H., Associate Director, Epidemiology and Oral Disease Prevention Program, National Institute of Dental Research, Bethesda, Maryland

Joseph W. Cullen, Ph.D., Chairman of the Advisory Committee, Deputy Director, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

J. David Erickson, D.D.S., M.P.H., Ph.D., Chief, Birth Defects and Genetic Diseases Branch, Centers for Disease Control, Atlanta, Georgia

Manning Feinleib, M.D., Dr.P.H., Director, National Center for Health Statistics, Hyattsville, Maryland

Jerome Jaffe, M.D., Director, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Michael McGinnis, M.D., M.A., M.P.P., Deputy Assistant Secretary for Health, Director, Office of Disease Prevention and Health Promotion, United States Public Health Service, Washington, D.C.

Robert Mecklenburg, D.D.S., M.P.H., Assistant Surgeon General, Chief Dental Officer, United States Public Health Service, Rockville, Maryland

Susan Sieber, Ph.D., Deputy Director, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Sumner J. Yaffe, M.D., Director, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, Bethesda, Maryland

The Advisory Committee was supported by the following technical experts in the areas listed below:

Carcinogenesis

William Blot, Ph.D. (Coordinator), Chief, Biostatistics Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Gayle Boyd, Ph.D., Research Psychologist, Division of Cancer Prevention and Control, National Cancer Institute, Silver Spring, Maryland

Virginia L. Ernster, Ph.D., Associate Professor of Epidemiology, University of California, San Francisco, California

Curtis Harris, M.D., Chief, Laboratory of Human Carcinogenesis, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Dietrich Hoffmann, Ph.D., Associate Director, Chemistry and Biochemistry, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York

Kenneth Rothman, Dr.P.H., Professor of Family and Community Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

David Schottenfeld, M.D., Chief, Division of Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, New York

Steven R. Tannenbaum, Ph.D., Professor of Toxicology and Food Chemistry, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts

David B. Thomas, M.D., Dr. P.H., Head, Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington

Non-Cancer Oral Effects

Arden G. Christen, D.D.S., M.S.D., M.A., Chairman, Department of Preventive Dentistry, Indiana University Dental School, Indianapolis, Indiana

Stephen B. Corbin, D.D.S., M.P.H., Chief, Dental Disease Prevention Activity, Center for Preventive Services, Centers for Disease Control, Rockville, Maryland

Robert O. Greer, Jr., D.D.S., Sc.D., Professor, Division of Oral Pathology and Oncology, University of Colorado Health Sciences Center, Denver, Colorado

Lireka P. Joseph, Dr.P.H., Medical Radiation Specialist, Food and Drug Administration, Rockville, Maryland

Stephen S. Kegeles, Ph.D., Professor, Department of Behavioral Sciences and Community Health, University of Connecticut Health Center, Farmington, Connecticut

Matthew Kinnard, Ph.D., Health Science Administrator, Periodontal and Soft Tissue Diseases Research Branch, National Institute of Dental Research, Bethesda, Maryland

Dushanka Kleinman, D.D.S., M.Sc.D., Special Assistant to the Associate Director for Program Coordination, Epidemiology and Oral Disease Prevention Program, National Institute of Dental Research, Bethesda, Maryland

Robert Mecklenburg, D.D.S., M.P.H. (Coordinator), Assistant Surgeon General, Chief Dental Officer, United States Public Health Service, Rockville, Maryland

Kathleen L. Schroeder, D.D.S., M.S., Assistant Professor, Department of Oral Biology, Ohio State University College of Dentistry, Columbus, Ohio

Addiction and Dependence

Catherine S. Bell, M.S. (Coordinator), Acting Chief, Prevention Research Branch, Division of Clinical Research, National Institute on Drug Abuse, Rockville, Maryland

Neal Benowitz, M.D., Associate Professor of Medicine, Chief of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, California

Anthony Biglan, Ph.D., Research Scientist, Oregon Research Institute, Eugene, Oregon

John Grabowski, Ph.D., Associate Professor, Department of Psychiatry, School of Medicine, Louisiana State University, Shreveport, Louisiana

Steven Gust, Ph.D., Research Associate, Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota

Jack Henningfield, Ph.D., Chief, Biology of Dependence and Abuse Potential Assessment Laboratory, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland

Lynn Kozlowski, Ph.D., Senior Scientist, The Smoking Research Program, Addiction Research Foundation, Toronto, Ontario, Canada

Norman A. Krasnegor, Ph.D., Chief, Human Learning and Behavioral Branch, Center for Research for Mothers and Children, National Institute for Child Health and Human Development, Bethesda, Maryland

Ovide Pomerleau, Ph.D., Chief of Psychology Service, Veterans Administration Medical Center, Newington, Connecticut

The following individuals prepared draft chapters or portions of the report as indicated:

Chapter I. Prevalence and Trends of Smokeless Tobacco Use in the United States

Gayle Boyd, Ph.D., Research Psychologist, Division of Cancer Prevention and Control, National Cancer Institute, Silver Spring, Maryland

Rebecca Cline, Ph.D., Senior Associate, Prospect Associates, Rockville, Maryland

Charles Darby, M.A., Technical Support Staff Coordinator for Addiction and Dependence Experts, Senior Associate, Prospect Associates, Rockville, Maryland

Margaret Mattson, Ph.D., Special Assistant for Science, Office of the Director, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

Chapter II. Carcinogenesis Associated With Smokeless Tobacco Use

William Blot, Ph.D., Chief, Biostatistics Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Virginia L. Ernster, Ph.D., Associate Professor of Epidemiology, University of California, San Francisco, California

Curtis Harris, M.D., Chief, Laboratory of Human Carcinogenesis, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

Stephen S. Hecht, Ph.D., Division of Chemical Carcinogenesis, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York

Dietrich Hoffmann, Ph.D., Associate Director, Chemistry and Biochemistry, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York

Kenneth Rothman, Dr.P.H., Professor of Family and Community Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

David Schottenfeld, M.D., Chief, Division of Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, New York

Steven R. Tannenbaum, Ph.D., Professor of Toxicology and Food Chemistry, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts

David B. Thomas, M.D., Dr.P.H., Head, Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington

Deborah M. Winn, Ph.D., Epidemiologist, Survey Planning and Development Branch, National Center for Health Statistics, Hyattsville, Maryland

Chapter III. Noncancerous and Precancerous Oral Health Effects Associated With Smokeless Tobacco Use

Stephen B. Corbin, D.D.S., M.P.H., Chief, Dental Disease Prevention Activity, Center for Preventive Services, Centers for Disease Control, Rockville, Maryland

Lireka P. Joseph, Dr.P.H., Medical Radiation Specialist, Food and Drug Administration, Rockville, Maryland

Dushanka Kleinman, D.D.S., M.Sc.D., Special Assistant to the Associate Director for Program Coordination, Epidemiology and Oral Disease Prevention Program, National Institute of Dental Research, Bethesda, Maryland

Chapter IV. Nicotine Exposure: Pharmacokinetics, Addiction, and Other Physiologic Effects

Neal Benowitz, M.D., Associate Professor of Medicine, Chief of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, California

Anthony Biglan, Ph.D., Research Scientist, Oregon Research Institute, Eugene, Oregon

Jack Henningfield, Ph.D., Chief, Biology of Dependence and Abuse Potential Assessment Laboratory, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland
Margaret Mattson, Ph.D., Special Assistant for Science, Office of the Director, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

The Advisory Committee and authors acknowledge with gratitude the following distinguished scientists, physicians, and others who lent their support in the development of this report by contributing critical reviews of the manuscript or assisting in other ways:

John Bailar, M.D., Ph.D., Lecturer, Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts
Enriqueta C. Bond, Ph.D., Director, Division of Health Promotion and Disease Prevention, Institute of Medicine, Washington, D.C.
Lester Breslow, M.D., M.P.H., Professor Emeritus, School of Public Health, University of California, Los Angeles, California
David M. Burns, M.D., Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of California, San Diego Medical Center, San Diego, California
Greg Connolly, D.M.D., M.P.H., Director, Division of Dental Health, Massachusetts Department of Public Health, Boston, Massachusetts
D. Layten Davis, Ph.D., Director, University of Kentucky, Tobacco and Health Research Institute, Lexington, Kentucky
Miriam Davis, Ph.D., Program Analyst, Office of Health Planning and Evaluation, Office of the Assistant Secretary for Health, Washington, D.C.
Vincent T. DeVita, Jr., M.D., Director, National Cancer Institute, Bethesda, Maryland
Joseph F. Fraumeni, Jr., M.D., Associate Director for Epidemiology and Biostatistics, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland
Thomas J. Glynn, Ph.D., Program Director for Smoking Research, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland
Peter Greenwald, M.D., Dr.P.H., Director, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland
Ellen R. Gritz, Ph.D., Director, Division of Cancer Control, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, California
Dianne G. Lindewall, Ph.D., Program Analyst, Office of Health Planning and Evaluation, Office of the Assistant Secretary for Health, Washington, D.C.
Marilyn M. Massey, M.P.H., Technical Support Staff Coordinator for the Advisory Committee, Senior Associate, Prospect Associates, Rockville, Maryland

Gardner C. McMillan, M.D., Associate Director for Etiology, Arteriosclerosis, and Hypertension, National Heart, Lung, and Blood Institute, Bethesda, Maryland

Jens J. Pindborg, D.D.S., Dr. Odont., Professor of Oral Pathology, Royal Dental College, Copenhagen, Panum Institute, Copenhagen, Denmark

John M. Pinney, Executive Director, Institute for the Study of Smoking Behavior and Policy, John F. Kennedy School of Government, Harvard University, Cambridge, Massachusetts

Earl S. Pollack, Sc.D., President, Pollack Associates Ltd., Bethesda, Maryland

Richard J. Riseberg, Chief Counsel, United States Public Health Service, Rockville, Maryland

Thomas L. Robertson, M.D., Chief, Cardiac Diseases Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland

Beatrice A. Rouse, Ph.D., Epidemiologist, Division of Epidemiology and Statistical Analysis, National Institute on Drug Abuse, Rockville, Maryland

Donald R. Shopland, Acting Director, Office on Smoking and Health, United States Public Health Service, Rockville, Maryland

Sol Silverman, Jr., M.A., D.D.S., Professor and Chairman of Oral Medicine, University of California, San Francisco, California

Chester Slaughter, M.A., Deputy Regional Inspector General for Analysis and Inspections, Office of the Inspector General, Dallas, Texas

K. W. Stephen, D.D.Sc., H.D.D.R.C.P.S., Head of Oral Medicine and Pathology, University of Glasgow, Glasgow, Scotland

Ronald W. Wilson, M.A., Director, Division of Epidemiology and Health Promotion, National Center for Health Statistics, Hyattsville, Maryland

Ernst L. Wynder, M.D., President, American Health Foundation, New York, New York

Maruta Zitans, M.Sc., Program Analyst, Office of the Inspector General, Washington, D.C.

The Advisory Committee and authors also acknowledge several organizations for their contributions in identifying relevant literature and/or in offering critical reviews of the manuscript.

Institute of Medicine, National Academy of Sciences, for providing through its Board on Health Promotion and Disease Prevention a critique of the Advisory Committee's review methods and drafts of the report.

International Agency for Research on Cancer (IARC), Lyon, France, for providing IARC Monograph No. 37 on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Habits Other Than Smoking; Betel-Quid and Areca-Nut Chewing and Some Related Nitrosamines, September 1985.

National Center for Health Statistics and National Institute on Drug Abuse, for providing data on the prevalence and trends of smokeless tobacco use in the United States.

Office on Smoking and Health, for bibliographic citations and other documents pertinent to the literature review.

Smokeless Tobacco Council, Inc. (Michael J. Kerrigan, President), for providing approximately 15,000 citations considered relevant by a number of the smokeless tobacco companies, including the collection of testimonies representing the smokeless tobacco industry's position concerning the health consequences of smokeless tobacco.

The Advisory Committee and authors also acknowledge the contributions of the following staff members and others who assisted in the preparation of the report:

Kathy Bauman, Editorial Assistant to the Deputy Director, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland

Julie Begun, Research Assistant, Prospect Associates, Rockville, Maryland

Barbara Clark, M.S., M.P.H., Technical Support Staff Coordinator for Non-Cancer Oral Effects Experts, Prospect Associates, Rockville, Maryland

Shelley Clark, Conference Coordinator, Prospect Associates, Rockville, Maryland

Nancy Cowan, Conference Coordinator, Prospect Associates, Rockville, Maryland

Kathleen Edmunds, Library Research Assistant, Prospect Associates, Rockville, Maryland

Robyn Ertwine, Librarian-Information Specialist, Prospect Associates, Rockville, Maryland

Catherine Fisher, Secretary, Prospect Associates, Rockville, Maryland

Barbara Hayden, Secretary, Prospect Associates, Rockville, Maryland

Douglas Hunter, Library Assistant, Prospect Associates, Rockville, Maryland

Karen Jacob, Editor, Prospect Associates, Rockville, Maryland

Margaret Johnson, Typist, Prospect Associates, Rockville, Maryland

Mary Johnson, Typist, Prospect Associates, Rockville, Maryland

Virginia Knill, Typist, Prospect Associates, Rockville, Maryland

Solomon Levy, M.P.H., Associate Director, Office of the Surgeon General, Rockville, Maryland

Paula Margus, Library Research Assistant, Prospect Associates, Rockville, Maryland

Nancy McCormick-Pickett, M.A., Technical Support Staff Coordinator for Carcinogenesis Experts, Prospect Associates, Rockville, Maryland

Lee McPherson, Typist, Prospect Associates, Rockville, Maryland

Robbie Morsette, Library Assistant, Prospect Associates, Rockville, Maryland
Elizabeth Mugge, Secretary to the Deputy Director of the Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland
Arthur Nelson, Library Research Assistant, Prospect Associates, Rockville, Maryland
Ro Nemeth-Coslett, Ph.D., Visiting Scientist, Biology of Dependence and Abuse Potential Assessment Laboratory, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland
Simon Plog, Typist, Prospect Associates, Rockville, Maryland
Nancy Rudner, M.S.N., M.P.H., Technical Support Staff Assistant, Prospect Associates, Rockville, Maryland
Estelle Schwalb, Technical Writer-Editor, Prospect Associates, Rockville, Maryland
Barbara Shapiro, Editor, Prospect Associates, Rockville, Maryland
John Shea, Ph.D., Technical Writer-Editor, Prospect Associates, Rockville, Maryland
Dorritt Silber, Secretary, Prospect Associates, Rockville, Maryland
Dori Steele, Proofreader, Prospect Associates, Rockville, Maryland
Deborah S. Swansburg, Program Officer, Institute of Medicine, National Academy of Sciences, Washington, D.C.

INTRODUCTION, OVERVIEW, AND CONCLUSIONS

DEVELOPMENT AND ORGANIZATION OF THE REPORT

This report from the Surgeon General's Advisory Committee on the Health Consequences of Using Smokeless Tobacco represents the first comprehensive assessment of the biomedical and behavioral literature describing experimental and human evidence on the health consequences of using smokeless tobacco. The content of this report is the work of numerous experts within the Department of Health and Human Services as well as distinguished scientists outside the organization.

Each chapter of the report was prepared based on manuscripts written by scientists who are recognized for their understanding of the specific content areas. Manuscripts were subjected to extensive peer review by a large number of experts in the specific areas of interest.

The report includes a "Preface" that presents the essence of the entire report and an "Introduction, Overview, and Conclusions." The body of the report consists of the following four chapters:

- Chapter 1—Prevalence and Trends of Smokeless Tobacco Use in the United States
- Chapter 2—Carcinogenesis Associated With Smokeless Tobacco Use
- Chapter 3—Noncancerous and Precancerous Oral Health Effects Associated With Smokeless Tobacco Use
- Chapter 4—Nicotine Exposure: Pharmacokinetics, Addiction, and Other Physiologic Effects

HISTORICAL PERSPECTIVE

The use of smokeless tobacco is a worldwide practice with numerous variations in the nature of the product used as well as in the customs associated with its use. In the United States, smokeless tobacco consists of chewing tobacco and snuff. The predominant mode of use of these nonsmoked tobaccos is oral, although they may be placed in or inhaled into the nasal cavity. Tobacco sniffing, however, has been and remains a rare practice in the United States.

Smokeless tobacco was used in the United States in the early 1600's when snuff made its way to the Jamestown Colony in Virginia through the efforts of John Rolfe in 1611 (1). Evidence of tobacco chewing, however, was not found until a century later in 1704 (2).

The use of tobacco, including smokeless tobacco, has been controversial since its introduction. In the past, tobacco use was considered by some as beneficial. As early as 3500 B.C., there are indications that tobacco was an article of established value to the inhabitants of Mexico and Peru. It appears that people who frequently lacked sufficient food alleviated their hunger pains by chewing tobacco (3). Smokeless tobacco was also thought to have several medicinal uses. Among Native Americans, for example, chewing tobacco was used to alleviate toothaches, disinfect cuts, and relieve the effects of snake, spider, and insect bites (4). Moreover, during the 19th and early 20th centuries in America, dental snuff was advertised to relieve toothache pain; to cure neuralgia, bleeding gums, and scurvy; and to preserve and whiten teeth and prevent decay (1).

On the other hand, tobacco use historically has had numerous adversaries, including the following (1):

- In 1590 in Japan, tobacco was prohibited. Users lost their property and were jailed.
- King James VI of Scotland in the early 1600's was a strong anti-smoking advocate who increased taxes on tobacco 4,000 percent in an attempt to reduce the quantity imported to England.
- In 1633, the Sultan Murad IV of Turkey made any use of tobacco a capital offense, punishable by death from hanging, beheading, or starvation. He maintained that tobacco caused infertility and reduced the fighting capabilities of his soldiers.
- The Russian Czar Michael Fedorovich, the first Romanov (1613-1645), prohibited the sale of tobacco, stating that users would be subjected to physical punishment and that persistent users would be killed.
- A Chinese law in 1683 threatened that anyone possessing tobacco would be beheaded.
- During the mid-1600's, Pope Urban VIII banned the use of snuff in churches, and Pope Innocent X attacked its use by priests in the Catholic Church.
- Other religious groups also banned snuff use: John Wesley, the founder of Methodism, attacked its use in Ireland; the Mormons, Seventh-Day Adventists, Parsees and Sikhs of India, Buddhist monks of Korea, members of the Tsai Li sect of China, and some Ethiopian Christian sects forbade the use of tobacco.

- Frederick the Great, King of Prussia, prevented his mother, the Dowager Queen of Prussia, from using snuff at his coronation in 1790.
- Louis XV, ruler of France from 1723 to 1774, banned snuff use from the Court of France.

Scientific observations concerning the health effects of smokeless tobacco use were first noted in 1761 by John Hill, a London physician and botanist who reported five cases of polypuses, a “swelling in the nostril that was hard, black and adherent with the symptoms of an open cancer” (5). He concluded that nasal cancer could develop as a consequence of tobacco snuff use (sniffing).

Evidence that suggested a possible association between smokeless tobacco use and oral conditions in North America and Europe was not reported until 1915 when Abbe identified several tobacco chewers among a series of oral cancer patients and commented that smokeless tobacco use may be a risk factor for this cancer (6). In the late 1930’s, Ahblom observed in Sweden that more patients with buccal, gingival, and “mandibular” cancers than with other cancers reported the use of snuff or chewing tobacco (7). In the United States, case reports of oral cancer among users of snuff or chewing tobacco appeared in the early 1940’s (8). The first epidemiologic study of smokeless tobacco was not conducted until the early 1950’s (9). Since that time, several scientists have described a pattern of increased risk of oral cancer among smokeless tobacco users.

Investigations of other possible health effects of smokeless tobacco use (e.g., noncancerous oral effects, addiction, and other physiologic consequences) are more recent subjects of scientific inquiry that have been undertaken primarily in the past two decades.

A brief review of the health consequences of smokeless tobacco was presented in the 1979 Surgeon General’s report on smoking and health (10). Since that review, the results of additional studies addressing the role of smokeless tobacco in health have become available and thus provide the basis of this current comprehensive review.

REVIEW METHODS

For the purpose of evaluating the scientific evidence to be included in this report, the Advisory Committee called upon the same criteria to determine causality as have been used for a number of Surgeon General’s reports on smoking for the past two decades. The following criteria were used as the primary guidelines for assessing whether any associations between smokeless tobacco use and each of the disease areas or health conditions under examination were likely to be causal in nature:

- Consistency of the association—similar observations by multiple investigators in different locations and situations, at different times, and using different methods of study.
- Strength of the association—high ratio of disease rate for the population exposed to the suspected risk factor compared to the population unexposed to the risk factor.
- Specificity of the association—associations with the exposure exist for a specific or limited set of diseases, and associations with the disease exist for a specific or limited set of exposures.
- Temporal relationship of the association—exposure to the suspected etiologic factor precedes the disease.
- Coherence of the association—epidemiologic observations are consonant with all else that is known about the disease.

In addition to these criteria, the general principles employed by the International Agency for Research on Cancer (IARC)* in evaluating the carcinogenic risk of chemicals or complex mixtures (table 1) were used as needed to supplement the primary causation criteria (11).

OVERVIEW

The use of smokeless tobacco products in the United States was widespread until the end of the 19th century. With the advent of antisputting laws, loss of social acceptability, and increased popularity of cigarette smoking, its use declined rapidly in this century. However, recent national data indicate a resurgence in smokeless tobacco habits with more than 12 million persons estimated as users of some form of smokeless tobacco in 1985. An upward trend in use is emerging, particularly among young males.

Given the evidence that smokeless tobacco is regaining popularity, serious questions have been raised about its adverse health effects. Most notably, this behavior has been linked to cancer, specifically, oral cancer. Analytic epidemiologic studies now indicate that the use of oral snuff increases the risk of oral cancer several fold and that among long-term snuff dippers the excess risk of cancers of the cheek and gum may reach nearly fiftyfold. This conclusion is consistent with the judgment of a recent working group of the IARC, which assessed the carcinogenic risk associated with tobacco habits other than smoking (11).

The conclusion that smokeless tobacco causes cancer results from several lines of evidence: the presence of high levels of carcinogens in smokeless tobacco; the metabolic conversion of products of smokeless

* The IARC was established in 1965 by the World Health Assembly as an independently financed organization within the framework of the World Health Organization. It conducts a program of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment.

**TABLE 1.—General Principles in Evaluating
Carcinogenic Risk of Chemicals or Complex Mixtures
(International Agency for Research on Cancer)**

- Evidence for carcinogenicity in experimental animals:
 - Qualitative aspects:
 - (a) Experimental parameters under which chemical was tested.
 - (b) Consistency with which chemical shown to be carcinogenic.
 - (c) Spectrum of neoplastic response.
 - (d) Stage of tumor formation in which chemical involved.
 - (e) Role of modifying factors.
 - Hormonal carcinogenesis.
 - Complex mixtures.
 - Quantitative aspects; increasing incidence of neoplasms with increasing exposure.
 - Evidence for activity in short-term tests:
 - Use of valid test system.
 - Sufficiently wide dose range and duration of exposure to the agent and appropriate metabolic system employed in test.
 - Use of appropriate controls.
 - Specification of the purity of the compound, and in the case of complex mixtures, source and representativeness of sample tested.
 - Evidence of carcinogenicity in humans:
 - For studies showing positive association:
 - (a) Existence of no identifiable bias.
 - (b) Possibility of positive confounding considered.
 - (c) Association unlikely to be due to chance alone.
 - (d) Association is strong.
 - (e) Existence of dose-response relationship.
 - For studies showing no association:
 - (a) Existence of no identifiable negative bias.
 - (b) Possibility of negative confounding considered.
 - (c) Possible effects of misclassification of exposure or outcome have been weighed.
-

tobacco into genotoxic agents; the consistency of the oral cancer-smokeless tobacco association across epidemiologic investigations conducted in diverse locations; the trend in increasing oral cancer risk with duration of exposure; the strength of the association with oral cancer; and the occurrence of the highest risks for cancers at the anatomic sites where the tobacco exposures are the greatest.

In addition, a number of clinical observations and studies show an association between smokeless tobacco use and some noncancerous and precancerous oral health conditions. The development of a portion of oral leukoplakias in both teenage and adult users can be attributed to the use of smokeless tobacco. The risk of developing these leukoplakic lesions increases with increased exposure, and a number of studies now suggest that some snuff-induced leukoplakias can undergo transforma-

tion to dysplasia and further to carcinoma. The evidence concerning the adverse health effects of smokeless tobacco use on other oral soft and hard tissues is only suggestive at this time.

The magnitude of blood nicotine levels resulting from smokeless tobacco use has been shown to be similar to that from cigarette smoking. Therefore, the nicotine-related health consequences of smoking would also be expected to result from smokeless tobacco use. Given the nicotine content of smokeless tobacco, the user's ability to sustain elevated blood levels of nicotine, and the well-established data implicating nicotine as an addictive substance, it is reasonable to expect that smokeless tobacco is capable of producing nicotine addiction in users.

There is also some suggestive evidence that nicotine may play a contributory or supportive role in the development of coronary artery and peripheral vascular disease, hypertension, peptic ulcer disease, and fetal mortality and morbidity.

The conclusions in this report on the relationship between smokeless tobacco use and cancer, noncancerous and precancerous oral conditions, and addiction and dependence are substantially in agreement with those published at a recent National Institutes of Health (NIH) Consensus Development Conference on the Health Implications of Smokeless Tobacco Use (12).

CONCLUSIONS

Prevalence and Trends of Smokeless Tobacco Use in the United States

1. Recent national data indicate that over 12 million persons used some form of smokeless tobacco (chewing tobacco and snuff) in 1985 and that approximately 6 million used smokeless tobacco weekly or more often. Use is increasing, particularly among young males.
2. The highest rates of use are seen among teenage and young adult males. A recent national survey indicates that 16 percent of males between 12 and 25 years of age have used some form of smokeless tobacco within the past year and that from one-third to one-half of these used smokeless tobacco at least once a week. Use by females of all ages is consistently less than that of males; about 2 percent have used smokeless tobacco in the last year.
3. State and local studies corroborate the national survey findings. The prevalence of smokeless tobacco use by youth and young adults varies widely by region, but use is not limited to a single region. In several parts of the country, as many as 25 to 35 percent of adolescent males have indicated current use of smokeless tobacco.

Carcinogenesis Associated With Smokeless Tobacco Use

1. The scientific evidence is strong that the use of smokeless tobacco can cause cancer in humans. The association between smokeless tobacco use and cancer is strongest for cancers of the oral cavity.
2. Oral cancer has been shown to occur several times more frequently among snuff dippers than among nontobacco users, and the excess risk of cancers of the cheek and gum may reach nearly fiftyfold among long-term snuff users.
3. Some investigations suggest that the use of chewing tobacco also may increase the risk of oral cancer.
4. Evidence for an association between smokeless tobacco use and cancers outside of the oral cavity in humans is sparse. Some investigations suggest that smokeless tobacco users may face increased risks of tumors of the upper aerodigestive tract, but results are currently inconclusive.
5. Experimental investigations have revealed potent carcinogens in snuff and chewing tobacco. These include nitrosamines, polycyclic aromatic hydrocarbons, and radiation-emitting polonium. The tobacco-specific nitrosamines N-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone have been detected in smokeless tobacco at levels 100 times higher than the regulated levels of other nitrosamines found in bacon, beer, and other foods. Animals exposed to these tobacco-specific nitrosamines, at levels approximating those thought to be accumulated during a human lifetime by daily smokeless tobacco users, have developed an excess of a variety of tumors. The nitrosamines can be metabolized by target tissues to compounds that can modify cellular genetic material.
6. Bioassays exposing animals to smokeless tobacco, however, have generally shown little or no increased tumor production, although some bioassays suggest that snuff may cause oral tumors when tested in animals that are infected with herpes simplex virus.

Noncancerous and Precancerous Oral Health Effects Associated With Smokeless Tobacco Use

1. Smokeless tobacco use is responsible for the development of a portion of oral leukoplakias in both teenage and adult users. The degree to which the use of smokeless tobacco affects the oral hard and soft tissues is variable depending on the site of action, type of smokeless tobacco product used, frequency and duration of use, predisposing factors, cofactors (such as smoking or concomitant gingival disease), and other factors not yet determined.

2. Dose response effects have been noted by a number of investigators. Longer use of smokeless tobacco results in a higher prevalence of leukoplakic lesions. Oral leukoplakias are commonly found at the site of tobacco placement.
3. Some snuff-induced oral leukoplakic lesions have been noted upon continued smokeless tobacco use to undergo transformation to a dysplastic state. A portion of these dysplastic lesions can further develop into carcinomas of either a verrucous or squamous cell variety.
4. Recent studies of the effects of smokeless tobacco use on gingival and periodontal tissues have resulted in equivocal findings. While gingival recession is a common outcome from use, gingivitis may or may not occur. Because longitudinal data are not available, the role of smokeless tobacco in the development and progression of gingivitis or periodontitis has not been confirmed.
5. The evidence concerning the effects of smokeless tobacco use on the salivary glands is inconclusive.
6. Negative health effects on the teeth from smokeless tobacco use are suspected but unconfirmed. Present evidence, albeit sparse, suggests that the combination of smokeless tobacco use in individuals with existing gingivitis may increase the prevalence of dental caries compared with nonusers without concomitant gingivitis. Reports of tooth abrasion or staining have not been substantiated through controlled studies; only case reports are available.

Nicotine Exposure: Pharmacokinetics, Addiction, and Other Physiologic Effects

1. The use of smokeless tobacco products can lead to nicotine dependence or addiction.
2. An examination of the pharmacokinetics of nicotine (i.e., nicotine absorption, distribution, and elimination) resulting from smoking and smokeless tobacco use indicates that the magnitude of nicotine exposure is similar for both.
3. Despite the complexities of tobacco smoke self-administration, systematic analysis has confirmed that the resulting addiction is similar to that produced and maintained by other addictive drugs in both humans and animals. Animals can learn to discriminate nicotine from other substances because of its effects on the central nervous system. These effects are related to the dose and rate of administration, as is also the case with other drugs of abuse.
4. It has been shown that nicotine functions as a reinforcer under a variety of conditions. It has been confirmed that nicotine can

function in all of the capacities that characterize a drug with a liability to widespread abuse. Additionally, as is the case with most other drugs of abuse, nicotine produces effects in the user that are considered desirable to the user. These effects are caused by the nicotine and not simply by the vehicle of delivery (tobacco or tobacco smoke).

5. Nicotine is similar in all critical measures to prototypic drugs of abuse such as morphine and cocaine. The methods and criteria used to establish these similarities are identical to those used for other drugs suspected of having the potential to produce abuse and physiologic dependence. Specifically, nicotine is psychoactive, producing transient dose-related changes in mood and feeling. It is a euphoriant that produces dose-related increases in scores on standard measures of euphoria. It is a reinforcer (or reward) in both human and animal intravenous self-administration paradigms, functioning as do other drugs of abuse. Additionally, nicotine through smoking produces the same effects, and it causes neuroadaptation leading to tolerance and physiologic dependence. Taken together, these results confirm the hypothesis that the role of nicotine in the compulsive use of tobacco is the same as the role of morphine in the compulsive use of opium derivatives or of cocaine in the compulsive use of coca derivatives.
6. The evidence that smokeless tobacco is addicting includes the pharmacologic role of nicotine dose in regulating tobacco intake; the commonalities between nicotine and other prototypic dependence-producing substances; the abuse liability and dependence potential of nicotine; and the direct, albeit limited at present, evidence that orally delivered nicotine retains the characteristics of an addictive drug.
7. Several other characteristics of tobacco products in general, including smokeless tobacco, may function to enhance further the number of persons who are afflicted by nicotine dependence: nicotine-delivering products are widely available and relatively inexpensive; and the self-administration of such products is legal, relatively well tolerated by society, and produces minimal disruption to cognitive and behavioral performance. Nicotine produces a variety of individual-specific therapeutic actions such as mood and performance enhancement; and the brief effects of nicotine ensure that conditioning occurs, because the behavior is associated with numerous concomitant environmental stimuli.
8. All commonly marketed and consumed smokeless tobacco products contain substantial quantities of nicotine. The nicotine is delivered to the central nervous system in addicting quantities when used in the fashion that each form is commonly used (or as recommended in smokeless tobacco marketing campaigns).

9. Since the exposure to nicotine from smokeless tobacco is similar in magnitude to nicotine exposure from cigarette smoking, the health consequences of smoking that are caused by nicotine also would be expected to be hazards of smokeless tobacco use. Areas of particular concern in which nicotine may play a contributory or supportive role in the pathogenesis of disease include coronary artery and peripheral vascular disease, hypertension, peptic ulcer disease, and fetal mortality and morbidity.

REFERENCES

- (1) Christen, A.G., Swanson, B.Z., Glover, E.D., and Henderson, A.H. Smokeless tobacco: The folklore and social history of snuffing, sneezing, dipping, and chewing. *J. Am. Dent. Assoc.* 105: 821-829, 1982.
- (2) Gottsegen, J.J. Tobacco. A Study of Its Consumption in the United States. New York, Pitman, 1940, p. 3.
- (3) Voges, E. The pleasures of tobacco—How it all began and the whole story. *Tobacco J. Int.* 1: 80-82, 1984.
- (4) Axton, W.F. Tobacco and Kentucky. Lexington, University Press of Kentucky, 1975, pp. 8, 25, 58-59.
- (5) Redmond, D.E. Tobacco and cancer: The first clinical report, 1761. *N. Engl. J. Med.* 282: 18-23, 1970.
- (6) Abbe, R. Cancer of the mouth. *New York Med. J.* 102: 1-2, 1915.
- (7) Ahblom, H.E. Predisposing factors for epitheliomas of the oral cavity, larynx, pharynx, and esophagus. *Acta Radiol.* 18: 163-185, 1937 (in Swedish).
- (8) Friedell, H.L., and Rosenthal, L.M. The etiologic role of chewing tobacco in cancer of the mouth. *JAMA* 116: 2130-2135, 1941.
- (9) Moore, G.E., Bissinger, L.L., and Proehl, E.C. Tobacco and intraoral cancer. *Surg. Forum* 3: 685-688, 1952.
- (10) U.S. Public Health Service. Smoking and Health. A Report of the Surgeon General. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health (DHEW Publication No. PHS 79-50066). Washington, D.C., U.S. Government Printing Office, 1979, pp. 13-38 to 13-41.
- (11) International Agency for Research on Cancer. Tobacco habits other than smoking: Betel-quid and areca-nut chewing and some related nitrosamines. *IARC Monogr.* 37: 291, 1985.
- (12) National Institutes of Health. Consensus Development Conference Statement on the Health Implications of Smokeless Tobacco Use, January 13-15, 1986.