THE CHEMICAL COMPONENTS OF TOBACCO AND TOBACCO SMOKE

SECOND EDITION

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Foreword

The following pages are an attempt to update a situation with regard to the composition of tobacco and tobacco smoke that has existed for almost five decades. Although it is suspected that the chemical components of tobacco and tobacco smoke may have been cataloged in-house at various U.S. and foreign tobacco companies as well as by various governmental agencies, no such catalog has been published since the 1968 review by the highly competent tobacco scientist R.L. Stedman of the U.S. Department of Agriculture (3797). One article published by a tobacco company prior to that of Stedman was a 1963 referenced monograph on tobacco and tobacco smoke components by Philip Morris, Inc. (2939). Its monograph was submitted to the 1964 Advisory Committee for use in preparation of its 1964 report to the U.S. Surgeon General. The Philip Morris monograph had been preceded by the 1959 published review by Johnstone and Plimmer (1971). In subsequent years, several tobacco and tobacco smoke publications dealt with specific types or classes of components, e.g., the 1964 compilation of the polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke by Elmenhorst and Reckzeh (1139), the 1969 review by Neurath on the nitrogen-containing components identified in tobacco smoke (2724), and the 1977 review by Schmeltz and Hoffmann on the nitrogen-containing components in both tobacco and tobacco smoke (3491). Several catalogs of the chemical components of only tobacco smoke have been published, e.g., the 1954 article by Kosak (2170), but the most recent one was that of Ishiguro and Sugawara (1884) in 1980. Since the 1968 Stedman article in which about 1200 tobacco and smoke components were listed, the number of identified tobacco and tobacco smoke components has increased sevenfold to almost 8600, a number that includes only about 500 of the many thousands of enzymes identified in the tobacco plant.

The references cited for a particular tobacco and/or tobacco smoke component may deal with its identification or with a variety of topics pertinent to the particular component. Such topics may include such simple items as the isolation and identification of a component, its characterization by classical chemical means such as the definition of the structure of solanesol isolated from flue-cured tobacco by Rowland et al. (3359), or the characterization of a component by spectrographic means such as UV, IR, NMR, MS, and chromatographic retention time, e.g., the identification by Snook et al. of many PAHs (3756–3758) and aza-arenes (3750) in cigarette mainstream smoke (MSS). Many references cited herein describe the search for and elucidation of the precursor in tobacco of a particular component in cigarette MSS (3616), e.g., the saturated aliphatic hydrocarbon precursors of the PAHs, including benzo[*a*]pyrene (B[*a*]P); the quantitation of the component on a per gram of tobacco basis or on its per cigarette MSS yield, particularly if the component is considered a health problem; and the improvements/developments in analytical technology to determine the per cigarette MSS and/or sidestream smoke (SSS) yield of the component. Also included in citations for a particular MSS, SSS, and environmental tobacco smoke (ETS) component are the publications of results of experimental studies on its biological activity plus discussions and/or assertions of its toxicity and/or tumorigenicity. While their number is much fewer than the opposite point of view, included are references to studies on the inhibition of adverse biological activity of a tobacco smoke component by another smoke component, e.g., the inhibition of mouse-skin tumorigenicity of B[*a*]P by *n*-hentriacontane and *n*-pentatriacontane (4314, 4336), the inhibition of *N*-nitrosodimethylamine (NDMA) mutagenicity by nicotine (2327a, 2327b), the inhibition of mouse-skin tumorigenicity of dibenz[*a,h*]anthracene (DB[*a,h*]A) by benz[*a*]anthracene (B[*a*]A) (3814), both classified as significant tobacco smoke tumorigens. Also cited are reports on the controversies over the extrapolation of the biological effect of a specific component administered individually vs. its biological effect when it is the component in a highly complex mixture such as MSS and is administered to a different species, by a different route, and at a dose level far in excess of its level in the complex mixture (1318a, 3300, 3627). Lastly, many studies are cited in which cigarette design technologies were generated to control the per cigarette MSS yield of FTC "tar" and one or more specific components of concern, e.g., reconstituted tobacco sheet, expanded tobacco, ventilated filters, filter-tip, and cigarette paper additives.

While some of the citations may seem obscure to a reader newly involved in tobacco and/or smoke research, they are included to elucidate the historical background and relationship to more recent studies, e.g., publications pertinent to 2-methyl-1,3-butadiene (isoprene), a fairly plentiful component of the vapor phase cigarette smoke. The publications include the 1913 report by Staudinger et al. (25A68) that pyrolysis of isoprene yielded a "tar." In 1918, the procedure to successfully generate tumors by animal skin painting was described (4361). Five years later, Kennaway (2073–2076) demonstrated the tumorigenicity of the pyrolysate "tar" from isoprene, and much later, Badger et al. (143) recorded the PAH content of an isoprene pyrolysate. Another example includes a series of references to the research results reported by Roffo that a tobacco "destructive distillate" was tumorigenic (3322, 3325), contained B[*a*]P (3316), and the B[*a*]P content and tumorigenicity of the "destructive distillate" were reduced by organic-solvent extraction of the tobacco prior to destructive distillation (3327).

Our goal was to present to the reader as many pertinent references that we could find for a particular component and permit the reader to decide which references to study. For some components, dozens of references are available, for other components only one or two. The multireferenced components are usually those considered to be involved in the health problems connected to tobacco smoking. Since the publication of the first edition of this book in late 2008, we have added to our Alphabetical Component Index and the appropriate major chapter tables nearly a thousand reported components of tobacco and/or tobacco smoke. References pertinent to these newly cataloged components and the earlier reported ones have been included in the Bibliography and in the appropriate major chapter tables devoted to functionality.

We express our deep appreciation to several scientific staff members of the Verband der Cigaretten-Industrie and the Beiträge zur Tabakforschung International. They reviewed the initial chapter of the draft of the first edition of our opus and made many meaningful suggestions and pointed out the need for several corrections. Most of their input was applied to that chapter and eventually extended to subsequent chapters as we wrote them. One needed correction that was described was a problem with the electronic address for a specific reference. It was found to be inaccessible at the time of the review. That was corrected, since the reference had multiple electronic addresses, the inaccessible one was replaced with an accessible and operative one. However, the finding triggered an examination of all the electronic addresses cited in the Bibliography section. Of the nearly 900 such addresses, three more were found to be inaccessible. Fortunately, each was part of a reference with multiple electronic addresses, and the inaccessible address for each was replaced with an accessible one.

We apologize to the reader for the omission not only of any tobacco or tobacco smoke component from the catalog but also any significant reference by one or more competent investigators who provided information pertinent to one or more specific components.

Acknowledgments

During the many years that this tobacco and tobacco smoke component catalog was being prepared, numerous components were discussed with colleagues, many of whom were involved either in tobacco and/or tobacco smoke research within the tobacco industry or outside of it. Much meaningful information was obtained during the many discussions, and such information has been incorporated into our effort. We greatly appreciate the input not only from those colleagues who are still with us but also from those who are not.

In the first group, we are extremely grateful to Fred W. Best, Michael F. Borgerding, N.M. Chopra, Christopher R.E. Coggins, William M. Coleman III, Lawrence C. Cook, James T. Dobbins Jr., Michael F. Dube, Curt R. Enzell, Charles R. Green, Paul Kotin, Brian M. Lawrence, Chin K. Lee, John C. Leffingwell, Robert A. Lloyd, Jr., William C. Luffman, Dwo Lynm, C.D. McGee, Alan B. Norman, Charles W. Nystrom, Michael W. Ogden, John H. Reynolds IV, Charles H. Risner, Charles E. Rix, Joseph N. Schumacher, Stephen B. Sears, Jeffery I. Seeman, Carr J. Smith, Thomas W. Stamey, Jr., David E. Townsend, and Jack L. White.

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We also wish to express our gratitude to those who, over the years, have provided us with much information on scientific publications and presentations. They include Charles W. Nystrom, Nell W. Sizemore, and the late Frank G. Colby, William W. Menz, and John J. Whalen. Particularly meaningful over the past decade has been the information provided by the extremely diligent Helen S. Chung of the R.J. Reynolds R&D Scientific Information Division.

One of us (T.A.P.) wishes to especially thank Patricia F. Perfetti for the encouragement and faith she has showed me as my wife, best friend, faithful colleague, and my partner in many happy and productive years of scientific research.

Authors

Alan Rodgman, MA, PhD, MCIC: Most of the original text of the following biography was written in 2003 for Alan Rodgman's nomination for the Tobacco Science Research Conference Lifetime Achievement Award. He was recipient of the 2003 award. In several places, the nominator's paragraphs have been slightly modified to include additional, more recent information plus a more recent picture than the 2003 one has been provided. The author of the 2003 nomination wrote:

> For here we are not afraid to follow truth wherever it may lead, nor to tolerate any error so long as reason is left free to combat it.
>
> **Thomas Jefferson, 1820**

The words penned long ago by Jefferson epitomize the life and professional career of Alan Rodgman.

For one year short of a half century, Dr. Rodgman has been at the forefront of tobacco science. His increasingly rare combination of keen scientific intellect, unceasing productivity, sense of tobacco science history, and unfailing attention to clear, concise, timely communication make him an ideal choice for the Tobacco Science Research Conference's (TSRC's) Lifetime Achievement Award. Not only has Alan Rodgman made his own prodigious, personal scientific contributions to tobacco and smoke chemistry and their related toxicology, but his mentoring of associates and many other tobacco scientists have allowed him to amplify his contributions far beyond those capable of any one man. Dr. Rodgman's professional "family tree" reads as a "Who's Who" in tobacco science.

Alan Rodgman was born in 1924 in Aberdare, Glamorgan County, Wales, to Arch and Margaret Llewellyn Rodgman. The family moved to Toronto, Ontario, Canada, in 1928. There he was educated at the grade and collegiate level. Because of the early death of his father when Rodgman was ten years old, he worked after school and on Saturdays at the children's and adult department of a local branch of the Toronto Public Library from 1937 to 1942. In 1945, Alan Rodgman entered the University of Toronto as recipient of the two highest mathematics, physics, and chemistry scholarships awarded in competition in 1942. Because of a University of Toronto rule on retaining no more than two competitive scholarships, a third chemistry and physics scholarship awarded to Rodgman reverted to the next highest candidate. The three-year period between earning the scholarships and their implementation was spent on active duty as a volunteer in the Royal Canadian Navy during World War II, with service on the North Atlantic Ocean.

Between 1945 and 1949, at the University of Toronto, Rodgman was awarded eight additional scholarships—one in mathematics, physics, and chemistry in 1946 and seven in chemistry in 1947, 1948, and 1949. His bachelor's thesis on *N*-nitrosamines in 1949, master's thesis on kinetics of the original Diels–Alder reaction in 1951, and doctoral thesis on oxymercuration–deoxymercuration in 1953 were conducted with Dr. George F. Wright* as his advisor. Rodgman taught the laboratory aspect of analytical chemistry during the first year of his master's period. His master's and doctoral research formed part of 11 publications coauthored between 1952 and 1959 with Dr. Wright who, by the way, from 1954 to 1959, preceded Dr. Dietrich Hoffmann as Dr. Ernst L. Wynder's tobacco smoke chemistry colleague.

Rodgman married Doris Curley in June 1947. They have three sons (Eric, Paul, and Mark), three daughters-in-law (Melody, Ella, and Sara), and seven grandchildren.

While pursuing his chemistry degrees, Rodgman conducted carcinogenesis and anticarcinogenesis research from 1947 to 1953 during summers, winter evenings, and weekends with Dr. Wilbur R. Franks, cancer research professor at the Banting and Best Department of Medical Research, University of Toronto. He conducted such research full-time to mid-1954 after receiving his doctorate in June 1953. Rodgman's first three scientific publications (on anticarcinogenesis) in 1947 and 1948 preceded the receipt of his bachelor's degree in chemistry in 1949. From 1951 to mid-1954, he also taught organic and physical chemistry plus mathematics for physical chemistry in evening courses sponsored by the Chemical Institute of Canada.

In mid-1954, Rodgman joined the Research Department of the R.J. Reynolds Tobacco Company as a senior research chemist. In October 1954, he initiated its program on cigarette smoke composition, personally conducting the laboratory research until 1967 and actively directing it and environmental tobacco smoke studies thereafter until 1987. Following successive promotions from senior research chemist to section head to division manager, he became director of research in 1976, and after an R&D reorganization in

* The lack of a period after Dr. Wright's middle initial is not a typographical error.

1980, he was appointed director of fundamental research. Rodgman became an American citizen in 1961.

After more than 60 years, Rodgman is still a member of the American Chemical Society and the Chemical Institute of Canada. Until 2006, he had been a member of the New York Academy of Sciences for over 40 years and also a member of Sigma Xi. He served on the editorial board of *Tobacco Science* as member and vice chairman (1963–1967); on the editorial board of *Beiträge zur Tabakforschung International* (1976–1987); on the Industry Technical Committee, Council for Tobacco Research (1955–1960); on the CORESTA Scientific Commission (1982–1985); and on several U.S. government committees, e.g., the Tobacco Working Group of the National Cancer Institute's Smoking and Health Program on the Less Hazardous Cigarette (1976–1977) and the U.S. Technical Study Group of the Cigarette Safety Act of 1984 (1984–1987). From 1960 to 1987, Rodgman served on numerous Tobacco Chemists' Research Conference (TCRC) committees. In 1972, he was involved in various aspects of the joint CORESTA/TCRC Conference in Williamsburg, Virginia. In 1976, he persuaded his company's management to continue its CORESTA membership. In the early 1980s, when a host site for the 1982 CORESTA Symposium did not materialize, Rodgman was instrumental in arranging for his company to sponsor the symposium in Winston-Salem, North Carolina. He served as its vice chairman.

Rodgman was the chairman for the 38th TCRC symposium entitled "Design of Low-'Tar' Cigarettes" held in 1984. On the occasion of TCRC's 50th conference in 1996, he coauthored with Charles R. Green a comprehensive review and presentation entitled "The Tobacco Chemists' Research Conference: A Half Century Forum for Advances in Analytical Methodology of Tobacco and Its Products." The following year at the 51st conference, he prepared a symposium paper and presentation on "FTC 'tar' and nicotine in cigarette mainstream smoke: A retrospective." In addition, Dr. Rodgman has presented many other original research papers at the conference.

In the journal *Tobacco Science*, he has published 13 scientific papers on tobacco smoke composition. Additionally, the 1986 volume of *Tobacco Science* was dedicated to Dr. Rodgman to honor his prolific career. In addition to serving as a reviewer for manuscripts submitted to *Tobacco Science* and *Beiträge zur Tabakforschung International*, Rodgman has served as a reviewer not only for manuscripts submitted to several other journals including *Recent Advances in Tobacco Science*, *Journal of Analytical and Applied Pyrolysis*, *Food and Chemical Toxicology*, and the *Journal of Organic Chemistry* but also for the page proofs of several well-known books on tobacco-related topics.

From 1954 to retirement and from retirement to 2004, Rodgman was involved in consulting activities on the scientific aspects of litigation against R.J. Reynolds Tobacco Company. Over 13,000 pages of his contributions are available at http://tobaccodocuments.org/bliley_rjr/list. Many of the more recent contributions were the consequence of the "Master Settlement" between the states and tobacco companies. Additionally, he has been a major contributor to the scientific content of *Beiträge zur Tabakforschung International*, both through submitted papers and as a volunteer editor. Dr. Rodgman has mined the wealth of documents previously considered proprietary to clarify the intent and content of tobacco and smoke research conducted by himself, his colleagues, and other scientists. The papers authored/coauthored by Rodgman during the last two decades include publications on environmental tobacco smoke (3255a); FTC "tar" and nicotine in cigarette mainstream smoke (3258); tobacco smoke components (3260); polycyclic aromatic hydrocarbons (3262, 3306a, 3306b, 5077); phenols (3712); "smoke pH" (3261); "IARC Group 2A carcinogens" (3713) and "IARC Group 2B carcinogens" (3714) reported in cigarette mainstream smoke; the effects of additives on cigarette mainstream smoke properties (3263, 3264, 3266); the problems with lists of tumorigens (3265, 3300, 5557); various tobacco substitutes (1375a); and the effect of expansion of tobacco on cigarette mainstream smoke properties (1375b).

At the 2002 CORESTA Congress held in New Orleans, Dr. Rodgman coauthored with Charles R. Green an invited speaker symposium paper entitled "Toxic chemicals in cigarette mainstream smoke—Hazard or hoopla." In this paper, the authors critically examined the proper listing and prioritizing of toxic chemicals in cigarette mainstream smoke. Moreover, the authors pointed to a number of disconcerting chemical and biological limitations in existing knowledge, which calls into question the veracity of such listed strategies for their oft-stated purposes. This example is included in Alan Rodgman's nomination to illustrate his lifelong pursuit of the truth.

In summary, there is no question that Alan Rodgman has dedicated his professional life to the achievement of the highest standards for tobacco science. Even with this nomination and the accompanying materials, it is impossible to convey to an outsider the tremendous impact that this person has made to our knowledge of tobacco and its smoke. Although his own personal scientific accomplishments are by themselves worthy of TSRC's Lifetime Achievement Award, the amplification of his life's work through influence on many other tobacco scientists is difficult to quantify. Beyond his many professional achievements is a man who is widely respected and personally liked both within and outside the tobacco science community.

Because his philosophy on publication authorship differed substantially from that of many academic, government agency, and health organization investigators, Rodgman did not insert his name as coauthor on the many articles on tobacco and smoke composition presented at conferences and/or published in peer-reviewed journals by his staff members. If he had done what many supervisors do, his list of publications between 1960 and 1987 would be increased by almost 200. However, his contributions to many of the studies are described in the Acknowledgment section of many of his staff/colleagues' publications.

Thomas Albert Perfetti, PhD was born in 1952 in Jeannette, Pennsylvania, the second son of Ruth Peters and Bruno Massimo Perfetti. He was one of five children. Perfetti received his elementary education in several schools in the Pittsburgh area. In 1970, he entered Indiana University of Pennsylvania (IUP). He earned a bachelor of science degree in chemistry in 1974. During his stay at IUP, he conducted cell transport research with Dr. Richard Hartline and synthesized numerous radiopharmaceuticals. Perfetti's first publication was on the preferential uptake of *d*-α-amino adipate by *Alcaligens denitrificans* in 1975.

In 1974, he entered the Virginia Polytechnic Institute and State University (VPI-SU), Blacksburg, Virginia. His doctoral thesis (1977), under Dr. Michael Ogliaruso, was on the electronic effects associated with the Woodward–Hoffman Rules. While pursuing his doctoral degree in physical organic chemistry, Perfetti worked as a research fellow for NASA, taught at organic chemistry labs, and tutored undergraduates. In 1976, Perfetti won the President's Award for Distinguished Teaching at VPI-SU.

Perfetti married Patricia Ann Finley, who graduated with him from the Chemistry Department at IUP, in 1975. They have two sons, Michael and David. The family now resides in Winston-Salem, North Carolina.

In late 1977, Dr. Perfetti joined the R.J. Reynolds Research Company (RJRT) as a research chemist. There, he initiated several research programs on tobacco and smoke chemistry, cigarette design, sensory science, flavor chemistry, and analytical method development. Perfetti was promoted from senior research chemist (1979), to senior staff scientist (1984), then to master scientist (1986), and finally to principal scientist (1991). He is a recognized expert in the areas of nicotine and menthol chemistry and in the area of innovation. As principal scientist, he worked with R.J. Reynolds-Nabisco and R.J. Reynolds International on corporate program development and program management issues. He also acted as a liaison on patent acquisitions, patent applications, and consulting activities on the scientific aspects of litigation against RJRT. Much of his career was spent in the laboratory, although he served as the manager of several divisions. Dr. Perfetti retired from RJRT in 2003. In that same year, he and his wife started Perfetti & Perfetti, LLC, a scientific consulting firm in Winston-Salem, North Carolina. Their company has done quite well with numerous national and international clients.

Perfetti has served as a reviewer for *Tobacco Science,* the *Journal of Food and Chemical Toxicology*, and *Beiträge zur Tabakforschung International*. He served on several Tobacco Chemists' Research Conference committees and contributed to two of its symposia (1987, 1993), one of which he chaired (1993).

Perfetti is a member of the American Chemical Society (ACS). He has served as assistant historian to the Division of the History of Chemistry. He is a member and fellow of the American Institute of Chemists and is a certified professional chemist. He was a cofounder and past president of the North Carolina Chromatography Discussion Group and former chairman of the Education Committee of the Central North Carolina Section of the ACS. Dr. Perfetti has been cited in *Who's Who in America*, *Who's Who in Science and Technology*, in the *International Directory of Distinguished Leadership*, and *Who's Who in American Leaders in America*. In 1993, Dr. Perfetti was presented with the Distinguished Alumni Award, Indiana University of Pennsylvania. In 1995, he and several other RJRT scientists were given the George Land World-Class Innovator Award for outstanding work in instilling the principles of innovation at RJRT Research and Development.

Over the last 32 years, Perfetti has made over 60 presentations and published numerous papers in peer-reviewed journal in the areas of biochemistry, tobacco and smoke chemistry, sensory perception, mathematics, and innovation. During his career at RJRT, he prepared more than 250 formal company research reports. He has written chapters for two books and has developed and presented five courses in the areas of cigarette design and innovation. Dr. Perfetti has 38 U.S. patents and hundreds of foreign patents.

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Introduction

> History balances the frustration of how far we have to go with the satisfaction of how far we have come. It teaches us tolerance for the human shortcomings and imperfections which are not uniquely of our generation, but of all time.
>
> **Lewis F. Powell, Jr. Associate Justice of the Supreme Court of the United States (1972–1987)**

INTENT OF THE WORK

Years from now, just as we were surprised how paltry was the number of identified tobacco smoke components cataloged in 1954 by Kosak (2170), others will no doubt have similar remarks concerning this catalog. We hope the reader will be satisfied rather than frustrated with the progress that has been made by tobacco scientists over the last 50+ years in furthering our knowledge base of components identified in tobacco and tobacco smoke. It should be noted the last published detailed catalog of tobacco and tobacco smoke components was that of Stedman (3797) in 1968.

CHEMICAL COMPOSITION OF TOBACCO

The Master Catalog, collected over a 50-year period, is our tabulation of all the information on the components identified in tobacco and smoke. The Master Catalog contains all of the information on components in tobacco and tobacco smoke that is contained in each chapter of this book as well as the information in the Bibliography and Alphabetical Component Index sections of this book. During the creation of this book, the information contained in the Master Catalog was searched to extract all of the components by functional group (alcohols, esters, aldehydes, etc.) to be included in the separate tables for each chapter of this book. The Bibliography was separated from the Master Catalog as a separate section of this book. An Alphabetical Components Index was created as a ready resource for readers to access particular information on each component and to locate the chapters and tables in the book chapters where that class of components is discussed. The original Master Catalog that we developed as such is not part of this book but was subdivided into numerous tables of components identified in tobacco and tobacco smoke by chemical functionality, the Bibliography, and the Alphabetical Components Index. This edition of our book catalogs nearly a thousand more tobacco and/or tobacco smoke components than were listed in the First Edition. Also, nearly a thousand more references pertinent to the newly reported components and to the previously reported ones are listed in the Bibliography.

The following, discussed in detail in Chapter 28, is a summary of the overall change in the number of components in our Index during the past 4 years, from 2008 to date:

Index Date	Tobacco Smoke	Tobacco	Tobacco and Tobacco Smoke	Subtotal	Smoke Isomers	Total
2012	6010	5595	2215	9390	192	9582
2008	5315	4994	1879	8430	192	8622

Tobacco is a fascinating organism. This plant, as all plants do, takes the simplest of molecules (carbon dioxide, nitrogen, and water), light, and a series of metals (as micronutrients) and through a sophisticated internal process converts these materials to complex molecules for plant growth regulation and maintenance. Tobacco has been called a chemical factory. It has been cultivated for the purpose of collecting nicotine for use as an insecticide and for starting material for numerous commercial chemicals such as the pyridines. More recently, it has been studied as a source of plant protein [Fraction 1 (F-1) and Fraction 2 (F-2) protein] (3974c). There are many different botanical classifications for tobacco plants. The genus *Nicotiana* has over 60 known species; each has been examined as to its genetic, physiological, botanical, and chemical characteristics (3972, 3973). Two tobacco species are grown commercially: *Nicotiana rustica* primarily for nicotine and solanesol collection; *Nicotiana tabacum* for use as in cigarette, pipe, cigar, snuff, and chewing tobaccos.

To date, nearly 5700 components have been identified in tobacco. The total appears at the end of the Alphabetical Components Index and represents an increase of more than 700 over the 4994 listed in the earlier version of our catalog [see p. 1784 in (5078)]. This number does not include the nontobacco components listed as added flavorants by Doull et al. (1053) and Baker and Bishop (172a) or the hundreds of enzyme and other proteinaceous components listed in our Master Catalog. This is a tremendous achievement compared to the number of tobacco components reported as 3044 in 1988 by Roberts (3215), reported as 2549 tobacco compounds in 1982 by Dube and Green (1067), the 200 identified compounds reported in 1960 (2338), the 199 organic compounds and 21 inorganic elements reported as identified in tobacco in 1959 (1971), and the accounting of less than 10 tobacco constituents by Frankenburg (1221) in 1946. It should be noted that in the classification by Frankenburg, the tobacco constituents listed were not individual compounds but classes of compounds such as alkaloids, proteins (soluble and insoluble fractions), nitrate-nitrogen, and amino nitrogen. It is estimated that literally tens of thousands of unidentified compounds are yet to be discovered in tobacco. This estimate is based upon the assumptions that there has already been thousands of organic, inorganic, and organometallic compounds identified in tobacco, that each plant contains hundreds of extremely complex compounds, e.g., various types of DNA and RNA, numerous types of complex enzymes, proteins, sugar, and amino acid oligomers, needed for plant growth, regulation, and maintenance, and that numerous fragments of these complex molecules have already been reported in tobacco.

If it were not for scientists' curiosity and the tremendous advances in analytical chemistry over the last 50–60 years, the need for this revised version of our 2008 catalog of compounds in tobacco and tobacco smoke would not be critical. Over the last 50–60 years, literally tens of thousands of scientific articles on varied topics in tobacco and tobacco smoke science have been written. Our understanding of these two areas of science has advanced tremendously in the recent past. As noted by Knipling [see Preface in Tso (3974c)],

> Pioneering tobacco research was the foundation of plant science at the dawn of modern development, in such areas as light, nutrition, genetics, growth control, disorders and metabolism. Tobacco research led to current advancements in plant biotechnology. In addition, tobacco plant research contributed significantly to public health research in radioactive elements, mycotoxins, and air pollutants. However, public support for tobacco research has today greatly declined to almost total elimination because of a sense of political correctness … tobacco is one of the most valuable research tools, and is a most abundant source of scientific information. Research with tobacco plants will contribute far beyond the frontiers of agricultural science: tobacco can be a source of food supply with nutrition value similar to that of milk; tobacco can be a source of health supplies including medical chemicals and various vaccines; tobacco can be a source of biofuel. All we need is to treat tobacco with respect; the use of tobacco is only in its initial stages.

For over 50 years, our Master Catalog of components identified in tobacco and smoke has been in the process of assembly. Each component has one or more corresponding references. The tobacco literature was diligently searched for components identified in tobacco and tobacco smoke. As new components in tobacco and tobacco smoke were reported by R.J. Reynolds Tobacco (RJRT) Co. R&D personnel and in the published scientific literature, they were entered into the Master Catalog. Data on components in mainstream smoke (MSS), sidestream smoke (SSS), and environmental tobacco smoke (ETS) were collected from studies on the smokes from a variety of tobacco types and blends and numerous forms of smoking articles, e.g., cigarettes, cigars, cigarillos, pipes. Data on tobacco components were collected from studies on numerous species of *Nicotiana* (primarily *N. tabacum*). The tobacco component data were collected from studies not only on all stages of plant development (seed to harvested plant) but also from tobacco processed in various ways (aged, fermented [various degrees], steamed, cut, rolled, expanded, converted to reconstituted sheet [by various methods], treated with additives) prior to use as a smoking material.

The Master Catalog contains an enormous variety of species from nearly every class of chemical components. We have separated and combined the identified components in tobacco and tobacco smoke into classes of components, e.g., hydrocarbons, alcohols, acids, esters, aza-arenes, and each class will be discussed in a separate chapter. For the reader's information, tobacco and tobacco smoke components possessing multifunctional groups will appear in each of the appropriate chapter lists but will be only tallied once as a tobacco component and/or a tobacco smoke component. For example, 2-furancarboxylic acid (2-furoic acid) is listed in the carboxylic acid chapter and the ether chapter; 4-hydroxy-3-methoxybenzaldehyde (vanillin) is listed in each of the aldehyde, ether, and phenol chapters. Also as an amendment to the First Edition of our catalog where multifunctional components were inserted into several major chapter tables, in this edition, the multifunctional components are listed in the Index as being cited in all the major chapter tables where they occur.

The Master Catalog and the chapters on the various classes of tobacco components do contain some items not identified as tobacco components per se. They include items that (1) are not identified components of untreated tobacco and/or its smoke but are individual compounds added to the tobacco in a flavor formulation to improve consumer acceptability of commercial products,* (2) are the pesticides, herbicides, nematicides, growth control agents, etc. (or their residues), that improve the agronomic situation for tobacco cultivation or have been found on tobacco, (3) are mycotoxic products of microorganisms found on tobacco plants, e.g., aflatoxins, and (4) thermal degradation products from (1), (2), and (3) found in tobacco smoke. Many of the components in (1) were identified as added tobacco ingredients in the reports by Doull et al. (1053), Baker and Bishop (172a), and Baker et al. (174b). Many of the components in (2) are retained in the tobacco after harvesting and curing, are transferred intact to the smoke, and in some cases, are degraded to compounds not usually expected in tobacco smoke. As noted previously, the items in (1) and (3) were not included in the 4200 identified tobacco components discussed earlier. As noted previously, the items in (1) and (3) were not included in the 4200 identified tobacco components discussed earlier. Also not included in our Master Catalog are the additives comprising mixtures from naturally occurring products, e.g., alfalfa extract, basil oil, honey. These will be discussed in the chapter on tobacco additives.

During the 1920s and 1930s, plant nutrition was an active area of research and tobacco served as the model in much of that work. The results of research on nitrogen assimilation,

* Among the flavor formulation compounds listed as tobacco ingredients by Baker and Bishop (172a), Baker et al. (174b), and Doull et al. (1053) was a substantial number of compounds reported as identified components of additive-free tobacco and/or its smoke [see Tables 1, 5, and 7A in (3266)]. That number was increased recently because of the identification of several additional listed flavor formulation compounds in flue-cured tobacco by Peng et al. (2917a) and in Perique tobacco by Leffingwell and Alford (2339a).

light as a factor in nitrogen fixation, and how weather contributed to nutrient uptake contributed greatly to our understanding of plant science. All these advancements seem trivial today in light of the sophisticated work in genomics but were nonetheless initially due to the pioneering work of scientists working with tobacco (3972, 3973).

The presence of some microelements in tobacco was reported as early as 1921. Today, nearly all of the common elements including alkali, alkali earth, heavy metal, and rare elements have been reported to be present in tobacco, e.g., Al, As, Ba, B, Cs, Cr, Co, Cu, F, Au, I, Pb, Li, Mg, Mn, Hg, Mo, Ni, Pt, Po, Ra, Rb, Se, Si, Ag, Sr, S, Ta, Ti, Sn, U, V, and Zn. Many heavy metal radioactive components have been reported in tobacco including those from the uranium series, e.g., ^{234}U, ^{226}Ra, ^{228}Ra, ^{222}Rn, ^{210}Po, and others, e.g., ^{38}Cl, ^{46}Sc, ^{134}Ce, ^{59}Fe, ^{40}K. The presence of such elements in tobacco may be accidental, acquired from soil or from other sources. Scientists curious to understand the role of these assorted elements conducted research studies from the 1920s in order to understand the role of each element in plant growth and development. The effect of boron on plant growth was first noted in 1929, zinc in 1942, and copper in 1942. The concept of metals as catalysts in plant growth advanced the areas of chemical catalysis and its use in industrial fermentation (3972, 3973). The transfer of elements, particularly some of the metallic ones noted earlier, from tobacco to its smoke has been studied since the mid-1950s, e.g., Cogbill and Hobbs (769).

Elemental isotopes have also been used in tobacco research for over 50 years. Studies with single, double, and even triple labeled compounds incorporating ^{15}N, ^{3}H, and ^{14}C were reported by personnel at the U.S. Department of Agriculture (USDA) in the early 1950s in their studies on plant metabolism (3972, 3973).

Tobacco is a very labor-intensive and sensitive crop. Hundreds of agronomic and physical processing steps occur from seed planting to final use in commercial products. The type of tobacco (flue-cured, burley, MD, Oriental) as well as dark air-cured tobacco and various cigar tobaccos and how the tobacco is produced and cured affect the type and level of chemical compounds in tobacco leaf and in smoke. Among the chemicals applied to tobacco are insecticides, acaricides, miticides, nematicides, and growth control agents, e.g., sucker-control and yellowing agents. These were developed to control pests and plant growth, to reduce labor, and ultimately to produce a better, healthier, and more profitable crop. Their number and types are large. Over the years, new chemical agents were developed and commercialized as others were either banned or found to be less effective. Nonetheless, some pesticide residues remain in the soil and are often transported to the plant. All the commercial pesticides (as well as herbicides) are tested thoroughly and can be safely used (822a). As an example, today, the most widely used sucker-control agents are fatty compounds, including fatty acids, alcohols, esters, and some of their derivatives. These sucker-control agents significantly inhibit axillary growth without causing undesirable side effects to the plant or the public (3972, 3973).

The genetic makeup of tobacco includes 25,000–50,000 genes. The gene mapping of tobacco is being conducted in the Plant Pathology Department, North Carolina State University Centennial Campus, College of Agricultural and Life Sciences, Raleigh, NC, in a project known as the Tobacco Genome Initiative (TGI). Its goal is to sequence and catalog more than 90% of the genome of cultivated tobacco, *N. tabacum*. Although tobacco has been cultivated for more than 500 years and is a crop of great economic significance, relatively little information exists on its genome structure and organization.

A complete tobacco gene catalog will provide information needed to investigate the physiological and genetic processes in the plant kingdom, in general, and in *N. tabacum* specifically. Understanding the genetic processes occurring within the tobacco plant could potentially provide valuable information on ways to reduce the harm associated with cigarette smoking and also provide information on agronomic traits associated with disease and pest resistance genes for use in improving traditional and molecular breeding projects aimed at enhancing the performance of tobacco as a crop. The plants within the agriculturally important *Solanaceae* family which includes tobacco, tomato, potato, eggplant, and pepper crop plants will all benefit from gene discovery in *N. tabacum*.

Available for public use are additional databases that contain listings of enzymes, enzymatic pathways, and reaction products of metabolic and catabolic processes occurring in tobacco species. Many of these are listed as references in our chapter catalogs:

- GenBank (tobacco): For references, see http://www.ncbi.nlm.nih.gov/Genbank/index.html (1282a).
- BRENDA: The Comprehensive Enzyme Information System, entry of hydroxymethylglutaryl-CoA reductase (NADPH) (EC-Number 1.1.1.34) Nicotiana, Kyoto Encyclopedia of Genes and Genomes (KEGG) Link 00100 Steroid Biosynthesis, see http://www.genome.jp/dbget-bin/show_pathway?map00100+1.1.1.34 (429c).
- BRENDA: The Comprehensive Enzyme Information System; http://www.genome.jp/dbget-bin/show_pathway?map00500+2.4.1.35 (429b).
- KEGG; see Kanehisa, M. and S. Goto: KEGG: Kyoto Encyclopedia of Genes and Genomes; *Nucleic Acids Res.* 28 (2000) 27–30 (429b).
- Lyon, G.D.: Host pathogen interactions & crop protection; Metabolic pathways of the diseased potato at http://www.scri.sari.ac.uk/publications/annualreports/98Indiv/21Metabo.pdf (429b).

Plant scientists have long known that all organic components are dynamic in nature and change in numerous ways when present in biological systems. Chemical, catalytic, enzymatic, and bacteriological processes occur continuously during plant growth in the field and until these biological processes are quenched at harvest and during processing. Tobacco scientists have extensively studied the metabolism and catabolism occurring in *Nicotiana* plants because the change or formation of each compound may affect its final quality and thus its usability. Organic compounds are formed, transformed, and interact during plant growth in the field, during postharvest handling processes of curing, aging, and fermentation, during manufacturing, including interaction with additives, and during blending (3972, 3973).

The chemical composition of the tobacco determines the chemical composition and yield of components in its tobacco smoke. For example, leaf protein (F-1 and F-2 protein) is abundant in tobacco and turns over and decomposes continuously to produce a vast array of protein subunits, amino acids, and amino acid oligomers (3974c).

Tobacco leaf protein by itself contributes little to smoking quality, but it is a major precursor of hundreds of tobacco smoke components, e.g., numerous nitrogenous compounds, amino acids. Similarly, other major tobacco components such as the carbohydrates, carboxylic acids, pigments, polyphenols, fatty compounds, phytosterols, and many primary or secondary compounds play a significant role in producing a myriad of tobacco smoke compounds (3972, 3973).

Tobacco has been used in one form or another in civilized society for nearly five centuries. Eventually in the late nineteenth century, investigations as to its composition began, but they were not particularly numerous. The major driving force in the escalation in the mid-twentieth century of studies on tobacco composition was the attempt to define (1) its components that contributed to the consumer acceptability of the taste and aroma of tobacco itself and its smoke and (2) the precursors in tobacco of the toxicants in its smoke.

The latter investigations were triggered by the following events: (1) The publication from 1950 to 1953 of the results from several retrospective studies on lung cancer in smokers and nonsmokers [Doll and Hill (1027), Mills and Porter (2556), McConnell et al. (2515), Sadowsky et al. (3375a), Schrek et al. (3529), Wynder and Graham (4306b)]. The results suggested an association between cigarette smoking and cancer of the lung, particularly the lung cancer tumor type defined as squamous cell carcinoma. (2) The 1953 presentation and publication by Wynder et al. (4306a) of their findings on the production of malignant tumors in a susceptible strain of mice skin painted daily with massive doses of solutions of cigarette smoke condensate (CSC) supposedly generated under conditions simulating the human smoking of a cigarette. These statistical and biological findings augmented by the results of additional similar studies led to an escalation in the research to define the composition of cigarette smoke and to determine which of its components were responsible for the observed biological response. When a particular class of components—the polycyclic aromatic hydrocarbons (PAHs)—was considered responsible, studies escalated to define the precursors in tobacco of the PAHs in its smoke.

Previous detailed reports on the composition of tobacco included those issued by Brückner in 1936 (451), Latimer in 1955 (2270), Johnstone and Plimmer in 1959 (1971), Shmuk in 1961 (3657), Stedman in 1968 (3797), Roberts et al. in 1975 (3224), Schmeltz and Hoffmann on nitrogen-containing tobacco components in 1977 (3491), and Enzell et al. on terpenoid-derived tobacco components between 1976 and the late 1980s (1149, 1150, 1156, 4089, 4090). One thing has become apparent since the mid-1950s: No other consumer product that involves a complex mixture has been defined in such detail as tobacco and/or its smoke, e.g., the number of components identified to date in tobacco is almost twice that of the number identified in coffee.

In the last 90 years, tobacco scientists have spent considerable time and effort determining and reporting on the chemical composition of tobacco. One of the first attempts at estimating the mass balance of the major and minor constituents of tobacco was that of Hobbs in 1972 (1665). Hobbs stated the following in his review:

> In order to understand; even approximately, the bearing of the various physicochemical processes on the character of the generated (*smoke*) aerosol it is essential to know in some detail the composition of the tobacco from which the aerosol is produced … It will be recognized that the use of different blending quantities of the several varieties of tobacco, or of different processing methods can markedly influence the quantitative composition of (*tobacco*), … but the differences are likely to be more quantitative than qualitative. (1665)

In his review, Hobbs included a figure illustrating the approximate chemical composition of blended cigarette tobacco. Figure 0.1 is a representation of those same data.

Table 4.1 summarizes the numbers of carboxylic acids and amino acids identified to date in tobacco and tobacco smoke. Their listing and references are presented in subsequent chapter tables (Tables 4.3 and 4.10).

The data that Hobbs used were collected over many years by scientists at Liggett and Myers Tobacco Company. Hobbs' data were subsequently reproduced by Green (1351, 1352b), in tabular form, see Table 0.1. Hobbs' original figure showed the approximate chemical composition of blended cigarette tobacco (at ∼12% moisture). The data from Green (1351, 1352b) were calculated on a dry weight basis.

The data in Table 0.1 show three columns. The original data by Hobbs (1665) are in the second column. Hobbs' data included water, humectants, and flavorants on the tobacco. Column three is the same data as in column two, but the data were recalculated to remove water, the added humectants, and the applied flavorants. As can be seen in column three, the carbohydrates (sugars, celluloses, pectic substances, starch, and pentosans) represent nearly 41% of the dry weight of tobacco. Lignin accounts for about 4% of the weight. The tobacco protein and amino acids represent about 10% of the dry tobacco weight. The volatile bases and alkaloids make up about 4% of the tobacco weight. Waxes and resins (the ether extractable portion of tobacco) represent about 10% of the dry tobacco weight. Metals (6%) and inorganic ions (1.8%) make up another 7.8% of the tobacco weight. The phenolics

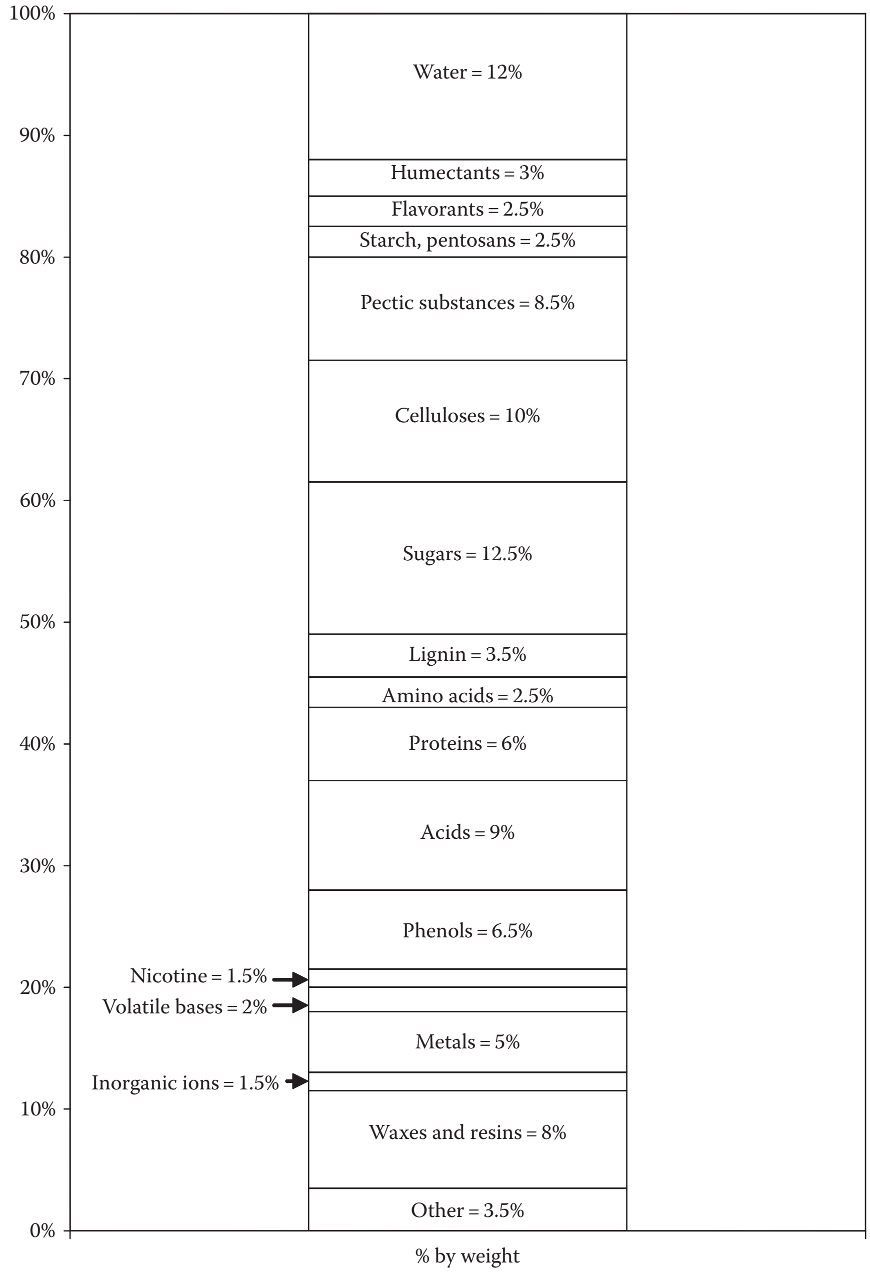

FIGURE 0.1 Approximate chemical composition of blended cigarette tobacco (1665).

and acids represent about 8% and 11% of the dry tobacco weight, respectively. Together, these tobacco constituents account for about 96% of the dry weight of tobacco. Hobbs (1665) added a category called "others" (at about 4%) which accounted for the remaining unaccounted for weight. Much of the "other" category was believed to be composed of dirt, sand, and other intractable materials.

To date, as indicated on the last page of our Alphabetical Component Index, 5596 separate components have been identified in tobacco. Table 0.2 contains three columns of information: the classification of the tobacco component(s), the average concentration of the component(s) in percent (%) dry weight of tobacco, and references to tables in the second edition of this book [Green (1351) and others that support the concentration data]. There are four broad classes of tobacco components in Table 0.2: hydrocarbons, oxygen-containing components, nitrogen-containing components, and miscellaneous components.

It must be noted that the majority of compounds found in tobacco are multifunctional. For example, polyfunctional *O*-containing compounds are counted in each functional group, e.g., propanoic acid, 2-hydroxy- (lactic acid) appears in the alcohol section and the acid section; benzoic acid, 4-hydroxy-3-methoxy- (vanillic acid) appears in the acid section, the phenol section, and the ether section. In Table 0.2, care was taken to count each tobacco isolate in only one of the component categories. Every attempt was made not to duplicate any of the 5596 tobacco compounds identified to date in tobacco. To accomplish this, a method for segregation of compounds, particularly those that were multifunctional,

TABLE 0.1
Approximate Chemical Composition of Blended Cigarette Tobacco (1665, 1351, 1352b)

Component	Wet Weight Blended Cigarette Tobacco, %	Dry Weight Tobacco (Only)[a], %
Carbohydrates		
Sugars	12.5	15.15
Celluloses	10.0	12.12
Pectic substances	8.5	10.36
Starch, pentosans	2.5	3.03
Water	12.0	0
Proteins and amino acids		
Proteins	6.0	7.27
Free amino acids	2.5	3.03
Bases		
Volatile bases	2.0	2.42
Nicotine	1.5	1.81
Waxes and resins	8.0	9.69
Metals	5.0	6.06
Phenols	6.5	7.87
Acids	9.0	10.90
Lignin	3.5	4.24
Humectants	3.0	0
Flavorants	2.5	0
Inorganic ions	1.5	1.81
Others	3.5	4.24
Total	100	100

[a] Percent dry weight = minus water, humectants, and added flavorants.

was used. The hierarchical system chosen for the segregation of the chemicals was patterned after the organization of chemical compounds in Beilstein [Heller (1990)]. That is, compounds without functional groups (i.e., the hydrocarbons) were followed by hydroxyl compounds, oxo compounds, carboxylic acids, amines, etc. As in Beilstein, the concept of parents and derivatives was followed. For example, phenol would be considered a parent. All substituted phenols were grouped with phenol as derivatives. Although, the strict rules used in Beilstein were not always applied, all of the 5596 compounds were accounted for in a logical manner.

The second column of data in Table 0.2 lists the average concentration of tobacco compounds. The values listed were obtained from several sources. Primarily, the concentration data were obtained from the present text, Rodgman and Perfetti (5078), Green (1351, 1352b), Hobbs (1665), various reports from the RJRT Company database (www.rjrt-doc.doc), Demole et al. (937–943), Dickerson et al. (965), Leffingwell (2337–2339, 2339a, 2339b, 2341), Lloyd et al. (2389), Roberts et al. (3215, 3219), Schumacher (3550, 3560, 3561), Schlotzhauer et al. (3458), Stedman (3797), Tso (3973, 3974a), Weeks (4159), and from years of personal experience (TAP) in tobacco science. In most cases, concentrations of the largest tobacco compounds (those greater than 0.05%) were obtained from literature sources. Although in a few cases, particularly those classes of compounds that had low to very low (0.001%–0.000001%) concentrations, e.g., anhydrides, quinones, oxazoles, aza-arenes, the concentrations were estimated.

Column three of Table 0.2 contains references to tables of data in this text and/or papers by Green (1351, 1352b) and others.

The chemical class of compounds in tobacco that has the largest mass is the oxygen-containing compounds (75.70%), followed by the nitrogen-containing compounds (12.98%), miscellaneous compounds (10.61%, including the category "Others" at 1.21%), and finally the hydrocarbons (0.71%). Within the oxygen-containing components, the largest single subclass of chemical components was the carbohydrates at 40.2%. There are 15.15% sugars, 12.12% celluloses, 10.36% pectins, and 3.03% starch. There are 9.8% carboxylic acids and 9.0% lipids (waxes) and resins in tobacco. In the lipids (waxes) and resins category, about 60% of the weight is lipids and 40% is resins. The lipids and resins category contain those compounds that prior to the 1950s were collected as part of the alcohol-ether-soluble fraction of tobacco. The phenolic category contains 8.3% of the dry mass of tobacco. About 2.25% of the weight of the phenolic category is lignin. The remainder of the weight from the oxygen-containing class of tobacco is composed of alcohols, phytosterols (and their derivatives), aldehydes, ketones, amino acids, esters, lactones, anhydrides, quinones, and ethers, ranging in levels from 2.0% to 0.0001% by weight of the dry mass of tobacco.

The two largest categories of compounds that contribute to the nitrogen-containing class of chemicals found in tobacco are the proteins and amino acids (6.4%) and the nitrogen heterocyclic compounds, which includes numerous types of tobacco alkaloids and related compounds (6.5%). The remainder of the weight from the nitrogen-containing class of tobacco is composed of amides, imides, *N*-nitrosamines, nitroalkanes, nitroarenes, nitrophenols, lactams, oxazoles, and aza-arenes. The mass of all of these remaining nitrogen-containing compounds represents only 0.08% of the dry weight of tobacco.

The third largest class of components found in tobacco was called "miscellaneous components" because it includes a broad range of chemical classes: sulfur-containing compounds; halogen-containing compounds; metals, nonmetals, and ions; pesticide residues; and the unknown components called "others." In the third class, the largest contributors to tobacco mass are the metals, nonmetals, and ions (7.2%). The halogen-containing compounds contribute 1.5% of the dry tobacco weight. Sulfur-containing compounds contribute 0.7% of the dry tobacco weight, and approximately 1.21% of the dry tobacco weight is compounds grouped as "others." Pesticide residues in tobacco contribute very little to the total tobacco mass (0.00001%).

The last class of components identified in tobacco is the hydrocarbons (alkanes, alkenes, alkynes, alicyclics, monocyclic aromatics, and polycyclic aromatics). The total mass of the hydrocarbons is only 0.71% of the dry weight of tobacco. The largest contributors to mass from this class of components are

TABLE 0.2
Distribution and Approximate Composition of Tobacco

Classification of the Tobacco Component	Average Concentration, %	Tables in Present Text and Other References
Hydrocarbons		
Alkanes	0.32	Table 1.10
Alkenes and alkynes	0.09	Table 1.11
Alicyclics	0.22	Table 1.12
Monocyclic aromatic	0.08	Table 1.13
Polycyclic aromatic	0.0001	Table 1.19, Stepanov et al. (5567)
Subtotals	0.71	
Oxygen-Containing Components		
Alcohols	1.7	Table 2.5
Phytosterols and derivatives	0.2	Table 2.7
Aldehydes	1.4	Table 3.12
Ketones	1.8	Table 3.13
Carboxylic acids	9.8	Table 4.3
Lipids (waxes) and resins	9.0	Green (1352b)
Amino acids	2.0	Table 4.10
Esters	0.9	Table 5.3
Lactones	0.001	Table 6.2
Anhydrides	0.0001	Table 7.1
Carbohydrates	40.2	Table 8.3
Celluloses: 13.3%		
Pectins: 11.4%		
Sugars: 14.1%		
Starch: 1.4%		
Total: 40.2%		
Phenols	8.3	Table 9.22
Lignin: 2.25%		
All other phenolics: 6.05%		
Quinones	0.001	Table 9.24
Ethers	0.4	Table 10.2
Subtotals	75.70	
Nitrogen-Containing Components		
Nitriles	0.0001	Table 11.2
Proteins, enzymes, and amines	6.4	Tables 12.2 and 22.2
Amides	0.06	Table 13.1
Imides	0.02	Table 14.1
N-Nitrosamines	0.002	Table 15.8
Nitroalkanes, nitroarenes, and nitrophenols	0.00001	Table 16.1
Nitrogen heterocyclic components (volatile bases) 4.5% [Monocyclic four-membered *N*-containing ring compounds, monocyclic five-membered *N*-containing ring compounds, compounds with multiple monocyclic five-membered *N*-containing ring, monocyclic six-membered *N*-containing ring compounds, compounds with a six-membered *N*-containing ring and a second five-membered *N*-containing ring, compounds with two or more six-membered *N*-containing rings]	6.5	Tables17.1, 17.3, 17.5, 17.6, 17.8, and 17.10
Alkaloids: 2.0%		
Lactams	0.0001	Table 17.13
Oxazoles	0.00001	Table 17.14
Aza-arene, aza-arene derivatives, and *N*-heterocyclic amines	0.000001	Tables 17.21, 17.23, and 17.31
Subtotals	12.98	

(*continued*)

TABLE 0.2 (continued)
Distribution and Approximate Composition of Tobacco

Classification of the Tobacco Component	Average Concentration, %	Tables in Present Text and Other References
Miscellaneous Components		
Sulfur-containing	0.7	Table 18.1
Halogen-containing and fixed gases	1.5	Table 18.4, Table 19.5
Metal, nonmetals, and ions	7.2	Tables 20.5 and 20.6
Pesticide residues	0.00001	Table 21.3, Binkley (5037)
All other compounds	1.205577	
Subtotals	10.61	
Grand total	100.00	

the alkanes (0.32%) and the alicyclics (0.22%). The alkenes and alkynes (0.09%), the monocyclic aromatics (0.08%), and the polycyclic aromatics (0.000002%) round out the other hydrocarbons that contribute to the dry weight of tobacco.

Figure 0.2 illustrates the approximate chemical composition of tobacco based on the data of Table 0.2.

Table 0.3 is a comparison of the reported concentrations of chemicals found in tobacco from Hobbs (1665) compared to similar data entries in Table 0.2 of this report.

There is close agreement between the estimates of the gross compositional tobacco data reported by Hobbs (1665) in 1972 *vs.* the data of Table 0.2. The differences between the Hobbs' data and the data of Table 0.2 could be from differences in tobacco types tested or from improvements in analytical separation, detection, and quantification technologies. The differences in the subtotals for carbohydrates, proteins, and amino acids; Hobbs' classification of bases; and most of the other chemical classes are generally different by less than 1–2 weight percent. Under the classification of "Others" for the data of this report (column three), there is about 2.9% dry weight of tobacco (i.e., 4.1%–1.2% [from Table 0.2] = 2.9%) that represents hundreds of minor tobacco constituents not accounted for in the components listed in column one of this table. It is quite remarkable how qualitatively similar the data are between the Hobbs data and those from Table 0.2. As Hobbs (1665) mentioned in 1972, any "differences (*in the chemical composition of tobacco*) are likely to be more quantitative than qualitative."

Because of the excellent fractionation and identification technologies developed during the early 1950s, the compositions of tobacco and tobacco smoke, both classified as highly complex mixtures, have been defined more completely than the composition of any other highly complex commercial product such as coffee. By year-end 1953, the many years of research by scientists using classical chemical techniques to define the composition of tobacco and its smoke provided meaningful information on the nature of over 300 tobacco components and fewer than 100 tobacco smoke components. Those involved in the pre-1954 research not only provided the cornerstone of our knowledge of the two compositions but also deserve the gratitude of their successors for the early information generated on tobacco and its smoke. This article is our tribute to those researchers who generated much meaningful knowledge on the composition of tobacco and tobacco smoke prior to 1954 despite the now known fractionation and analytical limitations of the so-called classical chemical techniques. It also notes the similarity of some of the early and more recent research results obtained on the chemical and biological properties of smoke condensate and several of its components from tobacco with those obtained by Roffo in the 1930s on a destructive distillate of tobacco.

The compilation of the catalog on the more than 8400 chemical components identified in tobacco and tobacco smoke provided an excellent assessment of the caliber of the research conducted since its escalation in the mid-1950s. The classical chemical analysis used before that date to isolate and characterize a component of a complex mixture was gradually augmented post-1953 by the inclusion of many different, new, and highly efficient separation and analytical technologies. Various types of chromatography coupled with various spectral technologies such as ultraviolet, infrared, nuclear magnetic resonance, and mass provided the means to identify more complex structures of components isolated in much lesser amounts than could be done by using the classical chemical approach. For example, inclusion of such technologies resulted in the increase of the number of identified chemical components in tobacco smoke from the fewer than 100 reported by Kosak in 1954 (2170) to the more than 5200 cataloged recently by Rodgman and Perfetti (5078). The manifold scientific skills generated and employed during those more than 50 years of research obviously deserve great commendation.

In the early part of the twentieth century until the mid 1950s, there was limited interest in the relationship between the majority of identified chemicals in tobacco and tobacco smoke and the varied asserted health issues associated with smoking in general, compared to the time after the mid-1950s. This limited interest may have been due to a lack of understanding of how to interpret the chemical data collected on the complex mixtures of tobacco and tobacco smoke in relation to biological endpoint data. On the other hand, early tobacco research concentrated on a greater understanding of the alkaloids in tobacco.

In early tobacco research, nicotine and other related tobacco alkaloids were regarded as toxic constituents of

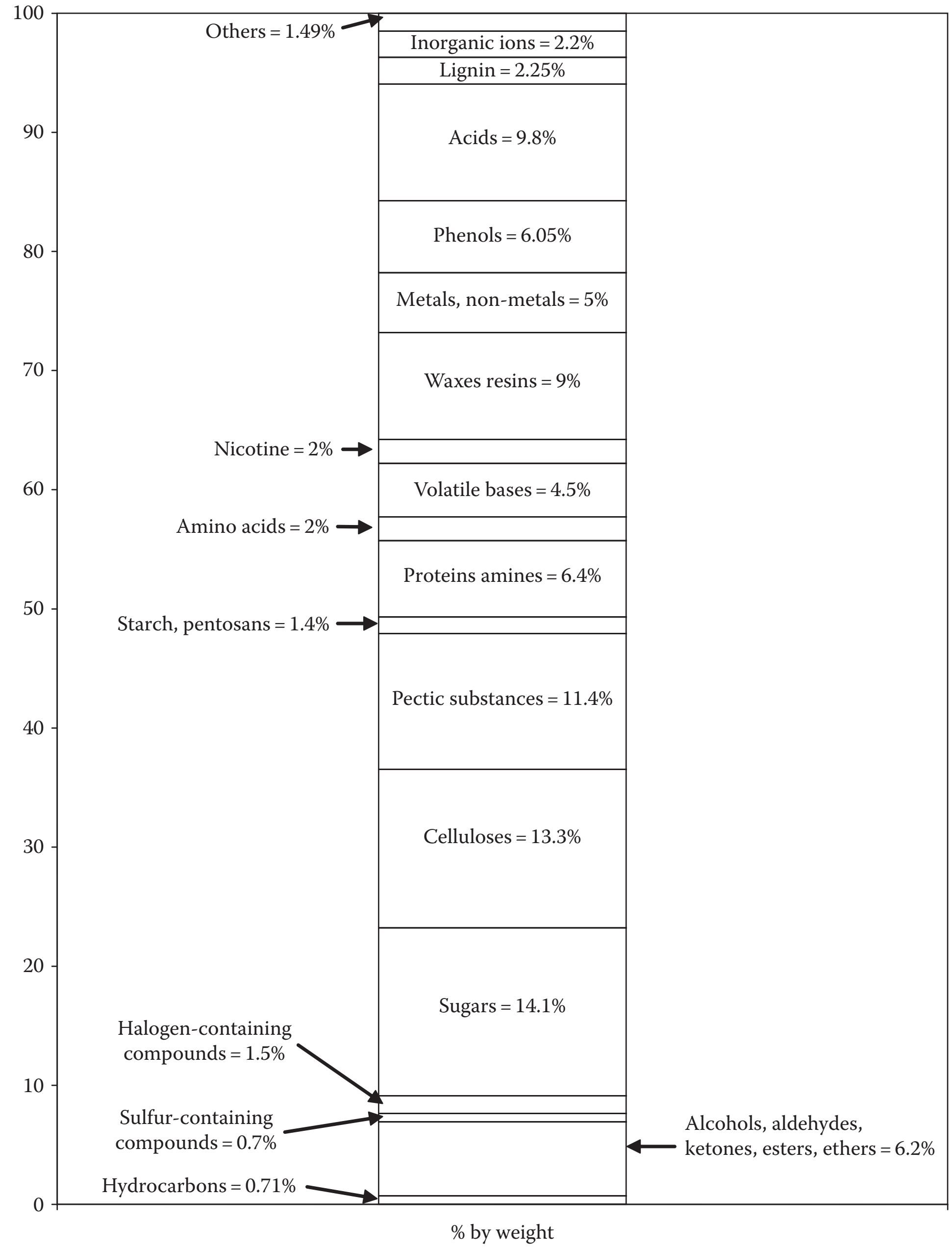

FIGURE 0.2 Approximate chemical composition of tobacco.

tobacco, and their presence in smoke was considered a health concern. Tobacco alkaloids were also important as raw materials for pesticides and as sources of raw material for the chemical industry. As a result, considerable effort was focused in the early years of tobacco research on nicotine and related tobacco alkaloids. This work included the development of new analytical determinations for tobacco alkaloids and tests to measure its toxicity and dependence of nicotine for smokers. Work in the area of breeding new tobacco lines was focused on two directions. Efforts were directed at developing low nicotine or nicotine-free tobaccos for health reasons and secondly, in the direction of tobaccos extremely high in nicotine, as a raw material for pesticides, chemicals, and pharmaceuticals.

During our cataloging of the chemical components of tobacco and tobacco smoke, it became apparent that the chemical research conducted on them from early in the 1800s to September 1953, the date of submission of the Kosak's manuscript for publication, also deserved considerable commendation. Considerable skill in classical chemical methods was used to isolate and characterize the tobacco and smoke components known by late 1953. In this article, the results of that research are summarized in an attempt to illustrate that not only should they not be minimized or disregarded but also the investigators who generated such meaningful results deserve considerable credit.

One of the stimuli cited by Kosak (2170) for the generation of his 1954 catalog of tobacco smoke components was the brief

TABLE 0.3
Comparison of Hobbs (1665) Data on Approximate Chemical Composition of Blended Cigarette Tobacco Compared to Similar Data of Table 0.2

Component	Hobbs Tobacco Data Dry Weight Basis, %	Dry Weight Tobacco Data from Table 0.2, %[a]
Carbohydrates		
Sugars	15.15	14.1
Celluloses	12.12	13.3
Pectic substances	10.36	11.4
Starch, pentosans	3.03	1.4
Subtotal	40.66	40.2
Proteins and amino acids		
Proteins, enzymes, and amines	7.27	6.4
Free amino acids	3.03	2.0
Subtotal	10.3	8.4
Bases		
Volatile bases	2.42	4.5
Nicotine	1.81	2.0
Subtotal	4.23	6.5
Lipids (waxes) and resins	9.69	9.0
Metals	6.06	5.0
Phenols	7.87	6.05
Acids	10.90	9.8
Lignin	4.24	2.25
Inorganic ions	1.81	2.2
Others	**4.24**	**4.1**
Total	100	100

1952 published report by Graham et al. (5202) on the induction of tumors in laboratory animals repeatedly painted with large doses of cigarette smoke tar, a report that was followed in early 1953 by a presentation at the American Association for Cancer Research (4306a) and then by a detailed publication in a peer-reviewed scientific journal in late 1953 (4306a). Wynder et al. (4306a) described many of the early studies on the effects of exposure of laboratory animals to various tars, including those derived from tobacco by smoking or extraction [E. Hoffmann et al. (1813), Helwig (1617, 5221), Bogen and Loomis (377), Cooper et al. (813), Campbell (579, 581), Schürch and Winterstein (3563), Taki (3865), Sugiura (5415), Flory (1206, 5178), and Shubik (3663)]. An early study reported in 1911 by Wacker and Schmincke (5446) preceded the development and description of the procedure to induce cancer in laboratory animals by skin painting with coal tar in 1915–1918 by Yamagiwa and Ichikawa (4361). As noted by Wynder et al. (4306a), each of the tobacco tar studies conducted after the Yamagiwa–Ichikawa reports suffered from one or more deficiencies such as a low number of daily or weekly paintings, low tar-painting dosage, inadequate smoking procedure for tar collection, and the like. However, seldom discussed is the fact that the Wynder et al. study involved a cigarette smoking procedure (35 mL puff, 2 s puff, 3 puff/min) different from the one in vogue since its elucidation (35 mL puff, 2 s puff, 1 puff/min) by Bradford et al. in 1936 (423b). Tripling the puff/min not only substantially increases the per-cigarette-tar yield but also drastically alters its composition, with substantial increases in several smoke components with known tumorigenicity to mouse skin, e.g., PAHs benzo[*a*]pyrene (B[*a*]P) and dibenz[*a,h*]anthracene (DB[*a,h*]A).

Other reports that triggered interest in the biological properties and chemical composition of CSC were the numerous publications between 1950 and 1953 on the epidemiology of lung cancer and cigarette smoking. They were presented in 1950 by Wynder and Graham (4306b), Doll and Hill (1026a), Levin et al. (2355), Mills and Porter (2556), and Schrek et al. (3529). These were followed in 1952 and 1953 by similar extensive studies conducted by Doll and Hill (1027), McConnell et al. (2515), Koulumies (4250), Lickint (5266), and Sadowsky et al. (3375a). It should be noted that the prospective method did not replace retrospective studies. Both approaches have their advantages and disadvantages. In the retrospective study, interviewers record the habits of smokers and controls; the prospective studies are better suited to survey larger groups of diseased and controls in terms of their environment, their behaviors, and specific diseases they contract.

Preceding these 1950–1953 epidemiological studies were several reported from 1912 to 1950, but in their 1950 report, Graham and Wynder (4306b) described in general several of the deficiencies of the earlier epidemiological studies, e.g., small sample size, lack of a control population, statistical procedure, tumor definition. Among the earlier studies were reports and/or comments on respiratory tract cancer by Adler (5096) in 1912, by Tylecote (5425) in 1927, by Lickint (5265) in 1935, by Arkin and Wagner (5101) in 1936, by Kennaway and Kennaway (5239, 5240) in 1936 and 1947, by Roffo (3322) in 1937, by Müller (5297) in 1939, by Ochsner and DeBakey (5316, 5317) in 1940 and 1941, and by Schairer and Schöninger (5370) in 1943.

The reports by Ochsner and DeBakey subsequently led to an interesting situation in the content of several U.S. Surgeon Generals' reports on smoking and health. From the late 1930s through the late 1960s, Ochsner, at that time one of the few eminent lung cancer surgeons in the United States, authored or coauthored over 40 articles and three books in which it was repeatedly asserted that the major cause of lung cancer was cigarette smoking. Despite his number of publications between the late 1930s and late 1963, the 1964 Advisory Committee to the U.S. Surgeon General (3999) and the 1979 (4005) and 1982 (4011) U.S. Surgeon Generals cited only one 1939 Ochsner-authored publication (5314) and one of his authored books, the 1954 edition (5315) on the relationship between lung cancer and cigarette smoking. Was the limitation of the citations of Ochsner's publications on cigarette smoking and lung cancer possibly due to either or both of the following situations?

1. Despite the repeated assertion that the major cause of lung cancer was cigarette smoking, Ochsner et al. frequently included other comments in the same articles, e.g., (a) the cause of the increasing incidence of cancer of the lung is not definite [see

p. 212 in (5317)], (b) the etiology of bronchogenic carcinoma is unknown (5320), and (c) the etiological picture (for bronchogenic carcinoma) is obscure. It is probable that there are a number of etiological factors in the production of this disease (5134).

2. Despite the repeated assertion that the major cause of lung cancer was cigarette smoking, the data on patients undergoing lung resection in the Ochsner Clinic because of lung cancer were summarized in several Ochsner et al.'s reports as follows: (a) In 129 resected cases, no factor was found which might bear a significant relationship to the occurrence of the disease. Neither occupation nor smoking habits, which some reports, including our own, have stressed as of possible etiological significance, seem of any special significance in this particular series (5318). (b) In the analysis of 147 resected cases, no etiological factor was found to bear a significant relationship to the occurrence of the disease. Both occupation and smoking, which had been particularly emphasized by some observers as possible etiological factors and which we were inclined previously to consider more seriously, were found to have no special significance in this analysis (5319).

CHEMICAL COMPONENTS OF TOBACCO AND TOBACCO SMOKE IDENTIFIED PRIOR TO 1954

Many components were identified in tobacco and/or tobacco smoke prior to the issuance of the 1954 Kosak's report (2170), the numerous epidemiological studies on tobacco smoking and respiratory cancer, and the 1953 report of tumor induction in laboratory animals by cigarette-tar painting (4306a). Most of the pre-1954 characterizations of such components were accomplished by the so-called classical chemical procedures. The components are listed in Table 0.4 with the identification and confirmation listed chronologically. If more than one study on a specific component was reported in a given year, the investigators in that year are listed alphabetically.

Examination of the data in Table 0.4 reveals the many investigators who contributed much meaningful information on tobacco and/or smoke composition prior to year-end 1953. They include the following: Brückner, Burkhard, Eulenberg, Frankenburg, Gabelya, Garner, Gottscho, Kipriyanov, Kissling, Kobel Lehmann, Molinari, Neuberg, Pfyl, Pontag, Preiss, Pyriki, Roffo, Schöller, Shmuk, Späth, Thoms, Vohl, and Wenusch. Each of them deserves much tribute for their contributions. Several of them continued to contribute to our knowledge of the composition of tobacco and/or tobacco smoke after 1953, e.g., Frankenburg, Garner, Gottscho, and Pyriki.

Compared to the fewer than 100 tobacco smoke components listed by Kosak (2170), Table 0.4 contains 325 chemical components identified and studied in tobacco prior to the publication of the Kosak's article. Included in 383 entries in Table 0.4 (as they were in the Kosak's tabulation) are several components originally assumed to be individual alkaloid-related components but subsequently were found to be known compounds or mixtures of known compounds, e.g., anodmine, gudham, lathrein, lohitam, obelin, poikiline, α-socratine, β-socratine, and γ-socratine (4208, 4209, 4210, 4211, 4213). They were not included in the count of the 325 identified tobacco components. The eventual characterization of anodmine, gudham, lathrein, lohitam, obelin, and the three socratines was described in 1955 by Kuffner et al. (2224). Their characterization of these supposedly alkaloid-related components was summarized by Johnstone and Plimmer (1971) in their 1959 review of tobacco and tobacco smoke composition. They wrote in 1959

> The constitution of these bases remained unknown until recently when investigators having access to original specimens were able to elucidate the identities of some of them by application of modern analytical techniques. γ-Socratine was found to be identical with *l*-nornicotine, and a crude mixture of α- and β-socratine (the only sample available), was shown to consist mainly of nicotyrine and 2,3′-dipyridyl with small quantities of nicotinic acid, nornicotine, and possibly anatabine (2224).

While noting that both ammonia and nicotine were previously identified as tobacco smoke components, Kosak elected not to list references to them because their number of references, in his opinion, was too numerous to list. Also the number of references to carbon dioxide and carbon monoxide was limited by Kosak (2170). Table 0.4 lists many of the pre-1954 references to ammonia, nicotine, carbon dioxide, and carbon monoxide in tobacco and/or tobacco smoke. Included in Table 0.4 are several pesticide residues, e.g., arsenic/arsenic (As) oxide, Toxaphene®, Lindane®, Parathion®, DDT, and TEPP (tetraethyl pyrophosphate), plus several pesticide residue degradation products, e.g., *o*,*p*′-DDD and *m*,*p*′-DDD, identified by Vinzant in 1951 (5439). Listed in Table 0.4 are a few compounds used as flavorants on tobacco products, most notably menthol which, however, occurs naturally in trace amounts in several tobacco types. Table 0.4 also cites numerous references to pre-1954 studies of a general nature. These include references to arsenical insecticides, alkaloids, aliphatic acids, aliphatic hydrocarbons amino acids, bases, tobacco distillates, tobacco fats, chlorophyll degradation products, enzymes (general information), hydrocarbons, hygroscopic agents, paraffins, pigments, sugars, tobacco combustion products, tobacco (general), tobacco smoke (general), and triglycerides. These items are not included in the total of 325.

Among metals, nonmetals, and ions, Kosak in his 1954 catalog listed only arsenic plus four ions as smoke components, and Kosak questioned the identification of each of the latter. Examination of Table 0.4 reveals that over 50 metals, nonmetals, and ions were identified in tobacco prior to late 1953. However, it was post-1953 when a concerted effort was made to determine the transfer of numerous metals from tobacco to tobacco smoke during the smoking process, e.g., the 1957 study by Cogbill and Hobbs (769). The references

TABLE 0.4
Chronology from 1800 to Late 1953 of Identified Items in Tobacco, Tobacco Smoke, and Tobacco Distillate

		References	
CAS No.	Name (per CA Collective Index)	Tobacco Smoke and/or Tobacco Distillate [Dry (Dr), Destructive (D)]	Tobacco
75-07-0	Acetaldehyde	1908 Brasch and Neuberg (5135)	1926 Neuberg and Kobel (2702a)
		1909 Brasch (5136)	1931 Neuberg and Burkard (2702)
		1931 Neuberg and Burkard (2702)	1936 Dixon et al. (5165)
		1933 Pfyl (2936)	
		1954 Kosak (2170)	
	Acetate	1939 Roffo (**D**) (3324, 5359)	
		1954 Kosak (2170)	
64-19-7	Acetic acid	1843 Zeise ([i]) (**Dr**) (4406)	1871 Vohl and Eulenberg (4064)
		1871 Vohl and Eulenberg (4064, 4065)	1884 Takayama (5419)
		1892 Abeles and Paschkis (18)	1909 Garner (1276)
		1929 Gabelya and Kipriyanov (**Dr**) (1263)	1924 Shmuk (5381)
		1931 Neuberg and Burkard (2702)	1929 Balabucha-Popzova (5114)
		1937 Bradford et al. (424)	1929 Shmuk (3655b)
		1939 Roffo (**D**) (3324, 5359)	1931 Yamafuji (5478)
		1950 Peterson (2934)	1935 Koenig (2154)
		1951 Garner (5189)	1936 Dixon et al. (5165)
		1952 James and Martin (1917)	1941 Sabetay et al. (3374)
		1954 Kosak (2170)	1951 Garner (5189)
	Acids, aliphatic	1931 Neuberg and Burkard (2702)	1930 Shmuk and Piatnicki (3655b)
		1937 Wenusch and Schöller (4214)	1931 Yamafuji (5478)
		1940 Haag (5207)	1943 Venkatarao et al. (4042b)
		1954 Kosak (2170)	1953 Wada and Kobashi (5447)
	Acids, amino-		1951 Roberts and Wood (5353)
			1952 Frankenburg and Gottscho (1223)
			1953 Pearse and Novellie (2911c)
			1953 Zacharius and Frankenburg (4398c)
	Acids, nonvolatile		1914 Garner et al. (5194)
			1931 Vickery and Pucher (5433)
			1933 Pucher and Vickery (3001a)
			1951 Garner (5189)
	Acids, phenolic	1939 Roffo (**D**) (3324, 5359)	
		1954 Kosak (2170)	
7440-34-8	Actinium		1937 Drobkov (5167)
56-41-7	*L*-α-Alanine		1952 Frankenburg and Gottscho (1223)
			1953 Pearse and Novellie (2911c)
			1953 Zacharius and Frankenburg (4398c)
107-95-9	β-Alanine		1953 Pearse and Novellie (2911c)
			1953 Zacharius and Frankenburg (4398c)
	Aldehydes		1953 Ross (3335)
	Alkaloids, tobacco or tobacco smoke	1931 Shmuk and Kolesnik (3659)	1901 Pictet and Rotschy (5332, 5333)
		1939 Wenusch (5457)	1908 Pictet and Court (4837a)
		1953 Latimer (2269)	1931 Ehrenstein (1116)
			1938 Marion (5271)
			1939 Späth and Kuffner (3761)
			1941 Jackson (17B18)
			1948 Frankenburg (1221)a
			1952 Badgett et al. (5111)
			1953 Tso and Jeffrey (3983a)
7429-90-5	Aluminum	1952 Bailey (160)	1932 Eisenmenger (5170)
			1938 McMurtrey and Robinson (5285)

TABLE 0.4 (continued)
Chronology from 1800 to Late 1953 of Identified Items in Tobacco, Tobacco Smoke, and Tobacco Distillate

CAS No.	Name (per CA Collective Index)	References: Tobacco Smoke and/or Tobacco Distillate [Dry (Dr), Destructive (D)]	References: Tobacco
			1938 Morgan and Street (5291)
			1944 LeCompte (20A57)
			1951 Garner (5189)
	Amines, aliphatic	1929 Gabelya and Kipriyanov (**Dr**) (1263)	
7664-41-7	Ammonia	1857 Vogel (4060, 4061)	1885 Müller-Thurgen (5298)
		1858 Vogel (4062)	1894 Behrens (5126)
		1871 Vohl and Eulenberg (4064, 4065)	1908 Pictet and Court (4837a)
		1879 Périgord (2928)	1914 Garner et al. (5194)
		1880 LeBon (2326)	1928 Shmuk (5382)
		1899 Thoms (3909)	1929 Gabelya and Kipriyanov (1263)
		1900 Thoms (3910)	1930 Smirnov and Izvoshtshikov (5396)
		1902 Pontag (2973)	1936 Dixon et al. (5165)
		1903 Pontag (2973)	1936 Preiss (2987)
		1908 Biederbeck (5129)	1937 Fromm (1244)
		1908 Lee (5263)	1939 Gaertner (5186)
		1908 Lehmann (2342a)	1939 Shmuk (5389)
		1909 Lehmann (2343)	1948 Pyriki (3022)
		1910 Toth and Krampera (3934)	1950 Molinari (2607)
		1911 Vaubel (4041)	1951 Garner (5189)
		1912 Anonymous (5099, 5100)	1952 Hough et al. (1835b)
		1928 Shmuk (5382)	1952 Jensen (1941)
		1929 Bogen (375)	
		1929 Gabelya and Kipriyanov (**Dr**) (1263)	
		1929 Koperina (2161)	
		1931 Gavrilov and Koperina (1277)	
		1931 Haley et al. (1489)	
		1931 Shmuk and Kolesnik (3659)	
		1932 Barta and Toole (197, 198)	
		1932 McNally (2524)	
		1933 Pfyl (2937)	
		1934 Barta (195)	
		1936 Bogen (376)	
		1936 Preiss (2986–2988)	
		1937 Bradford et al. (424)	
		1939 Dittmar (985–987)	
		1939 Roffo (**D**) (3324, 5359)	
		1939 Shmuk (5389)	
		1948 Pyriki (3022)	
		1950 Peterson (2934)	
		1951 Garner (5189)	
		1952 Larsen (2263)	
		1954 Kosak (2170)	
	Ammonium salts	1936 Cuvelier (5159)	
	Ammoresinol		1936 Späth and Zajic (3763)
9000-92-4	Amylase		1913 Oosthuizen and Shedd (5323)
			1937 Matsumina (5275)
			1942 Ward (5449)
			1946 Garner (5188)
			1951 Garner (5189)
			1951 Nakai and Inaba (5301)
			1953 Barrett et al. (5123)

(*continued*)

TABLE 0.4 (continued)
Chronology from 1800 to Late 1953 of Identified Items in Tobacco, Tobacco Smoke, and Tobacco Distillate

CAS No.	Name (per CA Collective Index)	References: Tobacco Smoke and/or Tobacco Distillate [Dry (Dr), Destructive (D)]	References: Tobacco
	Anabaseine		1939 Henry (5222)
	Anodmin = mixture of basic components of tobacco and its smoke (2224)	1935 Wenusch and Schöller (4210, 4211)	1935 Wenusch and Schöller (4210, 4211)
		1936 Wenusch and Schöller (5462)	
		1954 Kosak (2170)	
120-12-7	Anthracene	1939 Roffo (**D**) (3323, 3324, 5359)	
		1953 Cooper and Lindsey (818)	
		1954 Kosak (2170)	
7440-36-0	Antimony		1934 Heffer et al. (20A26)
147-81-9	Arabinose		1929 Gabelya and Kipriyanov (1263)
7004-12-8	Arginine		1933 Vickery et al. (5436)
			1935 Vickery et al. (5435)
			1951 Garner (5189)
			1953 Pearse and Novellie (2911c)
			1953 Zacharius and Frankenburg (4398c)
7440-38-2	Arsenic	1922 Leitch and Kennaway (5264)	1905 Boening (373)
		1927 Remington (3104)	1922 Leitch and Kennaway (5264)
		1932 McNally (2524)	1927 Remington (3104)
		1934 Gross and Nelson (1430)	1928 Popp (2978, 5338)
		1935 Bastedo (5124).	1934 Carey et al. (5142)
		1945 Thomas and Collier (3899)	1935 McMurtrey (5281)
		1947 Griffon and Delga (1395)	1938 McMurtrey (5283)
		1950 Daff and Kennaway (889, 5160)	1939 Barksdale (5119)
		1951 Daff et al. (889a)	1940 Barksdale (5120)
		1952 Goulden et al. (5201)	1941 McMurtrey (5284)
		1953 Monnet and Dupont (2609)	1942 Vucetich and Carratala (4070)
		1954 Kosak (2170)	1944 Vincent (5438)
			1947 Griffon and Delga (1395)
			1950 Daff and Kennaway (889, 5160)
			1951 Daff et al. (889a)
			1951 Garner (5189)
			1951 Oliver (5322)
			1952 Bunce (5139)
			1953 Monnet and Dupont (2609)
			1953 Wolff et al. (4273)
1327-53-3	Arsenic oxide (As_2O_3)	1927 Remington (3104)	1905 Boening (373)
		1932 McNally (2524)	1927 Remington (3104)
		1934 Gross and Nelson (1430)	1928 Popp (2978, 5338)
		1935 Bastedo (5124)	1934 Carey et al. (5142)
		1945 Thomas and Collier (3899)	1935 McMurtrey (5281)
		1947 Griffon and Delga (1395)	1938 McMurtrey (5283)
		1950 Daff and Kennaway (889, 5160)	1940 Barksdale (5120)
		1951 Daff et al. (889a)	1941 McMurtrey (5284)
		1952 Goulden et al. (5201)	1942 Vucetich and Carratala (4070)
		1953 Monnet and Dupont (2609)	1947 Griffon and Delga (1395)
		1954 Kosak (2170)	1950 Daff and Kennaway (889, 5160)
			1951 Daff et al. (889a)
			1951 Garner (5189)
			1953 Monnet and Dupont (2609)
	Arsenical insecticides		1901 Marlatt (5272)
			1908 Marlatt (5273)

TABLE 0.4 (continued)
Chronology from 1800 to Late 1953 of Identified Items in Tobacco, Tobacco Smoke, and Tobacco Distillate

		References	
CAS No.	Name (per CA Collective Index)	Tobacco Smoke and/or Tobacco Distillate [Dry (Dr), Destructive (D)]	Tobacco
50-81-7	Ascorbic acid		1947 Maton (2489)
			1951 Lona and Porzio-Giovanola (5267a)
			1951 Tombesi (3922)
7006-34-0	Asparagine		1894 Behrens (5126)
			1937 Vickery et al. (5437)
			1951 Garner (5189)
			1952 Frankenburg and Gottscho (1223)
			1953 Pearse and Novellie (2911c)
			1953 Zacharius and Frankenburg (4398c)
56-84-8	Aspartic acid		1952 Frankenburg and Gottscho (1223)
			1953 Pearse and Novellie (2911c)
			1953 Zacharius and Frankenburg (4398c)
275-51-4	Azulene	1947 Ikeda (1857)	
		1954 Kosak (2170)	
7440-39-3	Barium		1913 McHargue (5278)
			1913 Traetta-Mosca (5422)
			1916 Artis and Maxwell (5103)
			1916 Knight (5245)
			1921 Headden (5218)
	Bases	1940 Haag (5207)	1931 Yamafuji (5478)
			1934 Nito and Kitamura (5311)
100-52-7	Benzaldehyde	1931 Neuberg and Burkard (2702)	
		1954 Kosak (2170)	
	Benzenamine, alkyl- {coridine}		1871 Vohl and Eulenberg (4064)
	Benzenamine, alkyl- {rubidine}		1871 Vohl and Eulenberg (4064)
	Benzenamine, alkyl- {viridine}		1871 Vohl and Eulenberg (4064)
	Benzenamine, 4-(1,1-dimethylethyl)- {parvoline}		1871 Vohl and Eulenberg (4064)
53-19-0	Benzene, 1-chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]- {*o,p′*-DDD; *o,p′*-TDE}		1951 Vinzant (5439)
4329-12-8	Benzene, 1-chloro-3-[2,2-dichloro-1-(4-chlorophenyl)ethyl]- {*m,p′*-DDD}		1951 Vinzant (5439)
789-02-6	Benzene, 1-chloro-2-[2,2,2-trichloro-1-(4-chlorophenyl)ethyl]- {*o,p′*-DDT}		1951 Vinzant (5439)
50-29-3	Benzene, 1,1′-(2,2,2-trichloroethylidene) bis[4-chloro- {*p,p′*-DDT}		1951 Vinzant (5439)
100-21-0	1,4-Benzenedicarboxylic acid {terephthalic acid}		1946 Frankenburg (5180)
120-80-9	1,2-Benzenediol {catechol}	1893 Kissling (5243)	1935 Koenig (2154)
		1936 Molinari (2605)	
		1950 Molinari (2607)	
123-31-9	1,4-Benzenediol {hydroquinone}		1952 Volgunov (5440)
100-51-6	Benzenemethanol {benzyl alcohol}	1939 Wenusch (4202)	1939 Wenusch (4202)
65-85-0	Benzoic acid {benzenecarboxylic acid}	1931 Neuberg and Burkard (2702)	
		1939 Wenusch (4202)	
		1940 Haag (5207)	
		1954 Kosak (2170)	
99-50-3	Benzoic acid, 3,4-dihydroxy- {protocatechuic acid}		1929 Shmuk (3655b)
149-91-7	Benzoic acid, 3,4,5-trihydroxy- {gallic acid}		1929 Shmuk (3655b)
59-02-9	2*H*-1-Benzopyran-6-ol,3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)- {α-tocopherol}		1945 Riemenschneider et al. (3155)

(*continued*)

TABLE 0.4 (continued)
Chronology from 1800 to Late 1953 of Identified Items in Tobacco, Tobacco Smoke, and Tobacco Distillate

		References	
CAS No.	Name (per CA Collective Index)	Tobacco Smoke and/or Tobacco Distillate [Dry (Dr), Destructive (D)]	Tobacco
92-61-5	2*H*-1-Benzopyran-2-one, 7-hydroxy-6-methoxy- {scopoletin}		1948 Best (5127) 1953 Johanson (5235)
21637-25-2	4*H*-1-Benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-3-(β-*D*-glucofuranosyloxy)-5,7-dihydroxy- {isoquercetrin}		1935 Kurilo (5255) 1937 Kurilo (5256) 1950 Howard et al. (1837a)
117-39-5	4*H*-1-Benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy- {quercetrin}		1935 Kurilo (5255) 1936 Neuberg and Kobel (2704a) 1950 Howard et al. (1837a)
153-18-4	4*H*-1-Benzopyran-4-one, 3-[[6-*O*-(6-deoxy-α-*L*-mannopyranosyl)-β-*D*-glucopyranosyl] oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy- {rutin}		1931 Hasegawa (5217) 1935 Kobel and Neuberg (2153a) 1935 Neuberg and Kobel (5304) 1936 Neuberg and Kobel (2704a, 5305) 1944 Couch and Krewson (5156, 5157) 1944 Griffith et al. (5204) 1947 Couch (828b) 1949 Badgett et al. (5110) 1951 Garner (5189) 1951 Nio and Wada (5310)
480-10-4	4*H*-1-Benzopyran-4-one, 3-(β-*D*-glucopyranosyloxy)-5,7-dihydroxy-2-(4-hydroxyphenyl)- {kaempferol glycoside}		1953 Wada (4072a)
50-32-8	Benzo[*a*]pyrene	1937 Roffo (**D**) (3316) 1939 Roffo (**D**) (3323–3325, 5359) 1941 Roffo (**D**) (3326) 1942 Roffo (**D**) (3327) 1954 Kosak (2170)	
8001-35-2	Bicyclo[2.2.1]heptane, 2,2-dimethyl-3-methylene-, polychlorinated {Toxaphene®}		1951 Vinzant (5439)
507-70-0	Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, *endo*- {borneol}		1941 Sabetay et al. (3374)
366-18-7	2,2′-Bipyridine		1901 Pictet and Rotschy (5332) 1928 Shmuk (5382)
581-50-0	2,3′-Bipyridine		1928 Shmuk (5382) 1936 Späth and Zajic (3763) 1939 Späth and Biniecki (5403) 1946 Frankenburg (1221) 1952 Frankenburg and Gottscho (1223) 1953 Tso and Jeffrey (3983a)
581-49-7	2,3′-Bipyridine, 1,2,3,6-tetrahydro-, (S)- {*l*-anatabine}		1937 Späth and Kesztler (5406, 17B55) 1946 Frankenburg (1221) 1948 Shmuk (5390) 1953 Tso and Jeffrey (3983a)
5953-51-5	2,3′-Bipyridine, 1,2,3,6-tetrahydro-1-methyl-, (S)-		1937 Späth and Kesztler (5407) 1946 Frankenburg (1221)
7440-69-9	Bismuth		1934 Heffer et al. (20A26)
7440-42-8	Boron	1952 Bailey (160)	1923 Warrington (5450) 1926 Sommer and Lipman (5402) 1927 Swanback (5417) 1929 McMurtrey (5279) 1934 Van Schreven (5429) 1935 McMurtrey (5281)

TABLE 0.4 (continued)
Chronology from 1800 to Late 1953 of Identified Items in Tobacco, Tobacco Smoke, and Tobacco Distillate

CAS No.	Name (per CA Collective Index)	References: Tobacco Smoke and/or Tobacco Distillate [Dry (Dr), Destructive (D)]	References: Tobacco
			1938 McMurtrey (5283)
			1938 McMurtrey and Robinson (5285)
			1938 Morgan and Street (5291)
			1941 McMurtrey (5284)
			1950 Steinberg (5413)
			1951 Garner (5189)
			1952 Lashkevvich (5261)
123-72-8	Butanal	1908 Brasch and Neuberg (5135)	
		1909 Brasch (5136)	
		1931 Neuberg and Burkard (2702)	
		1954 Kosak (2170)	
107-89-1	Butanal, 3-hydroxy- {aldol}	1931 Neuberg and Burkard (2702)	
107-85-7	1-Butanamine, 3-methyl- {isoamyl amine}		1911 Ciamician and Ravenna (5147)
			1928 Shmuk (5382)
110-15-6	Butanedioic acid {succinic acid}	1939 Roffo (**D**) (3324, 5359)	1924 Shmuk (5381)
		1954 Kosak (2170)	1929 Shmuk (3655b)
			1930 Shmuk (5384)
6915-15-7	Butanedioic acid, hydroxy- {malic acid}		1809 Vauquelin5430
			1884 Takayama (5419)
			1894 Behrens (5126)
			1904 Kissling (5244)
			1924 Shmuk (5381)
			1929 Shmuk (3655b)
			1931 Yamafuji (5478)
			1930 Shmuk (5384)
			1935 Koenig (2154)
			1937 Pucher et al. (5342)
			1939 Shmuk (5389)
			1951 Bacon et al. (5109)
			1951 Garner (5189)
			1952 Bacon et al. (5109)
			1953 Phillips and Bacot (2947c)
			1953 Wright and Burton (5477)
16426-50-9	Butanedioic acid, hydroxy-, calcium salt		1937 Pucher et al. (5342)
			1951 Garner (5189)
869-06-7	Butanedioic acid, hydroxy-, magnesium salt		1937 Pucher et al. (5342)
			1951 Garner (5189)
585-09-1	Butanedioic acid, hydroxy-, potassium salt		1937 Pucher et al. (5342)
			1951 Garner (5189)
431-03-8	2,3-Butanedione	1935 Neuberg and Kobel (2704)	1929 Schmalfuss and Barthmeyer (5371)
		1939 Schmalfuss (3475)	1932 Schmalfuss and Schmalfuss (5372)
		1950 Schmalfuss (3475)	1935 Neuberg and Kobel (2704)
		1953 Sasaki (3413)	
		1954 Kosak (2170)	
107-92-6	Butanoic acid	1843 Zeise (4406)	1871 Vohl and Eulenberg (4064)
		1871 Vohl and Eulenberg (4064, 4065)	1909 Garner (1276)
		1900 Thoms (3910)	1924 Shmuk (5381)
		1904 Thoms (3912)	1929 Shmuk (3655b)
		1931 Neuberg and Burkard (2702)	
		1935 Wenusch (4185)	

(*continued*)