CHEMICAL AND BIOLOGICAL STUDIES

NEW CIGARETTE PROTOTYPES THAT HEAT INSTEAD OF BURN TOBACCO

R.J. REYNOLDS TOBACCO COMPANY
WINSTON-SALEM, NORTH CAROLINA

CHEMICAL AND BIOLOGICAL STUDIES ON NEW CIGARETTE PROTOTYPES THAT HEAT INSTEAD OF BURN TOBACCO

R.J. REYNOLDS TOBACCO COMPANY
Winston-Salem, North Carolina

This monograph is available to interested scientists and organizations. A complimentary copy is available upon submission of a written request on organization letterhead stationery.

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R.J. Reynolds Tobacco Co.
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Acknowledgment

The following reports were prepared by two groups of eminent, independent scientists. The first is a report of the Company's Scientific Advisory Board. The second is a report of a peer review Committee of twelve scientists who were convened under the auspices of Emory University and at the invitation of Dr. Gerald N. Wogan who chaired the Committee.

R. J. Reynolds Tobacco Company greatly appreciates their time, efforts and objective evaluations of the information reflected in this monograph.

These reports were not intended to be nor should they be viewed as an endorsement of the New Cigarette by the scientists. Similarly, any views expressed or conclusions reached by the scientists in respect to the New Cigarette or any other cigarette are their own and do not necessarily reflect the views of the Company.

Scientific Advisory Board Statement

STATEMENT OF THE SCIENTIFIC ADVISORY BOARD
OF R.J. REYNOLDS TOBACCO COMPANY

This monograph describes a new cigarette that warms or heats, rather than burns, tobacco and details the methodology and data from an extensive scientific program to assess the analytical chemistry and biological activity of this new cigarette, as compared to that of cigarettes that burn tobacco. The studies detailed in this monograph were conducted by qualified scientists using state-of-the-art procedures and equipment at R.J. Reynolds laboratories and at independent laboratories.

We, the members of R.J. Reynolds' Scientific Advisory Board, have reviewed the protocols and reported results of these studies. We have also had numerous opportunities to visit R.J. Reynolds' laboratories and talk with the scientists on the project.

Based upon our site visits, protocol reviews and the results presented to us, we have confidence in the data reported here. Scrupulous attention was paid to detail, and we believe that scientists in other laboratories will obtain the same results as those reported in this monograph, if they repeat these studies using the same methodology. The studies are reasonable to meet the Product Development Objectives for this NEW CIGARETTE.

The purpose of this monograph is not to make any claims about this NEW CIGARETTE. It is to provide to the scientific community information that was gathered through this rigorous research program. In our opinion, this volume is an accurate and comprehensive report of the extensive investigation of the analytical chemistry and of a comparison of the biological activity of this NEW CIGARETTE with reference cigarettes. It should be read as a scientific document and should be judged solely on its scientific merits.

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Preface

INTRODUCTION

The development of the NEW CIGARETTE represents a substantial commitment by R.J. Reynolds and its employees. This monograph is a compilation of the data from an extensive program to assess the chemistry and biological activity of a NEW CIGARETTE that heats, but does not burn, tobacco in comparison to reference cigarettes that burn tobacco. It presents the design and rationale for the testing program and describes a large number of studies conducted both at R.J. Reynolds and at independent contract laboratories.

Certain studies presented in this document exist in the open scientific literature. Others have been submitted to peer-reviewed journals for publication. This report presents these studies in a succinct manner under one cover. Details concerning laboratory methodology are not presented, but will appear in articles in scientific journals.

The studies reported in this monograph have used a series of prototypes that represent the evolution of the NEW CIGARETTE design. The testing of the actual cigarette to be marketed has been initiated, and the results of these studies will be made available to the scientific community upon their completion. The testing program for the market cigarette is at least as exhaustive as the program described in this monograph. The

conclusions from these studies are expected to be the same as those reported here.

This report begins with a perspective on the evolution and development of the NEW CIGARETTE design. This is followed by a detailed description of the NEW CIGARETTE, including the physical and functional configuration of its components.

Next is a discussion of the approach to the comparative assessment of the potential biological activity of the NEW CIGARETTE and reference cigarettes. This discussion provides the rationale for the overall program and the choice of its specific units.

Presentation of the data begins with a comparison of the mainstream smoke, sidestream smoke and environmental tobacco smoke chemistry of both the NEW CIGARETTE and a reference cigarette.

The final sections of this report present studies designed to compare the potential biological activity of the NEW CIGARETTE with that of reference cigarettes, based on tests widely used by scientists to study cigarettes. Data are presented from *in vitro* and *in vivo* genetic toxicology tests used to compare smoke from the NEW CIGARETTE and a reference cigarette. The NEW CIGARETTE and reference cigarettes are compared in several short-term and subchronic inhalation studies in laboratory animals.

Data comparing the NEW CIGARETTE and a reference cigarette in a study with human volunteers are also presented. These data include nicotine pharmacokinetics (plasma absorption and clearance) and urine mutagenicity.

A description of the NEW CIGARETTE's components and their chemical and physical characteristics, and a summary of their known biological activity, where appropriate, is presented in the final section of the monograph. This summary is based upon review of the literature and, in some cases, direct testing.

The assessment of the biological activity of this NEW CIGARETTE has used many of the test and experimental methods commonly deemed appropriate in the literature for the testing of cigarettes. Interpretation of the results of these tests is the

subject of vigorous debate at present, and we do not necessarily agree with the conclusions drawn by some. For the sake of completeness, however, the tests were performed, and the results are presented here to facilitate a broad, informed and objective evaluation of the NEW CIGARETTE by the scientific community.

Contents

Summary

I. THE NEW CIGARETTE

Through the years, significant changes have been introduced in the designs and raw materials used to manufacture cigarettes. In the early 1950s, most cigarettes produced in the United States were made from flue-cured, burley and Turkish tobaccos. They were 70 mm long and unfiltered. When smoked, these cigarettes produced an average of 40 mg of "tar" and 2.8 mg of nicotine by methods comparable to those used by the United States Federal Trade Commission (FTC). (The FTC methods became official in 1969.) In response to changing smoker demands, the vast majority of today's cigarettes are 85-100 mm long, have filters and yield an average of 11.5 mg of "tar" and 0.8 mg of nicotine. Some cigarettes now available produce less than 1.0 mg of "tar" as measured by the FTC method.

These "tar" and nicotine reductions have largely been achieved through innovations in cigarette design. These include the use of ventilated tobacco rods and filters, improved filtration systems, porous papers, puffed tobaccos and reconstituted tobacco sheet (produced from small tobacco pieces). Many of these reductions in "tar" and nicotine have come at the expense of flavor. Some smokers are unwilling to sacrifice flavor for reduced "tar." This has prompted a continuing effort to develop alternative cigarette designs.

Although most cigarette design modifications have occurred in recent decades, the search for alternative cigarette designs dates back to the early nineteenth century. Efforts failed for a variety of reasons, the most frequent being the

inability of the cigarette to provide satisfactory tobacco taste. Others did not sufficiently provide the characteristics of cigarette smoke. Although recent cigarette design alternatives have achieved the "tar" and nicotine reductions discussed above, current cigarette technology has been pushed close to its limits in reducing "tar" while providing acceptable flavor.

In response to this technological impasse and smokers' desires for cigarettes with acceptable taste that are low in "tar" and nicotine, R.J. Reynolds has developed a NEW CIGARETTE. This new design provides tobacco taste and enjoyment by warming, rather than burning, tobacco.

Following are the NEW CIGARETTE Product Development Objectives:

- To provide the tobacco taste and smoking pleasure of other cigarettes, as demanded by smokers, and to the degree possible:

  a) Simplify the mainstream and sidestream smoke chemistry by eliminating or reducing compounds produced by burning tobacco.

  b) Minimize the potential for biological activity, as measured by toxicological assays and tests frequently used to study cigarettes and cigarette smoke.

  c) Minimize environmental tobacco smoke and its potential annoyance.

The extensive scientific research program, summarized here and fully described in the following monograph, was designed to address objectives a, b and c.

Research and Development Guidelines

Consistent with the Product Development Objectives, following are the basic research and development guidelines for the NEW CIGARETTE:

1) To select components that would minimize biological activity of the smoke.

2) To coordinate the NEW CIGARETTE development with smoke composition studies to ensure that smoke composition was simpler and that specific compounds were reduced, compared to the reference cigarette.

3) To coordinate the development of the NEW CIGARETTE with results of genetic toxicology and inhalation

studies frequently used to study cigarette smoke, comparing the smoke from the NEW CIGARETTE with smoke from reference cigarettes to ensure reduced biological activity.

A large number of studies have been conducted comparing NEW CIGARETTE prototypes with reference cigarettes to confirm that the NEW CIGARETTE meets its Product Development Objectives. Except for three instances, the reference cigarettes used in these studies were standard reference cigarettes. All reference cigarettes were representative of low "tar" cigarettes but were not cigarettes that are currently marketed. The methodology, data and results of these studies have been reviewed by R.J. Reynolds' Scientific Advisory Board, as well as by other independent scientists. The testing of the NEW CIGARETTE that will be marketed has been initiated, and the results of these studies will be made available to the scientific community upon completion.

II. THE NEW CIGARETTE: STRUCTURE AND PROPERTIES

The NEW CIGARETTE uses a unique, patented cigarette design to produce smoke and tobacco taste by heating, rather than burning, tobacco. The smoke from the NEW CIGARETTE is produced by applying controlled heat to tobacco, spray-dried tobacco, flavor and glycerol. The heat is sufficient to volatilize, but not burn, these components. Because of the NEW CIGARETTE's design, almost 90% of the mainstream smoke particles leaving the mouth end of the cigarette are composed of glycerol and water. The NEW CIGARETTE's smoke (measured by a FTC-type comparison) contains nicotine in amounts lower than those found in fuller-flavor low-"tar" cigarettes (frequently called "Lights") currently on the market, but contains equivalent amounts of carbon monoxide.

Figure 1 shows a cross-section of the NEW CIGARETTE and its components. As the figure illustrates, the NEW CIGARETTE has two major sections:

1) The front-end piece, containing an insulated carbon heat source, tobacco and an aluminum capsule containing tobacco, flavor and glycerol.

2) The mouth-end piece, containing a two-part filtration system.

FIGURE 1

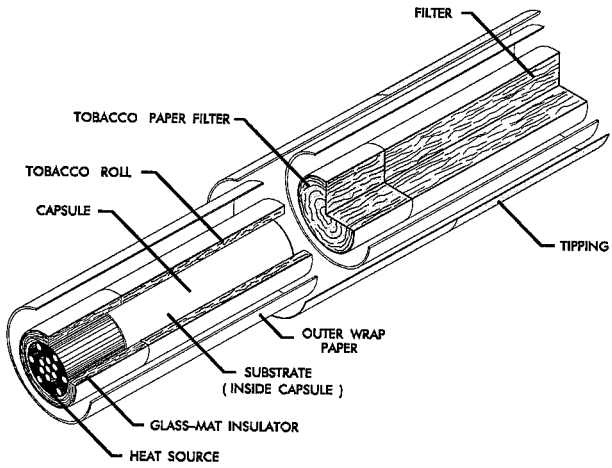

FIGURE 1 Diagram of the NEW CIGARETTE and its components. The carbon heat source fits into the aluminum capsule, which is surrounded by the tobacco roll. The tobacco-paper filter fits against the capsule and tobacco roll. The filter fits against the tobacco-paper filter.

The NEW CIGARETTE is lit and smoked similar to other cigarettes, but it does not burn tobacco and burns very little paper. Unlike other cigarettes, it does not burn down to a butt, nor does it produce loose ash. When the NEW CIGARETTE is lit, the only components that burn are the carbon heat source and approximately 6-8 mm of paper, which turns gray and simulates the ash of other cigarettes. Because the NEW CIGARETTE does not burn tobacco, sidestream smoke is greatly reduced.

When a smoker puffs the NEW CIGARETTE, heated air is drawn through an aluminum capsule, where it volatilizes glycerol, flavors from natural spray-dried tobacco, and a small amount of added flavor contained within a porous *alpha*-alumina substrate. Heated air also passes through and volatilizes natural tobacco flavor from a tobacco roll that surrounds the capsule. The vapor then passes through a tobacco-paper filter, which imparts additional tobacco flavor. The vapor is cooled within the tobacco-paper filter, allowing it to condense and form an aerosol that contains the particulate and vapor phases

of the mainstream smoke of the NEW CIGARETTE. Finally, the smoke passes through a polypropylene filter. The nicotine in the NEW CIGARETTE smoke comes only from the tobacco in the NEW CIGARETTE.

III. SMOKE CHEMISTRY ASSESSMENT

A two-part analytical assessment program was developed to compare the chemical composition of the smoke from the NEW CIGARETTE with that of a reference cigarette. The 1R4F reference cigarette from the Tobacco and Health Research Institute, University of Kentucky, was used as the reference. A NEW CIGARETTE developmental prototype (TM-6) was used for the smoke chemistry investigations. Best available methods were used to measure individual compounds or groups of compounds claimed to produce biological activity in cigarette smoke. Screening methods were used to measure, and when possible, identify all other smoke constituents that occurred at a level of 0.5 μg/cigarette and above.

Comparison of Total Particulate Matter, Nicotine and CO

The smoke from cigarettes that burn tobacco is an aerosol generated by cooling a mixture of hot gases produced by the combustion, pyrolysis and distillation of tobacco. In contrast, the NEW CIGARETTE smoke is an aerosol generated primarily by distilling and condensing glycerol and volatile tobacco constituents.

Mainstream smoke is the smoke that comes from the mouth end of the cigarette when it is puffed. Sidestream smoke comes from the lit end when the cigarette is not being puffed. Both mainstream and sidestream smoke are composed of a particulate phase and a vapor phase. The particulate and vapor phases of both mainstream and sidestream smoke were analyzed.

"Tar" is defined as mainstream Total Particulate Matter (TPM) minus nicotine and water. Though the NEW CIGARETTE produces smoke without burning tobacco, TPM can be collected through traditional "tar" measurement techniques. Its composition, however, differs dramatically from that of the "tar" produced by other cigarettes. Because of this difference in composition, TPM minus nicotine and water is referred to as

"nicotine-free, dry particulate matter" (NFDPM) for the NEW CIGARETTE, instead of "tar."

Table 1 shows that the TPM from a NEW CIGARETTE prototype and the 1R4F reference cigarette differ markedly in composition. The reference cigarette TPM is 27.9% glycerol, water and nicotine, with the remaining 72.2% composed of numerous other compounds (the sum exceeds 100% because of rounding). The TPM from the NEW CIGARETTE is 94.3% glycerol, propylene glycol, water and nicotine, with only 5.7% composed of other materials. These data are presented graphically in Figure 2.

TABLE 1 Composition of 1R4F and NEW CIGARETTE Total Particulate Matter

	1R4F Reference		NEW CIGARETTE	
	Amount (mg/cig)	% of TPM	Amount (mg/cig)	% of TPM
TPM	11.5	100	12.3	100
Nicotine	0.8	7	0.3	2.4
Water	1.3	11.3	6.3	51.2
Glycerol	1.1	9.6	4.6	37.4
Propylene Glycol	0.0	0.0	0.4	3.3
Other[a]	8.3	72.2	0.7	5.7

[a]Obtained by subtracting the nicotine, glycerol, water and propylene glycol values from the TPM.

FIGURE 2

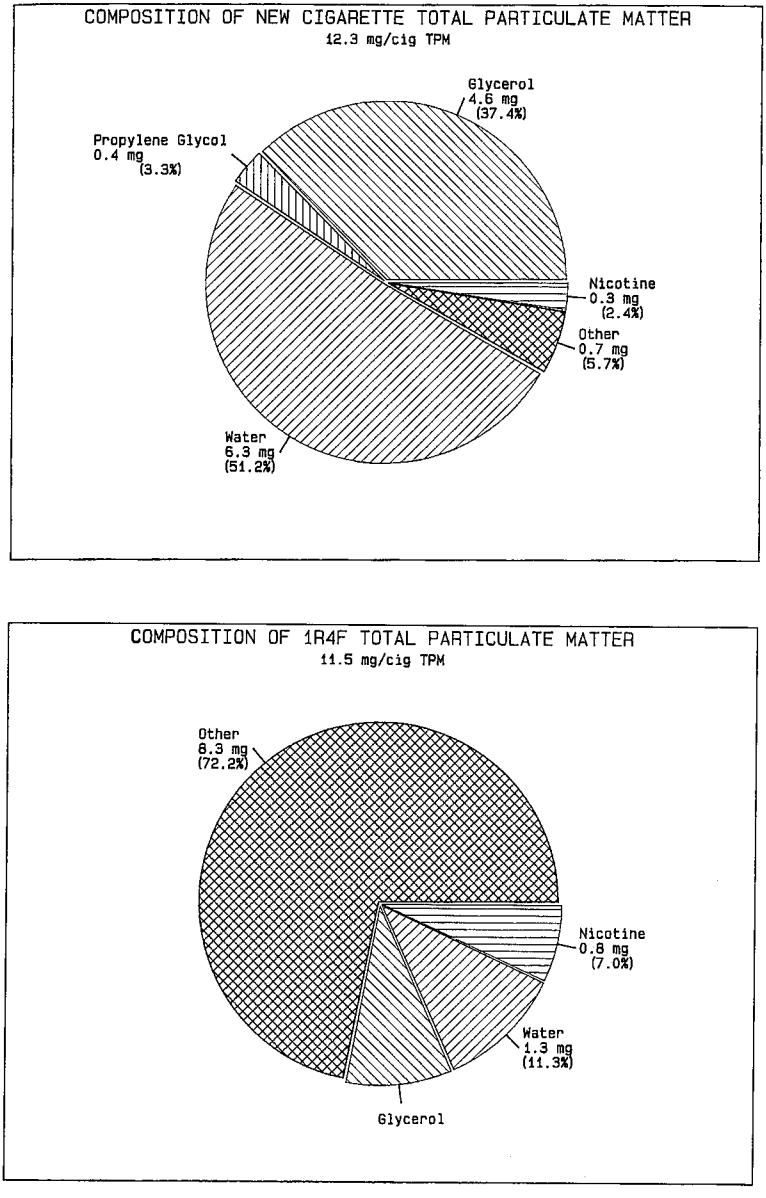

FIGURE 2 Illustration of the major constituents of the Total Particulate Matter (TPM) from the 1R4F reference cigarette and the NEW CIGARETTE prototype TM-6.

In the past, the FTC has reported "tar," nicotine and carbon monoxide values for cigarettes sold in the United States. Those values for the 1R4F reference cigarette and the NEW CIGARETTE are shown in Table 2 (the value for the NEW CIGARETTE is NFDPM, not "tar"). The sales-weighted average values (i.e., the average "tar" and nicotine level per cigarette sold) for the 12 leading "fuller-flavor, low-'tar'" (FFLT) brands sold in the United States also are shown in the table. These brands account for almost 20% of the total U.S. cigarette market.

TABLE 2 "Tar," Nicotine and Carbon Monoxide Data

	1R4F	NEW CIGARETTE	FFLT Sales-Weighted Average[a]
"Tar" (mg/cig)	9	—	10.5
NFDPM (mg/cig)[b]	—	6	—
Nicotine (mg/cig)	0.8	0.3	0.75
Carbon Monoxide (mg/cig)	11	12	12.4

[a]Sales-weighted average values for the 12 leading "fuller-flavor, low-'tar'" brands sold in the United States in 1987.
[b]Nicotine-free, dry particulate matter, not "tar."

Mainstream and Sidestream Smoke

Screening Analyses:

Both the particulate and vapor phases of mainstream and sidestream smoke from the 1R4F reference cigarette and the NEW CIGARETTE were subjected to gas-chromatographic analyses. The results are summarized in Figure 3. The number of compounds detected in the NEW CIGARETTE smoke was reduced 82-96% compared to the reference cigarette smoke, as shown in Figure 3. The amount (by weight) of the compounds detected was reduced from 84-97% compared to the reference cigarette.

FIGURE 3

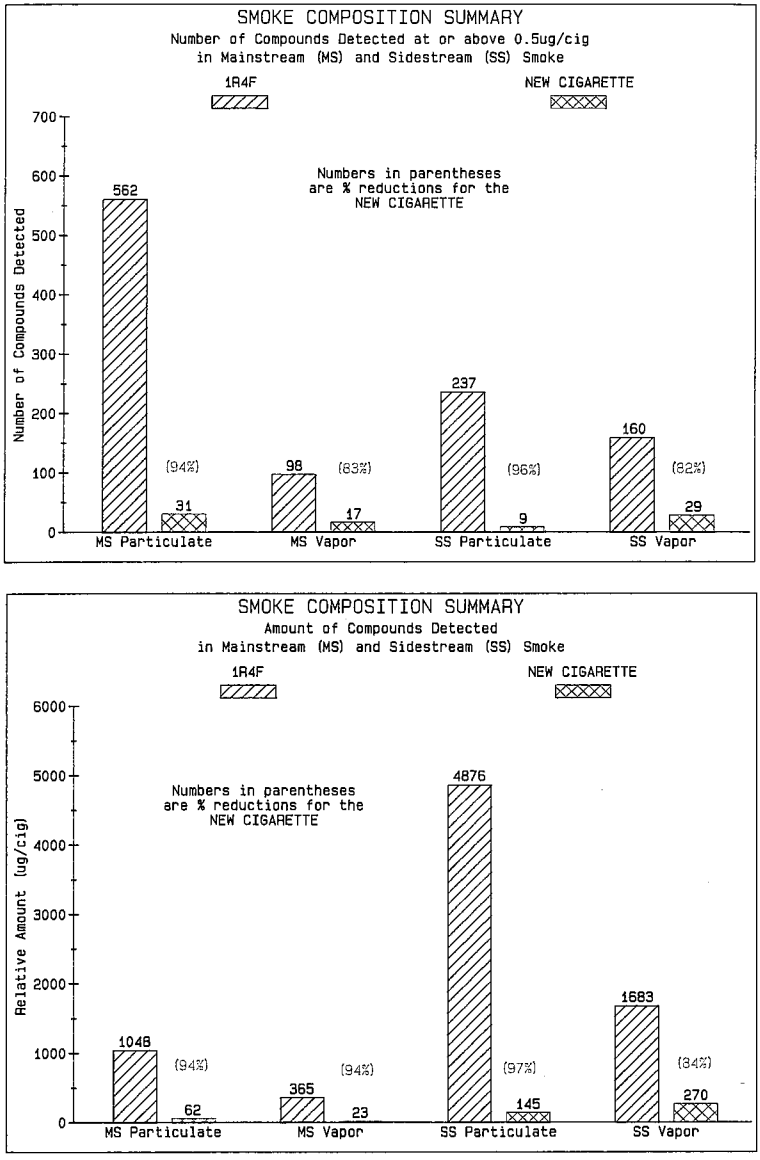

FIGURE 3 Illustration of the total number of compounds above 0.5 µg and their relative amounts detected in mainstream (MS) and sidestream smoke (SS) from the NEW CIGARETTE (TM-6) and the 1R4F reference cigarette. Data for both the particulate and vapor phases of the smoke are illustrated

for both cigarettes. The amounts are relative because peak areas were compared to an internal standard, assuming equivalent detector response. Mainstream particulate data include all compounds detected except nicotine, glycerol, propylene glycol, acetic acid and water. Mainstream vapor, sidestream particulate and sidestream vapor data include all compounds detected except water.

Specific Smoke Component Analyses:

Concentrations of specific smoke components were determined. Some of these components have been traditionally used as indicators for entire chemical classes including nitrosamines, polycyclic aromatic hydrocarbons and carbonyls. Amounts were substantially lower in both the mainstream and sidestream smokes from the NEW CIGARETTE compared to those from the 1R4F. These data are summarized in Table 3.

TABLE 3 Specific Component Reductions in Mainstream and Sidestream Smokes of the NEW CIGARETTE Compared to the 1R4F Reference

Compounds	Mainstream % Reduction	Sidestream % Reduction
Hydrogen Cyanide	99+	91
Nitrogen Oxides	95	96
Carbonyls[a]	91	88
Polycyclic Aromatic Hydrocarbons[a]	99	97
Nitrosamines[a]	97	94
Phenolics[a]	96	n.d.[b]

[a]Estimates for each class are based upon analytical determination of specific compounds.
[b]n.d. = Not determined.

Environmental Tobacco Smoke

Environmental Tobacco Smoke (ETS) is the combination of aged and diluted sidestream and exhaled smoke present in closed environments where people smoke. Seventeen substances were measured in ETS from the 1R4F reference cigarette and the NEW CIGARETTE. The NEW CIGARETTE achieved reductions ranging from 65-99% compared to the reference cigarette, as shown by the examples in Table 4.

TABLE 4 Reductions in the Environmental Tobacco Smoke from Smoking the NEW CIGARETTE Compared to a Reference Cigarette

Compound	% Reduction
Carbon Monoxide	65
Nitrogen Oxides	99
Ammonia	98
Nicotine	95
Carbonyls[a]	92
Nitrogen Heterocycles[a]	98

[a]Estimates for each class are based upon analytical determination of specific compounds for these classes.

IV. COMPARATIVE BIOLOGICAL ASSESSMENT: THE NEW CIGARETTE AND REFERENCE CIGARETTES

This section summarizes the results of an extensive research program designed to compare the biological activity of NEW CIGARETTE prototypes with that of cigarettes that burn tobacco. Using methodology reported in the literature to study cigarette smoke, studies were conducted both at R.J. Reynolds' research laboratories and at independent laboratories.

In Vitro Genetic Toxicity Profile

Mainstream and sidestream smoke condensates from the 1R4F reference cigarette and NEW CIGARETTE prototypes were individually compared in the following *in vitro* genetic toxicity assays:

1) Bacterial mutagenesis (Ames Assay) in *Salmonella typhimurium*

2) Gene mutations (Hypoxanthine Guanine Phosphoribosyl Transferase [HGPRT]) in Chinese hamster ovary (CHO) cells

3) Chromosomal aberrations in CHO cells

4) Sister chromatid exchanges in CHO cells

5) Unscheduled DNA synthesis in rat hepatocytes.

These studies indicated both the mainstream and sidestream smoke condensates from the reference cigarette were genotoxic in all assays except one (HGPRT). Those from the NEW CIGARETTE were not genotoxic in any of these assays. The data from these studies are summarized in Table 5.

TABLE 5 Summary of the *In Vitro* Genetic Toxicology Profile of the NEW CIGARETTE compared to the 1R4F Reference Cigarette[a]

	Sidestream		Mainstream	
Assay	Reference Cigarette	NEW CIGARETTE	Reference Cigarette	NEW CIGARETTE
Ames	Positive	Negative	Positive	Negative
HGPRT Gene Mutation	Negative	Negative	Negative	Negative
Chromosomal Aberrations	Positive	Negative	Positive	Negative
Sister Chromatid Exchanges	Positive	Negative	Positive	Negative
Unscheduled DNA Synthesis	Positive	Negative	Positive	Negative

[a]Complete data are presented in the monograph that follows this summary.

In Vivo Genetic Toxicity Profile

Reference cigarette mainstream smoke and NEW CIGARETTE mainstream smoke also were compared in the following *in vivo* genetic toxicity tests at the termination of a 90-day, nose-only inhalation study:

1) Sister chromatid exchanges in rat bone marrow cells
2) Chromosomal aberrations in rat bone marrow cells
3) Micronucleus assay in rat bone marrow cells
4) Mutagenicity of rat urine (Ames Strains TA-98 and TA-100) with and without metabolic activation of urine samples.

The smoke from the reference cigarette and that from the NEW CIGARETTE were not genotoxic in these assays. The data are summarized in Table 6.

TABLE 6 *In Vivo* Genetic Toxicology Profile of the NEW CIGARETTE Compared to the 1R4F Reference Cigarette[a]

Assay	Reference Cigarette	NEW CIGARETTE
Sister Chromatid Exchanges	Negative	Negative
Chromosomal Aberrations	Negative	Negative
Micronucleus Assay	Negative	Negative
Mutagenicity of Urine	Negative	Negative

[a]Data are from genetic toxicology assays from rats exposed to either NEW CIGARETTE smoke or reference cigarette smoke for one hour per day, five days per week for 13 weeks. Complete data are presented in the monograph that follows this summary.

Inhalation Studies

Seven nose-only inhalation studies were conducted to compare the effects of exposures of rats and hamsters to smoke from the NEW CIGARETTE with that from reference cigarettes. Although there were minor differences among the seven studies, all followed a standard protocol.

Each study used six groups of 15-40 animals of both sexes. Each group was exposed to one of three different concentrations of NEW CIGARETTE smoke or one of the same three concentrations of reference smoke. In addition, each study included a room-control group and a sham-exposed control group. Animals were continuously exposed to smoke for one hour per day, five or seven days per week. The seven studies included two 14-day studies in rats and one in hamsters (females only), and three 90-day studies in rats and one in hamsters.

The exposure apparatus was designed to permit daily calibration and measurement of smoke particle size and distribution, and concentrations of TPM, nicotine and carbon monoxide.

A series of observations and measurements was made to determine clinical appearance, body and selected organ weights, gross and histologic changes, hematology and clinical chemistry, pulmonary ventilation, blood concentrations of nicotine, cotinine and carboxyhemoglobin, and mortality.

Under the conditions of these studies, the smoke from the NEW CIGARETTE produced significantly fewer and less pronounced biological effects than did the reference smoke. This was consistent with the Product Development Objectives. Histologic changes in the respiratory tract were either absent or less frequent and less pronounced in the NEW CIGARETTE groups compared to the reference cigarette groups.

Plasma Nicotine in Rats

Because of the design of the NEW CIGARETTE and the much simpler chemistry of its smoke, a study was designed to determine whether nicotine from the NEW CIGARETTE is absorbed, metabolized and eliminated in a similar manner as that from reference cigarettes. Plasma nicotine absorption and nicotine and cotinine elimination were determined and related to pulmonary ventilation patterns and the amount of nicotine in the smoke.

Rats exposed to reference cigarette smoke showed decreased pulmonary ventilation compared to those exposed to NEW CIGARETTE smoke. After corrections were made for the varying amounts of smoke inhaled and differences in pulmonary ventilation, nicotine absorption was slightly higher from the NEW CIGARETTE than from the reference cigarette.

V. HUMAN SMOKING STUDIES

Studies were conducted to compare the NEW CIGARETTE and a reference cigarette with respect to human smoking behavior, nicotine pharmacokinetics and the mutagenicity of human urine. Various factors, including diet, alcohol consumption and use of tobacco products other than cigarettes smoked for the study, were controlled for all subjects.

Human Nicotine Pharmacokinetics and Smoking Behavior

Since the smoke from the NEW CIGARETTE is much simpler than that from cigarettes that burn tobacco, a study was designed to determine whether nicotine from the NEW CIGARETTE was absorbed, metabolized and eliminated by humans in a similar manner as that from other cigarettes. First, a study of the pharmacokinetics of intravenously administered nicotine was conducted to determine the relationship between administered nicotine and plasma nicotine. This was done to provide data required to determine the amount of nicotine absorbed when subjects smoked either the NEW CIGARETTE or the reference cigarette.

The data permitted calculation of the amount of nicotine absorbed while smoking either the NEW CIGARETTE or a reference cigarette, the rate of nicotine elimination, the nicotine plasma clearance, the rate of renal nicotine excretion, the rate of metabolic nicotine clearance and the proportion of nicotine metabolized to cotinine.

Smoking behavior (e.g., number, volume, duration and frequency of puffs) differed between the NEW CIGARETTE[1] and

[1]The NEW CIGARETTE prototype used in these studies was harder for the smoker to draw on than the actual market version. Additionally, only a small sample (40 + smokers) had smoking behavior measured, due to the complexity of such measurements. Finally, as has long been known, such behavioral comparisons have inherent limitations because no two smokers smoke the same way; in fact, no smoker smokes two cigarettes of the same type in exactly the same manner under all circumstances.

the reference cigarette. Smokers took more puffs, closer together in time, from the NEW CIGARETTE than from the reference cigarette. The average volume of individual puffs was the same. The net result was that a larger total volume of smoke was drawn from the NEW CIGARETTE than from the reference cigarette. With both the NEW CIGARETTE and the reference cigarette, the amount of nicotine from the cigarettes was correlated with the total puff volume. With both cigarettes, the amount of nicotine absorbed by smokers was correlated with the total puff volume. However, because of the lower amount of nicotine in the NEW CIGARETTE smoke compared to the reference cigarette smoke, less nicotine was absorbed by smokers smoking the NEW CIGARETTE.

The significant observations from the pharmacokinetic and smoking behavior study were:

1) Subjects smoking the reference cigarette and those smoking the NEW CIGARETTE had similar time patterns of plasma nicotine concentration.

2) Despite the change in smoking behavior, subjects smoking the NEW CIGARETTE always had lower plasma nicotine concentrations because of the smaller amount of nicotine in the smoke of the NEW CIGARETTE.

3) Nicotine elimination was independent of the type of cigarette.

4) There was no difference in the relative amounts of plasma cotinine, the major human nicotine metabolite, formed from nicotine absorbed from the reference cigarette and the NEW CIGARETTE. Cotinine elimination rates after smoking either cigarette were similar.

Human Urine Mutagenicity Studies

The urine of smokers has been reported to be more mutagenic than that of nonsmokers, as measured by the Ames bacterial mutagenicity assay. A study was conducted to determine the mutagenicity of urine from nonsmokers, NEW CIGARETTE smokers and reference cigarette smokers.

The study used a double-crossover design in which the subjects served as their own controls. Two groups of smokers and one nonsmoking group were used.

While the urine of all subjects, smokers and nonsmokers alike, was mutagenic, no mutagenic differences were observed

between the urine of smokers of the NEW CIGARETTE and that of nonsmokers. In addition, urine of smokers was significantly less mutagenic (equivalent to nonsmokers) when smoking the NEW CIGARETTE than when the same subjects smoked the reference cigarette. Data from this study are presented in Figure 4.

FIGURE 4

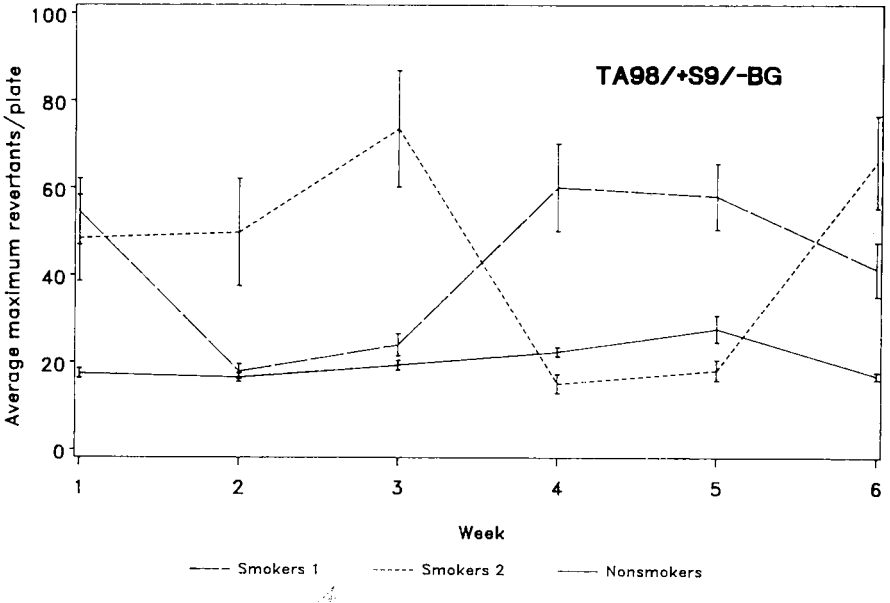

FIGURE 4 On day one, Smokers 1 changed from their regular brand of cigarette to the NEW CIGARETTE and Smokers 2 changed from their regular brand to the reference cigarette. The nonsmokers abstained from all tobacco usage. At week three, Smokers 1 changed from the NEW CIGARETTE to the reference cigarette and Smokers 2 changed from the reference cigarette to the NEW CIGARETTE. At week five, Smokers 2 switched back to the reference cigarette, while Smokers 1 continued to smoke the reference cigarette. The nonsmokers continued to abstain from tobacco products. The data presented used *Salmonella typhimurium* tester strain TA-98 (TA98) with metabolic activation (+ S9). *Beta*-glucuronidase was not included (− BG) in the study presented because it did not increase the sensitivity of the assay.

VI. NEW CIGARETTE COMPONENTS

Consistent with the Product Development Objectives, the components of the NEW CIGARETTE were designed and selected to minimize the potential for biological activity as they are used in the cigarette.

Component Selection Criteria

Components were selected based on their meeting the following criteria:

1) Literature review indicating no or very low known potential for biological activity at the usage levels

2) Evidence of minimal transfer of a chemical or other component to the smoker as measured by aerosol chemistry and other studies

3) A history of use by or exposure to human populations without reported and confirmed adverse effects

4) No evidence of genetic toxicity or adverse biological effects in inhalation studies using NEW CIGARETTE prototypes containing the component.

Following the literature reviews, all components that could be tested in such a manner were subjected to bacterial mutagenicity tests. Examples of components that could not be tested in these *in vitro* assays include aluminum, alumina and the papers. Those compounds found to be mutagenic were rejected. If nonmutagenic, they were subjected to a series of mammalian genetic toxicity assays. Materials found to be positive in any of these assays also were rejected. Glycerol, the principal aerosol-former, was subjected to both short-term and subchronic inhalation studies. All NEW CIGARETTE components were indirectly assayed in a genetic toxicology battery that tested NEW CIGARETTE smoke condensates, and in NEW CIGARETTE smoke inhalation studies. All components used in the NEW CIGARETTE meet the Product Development Objectives. Following are brief descriptions of the major components.

Components

Heat Source:

The heat source is a cylinder made of highly refined carbon. The materials and process used to manufacture it were specifically designed to ensure that the heat source produces

simple combustion products (primarily water and carbon dioxide) and that it minimizes production of carbon monoxide. After it is lit, the heat source produces negligible sidestream smoke and no loose ash.

Insulating Mat:

Surrounding the heat source is an insulating mat of specially designed and manufactured nonrespirable glass fiber. This mat insulates and maintains the integrity of the burning heat source and reduces heat loss.

The NEW CIGARETTE smoke aerosol has been evaluated by scanning electron microscopy, light microscopy and by graphite furnace atomization coupled with atomic absorption. No evidence of fibrous glass has been detected in any of these studies.

Flavor Capsule:

The flavor capsule is an aluminum cylinder that conducts heat and contains *alpha*-alumina substrate spheres. Because of the NEW CIGARETTE's design, smokers are not exposed to metallic aluminum from the capsule. Under normal conditions of use, the aluminum does not melt or degrade, nor can it be dislodged.

Tobacco Roll:

Surrounding the flavor capsule is a tobacco roll. The tobacco roll does not burn, but when heated, releases natural tobacco flavors.

Alpha-Alumina Substrate:

Contained within the aluminum capsule are *alpha*-alumina spheres that act as a porous substrate impregnated with the volatile, smoke-forming components of the NEW CIGARETTE (spray-dried tobacco, glycerol and flavor).

Analysis for aluminum in smoke condensates, within the limits of current methodology, indicates little or no likelihood of *alpha*-alumina occurring in NEW CIGARETTE smoke. A literature review of alumina toxicity revealed that acute, subchronic and chronic effects from inhalation exposures to *alpha*-alumina are minimal or nonexistent.

Spray-Dried Tobacco:

The *alpha*-alumina spheres contain a spray-dried water-extract of tobacco derived from tobacco blends similar to those in other cigarettes. When heated, the spray-dried tobacco releases natural tobacco flavors.

Flavor:

A small amount of added flavor is absorbed in the *alpha*-alumina substrate. When the NEW CIGARETTE is smoked, this flavor enhances the taste and aroma of the smoke.

Flavor selection was restricted to Generally Recognized as Safe (GRAS) materials, U.S. Food and Drug Administration (FDA) approved materials and flavor constituents of cigarette smoke with no known toxicity. In addition to providing the desired taste characteristics, the flavor used and the smoke condensates from NEW CIGARETTE prototypes containing this flavor were not shown to be genotoxic in a profile of *in vitro* genetic toxicity assays.

Glycerol:

Glycerol, the principal smoke-forming component in the NEW CIGARETTE, is contained within the pores of the alumina substrate. It was selected because of its low potential for biological activity, low vapor pressure, stability and taste characteristics. Glycerol is an important ingredient in other cigarettes. However, more is used in the NEW CIGARETTE than in other cigarettes.

Glycerol is a constituent of most foods and is a substrate of cellular metabolism. It is a structural backbone of stored fats in animal and plant cells, and of phospholipids, the principal building blocks of cell membranes in normal cells. Studies in experimental animals and animal tissues indicate that glycerol moves easily across the membranes of lung cells, becoming a part of the body's metabolic glycerol pool.

A review of the extensive body of literature on glycerol and the results of both genetic toxicology and inhalation studies in rats are detailed in this monograph.

Tobacco-Paper Filter:

Behind the aluminum capsule is a tobacco-paper filter made from tobacco and unbleached softwood kraft fiber. The

tobacco paper cools and filters the aerosol, and adds additional natural tobacco flavor to the smoke.

Polypropylene Filter:

Attached to the tobacco-paper filter is an additional filter made from polypropylene that also serves as the mouthpiece for the NEW CIGARETTE.

Polypropylene has been approved by the FDA for a variety of food contact uses. It is also extensively used in medical and pharmaceutical devices and in surgical and other items designed for human contact.

Papers:

The cigarette papers maintain the structural integrity of the NEW CIGARETTE. The outer-wrap is designed to burn back 6-8 mm to simulate the ash of other cigarettes. This small portion of the outer-wrap, and the insulator-mat inner-wrap beneath it, are the only papers that burn.

Adhesives:

Adhesives are used to bond the seams that join the components of the NEW CIGARETTE. When the NEW CIGARETTE is smoked, only a small amount of adhesive is burned (that on the first 6-8 mm of the outer-wrap and the insulation-mat inner-wrap).

Amorphous Silica Gel:

Amorphous silica gel, a nontoxic substance that has many varied uses in the food industry, is used as an aid in manufacturing the NEW CIGARETTE.

VII. ASSESSMENT SUMMARY

The research program summarized above and detailed in the monograph that follows represents an extensive investigation of the chemical and biological characteristics of the NEW CIGARETTE, compared with cigarettes that burn tobacco. The results of these studies indicate that the NEW CIGARETTE meets the specific Product Development Objectives.

How well the overall objective — to provide the tobacco taste and smoking pleasure of other cigarettes — has been met

will be determined in the marketplace. The data in this monograph indicate that the other three objectives have been met:

a) The chemistry of the smoke from the NEW CIGARETTE is much simpler than that of the 1R4F reference cigarette and many compounds involved in the controversy over smoking have been substantially reduced compared to the 1R4F reference cigarette.

b) Biological activity of the NEW CIGARETTE smoke is substantially less than that of reference cigarettes that burn tobacco, as measured by the assays used in the assessment program.

c) By eliminating the burning of tobacco, the NEW CIGARETTE produces negligible sidestream smoke. Both the sidestream smoke and environmental tobacco smoke from the NEW CIGARETTE are much simpler in chemical composition than those from reference cigarettes that burn tobacco.

Contents

SECTION 1.0 THE EVOLUTION OF THE CIGARETTE
(A HISTORICAL PERSPECTIVE)

1.0

The Evolution of the Cigarette (A Historical Perspective)

SUMMARY

As Heimann (1) has stated, "The tobacco tradition, like all mores, is evolutionary rather than revolutionary." The use of smoking materials can be traced back to antiquity. The widespread use of tobacco can be traced to the early New World explorers' discovery of the cultivation and use of tobacco by American Indians. Cigarettes were first made from cigar scraps as an inexpensive substitute for cigars in the 1700s and have gained widespread popularity among smokers. The first cigarette with widespread popularity in the United States was the CAMEL brand introduced by R.J. Reynolds in 1913.

A major innovation in cigarette design took place in 1954 with the introduction of the WINSTON cigarette by R.J. Reynolds. Its major design features consisted of a cigarette filter and the use of reconstituted sheet tobacco. Today filter cigarettes represent the vast majority of market entries and almost all cigarettes contain reconstituted tobacco. Innovations in cigarette design have led to the current mix of cigarette styles, which range from below 1 mg to about 29 mg "tar," as measured by the FTC method.

Even though a number of evolutionary steps in cigarette design have resulted in the development of ultra-low "tar" cigarettes, these cigarettes are only a minor proportion of the current market. To address the demand among smokers for even further reductions in "tar" and yet produce a cigarette that provides flavor and enjoyment to smokers, R.J. Reynolds reexamined cigarette design from a completely different perspective. This led to the design concept of the NEW CIGARETTE. The concept is based upon the same processes that take place in other cigarettes, but without burning tobacco. The process involves generating heat by burning a small, highly refined heat source to produce a smoke aerosol from glycerol and tobacco to duplicate the distillation of flavor from tobacco that occurs in other cigarettes.

A sustained effort was required to develop this design concept into an acceptable cigarette. Along with this effort was the requirement to develop entirely new methodology for the construction of the cigarette. This required experts from many fields to adapt existing methodology to cigarette manufacturing and to create entirely new methods of cigarette manufacture. Only recently has the required technology become available to mass-produce the NEW CIGARETTE, with its innovative design that heats but does not burn tobacco.

1.1 Historical Use of Tobacco

Archaeological studies indicate that smoking is an ancient custom. Various cultures, including the Greek and Roman, smoked pipes 1500 years before the appearance of tobacco. Several different materials were used for smoking, including oak leaves, mistletoe, rhododendron, hemp, menthol, belladonna and lavender (2). The current use of tobacco products can be traced to the Indian cultures first observed by Christopher Columbus during his voyage to the New World in 1492. He reported that natives cultivated tobacco and smoked it in pipes and chewed the leaf. Tobacco was cultivated by the Indians in much the same manner as it is cultivated today (Figure 1.1-1). However, the tobacco plant grown by the Indians was, by current standards, of poor quality with strong organoleptic characteristics.

FIGURE 1.1-1

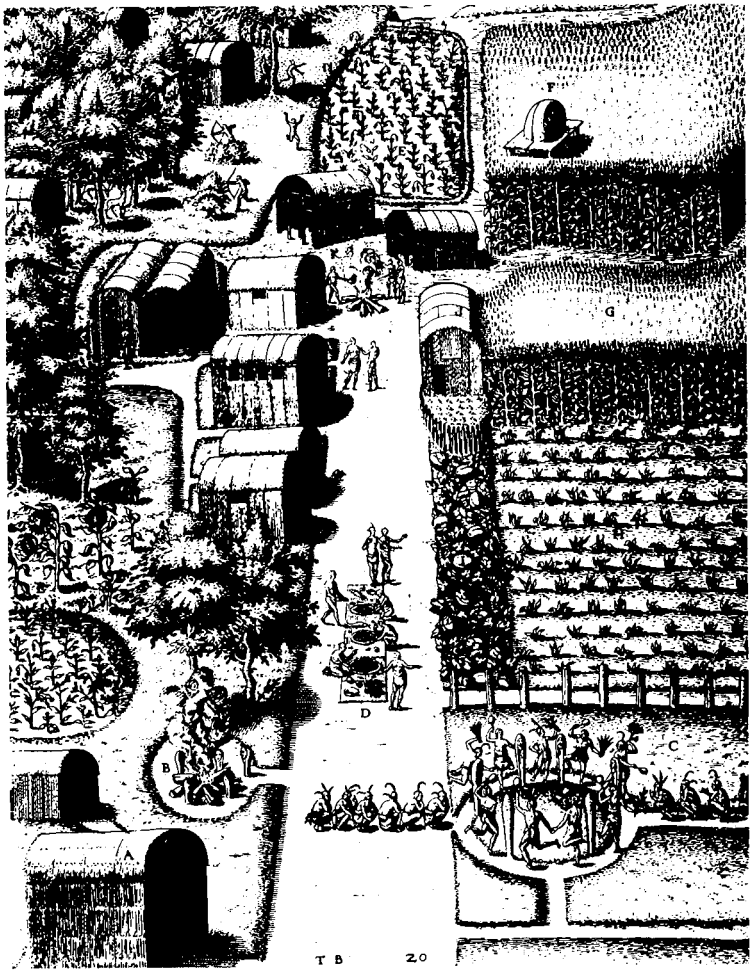

FIGURE 1.1-1 An illustration of Secota, an American Indian village near the coast of North Carolina, drawn in 1587. At the top of the middle section of the drawing is a tobacco field (E). Other crops illustrated include pumpkins (I) and corn (G,H). Used by permission of Arents Collections; The New York Public Library; Astor, Lenox and Tilden Foundations.

By the sixteenth century, tobacco was being used in Europe. Sir Walter Raleigh was a proponent of the smoking of tobacco in pipes, and the practice quickly spread. Commercial cultivation of the leaf in the United States was started through

the efforts of John Rolfe of Jamestown. He obtained seeds of *Nicotiana tabacum,* possibly from the Spanish colonies of Trinidad and Caracas. This plant, combined with the rich soils around Jamestown, led to the production of a highly prized tobacco. Rolfe's first shipment of tobacco to England was in 1613. In 1615-1616, 2,300 pounds of tobacco were shipped to England and by 1620, 40,000 pounds were exported. Growing the leaf became so popular as a source of income that in order to ensure a food supply, the deputy governor ordered each farmer to grow two acres of corn before he could cultivate tobacco.

Cultivation of tobacco quickly spread from the Jamestown area. Delaware was founded expressly to grow tobacco. George Calvert was given a land grant to grow tobacco along the Chesapeake Bay, and this later became the Maryland Colony. England quickly realized the profit potential from tobacco and declared it to be a royal monopoly of the Crown. Further restrictions and taxation of tobacco reduced the colonists' income and played no small part in fostering the American Revolution (3).

1.2 Commercialization of the Cigarette

The smoking of tobacco rolled in paper as a cigarette originated in Central America and had spread to the New Mexico Territory by the time the Santa Fe Trail was opened in the early 1820s. Beginning in the eary 1600s, Seville, Spain, was the first center of the cigar industry, and cigarettes were produced there from cigar scraps beginning in the 1700s. These early cigarettes were used by the poor in lieu of the more expensive cigars. Cigarettes spread in popularity in 1854-1856 during the Crimean War, when they found wide use among the soldiers (1).

Cigarette production in the United States began in the North soon after the Civil War and quickly spread to the South. By 1880, the total annual U.S. cigarette production was a half billion cigarettes. Expansion was hindered by the manual production of only four cigarettes per minute. A revolutionary development took place in 1881 when James Bonsack of Virginia patented the first cigarette-making machine (see Figure 1.2-1). This device could produce 120,000 cigarettes per day (3).

FIGURE 1.2-1

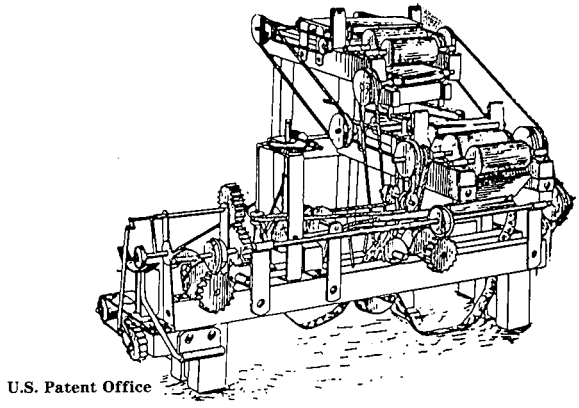

FIGURE 1.2-1 James Bonsack's 1881 patented cigarette machine. Technological advances have increased production from four cigarettes a minute made by hand to 250 a minute by the Bonsack machine to 8,000 a minute by modern cigarette machines.

The classic American-blend cigarette as we know it today was introduced in 1913 as the CAMEL brand by R.J. Reynolds of Winston-Salem, North Carolina (4). Before introduction of CAMEL, most American cigarettes consisted of either Turkish (Oriental) tobaccos or Virginia tobacco (flue-cured). CAMEL introduced a blend composed in most part of flue-cured tobacco mixed with Turkish and burley tobaccos. Flavors were also used to enhance CAMEL's tobacco taste. This product revolutionized the cigarette industry by providing a high-quality product with a superior flavor. Since the introduction of CAMEL, blended tobaccos have been used in virtually all cigarettes manufactured, along with flavors to complement the taste and aroma of the tobaccos.

1.3 Development of Filtered Cigarettes

The cigarette manufactured in the United States in the early 1950s was similar to those manufactured since the introduction of CAMEL. It was an unfiltered cigarette, usually 70 mm in length, containing the so-called American blend, i.e., a blend of flue-cured, burley, Oriental, and Maryland tobaccos. The market consisted of a dozen or so popular brands that produced 2.4-3.0 mg of nicotine in the smoke (as measured by a

procedure similar to the FTC method) and 35-40 mg of "tar." A few filter-tipped cigarettes were in the marketplace, but they constituted only 1-3% of sales. Figure 1.3-1 represents the construction of a classic unfiltered cigarette.

FIGURE 1.3-1

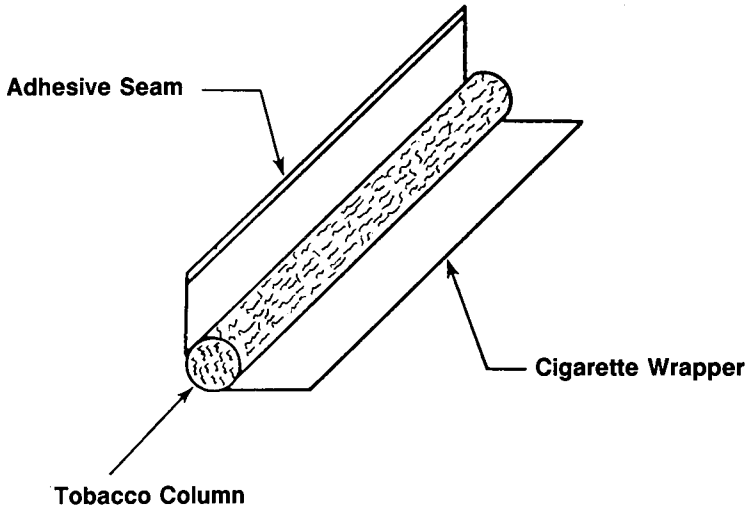

FIGURE 1.3-1 The basic construction of an unfiltered cigarette. The tobacco column or roll is composed of blended, shredded tobacco cut to specific lengths. The paper is wrapped around the column and sealed with an adhesive seam. Modified and used with permission from the Celanese Corporation (20).

In 1954, R.J. Reynolds introduced WINSTON, and this new cigarette was an immediate success. It embodied two major changes from previous cigarettes: first, it was filter-tipped with cellulose acetate as the filter material, and second, the blend included substantial levels of reconstituted tobacco sheet. Reconstituted tobacco is produced by extracting tobacco with water. The cellulose fibers of the tobacco are then used to form a base sheet to which the liquid extract is applied. These changes were gradually adopted and used by most other tobacco companies over the next few years. Today, filter-tipped cigarettes represent about 95% of the market (5), and reconstituted tobacco is used in virtually every cigarette brand on the market. Figure 1.3-2 illustrates the construction of a typical filter cigarette.

FIGURE 1.3-2

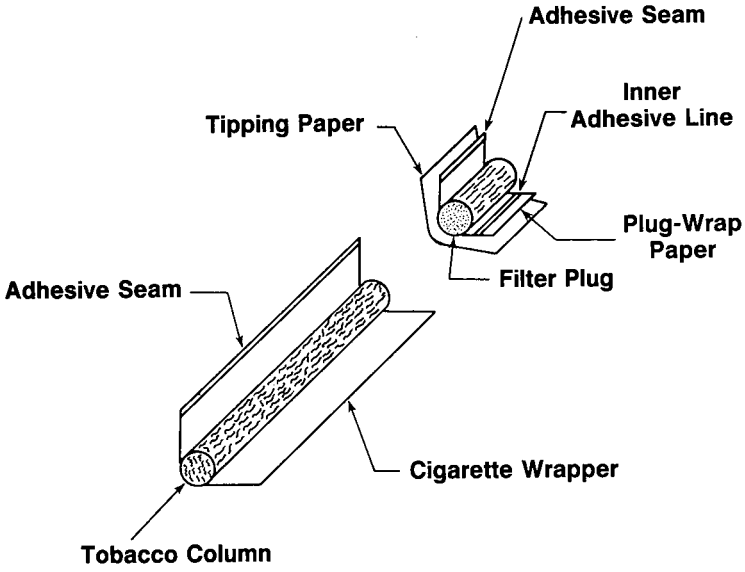

FIGURE 1.3-2 An illustration of a typical filtered cigarette. The "tobacco column" is constructed in a manner similar to the unfiltered cigarette. The filter or "plug" is made from a filamentous material wrapped in a paper "plug wrap." The "filter plug" is connected to the tobacco column by a tipping paper. Adhesives are used to hold the cigarette together. Modified and used with permission from the Celanese Corporation (20).

By increasing the level of reconstituted tobacco sheet and the filter efficiency, "tar" and nicotine levels (on a sales-weighted average basis, i.e., the average "tar" and nicotine level per cigarette sold) were reduced in response to consumer demand (Figure 1.3-3). As demand increased for heavier-bodied (thicker leaved) tobaccos, such as those used in the WINSTON cigarette brand, the supply of this tobacco was insufficient and lighter-bodied tobaccos were added to the heavier-bodied. Subsequent filtered cigarettes included both heavier- and lighter-bodied tobaccos. Since the lighter-bodied leaf has a greater filling capacity and decreases the total quantity of tobacco burned, this allowed further reductions in "tar" and nicotine. Filling capacity is the weight of tobacco needed to make a cigarette at a given firmness.

FIGURE 1.3-3

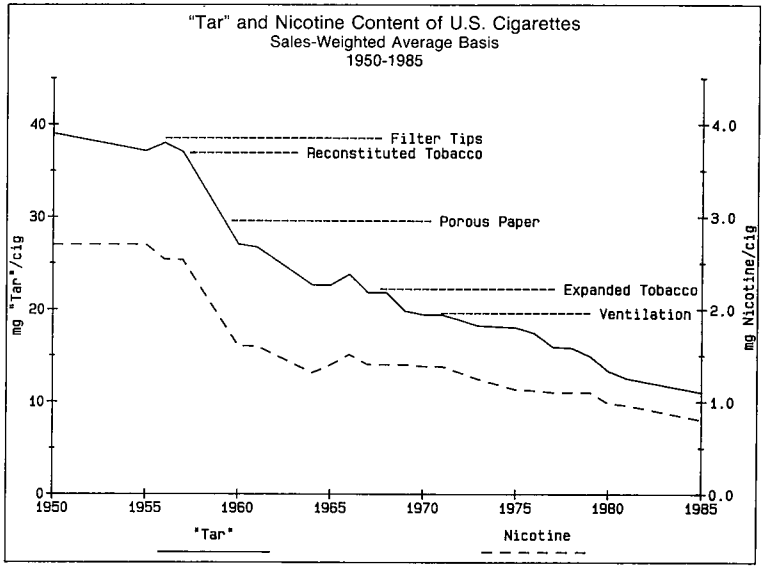

FIGURE 1.3-3 This figure shows the decline in the sales-weighted average "tar" and nicotine values of cigarettes sold in the United States from 1950-1985. The years in which significant technologies were first introduced are indicated.

1.3.1 *Other "Tar" and Nicotine Developments*

Over the years, a number of other product innovations have led to the introduction of cigarettes with increasingly lower "tar" and nicotine levels, as smokers have become more interested in those product characteristics (Figure 1.3-3). In the early 1960s, more porous cigarette paper was introduced; during the late 1960s, expanded or "puffed" tobacco appeared in cigarettes; the early 1970s saw the emergence of ventilated filter tips (Figure 1.3.1-1) as well as the gradual lengthening and increased efficiency of filters. Filter ventilation diminishes the amount of tobacco burned during a puff and dilutes the smoke with fresh air, decreasing "tar" and nicotine.

FIGURE 1.3.1-1

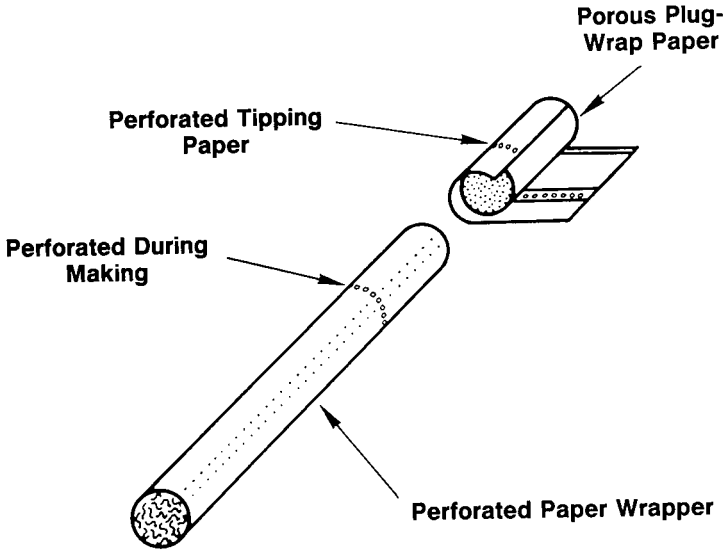

FIGURE 1.3.1-1 The basic construction of the "ventilated" cigarette. Ventilation through either perforation or increased porosity of the cigarette wrapper results in diminished burning of tobacco during the puff. Ventilation of the "wrapper" in front of the filter and ventilation of the "tipping paper"over the "filter plug" result in the air dilution of the smoke. Used with permission from the Celanese Corporation (20).

As consumer preferences have changed over the past 35 years, "tar" and nicotine levels (on a sales-weighted average basis) have been gradually reduced from nearly 37 mg and 2.6 mg, respectively, in 1954, to about 13 mg and 0.9 mg, respectively, in 1986. Cigarettes are now available that range from less than 1 mg to about 29 mg "tar."

1.4 Cigarettes That Burn Materials Other Than Tobacco

The long history of the search for additional types of cigarettes is illustrated by an 1839 U.S. patent suggesting the use of sunflower and rhubarb leaves as tobacco substitutes. Since then, most proposed additional designs have been based on burning natural or processed plant materials as a partial or complete substitute for tobacco filler. The list of alternatives considered includes fillers based on cornstalks, eucalyptus leaves, lettuce leaves, cocoa bean hulls, and many treated wood

and paper products. During both World Wars, large quantities of tobacco substitutes were used, usually mixed with some tobacco. These products were successful not because of taste, which was generally poor, but because the demand for cigarettes outstripped tobacco supplies (2, 6). For example, during the German occupation of Holland in World War II, cigarettes containing beech leaves, dried blackberries and fermented tussilago leaves were sold. The Vichy government in France developed a cigarette containing 65% tobacco, 25% Jerusalem artichoke and 10% chestnut leaves (2). Over the last 25 years, lettuce-based cigarettes were introduced by a number of companies but failed to gain consumer acceptance. R.J. Reynolds is among the many companies that have investigated a wide range of similar tobacco substitutes.

In the 1960s and 1970s, the primary focus of the worldwide search for additional cigarette designs turned to substitute fillers based on wood and paper derivatives. This effort culminated in the development of Cytrel by the Celanese Corporation in the United States and NSM ("new smoking material") by Imperial Tobacco and Imperial Chemical Industries in Great Britain (7, 8). In 1977, cigarettes containing blends of these substitutes with tobacco were unsuccessfully introduced in Great Britain by three leading British tobacco companies: namely, Imperial Tobacco, Gallaher and Rothmans. After six months, the combined market share of these products was only 1.5%, and it sank to well under 1% in less than a year. Within a few years, both Celanese and Imperial closed their production plants. Similar products were unsuccessfully introduced in West Germany by Bayer A.G., a large German-based chemical company, and Reemtsma Tobacco Products and Technology, Germany's largest tobacco manufacturer, as well as by other European companies (9-11).

Over the years, many companies have proposed cigarettes based on carbon. One of the oldest of these, a 2.5-inch-long stick of charcoal that contained a flavoring agent that distilled off during burning, was proposed in a 1959 U.S. patent (12). More recently, in the 1970s and early 1980s, Gallaher Limited, the British subsidiary of American Brands, obtained a series of U.S. patents on carbon-fiber substances impregnated with flavorants and smoke-forming agents (13-16). A number of other tobacco and nontobacco companies have also developed

carbon-based cigarettes over the last 15 years. However, no known commercial product of this type has ever been introduced, probably because of poor taste, potential fire hazards and other technical problems. Still others have proposed cigarettes that burned tobacco but blocked the smoke from reaching the smoker (17), and cigarettes that relied on air passages to reduce the amount of "tar" (18).

These efforts have failed for a variety of reasons. Most substitutes were unable to provide satisfactory tobacco taste. Cigarette fillers based on plant and wood materials also produced many of the same types of combustion products as tobacco or introduced many new compounds into the smoke. Other proposed products did not simulate the appearance or smoke of a cigarette well enough to gain consumer acceptance.

1.5 Development of the NEW CIGARETTE

The NEW CIGARETTE is the most recent of R.J. Reynolds' innovations that have greatly expanded the range of cigarette choices available to smokers. In response to consumer demand for cigarettes with lower "tar" and nicotine, R.J. Reynolds has produced a series of innovative cigarette designs over the past two decades. The success of R.J. Reynolds' ongoing efforts to reduce "tar" and nicotine is illustrated by several statistics. In WINSTON, for example, R.J. Reynolds has reduced "tar" more than 50% since its introduction while maintaining WINSTON's full flavor. In response to consumer demand for ultra-low "tar" cigarettes, R.J. Reynolds developed NOW in 1975 to offer tobacco taste with even lower "tar" and nicotine. Despite R.J. Reynolds' success in preserving cigarette flavor while reducing "tar," there is inevitably a trade-off in reduced flavor in ultra-low "tar" cigarettes. A large portion of today's smokers are unwilling to sacrifice full flavor in return for a cigarette with ultra-low "tar." The "tar" in some ultra-low styles is so low that it cannot reliably be measured by the standard FTC testing methodology (see Section 5.1.1.2). The overall market share of the ultra-low "tar" category peaked at 11% in 1980 and slowly declined to 8% by 1986.

Against this background, it was apparent that, although there was a great deal of demand among smokers for even further reductions in "tar," the ability of existing cigarette

design technology to respond to that demand, while still providing satisfactory flavor, was limited. In addition, increasing pressures were being imposed on smokers over social issues such as environmental tobacco smoke. There was a need for an entirely new approach to cigarette design and development.

R.J. Reynolds' Product Development Objectives for developing the NEW CIGARETTE were as follows:

- To provide the tobacco taste and smoking pleasure of other cigarettes, as demanded by smokers, and to the degree possible, to:

  a) Simplify the mainstream and sidestream smoke chemistry by eliminating or reducing compounds produced by burning tobacco.

  b) Minimize the potential for biological activity, as measured by toxicological assays and tests frequently used to study cigarettes and cigarette smoke

  c) Minimize environmental tobacco smoke and its potential annoyance

After a reexamination of the cigarette from a completely new perspective, the concept for the NEW CIGARETTE was conceived. The ingenious breakthrough that ultimately led to the NEW CIGARETTE occurred in the early 1980s when R.J. Reynolds' researchers discovered that a small carbon heat source, combined with an aluminum heat conductor, tobacco and glycerol, could produce smoke without burning the tobacco. The process by which this prototype functioned was similar to the process by which other cigarettes function, except no tobacco was burned to generate the required heat. (See Section 4.0 for a discussion of smoke formation in both the NEW CIGARETTE and other cigarettes.) The prototype that R.J. Reynolds' scientists constructed at that time was far removed from the final product, but it confirmed that the concept might form the basis for a cigarette that did not burn tobacco.

Even with the initial breakthrough, it took a sustained effort to develop a cigarette configuration suitable for commercial production and marketing. To develop the NEW CIGARETTE, the company brought in scientists, engineers and

consultants with expertise in several technical fields, including carbon production, aerosol release, heat transfer and ceramics. Hundreds of heat-source configurations, flavorants and materials to support the glycerol and tobaccos were evaluated. Outside suppliers were used to help develop the carbon heat source and new insulating materials and cigarette papers. State-of-the-art technology had to be used to fabricate the carbon heat source, the flavor capsule and other components of the cigarette.

Once the final product configuration was decided upon, more than three years were required to refine and test the cigarette, to design and build new production equipment to mass-produce it and to build a production plant. The extent to which the NEW CIGARETTE represents a technical and design breakthrough is illustrated by the number of patent applications (currently more than 20) that have been filed in the United States by R.J. Reynolds. These patent applications cover the cigarette, many of its components, the manufacturing process and the manufacturing equipment. To obtain the broadest patent coverage, R.J. Reynolds sought patent protection for many embodiments of the basic scientific discovery, including uses other than cigarettes. Patent protection also is being sought in more than 110 foreign countries.

The NEW CIGARETTE represents the next step in the evolution of cigarette design. The composition of the NEW CIGARETTE condensate is quite different from that of other cigarettes since tobacco is heated but not burned. Therefore, the NEW CIGARETTE produces little or no "tar" in the classic sense of "tar." This is discussed in detail in Section 4.1.1.1. Moreover, this NEW CIGARETTE design increases the possibilities for further evolution of cigarette design and performance.

1.6 Technological Feasibility of the NEW CIGARETTE

While R.J. Reynolds has historically been a leader in technological innovation in the cigarette industry, there is no doubt that the NEW CIGARETTE represents a very significant breakthrough. Other discoveries and technical advances have reduced "tar" and nicotine levels, but all cigarettes currently on the market burn tobacco. The NEW CIGARETTE does not.

Yet, it provides tobacco taste and enjoyment while preserving the rituals to which smokers have become accustomed.

The NEW CIGARETTE is the end product of an important scientific discovery by R.J. Reynolds in the early 1980s. The discovery of that product concept was the first step in the development of a commercially viable cigarette. Although the product concept had been discovered in the early 1980s, the component manufacturing technology and the cigarette production and packaging technology necessary to bring the NEW CIGARETTE to the market at a competitive price have only recently become available.

With the exception of the tobacco roll, no component of the NEW CIGARETTE was available at R.J. Reynolds or in the market when development of the NEW CIGARETTE began. The fuel element, the insulating jacket, the aluminum capsule, the substrate, the two-stage tobacco-paper/polypropylene filter and the various cigarette papers used in the NEW CIGARETTE were all developed during the course of this project.

Before the NEW CIGARETTE, no one had ever mass-produced a carbon product with the material properties, intricate hole configuration and tight tolerances of the NEW CIGARETTE heat source. The same is true of the thin-walled aluminum capsule, with its light weight, thickness tolerances and severe (30 mm-4.5 mm) length-to-diameter ratio. The *alpha*-alumina substrate likewise went a step beyond the *gamma*-alumina beads first developed for the auto industry in the mid-1970s for use in catalytic converters.

In these and other fields, significant technological advances were achieved with the development of the components of the NEW CIGARETTE. The same is true of the product assembly equipment used by R.J. Reynolds to produce the NEW CIGARETTE. All were specially developed, using computer-controlled machine tools, electronic segment-control innovations and state-of-the-art design techniques.

Importantly, R.J. Reynolds had to have a final cigarette design and components that could be mass-produced at low unit costs that would enable it to compete with other cigarette brands. The outside component and manufacturing equipment suppliers, along with R.J. Reynolds' research personnel and consultants, have achieved this goal at an enormous effort by the company.

How well the first Product Development Objective of providing the tobacco taste and smoking pleasure of other cigarettes has been met will be determined in the marketplace. However, the data in the following sections of this monograph clearly show that the other objectives have been met. Section 4 covers the simplified smoke chemistry and the reduced ETS of the NEW CIGARETTE as compared to a reference cigarette. Sections 5, 6 and 7 cover the reduced biological activity of the NEW CIGARETTE as compared to reference cigarettes.

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17) Ellis, C. D.; Dean, C.; Schachner, H.; Williamson, D. Smoking Device. U.S. Patent 3,258,015, 1966.
18) Helms, E. B. Smokers Draft Tube. U.S. Patent 2,349,551, 1944.
19) Hunt, F. J. Smoking Articles. U.S. Patent 3,863,644, 1975.
20) Browne, C. L. *The Design of Cigarettes.* Celanese Corporation, Charlotte, NC, 1981.

18) Helms, E. B. Smokers Draft Tube. U.S. Patent 2,349,551, 1944.
19) Hunt, F. J. Smoking Articles. U.S. Patent 3,863,644, 1975.
20) Browne, C. L. *The Design of Cigarettes.* Celanese Corporation, Charlotte, NC, 1981.

Contents

SECTION 2.0 CONCEPT AND COMPONENTS OF THE NEW CIGARETTE

2.0

Concept and Components of the NEW CIGARETTE

SUMMARY

The NEW CIGARETTE is based on a concept that allows a smoker to receive the tobacco taste, sensations and enjoyment of cigarettes without burning tobacco. The smoker lights and smokes the NEW CIGARETTE in a similar manner as other cigarettes.

The major components of the NEW CIGARETTE are tobacco, a carbon heat source, an aluminum capsule, spray-dried tobacco, glycerol, flavor, a tobacco-paper filter, a polypropylene filter and several sections of paper. Manufacture of the cigarette required a number of significant innovations both in the design and production of components and in the design of machines to make the cigarette.

This section presents the concept on which the NEW CIGARETTE is based, describes how the cigarette functions and describes the physical and chemical characteristics of the components in the NEW CIGARETTE. In many cases, a brief description of the manufacturing process is included.

Although there are a few references to the biological activity of certain components in this section, a detailed discussion of the biological activity of all components is presented in Section 8.

Based on literature reviews, toxicology studies conducted both at R.J. Reynolds and at independent contract laboratories, and an evaluation of the chemistry of the components and the smoke from the NEW CIGARETTE, the use of the components selected for the NEW CIGARETTE is consistent with achieving its Product Development Objectives (Section 1.5).

2.1 Concept of the NEW CIGARETTE

The NEW CIGARETTE is similar to other cigarettes in that it requires tobacco for taste and enjoyment. It is evolutionary in that it heats tobacco rather than burns it to release flavor. This is accomplished by applying enough controlled heat to warm the tobacco and release volatile, flavorful components, but not enough heat to burn and decompose the tobacco. The flavors are in an aerosol similar in appearance to the smoke produced by other cigarettes. This is accomplished by applying heat to a volatile liquid so that the liquid vaporizes and cools to form an aerosol. Three fundamental components are therefore necessary in the cigarette:

1) Tobacco
2) A volatile liquid to form the aerosol or smoke
3) A source of heat to warm the tobacco and vaporize the volatile liquid.

2.2 Illustration of the NEW CIGARETTE

A cross-sectional view of the NEW CIGARETTE is shown in Figure 2.2-1. The carbon heat source is inserted into an aluminum capsule. The aluminum capsule contains porous *alpha*-alumina spheres that are referred to as the substrate. The alumina substrate is impregnated with glycerol, spray-dried tobacco and flavor.

FIGURE 2.2-1

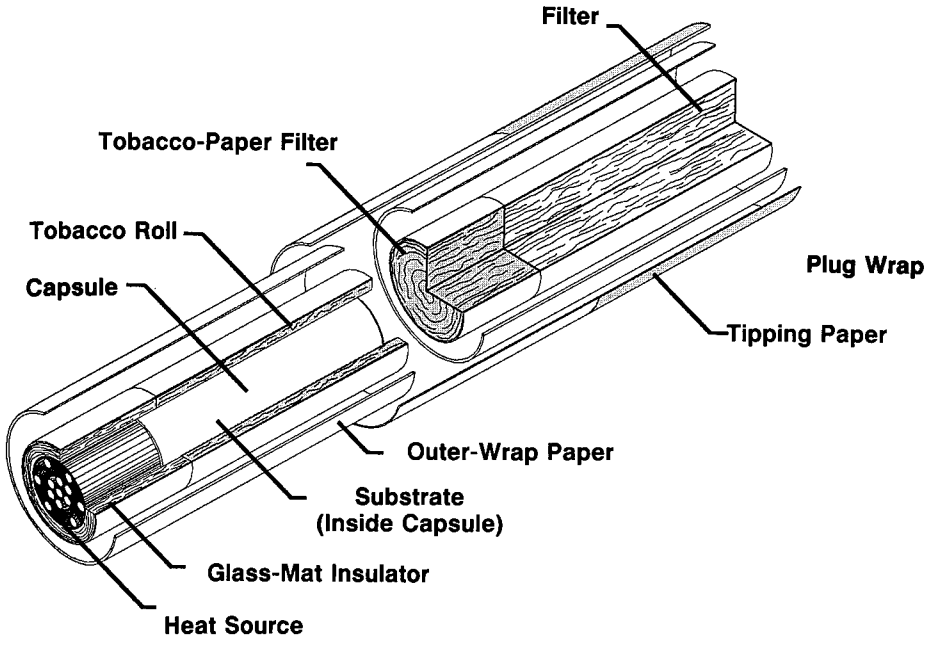

FIGURE 2.2-1 An illustration of the NEW CIGARETTE, diagramming its overall construction and its components.

The heat source is surrounded by a glass-mat insulator, and the capsule is surrounded by a roll of tobacco. An outer-wrap paper holds the heat source, glass mat, capsule and tobacco roll together forming the front portion of the cigarette. This front portion is connected to the mouth-end piece of the cigarette by another piece of paper termed tipping paper. The mouth-end piece is comprised of a tobacco-paper filter followed by a polypropylene filter. The function and composition of all components of the NEW CIGARETTE are described in detail in the following sections.

2.3 Performance of the NEW CIGARETTE

As the smoker lights the cigarette, the heat source ignites and begins to burn. With each puff, a portion of the incoming air is drawn through the passageways in the heat source and heats the aluminum capsule. The heat is transferred to the tobacco roll and the alumina substrate both during puffing and between puffs. Another portion of the incoming air is heated by the heat source. It passes through the glass mat and heats the tobacco roll directly. The heat transferred to the alumina substrate is sufficient to vaporize the glycerol, added flavor and the natural flavors, including nicotine, of the spray-dried tobacco. The heat transferred to the tobacco roll is sufficient to vaporize its natural flavors, including nicotine.

As the hot vapors exit the rear of the capsule and the tobacco roll, they enter the tobacco-paper filter, where they begin to cool. The less volatile components condense to form very small liquid particles. These small particles and the vapor in which they are entrained constitute the smoke that then passes through the polypropylene filter and out of the cigarette. This smoke provides the taste, sensations and enjoyment of other cigarettes without burning tobacco.

During smoking, the only parts of the cigarette that burn are the carbon heat source and a small amount of paper around the end of the cigarette. When the carbon burns, the major products are water and carbon oxides. Therefore, after the lighting puffs, virtually no sidestream smoke is emitted from the lit end of the NEW CIGARETTE when compared to other cigarettes. Since the tobacco and other components do not burn, the NEW CIGARETTE does not burn down and produce loose ash as do other cigarettes.

The insulator mat and paper that surround the heat source simulate the ash and fire cone of other cigarettes. The insulator mat also insulates the heat source, improving performance and lowering the propensity for this cigarette to accidentally ignite combustible substances it may contact.

2.4 Carbon Heat Source

2.4.1 *Function*

The heat source is necessary to heat the tobacco roll, the spray-dried tobacco, flavors and glycerol. It is specially designed for controlled heat transfer. Other than a small

amount of paper, it is the only component in the cigarette that burns. Carbon was selected as the heat source because of its simple products of combustion.

2.4.2 *Composition*

Very pure carbon and a sodium carboxymethylcellulose binder are the major raw materials used to make the NEW CIGARETTE heat source. The heat source is manufactured by extrusion of a mixture of water, carbon powder and sodium carboxymethylcellulose. The extruded material is cut into 10-mm sections that are dried and baked at a temperature in excess of 800°C. This process carbonizes the sodium carboxymethylcellulose binder and any potential residues of organic compounds. The structure of the heat source used in most of the studies reported in this monograph is shown in Figure 2.4.2-1.

FIGURE 2.4.2-1

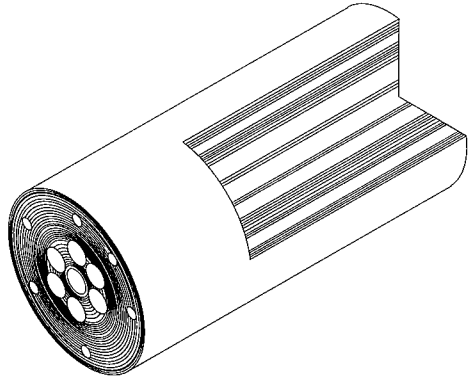

FIGURE 2.4.2-1 An illustration of the carbon heat source used in the NEW CIGARETTE. The heat source illustrated was used in most of the studies reported in this monograph. The cutaway illustrates the holes that pass through the heat source.

A review of the biological activity of carbon indicates its use is consistent with achieving the Product Development Objectives of the NEW CIGARETTE as described in Section 1.5.

2.5 Glass-Mat Insulator

2.5.1 *Function*

The glass-mat insulator insulates the heat source, reduces heat loss to the surrounding air, reduces propensity for the NEW CIGARETTE to ignite other materials, and enhances performance by directing heat flow into the capsule and the tobacco roll. Figure 2.2-1 illustrates the location of the glass-mat insulator in the cigarette.

2.5.2 *Composition*

The glass-mat insulator is made from glass fibers with an approximate average diameter of 8 μm. Respirable fibers are defined as those with a diameter $\leq$ 3 μm and up to 100-200 μm in length (1,2). Therefore, as defined by the World Health Organization and others, the diameter of the fibers in the glass-mat insulator exceed the respirable range. Figure 2.5.2-1 is a distribution plot of the fiber diameter for the glass mat. The glass-mat insulator consists of a specially designed glass manufactured by high temperature fusion of silicon dioxide and other materials. The inorganic raw materials used to manufacture the glass are similar to those used to prepare commonly encountered glass materials. Table 2.5.2-1 illustrates the general composition of several glasses in comparison to that used in the glass mat. Although the chemical composition of the glass in the glass mat is similar to that used in insulation fiberglass, the glass mat has a unique physical structure producing the required characteristics, as discussed below (see Section 8.2.1 for comments on the physical properties relative to the biological activity of fibers). Also, the glass fibers in the insulator mat of the NEW CIGARETTE are not coated with the binders used in insulation fiberglass. All glass contains varying levels of inorganic adventitious materials, generally oxides. To ensure that these materials are maintained at low levels, R.J. Reynolds has imposed limitations as part of the glass specifications. These limitations are detailed in Table 2.5.2-2.

FIGURE 2.5.2-1

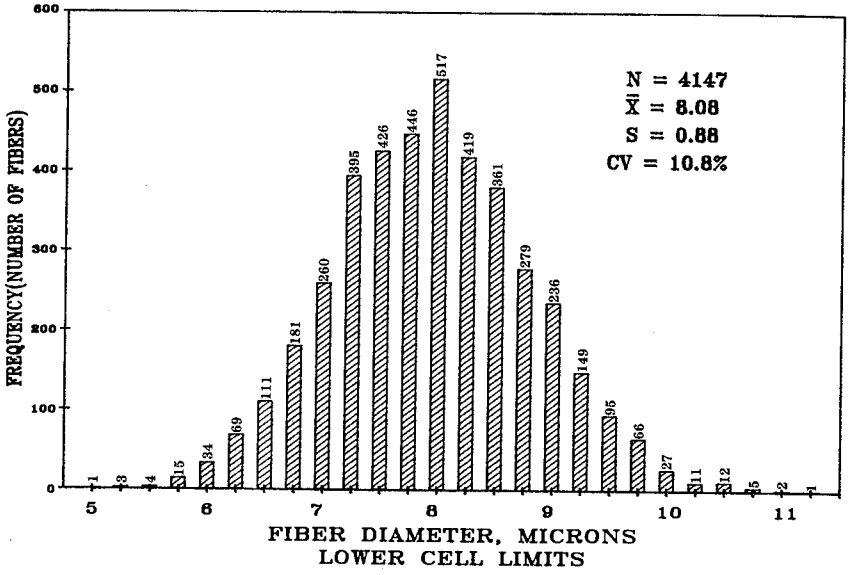

FIGURE 2.5.2-1 Plot of mean glass fiber diameter from production between November 1987 and March 1988 illustrating the lack of fibers below 3 um.

N = Sample size
$\overline{X}$ = Mean
S = Standard deviation
CV = Coefficient of variation

TABLE 2.5.2-1 Chemical Composition of Glass-Mat Insulator Compared to Other Common Glasses (Wt.%)[a]

Constituent	Glass Mat	Insulation Fiberglass	Structural Fiberglass	Tempered Ovenware	Glass Containers
SiO_2	65	65	53	75	70
Al_2O_3	4	4	14	1.5	3
B_2O_3	5	5	8	—	—
Na_2O	9	9	0.2	14	14
CaO	14	14	19	9.5	6

[a]Difference between total Wt.% presented and 100% represents minor constituents not listed in table.

TABLE 2.5.2-2 Maximum Levels of Specific Inorganic Oxides Allowed in the Glass for the Glass-Mat Insulator[a]

INORGANIC OXIDE	TARGET (% composition)	TARGET (ug oxide/g of glass)
SO_3	< 0.090	< 900
Cr_2O_3	< 0.015	< 150
NiO	n.d.[b]	n.d.
CdO	n.d.	n.d.
As_2O_3	< 0.008	< 80
V_2O_5	None	None
Li_2O	< 4	< 4,000
PbO	< 0.005	< 50

[a]Target values set by R.J. Reynolds for maximal levels of inorganic oxides
[b]Below limits of detection is represented by n.d.

After the raw materials are fused into molten glass, the glass is extruded into glass strands. Unlike production of insulation fiberglass, this process is carefully controlled to maintain a constant average strand diameter of approximately 8 μm. The continuous strand is chopped to a uniform 9.5 mm length for mat manufacture.

Mat manufacture is similar to other continuous sheet processes, such as those used in the paper industry. Proprietary processing aids are used in the production of the mat. The supplier has provided R.J. Reynolds with the potential residue levels that could occur on the glass mat. Even though these levels are probably exaggerated, they have been used in assessing the potential biological activity under the conditions of use

of the cigarette. Several of these materials are GRAS food substances. Others are currently used in the production of consumer products. Toxicological reviews of these compounds indicate that under the conditions and levels of use, they are consistent with achieving the design objectives for the NEW CIGARETTE (Section 1.5). For example, chemicals for which an accepted daily intake (ADI) has been established by governmental agencies occur at levels below the ADI with an additional 100-fold safety factor imposed upon the ADI. The mat also contains less than 5% pectin as a binder.

Figures 2.5.2-2 and 2.5.2-3 are photomicrographs of the glass-mat insulator. Both the uniformity of the fibers and the fiber size are apparent. At the higher magnification (Figure 2.5.2-3), sheets of pectin binder are evident. The glass strands appear to have lengths of hundreds of microns.

FIGURE 2.5.2-2

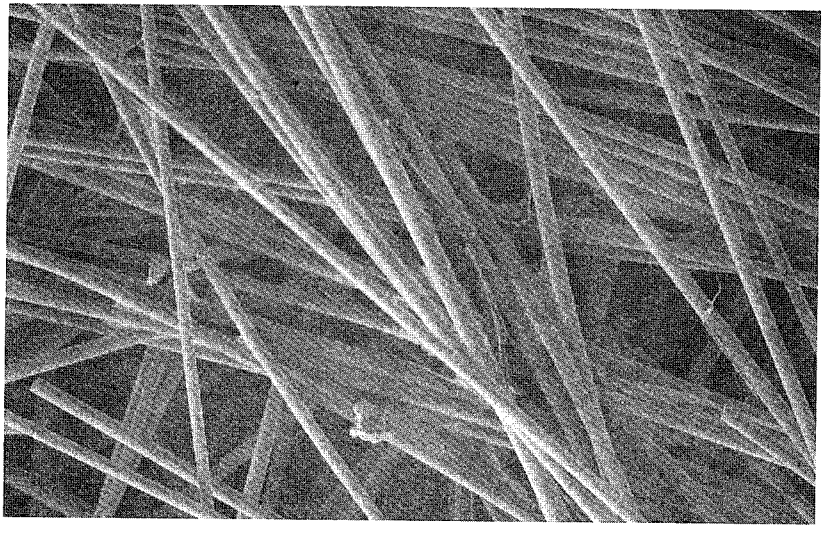

FIGURE 2.5.2-2 Photomicrograph of the glass fibers used to construct the glass-mat insulator used in the NEW CIGARETTE. Note the uniformity of fiber diameter.

FIGURE 2.5.2-3

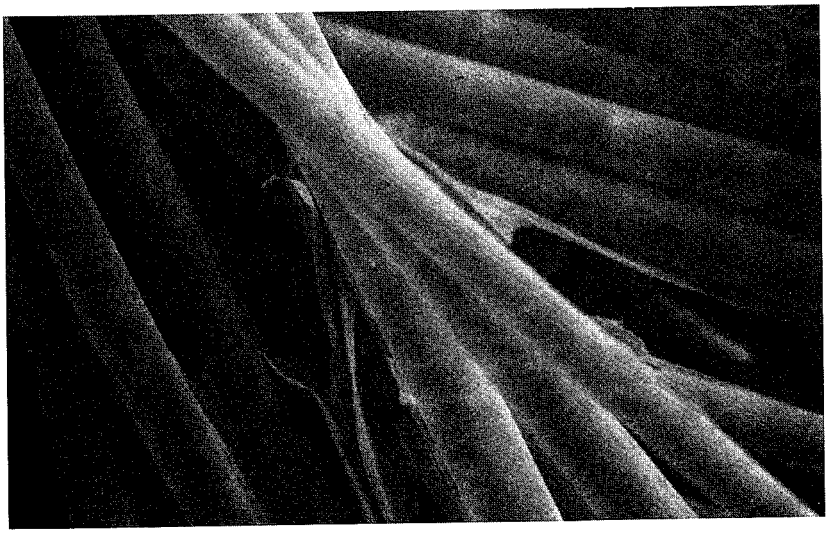

FIGURE 2.5.2-3 Photomicrograph at higher magnification of the fibers used to construct the glass-mat insulator used in the NEW CIGARETTE. The sheets of pectin binder can be seen between the strands of glass.

Although the fibers in the glass-mat insulator belong to the broad class of man-made vitreous fibers (MMVF) known as glass fibers, they are different from those in fiberglass. As illustrated in Table 2.5.2-1, the sodium oxide content of the mat glass is 45 times that employed in the manufacture of fiberglass destined for structural use. The fibrous glass used in the mat has a larger diameter and is much more consistent in diameter than insulation fiberglass because it is extruded. There is less propensity for dermal irritation when compared to insulation fiberglass because there are fewer broken ends. The glass has a soft, uniform feel, unlike the rigid, coarse, highly variable insulation fiberglass. Also unlike insulation fiberglass, the glass fibers used in the NEW CIGARETTE are not coated with chemical resins, such as phenol formaldehyde, commonly used on insulation fiberglass.

The biological activity of glass fibers is reviewed in detail in Section 8.14.1. This review indicates that the use of the glass-mat insulator is consistent with achieving the Product Development Objectives for the NEW CIGARETTE (Section 1.5).

2.6 Aluminum Capsule

2.6.1 *Function*

The aluminum capsule, illustrated in Figure 2.6.1-1, serves many functions. It contains the substrate material, holds the heat source and provides conductive heat transfer. Its ability to transfer heat conductively, both during the puff and between puffs, is an important element of the cigarette's heat-transfer system. This ensures that sufficient heat exists to vaporize the glycerol, spray-dried tobacco components and flavors in the capsule, and to heat the tobacco surrounding the capsule.

PLATE 2.6.1-1

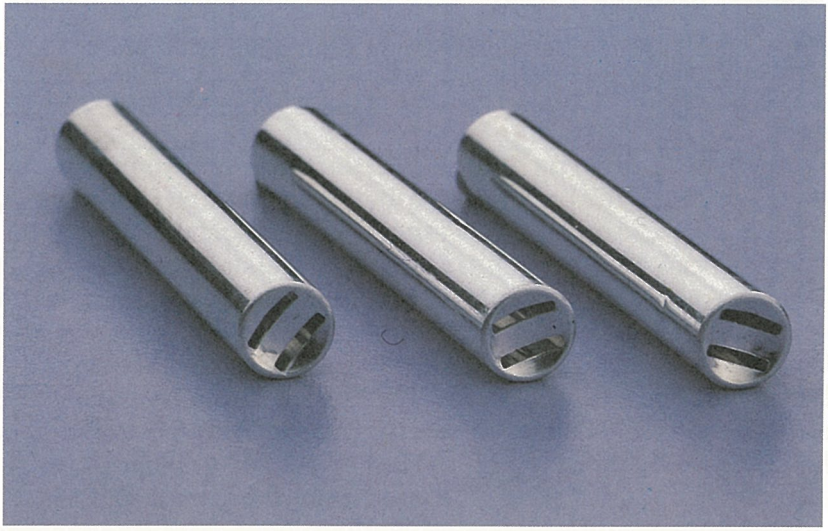

PLATE 2.6.1-1 Photograph of the aluminum capsule used in the NEW CIGARETTE. The capsule is a hollow tube closed at one end. Two slits are made in the closed end of the capsule.

The biological activity of aluminum is reviewed in Section 8. This review indicates that the use of aluminum is consistent

with achieving the Product Development Objectives for the NEW CIGARETTE (See Section 1.5).

2.6.2 *Composition*

The capsule may be made of either of two government numbered alloys: Alloy 3003 or Alloy 1100. Typical applications for both alloys are found where good formability and high corrosion resistance are required. These include cooking utensils, and food handling and storage containers, among others. Alloy 3003 has a density of 2.73 gm/cm^3 at 20°C and melts at 654°C. The corresponding values for Alloy 1100 are 2.71 gm/cm^3 and 657°C. The chemical composition limits for these alloys, according to U.S. government specifications, are presented in Table 2.6.2-1.

TABLE 2.6.2-1 Chemical Composition Limits For Aluminum Alloys[a]

	% Composition Limits	
Element	3003	1100
Al	—[b]	99 min
Mn	1.5 max 1.0 min	0.05 max —
Si	0.6 max	1.0 max
Fe	0.7 max	combined
Cu	0.2 max	0.2 max
Zn	0.1 max	0.1 max
Other Elements	0.15 Total	0.15 Total

[a]Source: Lyman, T., editor. Metals Handbook, 8th Ed., Vol. 1, Properties and Selections of Metals. Metals Park, Ohio: American Society for Metals; 1961: p. 936-940.
[b]Aluminum content not formally specified.

The capsule is manufactured by a specially developed metal-drawing process. To remove potential residues, the capsules are washed in a highly volatile, inert solvent.

2.7 Alumina Substrate

2.7.1 *Function*

The substrate is the material within which glycerol, flavors and spray-dried tobacco are absorbed. It is composed of porous, *alpha*-alumina spheres. They are maintained within the capsule by the heat source. The volatile aerosol-forming materials reside within the pores of the alumina until sufficient heat is delivered for vaporization. The alumina itself is

thermally stable and readily withstands the temperatures to which it is exposed. The use of *alpha*-alumina has been carefully reviewed for potential biological activity under the conditions of use and found to be consistent with the Product Development Objectives of the NEW CIGARETTE (see Section 1.5). The review is presented in Section 8.14.3.

2.7.2 *Composition*

Alumina is a form of aluminum oxide with the chemical formula Al_2O_3 (CAS# 1344-28-1) and a molecular weight of 101.94. It is 52.91% aluminum and 47.08% oxygen. In nature, it occurs in hydrated forms such as bauxite, bayerite, boehmite, diaspore and gibbsite. Naturally occurring *alpha*-alumina is known as corundum.

Excluding the hydrated species, alumina can exist in eight forms: *alpha, chi, eta, delta, iota, theta, kappa* and *gamma*. Only the *alpha* form is used in the NEW CIGARETTE. *Alpha*-alumina is a stable phase of aluminum oxide (Al_2O_3) having a rhombohedral crystalline lattice. The structure essentially consists of hexagonally packed oxygen ions forming layers parallel to the lattice plane. Generally speaking, the crystalline arrangement consists of alternating layers of oxygen and aluminum ions in which the coordination number of the aluminum ion is six. The structure is extremely stable and does not change over a temperature range from 25°C to at least 2000°C. Its melting point is 2015°C and its boiling point is 2980°C. Figure 2.7.2-1 is a magnified view (10X) of the alumina spheres used in the capsule. Figure 2.7.2-2 is an electron micrograph illustrating the microstructure of the sphere surface. At the 10,000X magnification, the *alpha*-alumina structure and the pores in the spheres are apparent.

FIGURE 2.7.2-1

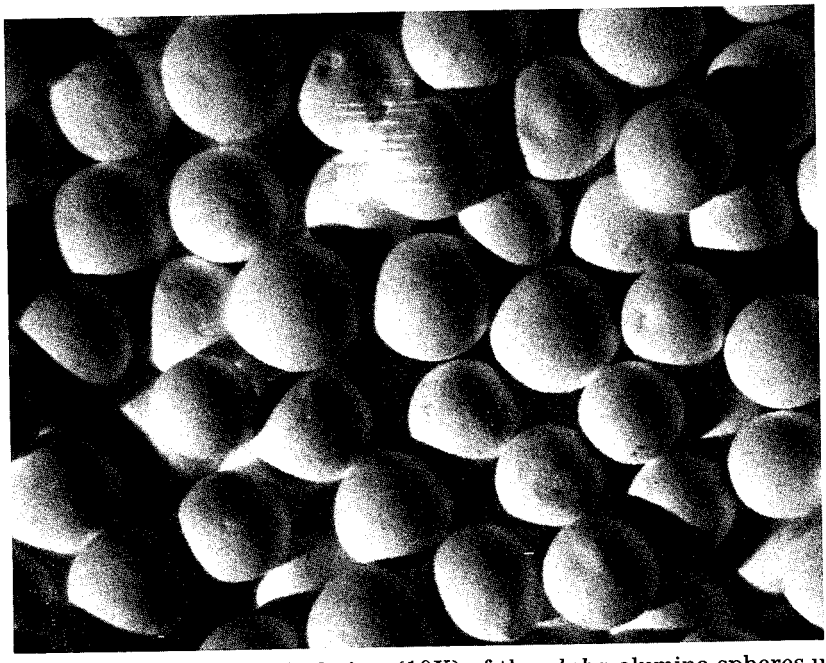

FIGURE 2.7.2-1 A magnified view (10X) of the *alpha*-alumina spheres used in the capsule of the NEW CIGARETTE.

FIGURE 2.7.2-2

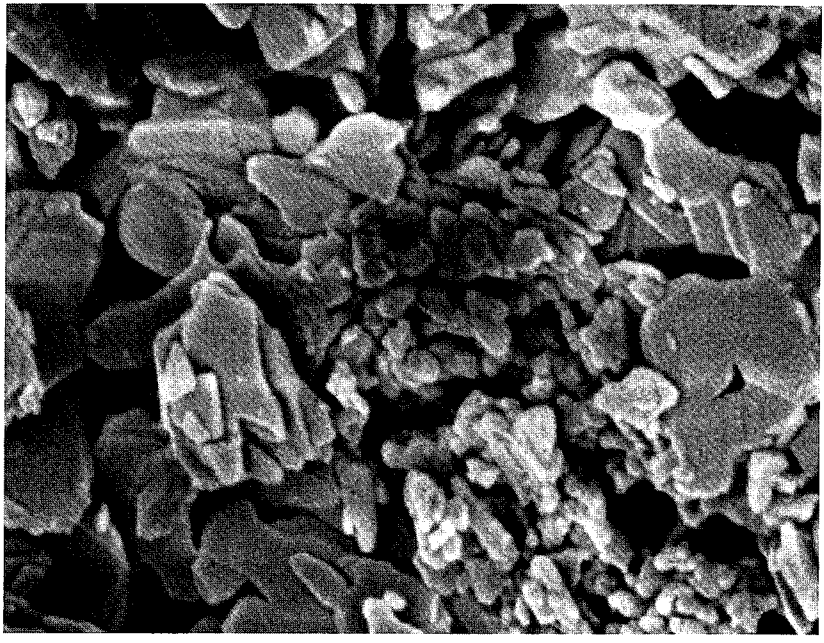

FIGURE 2.7.2-2 A magnified view (10,000X) of an *alpha*-alumina sphere used in the NEW CIGARETTE. Note the porous structure of the sphere.

The *alpha* form of alumina is produced for R.J. Reynolds by independent contractors using proprietary processes involving sintering at much higher temperatures than those produced by the hot gases from the heat source. R.J. Reynolds' specifications for *alpha*-alumina spheres exclude the presence of the *beta* or *gamma* forms of alumina, since *gamma*-alumina has been reported to be fibrogenic in some animal studies. The alumina spheres used in the cigarette are subject to the additional specifications of at least 94% *alpha*-alumina and no more than 6% mullite. Mullite is a compound of Al_2O_3 and SiO_2. The silicon dioxide reacts with the alumina and is bound into a specific crystalline structure. The total silicon level is specified at no greater than 2%. No "free" silicon dioxide is permitted and none has been detected by use of X-ray diffraction techniques. The spheres do not transform chemically, disintegrate physically or emit particles upon being subjected to heat in the

cigarette. Any particles that might occur through either breakage or other process should be filtered by the tobacco-paper plug and polypropylene filter.

2.8 Silica Gel

2.8.1 *Function*

Amorphous silica gel is used as a manufacturing aid with the alumina substrate. Silica gel was chosen because of its performance and its low potential for biological activity. The amount of silica gel is less than 2.5 mg silica gel/capsule.

2.8.2 *Composition*

Silica gel is made by reacting a soluble alkali silicate with an acid. This results in a hydrogel that is approximately 70% water and silicon dioxide; sodium sulfate is a by-product. The hydrogel is washed to remove the salt and then dried and ground into a fine powder. The powder contains 96% silicon dioxide as a minimum and approximately 0.7% sodium oxide and 0.5% sodium sulfate. The level of trace impurities, such as calcium, magnesium and iron, depends on the purity of the starting material. There is no crystalline silica in the silica gel.

The biological activity of silica gel is reviewed in Section 8.14.6. This review indicates that silica gel, under the conditions of use in the NEW CIGARETTE, is consistent with achieving the Product Development Objectives for the NEW CIGARETTE (see Section 1.5).

2.9 Spray-Dried Tobacco

2.9.1 *Function*

The spray-dried tobacco, together with the tobacco roll and tobacco-paper filter, provides the taste, smoking sensations and enjoyment similar to that from other cigarettes. The spray-dried tobacco is applied to the substrate along with glycerol and added flavors. During smoking, heat provided by the heat source volatilizes the flavors, including nicotine, in the spray-dried tobacco. These tobacco flavors become part of the smoke. The use of spray-dried tobacco is consistent with the Product Development Objectives of the NEW CIGARETTE, and makes an essential contribution to the tobacco taste and flavor of the NEW CIGARETTE. PLATE 2.9.1-1 illustrates the spray-dried

tobacco and the *alpha*-alumina spheres after the addition of the spray-dried tobacco.

PLATE 2.9.1-1

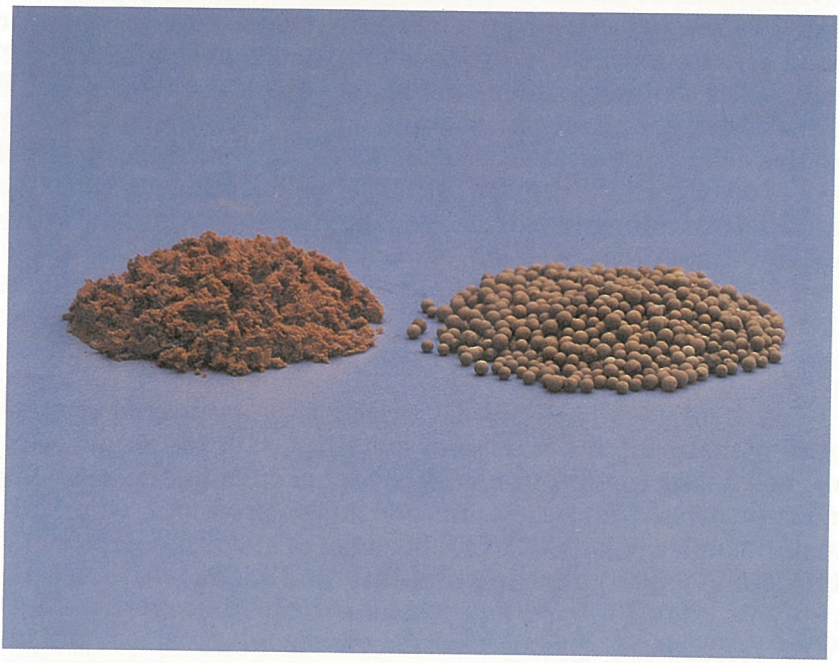

PLATE 2.9.1-1 The spray-dried tobacco is shown on the left in this photograph. The tobacco has the consistency of a fine powder. The *alpha*-alumina substrate, after the application of the spray-dried tobacco and glycerol, is shown on the right. The spray-dried tobacco is adsorbed into the alumina.

2.9.2 *Composition*

The raw materials for the spray-dried tobacco can be any of several tobacco blends. The choice of blend is based on the smoking quality of the cigarette as determined by a sensory panel. To produce the spray-dried tobacco, a blend of cut tobacco is slurried in water and filtered. The filtrate is put through a commercial spray-drying unit to produce the final product, a powder that looks and smells very much like finely ground tobacco. The extraction and spray-drying processes produce a tobacco from which the cellulose and other water insoluble materials have been removed. This is important since the cellulosic materials cannot withstand the temperatures

inside the capsule without decomposing and producing an off-taste.

The process of extracting tobacco with water and other solvents has been used in the cigarette industry for many years. Reconstituted tobacco, used in virtually every cigarette brand on the market, is produced by extracting tobacco with water. The cellulose fibers are used to form a base sheet to which the liquid extract is applied and then dried. The end product is a "regenerated" or "reconstituted" tobacco. The process used for the NEW CIGARETTE is the same, except the liquid extract is spray-dried and applied to an alumina base instead of cellulose.

2.10 GLYCEROL

2.10.1 *Function*

Glycerol is the NEW CIGARETTE's principal aerosol-forming material and is a major constituent of the smoke. Glycerol has a long history of use in the tobacco industry, as well as in many other industries and consumer products. Glycerol is used in the NEW CIGARETTE because of its organoleptic characteristics, vapor pressure, stability and history of use.

2.10.2 *Composition*

Glycerol (CAS #56-81-5) (glycerin; 1, 2, 3 propanetriol; trihydroxypropane) is a three-carbon trihydric alcohol with the chemical formula $CH_2OH\text{-}CHOH\text{-}CH_2OH$. Occurring extensively in nature, glycerol is a neutral, colorless, syrupy liquid that has a sweet taste. It is hygroscopic and miscible with water and alcohol, but is insoluble in chloroform, ether, and both fixed and volatile oils. Glycerol has a molecular weight of 92.08; its specific gravity is approximately 1.25 (at 95% concentration); it boils at 290°C at atmospheric pressure.

Glycerol is a natural constituent of both animals and plants. Many foods consumed by humans and food-producing animals contain glycerol in the form of glycerides, i.e., triglycerides. Glycerol moieties are the building blocks used by animals and plants to synthesize more complex lipid structures, such as the triglycerides and phospholipids. Animal and vegetable fats contain about 10% by weight of glycerol.

Glycerol has a long history of use by humans in medicinal drugs applied topically, inhaled, instilled and ingested. It is

also used in intravenous medical therapy. It is used as a food ingredient and in cosmetics and tobacco products. Its safety for use in foods has been reviewed extensively as part of FDA's review of food substances that are Generally Recognized As Safe (GRAS). In 1975, the Federation of American Societies for Experimental Biology (FASEB) (3) prepared a review for the FDA. This was followed in 1984 by a review by the Flavor Extract Manufacturers' Association of the United States (4). The use of glycerol is approved by FDA either as GRAS or by regulation under Title 21, *Code of Federal Regulations.*

Genetic toxicology studies and subchronic inhalation studies on glycerol, either performed or supported by R.J. Reynolds, are discussed in Section 8.14.4.1 along with a comprehensive literature review in Section 8.14.4.2. The data in Section 8 indicate that the use of glycerol is consistent with achieving the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

2.11 FLAVOR

2.11.1 *Function*

A small amount of flavor is added to the NEW CIGARETTE to enhance the taste of its tobacco components and to provide a pleasing aroma to the smoke aerosol. In this respect, the NEW CIGARETTE flavor helps provide the smoker with the taste, sensations and enjoyment of other cigarettes. The flavor is located primarily in the alumina substrate, but the tobacco roll and tobacco-paper filter may optionally contain added flavor. As heat is delivered from the heat source to the capsule and substrate, the added flavor and the natural flavors of the spray-dried tobacco are volatilized and become part of the aerosol. As the tobacco roll warms from the heat of the capsule and the heated air drawn through it, the volatile natural tobacco components, as well as any added flavors, are released.

One naturally occurring tobacco flavor that is not added to the NEW CIGARETTE is nicotine. The only source of nicotine in the NEW CIGARETTE is the naturally occurring nicotine in the spray-dried tobacco, tobacco roll and tobacco-paper filter used in the NEW CIGARETTE.

During the development of the NEW CIGARETTE, a variety of flavors were investigated. The specific flavor used in the cigarette, like those used in food and other consumer products,

is proprietary. The testing program associated with flavor is discussed in Sections 3.2 and 8.6. The flavor used in the NEW CIGARETTE is consistent with achieving the Product Development Objectives of the NEW CIGARETTE as presented in Section 1.5.

2.11.2 *Composition*

As in most consumer products, the flavor used in the NEW CIGARETTE is proprietary and its formula is a closely guarded secret. However, several statements concerning the flavor can be made. The quantity of flavoring material required to achieve the desired organoleptic effects is very small. A product would be both unpalatable and unacceptable if too much flavor were added. Most of the flavor ingredients occur naturally in foods and are either natural extracts or are chemically identical to substances found in natural products intended for human consumption.

Propylene glycol is used as a flavor solvent in the NEW CIGARETTE. A 90-day subchronic nose-only inhalation study using rats was conducted by an independent contract laboratory. The results of this study are summarized in Section 8.14.8.1.

2.12 Tobacco Roll

2.12.1 *Function*

The tobacco roll surrounding the aluminum capsule is an important source of tobacco taste and flavor and helps retain the heat in the capsule. The tobacco is not burned, but because of its exposure to heat from both the capsule and the heat source, it becomes sufficiently warm during smoking to release volatile components such as essential oils and other flavor compounds, including nicotine, into the aerosol. It also provides the required tobacco aroma to the cigarette. The use of a heated roll of tobacco is consistent with the Product Development Objectives for the NEW CIGARETTE and has been found to play an essential role in providing tobacco taste and flavor in the NEW CIGARETTE.

2.12.2 *Composition*

Manufactured by a standard cigarette-making machine, the tobacco roll is made from standard high-quality tobaccos and

may be formulated from a variety of blends. The choice of blend is determined by the desired organoleptic characteristics. The tobacco roll is pictured in Plate 2.12.2-1.

PLATE 2.12.2-1

PLATE 2.12.2-1 Photograph of a NEW CIGARETTE broken open near its center. The tobacco roll surrounding the aluminum capsule and the tobacco-paper filter are clearly visible. The *alpha*-alumina spheres containing the spray-dried tobacco can be seen through the slots of the aluminum capsule.

2.13 Tobacco-Paper Filter

2.13.1 *Function*

Located between the polypropylene filter and the tobacco roll, the tobacco-paper filter is the first part of the NEW CIGARETTE's novel, two-part filtering system. The tobacco filter has three primary functions. First, it serves as a traditional filter, providing an additional barrier between the components and the smoker. Second, it cools the aerosol. Third, it adds additional tobacco taste to the smoke from the NEW CIGARETTE. An optional fourth function is to carry added flavors. The use of a tobacco-paper filter is consistent with the Product Development Objectives of the NEW CIGARETTE and makes a

measurable contribution to the tobacco taste and flavor of the NEW CIGARETTE.

2.13.2 *Composition*

The tobacco-paper filter is a thin, tobacco-paper sheet that has been crimped and folded into a cylinder. It is illustrated in Plate 2.13.2-1. The tobacco filter's folded and crimped surfaces serve as areas for interception and impaction for particles making their way through the tobacco roll and capsule. As the aerosol passes through the tobacco filter, heat energy is dissipated, resulting in a cooler aerosol before it enters the polypropylene filter.

PLATE 2.13.2-1

PLATE 2.13.2-1 Photograph of the assembled tobacco-paper filter (foreground) and the tobacco-paper used to construct it.

The major components of the tobacco-paper filter are tobacco fiber and unbleached softwood kraft. Therefore the tobacco-paper filter is composed primarily of naturally occurring, cellulose-based materials. To fabricate the tobacco paper,

tobacco stems are mixed with water to form a slurry, which is pulped and filtered to extract the water-soluble components. The fiber that remains and the unbleached softwood kraft form a base paper to which a portion of the aqueous extract may be added. The tobacco-paper filter is a source of natural tobacco flavor.

2.14 POLYPROPYLENE FILTER

2.14.1 *Function*

A specifically designed polypropylene filter (Figure 2.14.1-1) completes the unique aerosol filtering system of the NEW CIGARETTE. The physical and chemical characteristics of this filter result in efficient filtration of any potential particles and fibers without loss of the aromas and flavors present in the smoke aerosol. In addition, passing through the polypropylene filter further cools the aerosol to the point it is pleasant to the smoker.

Polypropylene is generally considered a nontoxic material, and its use in the NEW CIGARETTE is consistent with the Product Development Objectives of the NEW CIGARETTE (Section 1.5). The biological activity of polypropylene is reviewed in Section 8.14.5.

2.14.2 *Composition*

The polypropylene granules used to make the fabric for the NEW CIGARETTE's filter are composed of approximately 99.8% polypropylene. Polypropylene is virtually inert chemically and is extremely nonpolar. In addition, polypropylene has a very low level of toxicity (see Section 8.14.5) and is approved by the FDA for use as a food-contact packaging component. The remaining ingredients are proprietary to the supplier, but general comments can be made. The polypropylene contains a stabilizer against ultraviolet light and an antioxidant, both of which are approved by the FDA as antioxidants and/or stabilizers in polymers used to package, transport or hold food. Viscosity control of the molten polypropylene is achieved through the use of a third agent, none of which remains in the polypropylene. A residue of a reaction product is present at a level less than 50 ppm. This compound is approved by the FDA for indirect food contact applications. The final ingredient, which is a GRAS compound, functions as

a lubricant for the polypropylene during manufacture. The NEW CIGARETTE's polypropylene filter does not contain any plasticizers.

There is ample space in the polypropylene filter for the diffusion of the gas stream as it flows through the filter, decreasing the aerosol velocity. The physical construction of the polypropylene filter allows it to filter various particles and fibers that might potentially be in the aerosol. The travel or path of a material through the filter is a function of its diameter, density and length. The average diameter of the spherical aerosol particles is 0.2–0.3 um, and since they are composed mainly of glycerol and water, their density is near 1.0. Therefore, while most of the aerosol traverses the tobacco-paper and polypropylene filters relatively intact, any larger, denser particles and fibers should be removed. Filtration occurs through impaction and interception with the many polypropylene fibers in the filter, as well as the many folds and pleats in the polypropylene fabric and tobacco paper. In addition, the numerous spaces in the polypropylene filter encourage slowing of the aerosol so that any larger, heavier particles should "settle out" and be deposited within the filter.

The physical form of the material used by R.J. Reynolds to fabricate the polypropylene filter is a weblike fabric sheet made from thick fibers (Figure 2.14.1-1). The fibers spread out in all directions, however, and are not woven, but are laid down on top of each other, producing a fabric that resists collapse and possesses inherent firmness. The fabric sheet is produced by a melt-blown manufacturing process producing large fibers, which adhere to form a web. No cross-linking agents are used in this process.

PLATE 2.14.1-1

PLATE 2.14.1-1 Photograph of an assembled polypropylene cigarette filter (foreground) and the polypropylene fabric used to construct the filter. The web-like strands of the polypropylene fabric are easily visible.

2.15 PAPERS

2.15.1 *Function*

The NEW CIGARETTE differs from other cigarettes in both the number and function of the various papers. Other filter cigarettes generally have three papers: the plug wrap around the filter, the cigarette or tobacco paper, and the tipping paper connecting the filter to the tobacco roll (see Figure 1.3-2). During the manufacturing process of other filter cigarettes, the plug wrap is used to encase the filter so it can be cut to size and joined to the tobacco roll. The plug wrap and the tipping paper are generally nonporous so very little air passes through these papers during smoking. To control air dilution for the particular cigarette being manufactured, lasers are used to burn holes through the plug wrap and tipping paper. A porous cigarette paper wraps the blended tobaccos, forming the tobacco roll.

The tipping paper then joins the tobacco roll and the filter, completing the cigarette.

There are seven papers used in fabricating the NEW CIGARETTE: the filter plug-wrap, the tobacco-paper filter plug-wrap, the combining plug-wrap, the tobacco-roll inner-wrap, the insulator-mat inner-wrap, the cigarette outer-wrap, and the tipping over-wrap (Figure 2.15.1-1). The filter plug-wrap is used to wrap the polypropylene filter. The tobacco-paper filter plug-wrap encloses the tobacco-paper filter. This allows the two pieces to be joined with the combining plug-wrap, forming a single filter piece. The tobacco-roll inner-wrap holds the tobacco roll around the aluminum capsule; the insulator-mat inner-wrap encircles the insulation jacket. A special outer cigarette wrap, discussed below, forms a second layer of paper for the aluminum capsule, tobacco roll, heat source and insulator mat, and unites these components into a single rod. The tipping over-wrap then combines the filter components and the tobacco component into a single unit, thus forming the NEW CIGARETTE.

FIGURE 2.15.1-1

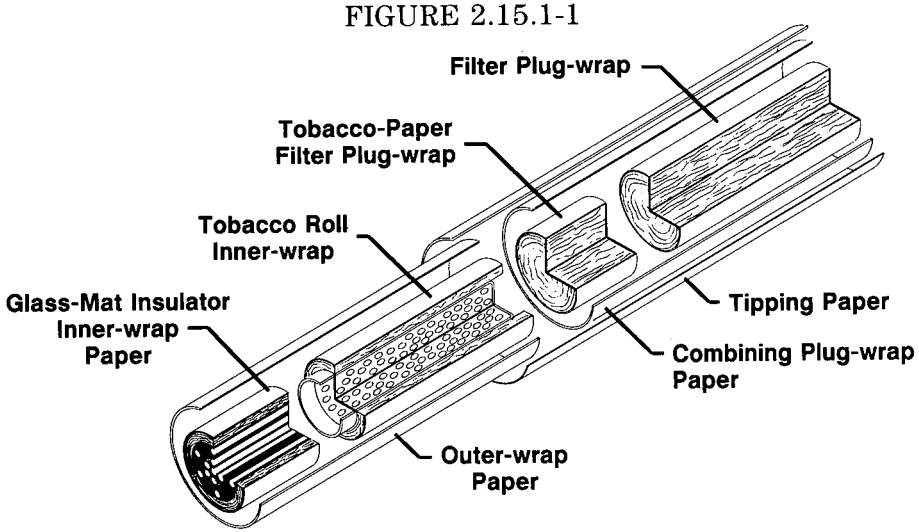

FIGURE 2.15.1-1 Illustration of the NEW CIGARETTE demonstrating the placement of the seven papers used in its construction.

The outer-wrap paper was specifically designed for the NEW CIGARETTE. An important characteristic is that it has been designed to burn for only 6-8 mm. This small portion of the outer-wrap paper and the insulator-mat inner-wrap paper is the only paper that burns. Once the papers burn back over the length of the heat source, the heat is no longer sufficient to support paper combustion.

When the NEW CIGARETTE is smoked, the outer wrap, insulator-mat inner-wrap, and insulator mat surrounding the heat source provide a strong cohesive ash that simulates the ash and fire cone of other cigarettes.

The papers selected for use in the NEW CIGARETTE are consistent with achieving the Product Development Objectives of the NEW CIGARETTE (Section 1.5).

2.15.2 *Composition*

Since the formulations for the various papers used in the NEW CIGARETTE are proprietary information to the supplier, the exact compositions cannot be disclosed. However, some general comments can be made. The major component of all the papers is bleached softwood kraft fiber, a naturally occurring cellulose-based material. Softwood kraft fiber is also used in other cigarette papers that do not burn, such as the plug wrap and tipping papers.

Various agents are added to the softwood base to give the finished paper opacity and a pure white color. Additional agents are used to produce the desired porosity, burn and ash characteristics. Most of these components have been reviewed by the FDA and/or OSHA and the American Conference of Governmental Industrial Hygienists.

2.16 ADHESIVES

2.16.1 *Function*

The adhesives used in manufacturing the NEW CIGARETTE all have a history of use in cigarette manufacturing. The function of the adhesives is to hold together the seams of the papers that surround the various components of the NEW CIGARETTE, to help maintain the position of the components, and to bind the complete filter-piece to the cigarette rod. Adhesive is placed along the seam lines of the papers that encircle

and wrap the NEW CIGARETTE's components; around the bottom edge of the tipping over-wrap that unites the filter piece with the cigarette; and along the centerline, opposite the seamline, of such papers as the combining plug-wrap, tipping over-wrap, and the outer wrap.

Since the NEW CIGARETTE has limited burn-back, only the adhesive used on the first 7 mm of the outer wrap and insulator-mat inner-wrap seamlines and centerline is pyrolyzed. R.J. Reynolds estimates this at approximately 240 µg adhesive per cigarette smoked. The adhesives used are consistent with the Product Development Objectives of the NEW CIGARETTE (Section 1.5).

2.16.2 *Composition*

As with the flavors and the papers, the composition of the adhesives used in manufacturing the NEW CIGARETTE is proprietary information and cannot be disclosed.

2.17 Significant Innovations in the NEW CIGARETTE

The most significant innovation in the NEW CIGARETTE is the overall concept that allows the smoker to receive the tobacco taste, sensations and enjoyment of other cigarettes without burning tobacco. Reducing the concept to a practical design that could be produced at a reasonable cost required a number of significant innovations, both in the design and production of the components and in the design of machines to make the cigarette. Some of these innovations are discussed below.

One key to the NEW CIGARETTE design is its small, high-purity, carbon heat source. Without development of this novel component, the NEW CIGARETTE would not be possible. The small carbon heat source permits rapid heat transfer to the capsule and the tobacco roll, which produces smoke and flavor from the first puff. While small, the heat source allows the NEW CIGARETTE to burn as long as other cigarettes and produces enough controlled heat to provide the desired amount of tobacco taste, flavor and smoke.

As shown in Figure 2.4.2-1, the NEW CIGARETTE's heat source includes small holes spaced around its outer edge, and larger holes near the center. This multihole pattern was developed to minimize the amount of carbon monoxide contained in

the smoke. The hole configuration illustrated was used with the majority of the NEW CIGARETTE prototypes discussed in this monograph, but may change to improve product performance.

The heat source is made by a process that required developing new carbon-processing technology. This new process produces a high-purity heat source that generates a minimal quantity of combustion products and virtually no sidestream smoke.

The NEW CIGARETTE's configuration, covered by pending patent applications, helps distribute heat to the tobacco roll and the alumina spheres at a much lower temperature than that of the burning heat source. The capsule itself is thin-walled and is made by a new process using high-speed equipment. The placement of the nonburning tobacco roll around the flavor capsule maximizes controlled heat transfer to the tobacco and release of tobacco flavors.

Another innovative aspect of the NEW CIGARETTE is the insulating jacket around the heat source. This component reduces heat loss to the air, helping to channel heat toward the tobacco roll and flavor capsule. It also minimizes the exposure of the burning heat source to its environment. This component was specially developed for R.J. Reynolds to be used in the NEW CIGARETTE. In addition, the tobacco roll is wrapped with a new cigarette paper, developed in conjunction with one of the company's outside suppliers.

The *alpha*-alumina substrate used to hold the glycerol, spray-dried tobacco and flavor is also important. This material was specially developed to release the glycerol and other volatile materials with optimal taste characteristics. The alumina is covered by pending patent applications.

Finally, the commercial introduction of the NEW CIGARETTE, at a competitive price, would not be possible without the development of revolutionary new assembly equipment specially designed to produce the NEW CIGARETTE in commercial quantities. This assembly equipment, which was designed and developed in conjunction with outside equipment suppliers, was built using state-of-the-art computer-controlled design and machine-tool technology. It operates at tolerances that have only recently been made available in high-speed cigarette production equipment. The assembly equipment is covered by pending patent applications.

REFERENCES

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3) Federation of American Societies for Experimental Biology (FASEB). *Evaluation of Health Aspects of Glycerin and Glycerides as Food Ingredients.* Life Sci. Res. Off., SCOGS-30, 1975.
4) Flavor Extract Manufacturers' Association. *Scientific Literature Review of Propylene Glycol, Glycerol and Related Substances in Flavor Usage.* Natl. Tech. Inform. Serv., PB 85-141083, 1984.

Contents

SECTION 3. COMPARATIVE APPROACH TO THE EVALUATION OF THE POTENTIAL TOXICOLOGY OF THE NEW CIGARETTE COMPARED TO REFERENCE CIGARETTES

3.5 NEW CIGARETTE Prototypes and Reference Cigarettes Used in the Testing Program

A number of NEW CIGARETTE prototypes were used in the chemical and biological testing programs. While more than 200 prototypes have been screened for bacterial mutagenicity, six prototypes have been tested in the overall program. These six NEW CIGARETTE prototypes were termed "Test Models" and numbered sequentially, *i.e.*, Test Model 1 (TM-1) through Test Model 6 (TM-6). Of these six prototypes, TM-6 has been most extensively tested. The prototype used in the human studies was termed HS-1. Additional prototypes, TM-7, TM-8 and TM-9, were used for the genetic toxicology of mainstream and sidestream smoke.

Although the 1R4F reference cigarette was used for the majority of the studies reported here, several different reference cigarettes have been used in the testing program. The choice of reference cigarette, in major part, depended upon the type of study. For instance, in certain inhalation studies, reference cigarettes were constructed that closely matched the NEW CIGARETTE prototype in terms of TPM and nicotine. This allowed the animals in both the NEW CIGARETTE and reference cigarette groups to be exposed to equivalent levels of both TPM and nicotine. The human studies are another example of the use of a different reference cigarette. The 1R4F cigarette is not pleasant to smoke. To ensure that the reference smokers did not change their smoking behavior in response to an unpleasant tasting cigarette, a reference with smoking qualities similar to commercial brands was constructed. The reference cigarettes used during the testing program are described in Section 3.5.4.

3.5.1 *NEW CIGARETTE Prototypes Used in the Genetic Toxicology Program*

3.5.1.1 *NEW CIGARETTE Prototypes Used in the* In Vitro *Genetic Toxicology Program*

The NEW CIGARETTE prototypes used in the *in vitro* genetic toxicology battery employing smoke condensates are listed in Table 3.5.1.1-1. With the exception of TM-2, all prototypes were tested in the complete battery. TM-2 was not tested in the battery since it was almost identical to TM-1.

TABLE 3.5.1.1-1 *In Vitro* Genetic Toxicology Program for Smoke Condensates from NEW CIGARETTE Test Models

Test Model[a]	Ames Assay	Laboratory	SCE[b] Assay	Laboratory	CA[c] Assay	Laboratory	HGRPT[d] Assay	Laboratory	UDS[e] Assay	Laboratory
TM-1	Yes	RJ Reynolds	Yes	RJ Reynolds, SRI Internat[f]	Yes	RJ Reynolds SRI Internat	Yes	RJ Reynolds SRI Internat	Yes	RJ Reynolds SRI Internat
TM-2	Yes	RJ Reynolds	No	—	No	—	No	—	No	—
TM-3	Yes	RJ Reynolds	Yes	SRI Internat.	Yes	SRI Internat	Yes	SRI Internat	Yes	SRI Internat
TM-4	Yes	RJ Reynolds	Yes	SRI Internat	Yes	SRI Internat	Yes	SRI Internat	Yes	SRI Internat
TM-5	Yes	SRI Internat	Yes	Hazleton[g]	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat
TM-6	Yes	RJ Reynolds	Yes	Hazleton	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat
HS-1	Yes	RJ Reynolds	Yes	RJ Reynolds	Yes	RJ Reynolds	Yes	SRI Internat	Yes	SRI Internat
TM-7	Yes	RJ Reynolds	Yes	Hazleton	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat
TM-8	Yes	RJ Reynolds	Yes	Hazleton	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat
TM-9	Yes	RJ Reynolds	Yes	Hazleton	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat

[a]Test Models described in Table 3.5.3-1. All Test Models were compared to the 1R4F reference cigarette.
[b]SCE = sister chromatid exchange in CHO cells.
[c]CA = chromosomal aberration in CHO cells.
[d]HGPRT = hypoxanthine guanine phosphoribosyl transferase in CHO or V79 cells.
[e]UDS = unscheduled DNA synthesis in isolated rat hepatocytes.
[f]SRI International, Menlo Park, California.
[g]Hazleton America, Vienna, Virginia.

3.5.1.2 *NEW CIGARETTE Prototypes Used in the* In Vitro *Genetic Toxicology Program for Sidestream Smoke*

TM-7, TM-8 and TM-9 were used in the genetic toxicology battery for sidestream smoke. This program is outlined in Table 3.5.1.2-1.

TABLE 3.5.1.2-1 *In Vitro* Genetic Toxicology Program for Sidestream Smoke from NEW CIGARETTE Test Models

Test Model[a]	Ames Assay	Laboratory	SCE[b] Assay	Laboratory	CA[c] Assay	Laboratory	HGRPT[d] Assay	Laboratory	UDS[e] Assay	Laboratory
TM-7	Yes	RJ Reynolds	Yes	Hazleton[g]	Yes	Hazleton	Yes	SRI Internat[f]	Yes	SRI Internat
TM-8	Yes	RJ Reynolds	Yes	Hazleton	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat
TM-9	Yes	RJ Reynolds	Yes	Hazleton	Yes	Hazleton	Yes	SRI Internat	Yes	SRI Internat

[a]Test Models described in Table 3.5.3-1. All Test Models were compared to the 1R4F reference cigarette.
[b]SCE = sister chromatid exchange in CHO cells.
[c]CA = chromosomal aberration in CHO cells.
[d]HGPRT = hypoxanthine guanine phosphoribosyl transferase in CHO or V79 cells.
[e]UDS = unscheduled DNA synthesis in isolated rat hepatocytes.
[f]SRI International, Menlo Park, California.
[g]Hazleton America, Vienna, Virginia.

3.5.1.3 *NEW CIGARETTE Prototype Used in the Human Studies*

The human study program was divided into pharmacokinetic and urine mutagenicity programs. The NEW CIGARETTE prototype used in these studies was termed HS-1. It was similar to TM-6. The reference cigarette used in the study was RJRT-3.

3.5.1.4 *NEW CIGARETTE Prototype Used in the* In Vivo *Genetic Toxicology Program*

TM-6 was the NEW CIGARETTE prototype used in the *in vivo* genetic toxicology battery. The program is outlined in Table 3.5.1.4-1. The 1R4F was the reference used in this study.

TABLE 3.5.1.4-1 *In Vivo* Genetic Toxicology Program for NEW CIGARETTE Test Models[a]

Test Model[b]	Reference Cigarette	SCE[c] Assay	CA[d] Assay	Micronucleus Assay	Urine Mutagenicity
TM-6	1R4F	Yes	Yes	Yes	Yes

[a]All assays done at R.J. Reynolds.
[b]Test Model described in Table 3.5.3-1. Test Model was compared to 1R4F reference cigarette.
[c]SCE = sister chromatid exchange.
[d]CA = chromosomal aberration.

3.5.2. *NEW CIGARETTE Prototypes Used in the Inhalation Toxicology Program*

Table 3.5.2-1 outlines the NEW CIGARETTE prototypes used in the various inhalation studies. It also presents the reference cigarettes used for comparison with each test model.

TABLE 3.5.2-1 Inhalation Toxicology Program for NEW CIGARETTE Test Models

Test Model[a,b]	Reference[c] Cigarette	Study Duration[d]	Species	Laboratory
TM-2	RJRT-1	14 days	Rat	R.J. Reynolds
TM-3	RJRT-2	90 days	Rat	R.J. Reynolds
TM-4	1R4F	90 days	Rat	Battelle, NW
TM-5	1R4F	14 days	Hamster	R.J. Reynolds
TM-5	1R4F	90 days	Hamster	Battelle, NW
TM-6	1R4F	90 days	Rat	R.J. Reynolds

[a]TM-1 was used in an initial preliminary 14-day inhalation study to develop methodology.
[b]Test Models described in Section 3.5.3.
[c]Reference cigarettes described in Section 3.5.4.
[d]Typical study used a one-hour-per-day, five-days-per-week exposure. TM-1 and TM-2 used seven-days-per-week exposure.

3.5.3 *Description of the NEW CIGARETTE Prototypes Used in the Testing Program*

Table 3.5.3-1 presents the 10 NEW CIGARETTE test models used in the chemical and biological studies. TM-1 was the first test model used in the testing program. TM-2 was similar to TM-1, except for the heat source processing and the configuration of the aluminum capsule. TM-3 differed from TM-2 in respect to the heat source configuration, the quantity of alumina and spray-dried tobacco, and the flavor. TM-4 differed from TM-3 in the quantity of alumina and spray-dried tobacco and the flavor. TM-5 had a different heat source configuration, quantity of alumina, glycerol and spray-dried tobacco, and a different paper, compared to TM-4. TM-5 also had a polypropylene cigarette filter instead of a cellulose acetate filter. TM-6 differed from TM-5 with respect to the quantity of glycerol and spray-dried tobacco, the flavor, the chemical composition of the glass in the insulator mat and the inclusion of the tobacco-paper filter. HS-1 was similar to TM-6. TM-7 differed from TM-6 in the spray-dried tobacco, flavor, chemical composition of the glass in the insulator mat and the tobacco

blend in the tobacco roll. TM-8 differed from TM-7 in the amount of glycerol and tobacco blend in the tobacco roll. TM-8 differed from TM-7 only in the flavor used.

Three additional test models (TM-7 through TM-9) were used in the genetic toxicology program. The genetic toxicology battery was conducted on both mainstream and sidestream condensates from these models. No inhalation studies were done with these three prototypes.

TABLE 3.5.3-1 NEW CIGARETTE Prototype Descriptions

	Prototypes									
Physical Data	TM-1	TM-2	TM-3	TM-4	TM-5	TM-6	HS-1	TM-7	TM-8	TM-9
Heat Source[a]	A	B	C	C	D	D	D	D	D	D
Capsule[b]	A	B	B	B	B	B	B	B	B	B
Substrate Composition										
- Alumina[c]	A	A	B	C	D	D	D	D	D	D
- Glycerol[d]	A	A	A	A	B	C	C	C	D	C
- Spray-Dried Tobacco[e]	A	A	B	C	D	E	E	F	F	F
- Flavors[f]	A	A	B	C	D	E	E	F	F	G
Insulator Mat[g]	A	A	A	A	A	B	A	C	C	C
Filter[h]	A	A	A	A	B	B	B	B	B	B
Tobacco-Paper Filter[i]	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Tobacco Roll[j]	A	A	B	B	B	B	B	C	B	B
Paper[k]	A	A	A	A	B	B	B	B	B	B
	Smoke Aerosol Data[l]									
TPM (mg/cig)	11.5	8.7	11.5	11.5	13.2	10.6	10.2	13.2	11.1	12.7
Nicotine (mg/cig)	0.38	0.48	0.47	0.40	0.38	0.30	0.34	0.32	0.30	0.31
Glycerol (mg/cig)	4.8	3.8	5.2	5.5	5.0	4.0	3.9	5.7	4.6	5.6
Water (mg/cig)	4.3	2.2	2.4	2.7	5.0	3.7	—	5.6	5.0	5.9
CO (mg/cig)	21.6	9.1	12.3	13.8	11.9	11.7	9.9	17.2	17.8	17.6
CO_2(mg/cig)	31.3	22.7	—	—	35.5	30.0	30.7	—	—	—

[a]Letters represent different configurations and processing.
[b]Letters represent different configurations.
[c]Letters represent different mesh size and processing.
[d]Letters represent different quantities.
[e]Letters represent different quantities and tobacco blends.
[f]Letters represent different flavors and locations within the cigarette.
[g]Letters represent different chemical composition.
[h]"A" represents cellulose acetate and "B" represents polypropylene.
[i]Represents the absence (No) or presence (Yes) of tobacco-paper filter.
[j]Letters represent different tobacco blends.
[k]Letters represent different papers.
[l]Data represent smoke analyses under FTC smoking conditions modified because the NEW CIGARETTE does not burn down.

3.5.4 *Description of the Reference Cigarettes Used in the Testing Program*

3.5.4.1 *The 2A1 Reference Cigarette from the Tobacco and Health Research Institute*

The reference cigarette used in the preliminary 14-day study with TM-1 was the 2A1 Kentucky reference cigarette. It is readily available to researchers through the Tobacco and Health Research Institute in Lexington, Kentucky. It should be pointed out that this cigarette is unfiltered and, therefore, does not represent the majority of the currently marketed cigarettes.

Specifications provided by the Tobacco and Health Research Institute for this cigarette are listed below in Tables 3.5.4.1-1 and 3.5.4.1-2. The Tobacco and Health Research Institute states that this cigarette was blended from low-nicotine flue-cured and low-nicotine burley tobacco.

TABLE 3.5.4.1-1 Selected Physical Data for the 2A1 Reference Cigarette[a]

Rod Weight (gm/cig)	Draw Resistance (cm of H_2O)	Length (mm/cig)	Circumference (mm/cig)	Paper Porosity (sec/50cc)
1.15	7.4	85.4	24.9	46.1

[a]Source: "The Reference and Research Cigarette Series," Sullivan, S. L., ed., University of Kentucky Printing Services, 1984.

TABLE 3.5.4.1-2 Smoke analysis (FTC Method) for the 2A1 Reference Cigarette[a]

Butt Length (mm)	TPM (mg/cig)	FTC "Tar" (mg/cig)	Nicotine (mg/cig)	CO (mg/cig)	CO_2 (mg/cig)	Water (mg/cig)	Puff Count (puffs/cig)
23	41.3	36.4	0.48	21.5	62.4	4.38	10.6
30	35.0	31.8	0.42	17.9	52.6	2.85	9.2

[a]Source: (See Table 3.5.4.1-1).

3.5.4.2 *The 1R4F Reference Cigarette from the Tobacco and Health Institute*

The reference cigarette used in the inhalation studies of TM-4, TM-5 and TM-6 and in the genetic toxicology program

was the 1R4F, obtained from the Tobacco and Health Research Institute, Lexington, Kentucky. The 1R4F is a filtered cigarette that is air-diluted. It is described in Tables 3.5.4.2-1, 3.5.4.2-2 and 3.5.4.2-3.

TABLE 3.5.4.2-1 Composition of the 1R4F Reference Cigarette[a]

Tobacco Type	Percent Composition
Flue-cured	32.54
Burley	20.04
Oriental	11.09
Maryland	1.06
Reconstituted (Schweitzer)	27.17
Glycerol	2.80
Isosweet (sugar)	5.30

[a]Source: "The Reference and Research Cigarette Series," Sullivan, S. L. ed., University of Kentucky Printing Services, 1984.

TABLE 3.5.4.2-2 Physical Data for the 1R4F Reference Cigarette[a]

Cigarette Rod Weight (gm/cig)	Static Burn (sec/40 mm)	Length (mm/cig)	Circumference (mm/cig)	Paper Porosity (sec/50 cc)
1.072	552	84.0	25.0	22.0

[a]Source: "The Reference and Research Cigarette Series," Sullivan, S. L. ed., University of Kentucky Printing Services, 1984.

TABLE 3.5.4.2-3 Smoke Analysis for the 1R4F Kentucky Reference Cigarette[a,b]

TPM (mg/cig)	"Tar" (mg/cig)	Nicotine (mg/cig)	Water (mg/cig)	CO (mg/cig)	CO_2 (mg/cig)	Puff Count (puffs/cig)
10.8	9.2	0.8	0.9	11.6	41.9	9.2

[a]Source: "The Reference and Research Cigarette Series," Sullivan, S. L. ed., University of Kentucky Printing Services, 1984.
[b]Cigarettes smoked by FTC procedures to a butt length of 35 mm.

3.5.4.3 *The RJRT-1 Reference Cigarette*

The 1R4F reference cigarette did not match the TPM, nicotine and CO levels of TM-2. To match these smoke characteristics, an in-house reference cigarette (RJRT-1) was manufactured. This reference cigarette allowed a closer match of all three components in this inhalation study, in contrast to the previous study. RJRT-1 was a classically manufactured cigarette composed of blended tobaccos including flue-cured, Turkish, burley and reconstituted sheet. The tobacco was cased with a standard casing that is proprietary.

Specifications for the RJRT-1 reference cigarette are described in Tables 3.5.4.3-1 and 3.5.4.3-2.

TABLE 3.5.4.3-1 Selected Physical Data for the RJRT-1 Reference Cigarette

Total Weight (gm/cig)	Tobacco Rod Length (mm/cig)	Total Rod Length (mm/cig)	Circumference (mm/cig)	Air Dilution (%)
0.98	57	84	24.8	0

TABLE 3.5.4.3-2 Smoke Analysis (FTC Method) for the RJRT-1 Reference Cigarette[a,b]

Butt Length (mm)	TPM (mg/cig)	FTC"Tar" (mg/cig)	Nicotine (mg)	Water (mg/cig)	Puff Count (puffs/cig)	CO (mg/cig)	CO_2 (mg/cig)
34	9.8 ± 0.2	8.0 ± 0.2	0.56 ± 0.20	1.2 ± 0.2	7.0 ± 0.1	13.0	40.0

[a]Cigarettes were conditioned at 75° F/60% RH before smoking.
[b]Data represent the mean ± S.D. for replicate smokings of 50 cigarettes.

3.5.4.4 *The RJRT-2 Reference Cigarette*

The RJRT-2 reference cigarette was designed and constructed at R.J. Reynolds. It was designed to yield TPM, nicotine and carbon monoxide levels closely approximating that of TM-3. It was a classically designed filter cigarette. The exact tobacco composition of RJRT-2 is proprietary, but it consisted of Turkish, flue-cured, burley and reconstituted sheet tobaccos.

The tobaccos were cased with a standard casing that is proprietary. The characteristics of the RJRT-2 reference cigarette are described in Tables 3.5.4.4-1 and 3.5.4.4-2.

TABLE 3.5.4.4-1 Physical Specifications of the RJRT-2 Reference Cigarette

Cig. Rod Weight (gm/cig)	Total Rod Length (mm/cig)	Circumf. (mm/cig)	Air Dilution Paper(%)	Air Dilution (Filter)(%)	Air Dilution (Total)(%)	Filter Length (mm)
0.89	84	24.8	4.5	6.4	10.9	21.0

TABLE 3.5.4.4-2 Smoke Analysis of the RJRT-2 Reference Cigarette[a]

Butt Length (mm)	TPM[b] (mg)	Nicotine (mg)	FTC "Tar"[b] (mg)	CO (mg)	Water (mg)	Puff Count puffs/cig
28	20.0	0.44	16.8	19.7	2.8	9.5
35	15.7	0.37	14.0	16.7	1.4	8.4
45[c]	11.5	0.27	10.2	12.2	1.1	6.7

[a]Data was acquired at standard FTC smoking conditions.
[b]TPM = Total Particulate Matter; "Tar" = Standard FTC; "Tar" number = TPM minus water minus nicotine.
[c]Data at a 45mm butt length provided because cigarettes were smoked to this butt length during inhalation exposures.

3.5.4.5 *The RJRT-3 Reference Cigarette*

The RJRT-3 reference cigarette was used in the human studies for comparison to HS-1. It was a standard American-blend cigarette consisting of Turkish, flue-cured, burley and reconstituted tobaccos. The tobaccos were cased with a standard casing that is proprietary. The characteristics of the RJRT-3 reference cigarette are described in Tables 3.5.4.5-1 and 3.5.4.5-2.

TABLE 3.5.4.5-1 Physical Specifications of the RJRT-3 Reference Cigarette

Cig. Rod Weight (gm/cig)	Total Rod Length (mm/cig)	Circumf. (mm/cig)	Air Dilution Paper(%)	Air Dilution (Filter)(%)	Air Dilution (Total)(%)	Filter Length (mm)
0.99	85	24.8	6.3	24.8	31.1	21.0

TABLE 3.5.4.5-2 Smoke Analysis of the RJRT-3 Reference Cigarette[a]

Butt Length (mm)	TPM[b] (mg)	Nicotine (mg)	FTC "Tar"[b] (mg/cig)	CO (mg)	Water (mg)	Puff Count puffs/cig.
35	10.6	0.66	7.8	12.2	1.1	—

[a]Data was acquired at standard FTC smoking conditions.
[b]TPM = Total Particulate Matter; "Tar" = Standard FTC; "Tar" number = TPM minus water minus nicotine.

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4.0

Chemical Composition of NEW CIGARETTE Smoke

SUMMARY

Comparison of the mainstream and sidestream smokes from NEW CIGARETTE prototype TM-6 with those from a reference cigarette, the 1R4F, reveals the following:

1) The bulk (92%) of the mainstream particulate phase from the TM-6 is composed of water, glycerol and propylene glycol, compared to 21% for the 1R4F reference cigarette (see Section 4.2.1 and Table 4.2.1-1).

2) The amount of nicotine, as measured with the modified FTC procedure, in the mainstream smoke from TM-6 is about 59% less (0.33 versus 0.80 mg/cig) than that from the 1R4F reference; the amount of carbon monoxide is equivalent.

3) As indicated by results from smoke comparison studies, the mainstream and sidestream smoke compositions from TM-6 are much less complex than those from the 1R4F in terms of number of components detected and total relative amount of material detected (see Sections 4.2 and 4.5). Data from Sections 4.2 and 4.5 are summarized in the table below:

Smoke Composition Summary

Smoke Stream	Number Detected			Amount (μg/cig)		
	1R4F	TM-6	% Change	1R4F	TM-6	% Change
MS particulate phase	562	31	−94	1048	62	−94
MS vapor phase	98	17	−83	365	23	−94
SS particulate phase	237	9	−96	4877	145	−97
SS vapor phase	160	29	−82	1682	269	−84

4) Quantities of specific smoke components, some of which have been traditionally used as indicators, including nitrosamines, polycyclic aromatic hydrocarbons and carbonyls, are substantially lower in both the mainstream and sidestream smokes from prototype TM-6 compared to those from 1R4F (see Section 4.3 and Table 4.3-1, and Section 4.5.4 and Table 4.5.4-1). Some of the data are summarized in the table below:

Specific Component Reductions in Mainstream and Sidestream Smoke

Compounds	Mainstream % Reduction	Sidestream % Reduction
HCN	99+	91
NOx	95	96
Carbonyls	91	88
Polycyclic Aromatic Hydrocarbons	99	97
Nitrosamines	97	94
Phenolics	96	n.d.*

*n.d. = Not determined

5) Measured quantities of environmental tobacco smoke, generated either by machine- or human-smoked cigarettes, are much lower for the NEW CIGARETTE prototype TM-6 than for the 1R4F reference cigarette. Measured components were reduced by 65-99% for TM-6 (see Section 4.6).

4.0 BACKGROUND

The qualitative composition of tobacco and tobacco smoke has been an active research field for many years. In 1954, Kosak (1) cataloged the known components of tobacco smoke and listed some 100 components that had been reported in the literature. Subsequently it was shown that some of these were not individual entities but were mixtures. By 1987, the number

of tobacco smoke components reported in the literature had increased to over 4500.

During this same time a variety of analytical methods for specific tobacco and tobacco-smoke components were also developed. These included methods for the following:

1) Nicotine and nornicotine in tobacco (2)
2) Humectants in tobacco (3-5) and tobacco smoke (6,7)
3) Ammonia (8) and nitrogen oxides (9) in smoke
4) The simple carbonyl compounds (10-13)

With the availability at R.J. Reynolds of a test chamber designed for multiple-mode operation in 1985 (14), the determination of the levels of components (15) in environmental tobacco smoke became possible.

R.J. Reynolds has utilized the technologies and analytical methods developed and used over the years in the tobacco and tobacco-smoke studies in concert with more recently developed techniques to examine the chemical characteristics of mainstream, sidestream and environmental tobacco smokes from NEW CIGARETTE prototypes and to compare these characteristics with those of the smokes similarly generated from a reference cigarette, the 1R4F from the Tobacco and Health Institute at the University of Kentucky. The 1R4F reference cigarette is described in Section 3.5.4.2.

When other cigarettes are smoked, a portion of the tobacco and cigarette paper of the lighted cigarette is consumed during the puff. This generates a dense fire cone and gaseous products (carbon monoxide, carbon dioxide, water, nitrogen oxides, etc.). During the puff, these hot gaseous components plus air, heated as it enters the cigarette at the char line between the fire cone and the tobacco rod, traverse the tobacco rod from the fire cone-tobacco rod interface to the mouth end of the cigarette and heat the tobacco enroute. The tobacco-rod temperature decreases exponentially from about 900°C at the fire cone-tobacco rod interface (16) to near room temperature at the mouth end of the cigarette. A few millimeters ahead of the fire cone-tobacco rod interface, *i.e.*, toward the mouth end of the cigarette, a short (3-5 mm) section of the tobacco rod is heated to a temperature range of about 400°-700°C. It is in this region of the cigarette that the great number and variety of smoke components, including the flavorful ones such as nicotine, are generated from the heated tobacco components that

undergo processes such as vaporization, decomposition, hydration, dehydration, aromatization, oxidation, reduction, and reaction between generated smoke components and fragments. Because of the temperature, these reaction products volatilize and enter the vapor phase, joining with simpler combustion products generated in the fire cone. They continue toward the mouth end of the cigarette, are cooled, and condense to form liquid particles. Since liquid particles in a gas stream constitute an aerosol, cigarette smoke, by definition, is an aerosol. As the aerosol proceeds toward the mouth end of the cigarette, under the influence of the puff, some particles successfully traverse the tobacco rod and filter tip, some successfully traverse the tobacco rod but are removed from the smoke stream by the filter tip, and others are filtered out by the tobacco rod itself. These latter particles and the tobacco on which they are deposited participate in the same sequence of events during the next puff.

Detailed reviews of cigarette mainstream smoke formation and transport, and of the aerosol nature of cigarette mainstream smoke were presented in 1981 by Baker (17) and in 1986 by Ingebrethsen (18). Recently, Baker (19) provided additional information on the processes occurring in a burning cigarette.

When the NEW CIGARETTE is smoked, smoke is generated in an analogous manner. Heat from the heat source enters the aluminum capsule where it vaporizes glycerol, flavors and volatile flavor components (including nicotine) of the spray-dried tobacco. Natural tobacco flavors are also released from the tobacco roll. The resulting mixture of heated gases cools rapidly as it passes through the tobacco-paper filter and the mouth-end piece. The less volatile components condense to form numerous small particles that remain entrained in the gas stream. Unlike other cigarettes, no tobacco is burned in generating the NEW CIGARETTE smoke. The aerosol particles are primarily the result of simple vaporization and condensation. The carbon heat source and a small amount of paper are the only components in the NEW CIGARETTE that actually burn, producing predominantly carbon dioxide, some carbon monoxide and trace amounts of other materials. In contrast to other cigarettes where the tobacco is heated to temperatures up to

900 + °C during the puff, the spray-dried tobacco in the capsule and the other tobaccos in the NEW CIGARETTE are seldom, if ever, exposed to temperatures in excess of 300°C (see section 4.7 for temperature measurements).

When other cigarettes smolder between puffs, tobacco is consumed as the fire-cone front moves toward the mouth end of the cigarette. Heat is transferred to the tobacco ahead of the fire cone, and reactions similar to those described above occur. Reaction products in the vapor phase exit the cigarette through the brown portion of the char line closest to the mouth end of the cigarette. They also exit the cigarette through a few millimeters of the cigarette paper just ahead (toward the mouth end) of this brown char line. They are cooled on contact with air and form liquid particles, termed the sidestream smoke aerosol. These phenomena have been described in detail by Baker (19).

In contrast, because no tobacco burns when the NEW CIGARETTE smolders, very little sidestream smoke is produced. The small amount that is produced comes primarily from the smolder of a short section of paper that burns when the cigarette is first lit. Some arises by vaporization of materials in the capsule and the tobacco roll, and the remainder arises from the burning heat source, which mostly generates carbon oxides.

This chapter describes and compares the chemical analysis of the smokes generated by the 1R4F reference cigarette and by a NEW CIGARETTE prototype, TM-6. As in other sections of this monograph, this section does not include any data, other than Federal Trade Commission (FTC) reportable data, on smoke generated by cigarettes currently marketed. It includes data on mainstream smoke (MS) (see Section 4.4), sidestream smoke (SS) (see Section 4.5) and environmental tobacco smoke (ETS) (see Section 4.6). It also attempts to explain how and why the NEW CIGARETTE design has such a profound effect on smoke composition (see Section 4.8).

4.1 Major FTC Reportable Constituents Compared to Other Cigarettes: Phase I Chemistry

For a number of years the FTC has analyzed and reported the "tar" and nicotine (20) and carbon monoxide (CO) (21) for mainstream smoke of most cigarette brands sold in the United States. This section describes how each of these analyses is

higher level for TM-6 than 1R4F. The per cigarette quantities for the remaining 29 components were substantially less for prototype TM-6 than for the 1R4F reference cigarette.[1]

In addition to the compounds listed in Table 4.3-1, attempts have been made to determine the known tobacco smoke constituents 2-naphthalenamine and 1,1'-biphenyl-4-amine. To date, these compounds have not been detected in the smoke from either 1R4F or TM-6. Work is in progress to further develop the analytical method.

TABLE 4.3-1 Specific Mainstream Components

Compound Name	CAS Number	Amount 1R4F	Amount TM-6	% Change TM-6
Nicotine (mg/cig)	54115	0.79	0.3	−62.0
Carbon monoxide (mg/cig)	630080	11.3	11.7	3.5
Carbon dioxide (mg/cig)	124389	41.9	32.9	−21.5
Hydrogen Cyanide (μg/cig)	74908	89.0	n.d.	−99.9+
NOx (μg/cig)	—	234.0	11.0	−95.3
Ammonia (μg/cig)	7664417	18.0	17.0	−5.6
Acetaldehyde (μg/cig)	76070	627.0	41.0	−93.5
Acrolein (μg/cig)	107028	73.0	10.0	−86.3
Formaldehyde (μg/cig)	50000	17.0	11.0	−35.3
Benzene (μg/cig)	71432	45.2	3.3	−92.7
Toluene (μg/cig)	108883	68.1	3.3	−95.2
Styrene (μg/cig)	100425	2.1	0.18	−91.4
Benz[a]anthracene (ng/cig)	56553	10.5	0.1	−99.0
Benzo[a]pyrene (ng/cig)	50328	9.2	0.08	−99.1
NNN (ng/cig)[a,b]	16543558	101.0	8.5	−91.6
NNK (ng/cig)[c]	64173371	84.0	2.4	−97.1
NAT (ng/cig)[d]	71608134	114.0	11.4	−90.0
NAB (ng/cig)[e]	1133548	18.0	1.1	−93.9
DMNA (ng/cig)[f]	62759	n.d.	n.d.	—
EMNA (ng/cig)[g]	10595956	n.d.	n.d.	—
DENA (ng/cig)[h]	55185	n.d.	n.d.	—
NPYR (ng/cig)[i]	930552	14.0	0.6	−95.7
Phenol (μg/cig)	108952	6.8	.27	−96.0
o-Cresol (μg/cig)	95487	1.8	0.03	−98.3
m-Cresol (μg/cig)	108394	1.6	n.d.	−99.9+
p-Cresol (μg/cig)	106445	4.1	0.12	−97.1

[1]When preliminary data on a cigarette yielding 1 mg "tar" by the FTC method are compared with the TM-6 data in Table 4.3-1, some of the compounds that are lower in TM-6 as compared with IR4F are at or above the levels found for the 1 mg "tar" cigarette.

TABLE 4.3-1 (continued)

Compound Name	CAS Number	Amount 1R4F	Amount TM-6	% Change TM-6
Catechol (μg/cig)	120809	38.0	1.6	−95.8
Hydroquinone (μg/cig)	123319	37.0	1.3	−96.5
Resorcinol (μg/cig)	108463	3.0	0.8	−73.3
Pyridine (ng/cig)	110861	2096.0	135.0	−93.6
Quinoline (ng/cig)	91225	235.0	102.0	−56.6
Acrylonitrile (μg/cig)	107131	7.6	n.d.	−99.9+
Acrylamide (μg/cig)	79061	1.1	2.2	100.0
Acetamide (μg/cig)	60355	2.2	1.8	−18.2

*n.d. = Not detected

[a]R.J. Reynolds R&D personnel appreciate the input and discussion with American Health Foundation personnel, particularly Dr. K. D. Brunnemann, on analytical methods to determine nitrosamine levels in cigarette smoke.

[b]NNN = N-Nitrosonornicotine
[c]NNK = 4-Methylnitrosoamino-1-(3-pyridinyl)-1-butanone
[d]NAT = N-Nitrosoanatabine
[e]NAB = N-Nitrosoanabasine
[f]DMNA = Dimethylnitrosamine
[g]EMNA = Ethylmethylnitrosamine
[h]DENA = Diethylnitrosamine
[i]NPYR = Nitrosopyrrolidine

4.4 Elemental Analysis of Mainstream Smoke TPM

The specific mainstream smoke component analyses described in Section 4.3 constitute a more complete quantitative assessment of mainstream smoke than is generally found in the literature. This is true both in terms of the number of components evaluated and in the diversity of chemical classes represented. Although such analyses provide detailed information on individual compounds, they do not yield an overall measure of composition comparable in scope to the spectrophotometric "tar" determination (Section 4.1.1.2). As a further comparison of the mainstream particulate phases of the two cigarettes, elemental analyses were performed to determine carbon, hydrogen and nitrogen (C,H,N) content.

To determine the C,H,N content, mainstream smoke TPM was collected by electrostatic precipitation, as described in Section 4.1.1.3. Elemental analysis of this material was accomplished with a Perkin-Elmer Model 240C Elemental Analyzer.

TABLE 4.6.1-1 Sidestream ETS Measurements

	Two-Hour Integrated Concentrations Per Cigarette				
	1R4F		TM-6		
Analyte	Mean	S.D.	Mean	S.D.	% Reduction
CO (ppm)	2.34	0.07	0.45	0.01	80.8
NOx (ppm)	0.08	0.01	n.d.*	—	99.9+
CO_2 (ppm)	11.00	0.66	4.42	0.22	59.8
FID (ppm)[a]	0.80	0.03	0.03	0.01	96.3
Piezobalance Particles ($\mu g/m^3$)	326.00	10.68	2.07	0.80	99.4
RAM-1 ($\mu g/m^3$)[b]	471.00	16.82	3.04	1.87	99.4
CNC (number/cc)[c]	59186	4344	7086	556	88.0
Gravimetric Particles ($\mu g/m^3$)	287.00	12.87	4.17	2.59	98.6
Nicotine ($\mu g/m^3$)	34.30	2.20	2.00	0.32	94.2
Formaldehyde (μg)	79.90	9.07	16.60	3.10	79.2
Acetaldehyde (μg)	196.00	21.44	19.80	3.92	89.9
Acrolein (μg)	27.20	2.75	2.70	1.06	90.1
Propionaldehyde (μg)	49.74	3.04	6.20	2.40	87.5
Ethylpyridines (ppb)	3.89	0.27	0.15	0.01	96.1
Pyridine (ppb)	9.95	1.27	0.34	0.03	96.6
Cyanopyridine (ppb)	1.77	0.16	0.14	0.01	92.1
Picolines (ppb)	8.50	2.20	0.71	0.13	91.7
Vinylpyridine (ppb)	4.89	0.34	0.19	0.01	96.1
Ammonia (ppb)	691.17	97.57	23.00	3.92	96.7

*n.d. = Not detected
[a]FID = Flame ionization detector is a measure of total volatile organic compounds.
[b]RAM-1 = Real time aerosol monitor measures mass of particles by a light-scattering technique.
[c]CNC = Condensation nucleus counter

4.6.2 *Total ETS Study*

This study was conducted in essentially the same way as the ETS sidestream study described in Section 4.6.1 except for the method of sidestream-smoke generation. In this total ETS study, two human subjects were positioned inside the chamber and allowed to smoke normally, except that they were cued to take one puff every 60 sec. Baseline data were generated on atmospheric components plus the contribution of respiration products from the smokers. The smokers were their own background controls. Total ETS data, corrected for atmospheric and smoker respiration products, are summarized in Table 4.6.2-1. For the smoke entities measured, the percent reductions

observed in the total ETS for TM-6, relative to the 1R4F reference, are not only significant (65-99%), but also very similar to those observed in the ETS sidestream study (Section 4.6.1).

TABLE 4.6.2-1 ETS Measurements

	Two-Hour Integrated Concentrations Per Cigarette				
	1R4F		TM-6		
Analyte	Mean	S.D.	Mean	S.D.	% Reduction
CO (ppm)	2.37	0.09	0.84	0.06	64.6
NOx (ppm)	0.07	0.01	n.d.	—	99.9+
CO_2 (ppm)	10.04	5.79	2.71	7.83	73.0
FID (ppm)[a]	0.73	0.03	0.01	0.01	98.6
Piezobalance Particles ($\mu g/m^3$)	448.89	17.41	5.04	1.67	98.9
RAM-1 ($\mu g/m^3$)[b]	1075.82	51.33	8.90	3.07	99.2
CNC (number/cc)[c]	48390	1791	8580	544	82.3
Gravimetric Particles ($\mu g/m^3$)	419.80	15.32	18.20	2.39	95.7
Nicotine ($\mu g/m^3$)	24.44	1.59	1.32	0.39	94.6
Formaldehyde (μg)	63.52	6.52	10.82	1.88	83.0
Acetaldehyde (μg)	158.20	54.94	16.80	7.71	89.4
Acetone (μg)	110.90	69.40	n.d. *	—	99.9+
Acrolein (μg)	31.22	2.88	1.72	2.75	94.5
Propionaldehyde (μg)	45.40	3.58	2.36	3.14	94.8
Ethylpyridines (ppb)	3.23	1.32	0.04	0.04	98.8
Pyridine (ppb)	9.46	3.04	0.23	0.11	97.6
Cyanopyridine (ppb)	2.84	1.57	0.05	0.06	98.2
Picolines (ppb)	9.00	3.19	0.30	0.18	96.7
Vinylpyridine (ppb)	3.19	1.14	0.02	0.03	99.4
Ammonia (ppb)	351.83	168.60	7.97	62.22	97.7

*n.d. = Not detected
[a]FID = Flame ionization detector is a measure of total volatile organic compounds.
[b]RAM-1 = Real time aerosol monitor measures mass of particles by a light-scattering technique.
[c]CNC = Condensation nucleus counter

4.7 Temperature Measurements

Temperature measurements were made at several points in the NEW CIGARETTE during smoking. The data, summarized in Table 4.7-1, were obtained under the stressed conditions of taking a 50-cc puff of 2-sec duration every 30-sec. Because the temperature at any point is a function of puff number, temperature ranges are given in the table. Heat source measurements were acquired with an infrared thermometer (IR Heat Spy, Model HSM-673, Wahl Instruments Inc., Culver City, CA) focused at selected points. Capsule surface and exit gas temperatures were measured with Type "E" thermocouples (Omega

6.0

Comparative Toxicological Evaluation of NEW CIGARETTE Prototype Smoke: Inhalation Studies with Experimental Animals

SUMMARY

Seven inhalation studies have been completed that compare NEW CIGARETTE prototypes with reference cigarettes. Based on the respiratory physiology results, the NEW CIGARETTE showed significantly less depression in minute ventilation than the reference cigarette. The histopathology results demonstrated fewer significant changes with the NEW CIGARETTE than with the reference cigarettes. An example being the absence of pigmented macrophages (including aggregates) in lung alveoli of animals exposed to NEW CIGARETTE smoke, whereas pigmented macrophages were seen in animals exposed to reference cigarette smoke during subchronic inhalation studies. Where histologic changes were observed with both cigarettes, these changes were less severe and less frequent with the NEW CIGARETTE. For example, the squamous metaplasia observed in the larynx is focal and minimal in rats exposed to NEW CIGARETTE smoke and is seen only at the base of the epiglottis. Larynges from rats in the NEW CIGARETTE low-exposure group are indistinguishable from the

larynges from controls. The metaplastic change noted from the NEW CIGARETTE completely regresses six weeks after termination of smoke exposure. The squamous metaplasia in reference smoke-exposed animals was observed in animals from all exposure groups, and it was more severe and located throughout the larynx. The squamous metaplasia in reference cigarette exposed rats does not completely regress during the six-week recovery period.

The changes observed indicate that in two different species (rats and hamsters) evaluated by three different laboratories (R.J. Reynolds and two independent laboratories) there is a substantial decrease in the biological activity produced by exposure to smoke from the NEW CIGARETTE when compared with smoke from reference cigarettes.

6.1 Use of Inhalation Studies in Product Development

Inhalation studies were included for product development and assessment to provide a comparison of biological activity between the smoke from the NEW CIGARETTE and a reference cigarette. The comparison was based on biological changes produced by either cigarette. This approach provides a comparison of biological activity between various prototypes of the NEW CIGARETTE and reference cigarettes. To evaluate the potential for biological activity, a protocol was designed to compare the NEW CIGARETTE with the reference cigarette. This protocol is similar to those published in the scientific literature and conforms with accepted principles of inhalation toxicology.

6.1.1 *Components*

Inhalation studies with the NEW CIGARETTE components consisted of a 14-day continuous dosing study and a 90-day subchronic study on glycerol (see Section 8.14.4.1.2) and a 90-day subchronic study on propylene glycol (see Section 8.14.8.1). An additional 14-day inhalation study was performed on an aerosol-forming mixture. No further studies were done on this mixture because it did not fully meet product performance standards. Emphasis was placed on glycerol because glycerol and water constitute approximately 90% of the total smoke constituents from the NEW CIGARETTE.

7.0

Comparative Study of Humans Smoking the NEW CIGARETTE and a Reference Cigarette

SUMMARY

Since the smoke from the NEW CIGARETTE is much simpler than that of reference cigarettes that burn tobacco, studies were conducted to compare the NEW CIGARETTE and a reference cigarette in terms of nicotine pharmacokinetics, human smoking behavior and the mutagenicity of human urine. Various factors, including diet, alcohol consumption and use of tobacco products other than cigarettes smoked for the study, were controlled for all subjects.

Data from the human smoking behavior study showed that smokers took more puffs, closer together in time, from the NEW CIGARETTE than from the reference cigarette. The average volume of individual puffs was the same. With both the NEW CIGARETTE and the reference cigarette, the amount of nicotine from the cigarettes was correlated with the total puff volume. The pharmacokinetics study was designed to determine whether nicotine from the NEW CIGARETTE was absorbed, metabolized and eliminated by humans in a similar manner as that from other cigarettes. These data were correlated with the human smoking behavior data and permitted calculation of: the amount of nicotine absorbed while smoking

either the NEW CIGARETTE or a reference cigarette, the rate of nicotine elimination, the nicotine plasma clearance, the rate of renal nicotine excretion, the rate of metabolic nicotine clearance and the proportion of nicotine metabolized to cotinine.

Subjects smoking the reference cigarette and those smoking the NEW CIGARETTE had similar time patterns of plasma nicotine concentration. Despite the change in smoking behavior, subjects smoking the NEW CIGARETTE consistently had lower plasma nicotine concentrations because of the smaller amount of nicotine in the smoke of the NEW CIGARETTE. Nicotine elimination was independent of the type of cigarette. There was no difference in the relative amounts of plasma cotinine, the major human nicotine metabolite, formed from nicotine absorbed from the reference cigarette and the NEW CIGARETTE. Cotinine elimination rates after smoking either cigarette were similar.

The urine of smokers has been reported to be more mutagenic than that of nonsmokers, as measured by the Ames bacterial mutagenicity assay. The human urine mutagenicity study was conducted to determine the mutagenicity of urine from nonsmokers, NEW CIGARETTE smokers and reference cigarette smokers. The study used a double-crossover design in which the subjects served as their own controls. Two groups of smokers and one nonsmoking group were used.

While the urine of all subjects, smokers and nonsmokers alike, was mutagenic, no mutagenic differences were observed between the urine of smokers of the NEW CIGARETTE and that of nonsmokers. In addition, the urine of smokers was significantly less mutagenic (equivalent to nonsmokers) when smoking the NEW CIGARETTE than when the same subjects smoked the reference cigarette.

7.1 INTRODUCTION

The human smoking studies were designed to compare the NEW CIGARETTE with a reference cigarette in terms of nicotine pharmacokinetics, urine mutagenicity, smoking behavior and selected biochemical observations. These measurements were made on smokers smoking both cigarettes freely. This approach allowed various smoking behaviors and methods to be expressed.

cigarette) blood sample drawn. All plasma and urine samples were analyzed for nicotine and cotinine by gas chromatography with nitrogen/phosphorus-sensitive detection (12).

Human puffing patterns ("puff-profiles") were monitored on-line during all phases of the human study for both cigarettes. Figure 7.3.4.1-1 illustrates puff-profile measurements schematically. Puff-profiles were measured with a system modeled after techniques first described by Cuzin (13) and further developed at R.J. Reynolds.

FIGURE 7.3.4.1-1

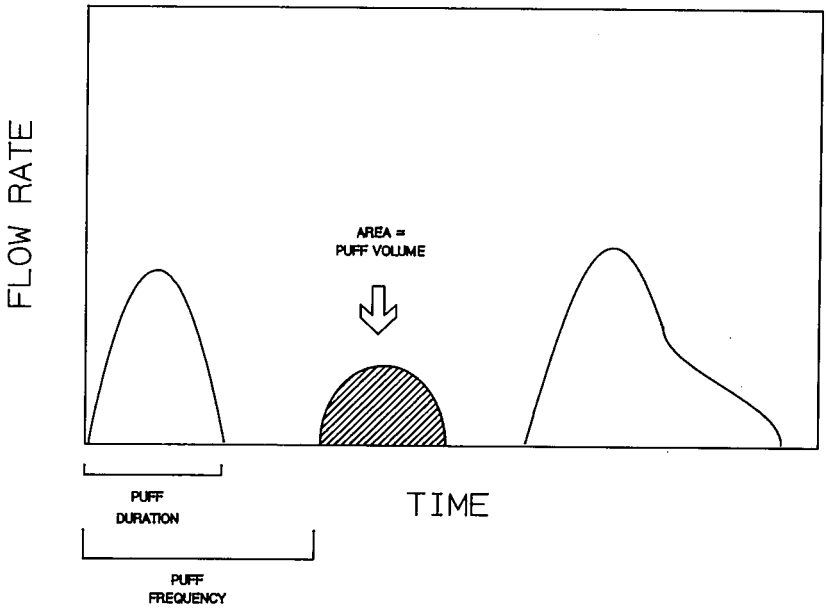

FIGURE 7.3.4.1-1 The measurement of puffing behavior basically consists of measuring the flow rate of smoke exiting the mouth end of the cigarette at discrete time points. The hypothetical puffs shown demonstrate basic puff properties: puff duration (the time from beginning to end of a puff), puff frequency (the time from the beginning of a puff to the beginning of the next), and puff volume (area under the flow vs. time curve). In smokers, these properties vary from puff to puff. The "shape" of the flow vs. time curve also varies from puff to puff.

Briefly, a small, tubular, plastic sensor (illustrated in Figure 7.3.4.1-2) was attached to the filter end of the cigarette. The sensor has a restrictive orifice in its center. Each side of the sensor (fore and aft of the restrictive orifice) was connected to pressure transducers (monitored by a computer) capable of detecting small pressure changes during puffing. The pressure measurements were converted to volumetric flow

rates by calculation. Sensor calibration and continuous sampling by the computer provide a record of a smoker's puff-profile. Puff-profiles describe how a particular cigarette was smoked, including:

1) Number of puffs taken

2) Volume of puffs (ml), including the "profile" of the puffs; the profile is generated by a plot of flow rate versus time

3) Frequency of puffs (sec), which is defined as the time from the start of one puff to the start of the next puff

4) Temporal duration of puffs (sec)

5) Total puff volume (ml)

6) Time alight (sec), which is defined as total time from start of the lighting puff to the end of the last puff.

FIGURE 7.3.4.1-2

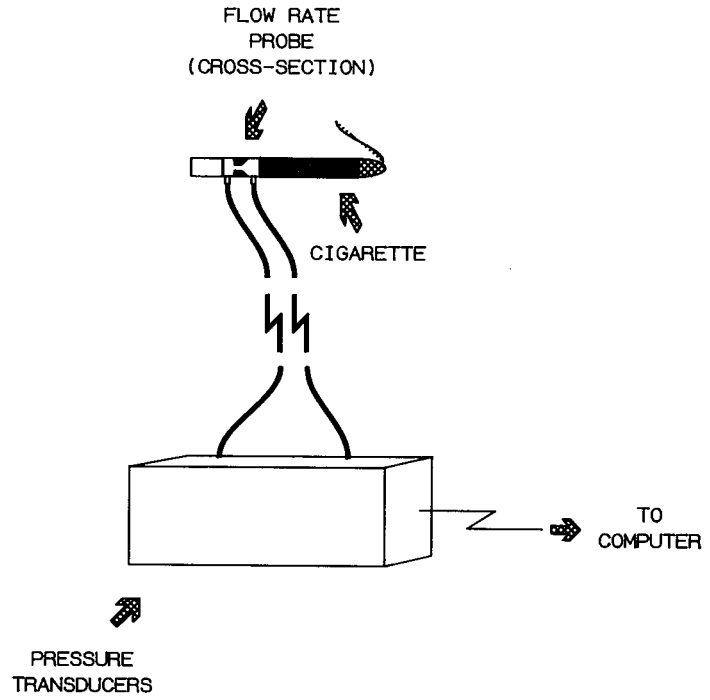

FIGURE 7.3.4.1-2 Schematic diagram of the flow-rate probe used to determine human cigarette puffing patterns ("puff-profiles"). Operation of the system is described in the text.

Yields of smoke components from cigarettes smoked by subjects were determined by replicating measured smoking behaviors via a computer-controlled smoking machine (patent pending). Referred to in the text as the "human-mimic smoking machine," the device is a 10-port, hydraulically driven smoking machine, that can accurately duplicate the flow-rate profiles of an individual's puffs, while accurately maintaining the puff durations and interpuff intervals. The human-mimic

Contents

SECTION 8.0 EVALUATION OF THE POTENTIAL TOXICITY ASSOCIATED WITH THE COMPONENTS OF THE NEW CIGARETTE PROTOTYPES

8.0

Evaluation of the Potential Toxicity Associated with the Components of the NEW CIGARETTE Prototypes

SUMMARY

This section presents an overview of literature reviews and studies associated with the assessment of the potential biological activity of specific components of the NEW CIGARETTE. Being an overview, it does not present detailed literature reviews of every study associated with this assessment. Also, a detailed discussion of certain components is not possible because of the proprietary nature of the components' constituents. However, an attempt is made to indicate the types of information upon which the assessments were based.

The assessment of potential toxicity of the NEW CIGARETTE components has been described in Section 3. Basically, this approach used a decision-tree system. Components not normally used in cigarettes now on the market were considered suitable if the literature indicated little or no risk to humans under the conditions of their use in the NEW CIGARETTE and if there was a history of human exposure without reported and confirmed adverse effects. All components with suitable physiochemical characteristics were tested in a genetic toxicology battery, as were smoke-aerosol condensates from prototypes containing the components. Certain components were tested in

short-term and subchronic inhalation studies. NEW CIGARETTE prototypes containing the components were tested in subchronic inhalation studies.

The results of the studies and literature reviews indicate that the use of these components, under the conditions in which they are used in the NEW CIGARETTE, is consistent with meeting the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

8.1 Carbon Heat Source

The heat source is primarily manufactured from wood pulp, a common cellulosic material, as discussed in Section 2.4. A high-temperature-baking step (>800°C) is used to carbonize adventitious organic compounds that could occur in the heat source. This step eliminates their potential to enter the smoke aerosol produced by the cigarette. The burning of the purified carbon results in the formation of carbon dioxide, carbon monoxide and water as the major products. Small amounts of other materials may be produced. If these materials became a part of the smoke aerosol at potential biologically relevant levels, they have been detected by the aerosol chemistry program described in Section 4. A portion of the carbon monoxide and carbon dioxide produced by the burning of the purified carbon becomes part of the the NEW CIGARETTE smoke inhaled by the smoker. The amounts, however, are less than in many (though not all) cigarettes commercially available today and even these levels appear susceptible to reduction with further refinements in the NEW CIGARETTE technology. The use of a purified carbon heat source in the NEW CIGARETTE is, therefore, considered consistent with meeting its Product Development Objectives (see Section 1.5).

8.2 Glass-Mat Insulator

A careful review of the scientific literature and analytical studies on the mainstream smoke of the NEW CIGARETTE indicates that the glass-mat insulator meets the Project Development Objectives (see Section 1.5). This conclusion is based upon the physical and chemical characteristics of the glass fiber in the glass-mat insulator and upon the filtration afforded by the design of the NEW CIGARETTE. In addition,

no fiber-associated toxicity was evident in any of the animal studies conducted at R.J. Reynolds or at the independent contract laboratories.

The glass-mat insulator used in the NEW CIGARETTE has been specially designed to minimize the potential for biological activity, based upon scientific findings from experimental studies in animals and from observational studies of humans. These findings indicate that the physical characteristics of fibers, especially diameter, are important determinants of respirability. Respirable fibers are usually defined as those having diameters less than or equal to 3 μm and lengths of 100–200 μm (1,2). The fiber diameter in the glass-mat insulator is specified to be 8 μm, more than twice the diameter of respirable fibers. The continuous-strand fibers are also chopped to a uniform length of 9.5 μm for mat manufacture. In addition, the fibers do not break longitudinally to form smaller diameter fibers. They break only transversely, and thereby maintain their non-respirable diameter. Specifications have been set for the glass-mat insulator chemical composition to limit the occurrence of specific oxides (see Section 2.5.2).

The components of the NEW CIGARETTE have also been configured to provide extensive filtration, which further reduces the potential for any fibers to enter the mainstream smoke. Chemical and microscopic analyses of the aerosol have presented no evidence that glass fibers occur in the mainstream smoke.

Studies in experimental animals and epidemiological studies of humans indicate that glass fibers with the physical and chemical characteristics of the glass-mat insulator are not associated with an increase in either morbidity or mortality under realistic exposure conditions. The International Agency for Research on Cancer has determined that the data on continuous-filament glass fiber are inadequate to show a carcinogenic effect in either animals or humans. The National Institute for Occupational Safety and Health limits airborne concentrations determined as total fibrous dust to a time-weighted average of 5 mg/m^3. The American Conference of Governmental Industrial Hygienists considers glass fiber to be a nuisance dust.

8.2.1 *Design Characteristics of the Glass-Mat Insulator*

Information available in the scientific literature aids in the design of glass fibers to minimize their potential to produce biological activity in specific consumer products. This information has been used in the design of the glass fibers used in the glass-mat insulator of the NEW CIGARETTE.

8.2.1.1 *Design Characteristics of the NEW CIGARETTE to Eliminate Mainstream Fibers*

The NEW CIGARETTE has been designed to minimize the potential for glass fibers to enter the smoke aerosol. Within the mat, the pectin binder holds the fibers together and reduces the occurrence of loose fibers. Any potential loose fibers would encounter a variety of filtration sites within the cigarette. For example, the glass-mat insulator itself acts as an initial filter to remove glass fibers. The charcoal of the heat source blocks the entry of fibers into the main air-flow of the cigarette. If any fibers were to enter the main air-flow by this route, they would encounter the alumina beads within the capsule and would potentially be removed by impaction upon and interception by these beads. If a stray fiber were to escape filtration within the capsule, it would then encounter the filtration system of the mouth-end piece.

The potential occurrence of stray fibers that escaped filtration within the glass-mat insulator and entered the bypass airstream around the heat source would result in their passing into the tobacco roll. The tobacco roll acts as a filtration device, which decreases the potential for the fibers to enter the mainstream air flow. Any fiber that escaped the filtration of the tobacco roll and entered into the mainstream air-flow would then face the filtration system in the mouth-end piece.

The mouth-end piece consists of the tobacco-paper filter and the polypropylene filter. Any fiber that escaped through the folds of the tobacco-paper filter would confront a circuitous passage through the polypropylene filter. This filter is a random maze of polypropylene strands that decreases the laminar flow of the airstream. This decrease results in diminution of the linear orientation of the fiber and increases the capture potential of the filter by both impaction and interception. The polypropylene strands are coated with a layer of glycerol, and as the cigarette is smoked, the glycerol content of the filter

increases. The glycerol results in a syrupy liquid coating on the polypropylene strands and should increase the fiber capture potential of the filter. The basic design of the cigarette results in several layers of filtration that dramatically reduce the potential for loose fibers to occur in the aerosol.

8.2.1.2 *Design Characteristics to Minimize Respirability of the Glass Fibers in the Insulator Mat*

The diameter of the glass fibers in the glass-mat insulator effectively eliminates the potential of alveolar deposition and related biological activity in that area of the pulmonary system. To ensure that the glass fibers of the mat are not respirable, the fiber diameter is specified to be 8 μm. This is more than twice the diameter of respirable fibers, which have been defined as those fibers $\leq$ 3 μm in diameter and 100-200 μm in length (1,2). To ensure careful control of the diameter of the glass strands, specific manufacturing processes were mandated. The glass strands are manufactured by a carefully controlled extrusion process that produces a uniform diameter. This is in contrast to the more common production of glass wool. Figure 2.5.2-1 presents a distribution plot of the fiber diameter for sample batches of glass fibers used in the insulator mat.

Glass fibers have a random amorphous, noncrystalline structure. Unlike asbestos, they break only transversely and not longitudinally. Therefore, glass fibers manufactured to a specific diameter will retain that diameter although they can be broken to shorter lengths under mechanical stress. The minimal length is determined by several factors. As a fiber becomes shorter, its resistance to breakage becomes greater. Figure 8.2.1.2-1 illustrates glass fibers from the insulator mat that have been extensively ball-milled. It is evident that, although the glass fibers have been broken to shorter lengths, their diameter has not been decreased.

FIGURE 8.2.1.2-1

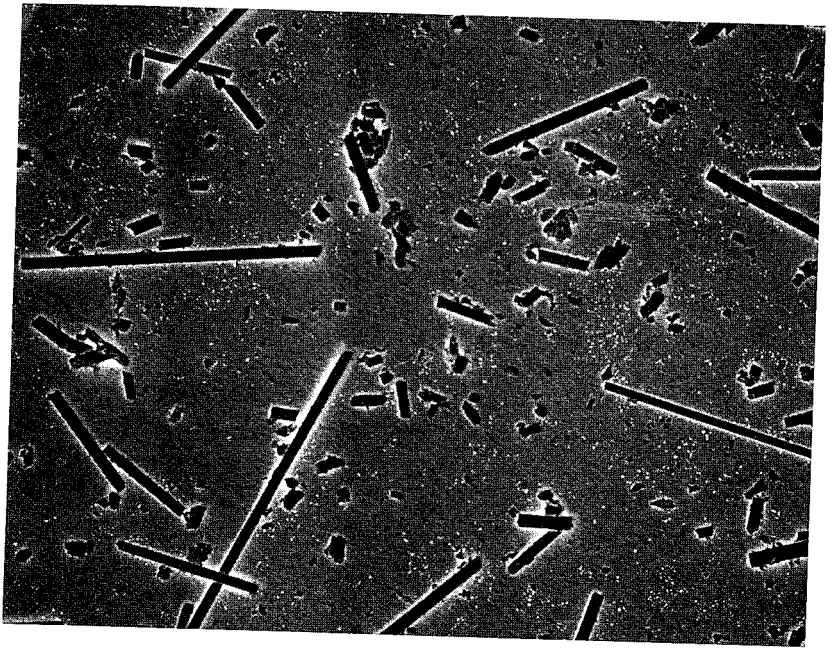

FIGURE 8.2.1.2-1 Ball-milled glass fibers illustrating that glass fibers can be mechanically broken to shorter lengths, but not broken to smaller diameters.

8.2.1.3 *Design Characteristics to Reduce Oxides*

As discussed in Section 2.5.2 of this document and illustrated in Table 2.5.2-2, the chemical composition of the glass is controlled to limit the occurrence of specific oxides. This ensures, to the extent possible, that dissolution of the fiber results in the production of essentially nontoxic products.

8.2.2 *Examination of the Aerosol for Fibers*

Studies have presented no evidence that glass fibers occur in the mainstream smoke of the NEW CIGARETTE. As discussed in the previous sections, the design of the cigarette and the nature of the glass fiber make it highly unlikely that any fibers would be present in the mainstream aerosol. Nevertheless, the aerosol has been examined for evidence of glass fibers. This examination included:

1) Aerosol chemistry analysis to detect the presence of silicon, the major constituent of glass

2) Scanning electron microscopic analysis for aerosol fibers in smoke condensates, done by R.J. Reynolds and by independent contract laboratories.

8.2.2.1 *Chemical Analysis for Silicon*

Existing analytical methodology was not adequate to analyze cigarette-smoke condensate for trace quantities of silicon. Therefore, a method was developed using graphite furnace atomization coupled with atomic absorption spectroscopy as the method of determination.

A calibration curve was developed using Certified Standard Reference Material 78a, obtained from the National Bureau of Standards. This standard has a SiO_2 content of 19.4 $\pm$ 0.1%. The standard was ground in a tungsten carbide container so that it passed a 325-mesh sieve. The ground material was prepared as a slurry in a mixture of methanol (added to account for the solvent used to wash the smoke condensate from the collection device), glycerol and water to represent the matrix present when the NEW CIGARETTE prototypes were analyzed. The calibration curve, together with appropriate confidence intervals, is shown in Figure 8.2.2.1-1.

FIGURE 8.2.2.1-1

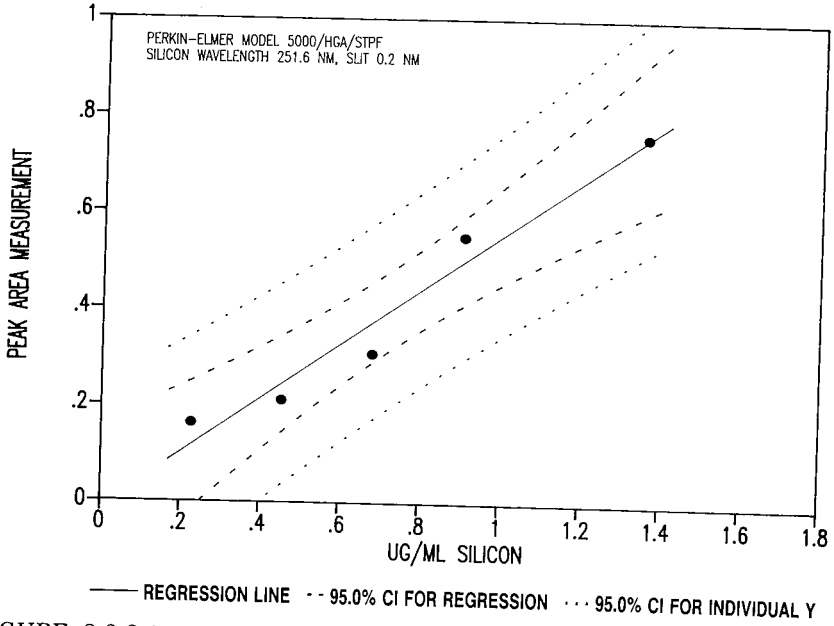

FIGURE 8.2.2.1-1 Calibration curve for NBS-78A silicon standard. The silicon standards were made up in a glycerol-water matrix to mimic the smoke condensate from the NEW CIGARETTE. The standards were analyzed by graphite furnace atomization coupled with atomic absorption spectroscopy.

To analyze smoke condensates, cigarettes were smoked under different conditions, and the condensates were collected by electrostatic precipitation. To minimize background contamination, Teflon sleeves were used on all ground-glass joints in the apparatus, and plasticware was used to transfer the slurries. Results of typical analyses are shown in Table 8.2.2.1-1.

TABLE 8.2.2.1-1 Aerosol Silicon Analyses [a,b,c,d,e,f,g,h]

Study	Sample Description	Smoking Conditions	Amount Found (µg/cig)	Standard Deviation (µg/cig)	Limit of Detection [e] (Instrument) (µg/cig)	Limit of Detection [f,g] (Method) (µg/cig)	Limit of Quantitation [f,g] (µg/cig)	N
TM-5/1R4F	TM-5	FTC	n.d	—	0.113	—	—	6
Comparison	1R4F	FTC	n.d	—	0.113	—	—	7
	Blank	FTC	n.d	—	0.113	—	—	6
Prototype	Prototype A	FTC	0.15	0.01	0.10	0.10	0.24	6
Comparison	Prototype B	FTC	0.20	0.05	0.10	0.10	0.24	5
	Blank	FTC	0.04	0.02	0.10	0.10	0.24	5
	No Silica							
Silica Gel	Gel	Stressed	0.19	0.02	0.10	0.06	0.13	6
Comparison	Silica Gel	Stressed	0.20	0.02	0.10	0.06	0.13	6
	Blank	Stressed	0.03	0.01	0.10	0.06	0.13	6

[a]n.d. = Not detected.
[b]Condensate from 100 cigarettes was collected for each sample.
[c]Quantitation was accomplished using the regression equation from the calibration curve.
[d]FTC smoking conditions consist of taking a 35-ml puff of 2-second duration every 60 seconds. Stressed smoking conditions consist of taking a 75-ml puff of 2-seconds duration every 35 seconds.
[e]Miller, J. C. and Miller, J. N., "Statistics for Analytical Chemistry," John Wiley & Sons: New York, 1984.
[f]Taylor, J. K., "Quality Assurance of Chemical Measurements," Lewis Publishers, Inc., 1987.
[g]American Chemical Society Committee Report, "Principles of Environmental Measurement," Anal. Chem. 55, 2210, 1983.
[h]See sections 2.8, 8.11 and 8.14.6 for discussions of the function and biological activity of the silica gel.

Examination of the data indicates that, even with the improved methodology, little or no silicon can be detected in the aerosol samples. In the study comparing prototypes A and B, where the cigarettes were smoked under FTC conditions, the amount of silicon determined was approximately 0.2 μg/cig for both prototypes. In the silica-gel study, where the cigarettes were smoked under the highly stressed conditions of a 75-cc puff of 2-second duration every 35 seconds, the silicon values determined were also 0.2 μg/cig. Since the stressed conditions (which are not generally attained by a human smoker) produce more condensate than do the FTC conditions (25.0 for the stressed smoking conditions versus 14.9 for the FTC conditions), one would expect a corresponding increase in the amount of silicon determined, if the silicon value were real. Since no increase was observed, there is a strong probability that the value is not real. This would not be surprising since these values are in the "gray area" of detectability based upon the limits of quantitation.

Assuming that the determined silicon values are real (an unlikely assumption based on the discussion in the previous paragraph) and assuming all silicon comes from the glass fiber, it is possible to calculate the maximum amount of glass fiber that could be present in the aerosol.

The glass fiber used in these prototypes has a maximum SiO_2 content of 65%. Assuming that the 0.2 μg of silicon measured under stressed smoking conditions comes from the glass fiber, the maximum amount of glass fiber present would be 0.66 μg/cigarette. Therefore, a 70-kg smoker smoking 60 cigarettes per day would be exposed to 0.566 μg/kg/day. The threshold limit value (TLV) established by the American Conference of Governmental Industrial Hygienists (ACGIH) for workers exposed to fiberglass is 10 mg/m^3 per eight-hour workday. Thus, a 70-kg worker transpiring 10 m^3 of air per day is allowed to be exposed to 1429 μg/kg/day. This is 2525 times more than the maximum amount the same worker would receive from smoking 60 NEW CIGARETTE prototypes in a day. Several factors limit the TLV-based risk-assessment. First, the TLV for glass fibers was set several years ago. New data could result in a change in the TLV. Second, the 10 mg/m^3 TLV is a gravimetric determination, and such determinations do not necessarily reflect fiber concentration. For example, when

equivalent *numbers* of small fibers and large fibers are weighed, the weight of the small fiber will be less than that of the large fiber. Likewise, identical *weights* of small fibers and large fibers may result in a greater number of small fibers than large fibers.

8.2.2.2 *Microscopic Examination of the Aerosol for Fibers*

Scanning electron microscopic (SEM) examination of prototype aerosols has been done both at R. J. Reynolds and at contract laboratories. Positive controls were prepared by ball milling the glass-fiber mat to produce a fiber length as small as possible. This ground material was slurried in a mixture of methanol, glycerol and water. Filtration of these slurries gave samples of known concentrations.

To date, SEM analysis has shown no evidence of fibers being present in any of the aerosols. However, because of variable results obtained with the positive controls, the SEM assay cannot be considered totally definitive, and refinements of the technique continue.

8.2.3 *Toxicology of Glass Fibers*

As discussed above, there is no chemical or physical evidence that any glass fiber gets into the aerosol. No glass-associated pathology has been observed in the inhalation studies (see Section 6). A review of glass-fiber toxicology is presented in the Appendix (Section 8.14.1), emphasizing what is currently known about man-made vitreous fibers.

REFERENCES

1) World Health Organization; International Agency for Research on Cancer. *Biological Effects of Man-Made Mineral Fibres.* World Health Organ., EURO Rept. Stud. 81, 1983.
2) Timbrell, V. Aerodynamic Considerations and Other Aspects of Glass Fiber. In: *Occupational Exposure to Fibrous Glass: Proceedings of A Symposium.* U.S. Dept. HEW (NIOSH) Publ. No. 76-151: 33-50, 1976.

8.3 ALUMINUM CAPSULE

The capsule is constructed of aluminum to assure minimal potential for biological activity, while maintaining adequate heat transfer. Its use in the cigarette does not result in disruption of the capsule that would produce aluminum particles.

The capsule is not exposed to temperatures high enough to melt the aluminum. The capsule's location within the cigarette makes the capsule impossible to dislodge during smoking. As part of the manufacturing process, the capsule is cleaned of any contaminants and lubricants by a high-vapor-pressure inert solvent before use in the cigarette. Residual solvent evaporates from the capsule before it is incorporated into the cigarette. Chemical analysis of the smoke aerosol from the NEW CIGARETTE for aluminum is discussed in Section 8.4.1.

Aluminum is an abundant element, and small quantities occur naturally in foods. Certain forms of aluminum are permitted as food additives. Aluminum hydroxide is used in over-the-counter antacid. Aluminum hydrochloride is used as an antiperspirant. Aluminum compounds are used as flocculents in drinking water, and aluminum cooking utensils are in common use. No adverse effects from these multiple exposures to aluminum have been reported, with the possible exception of effects in individuals undergoing kidney dialysis, as discussed in Section 8.14.2. Aluminum toxicity studies have been limited because of aluminum's poor absorption in the metallic form. Aluminum toxicity is reviewed in Section 8.14.2. These data, considered as a whole, indicate that the use of an aluminum capsule in the NEW CIGARETTE is consistent with the Product Development Objectives (see Section 1.5).

8.4 Alumina Substrate

Alpha-alumina, a form of alumina (Al_2O_3) with a very low potential for adverse biological activity, was selected as the substrate in the NEW CIGARETTE. Because the *alpha*-alumina spheres are contained within the aluminum capsule, and because of the NEW CIGARETTE's extensive filtration system, the potential for *alpha*-alumina to migrate into the aerosol is extremely low.

When evaluating toxicity data related to the various forms of alumina, it is important to keep in mind factors such as crystalline structure, purity, particle shape and size, and any other particles that may occur concurrently with various forms of alumina. Each of these factors can affect the biological activity of this compound. Only *alpha*-alumina is used in the NEW CIGARETTE. This form of alumina is nonfibrous in

nature. The biological activity of *alpha*-alumina is reviewed in Section 8.14.3.

8.4.1 *Chemical Analysis of the Aerosol for Aluminum*

The condensate from several NEW CIGARETTE prototypes has been carefully examined for the presence of aluminum. There are two principal sources for the potential occurrence of aluminum in the NEW CIGARETTE aerosol: the aluminum capsule and the alumina substrate. Based on the discussion in the previous sections of this report, it is highly unlikely that any of these materials would actually become part of the aerosol. Nevertheless, the condensate from several prototypes has been analyzed for aluminum.

Existing analytical methodology was not adequate to analyze smoke condensates for trace quantities of aluminum. Therefore, a method was developed using graphite furnace atomization coupled with atomic absorption spectroscopy as the end determination. This is the same methodology used to analyze for silicon, and it parallels the method developed for silicon (see Section 8.2.2.1 for a discussion of the silicon analysis).

A calibration curve was developed using Certified Standard Reference Material 1412, obtained from the National Bureau of Standards. This standard has an aluminum oxide (Al_2O_3) content of $7.52 \pm 0.24\%$. The standard was ground in a tungsten carbide container so it would pass through a 325-mesh sieve. The ground material was prepared as a slurry in a mixture of methanol (to mimic the condensate-extraction solvent), glycerol and water to represent the matrix present when the NEW CIGARETTE prototypes were analyzed. The resulting calibration curve, together with appropriate confidence intervals, is presented in Figure 8.4.1-1.

FIGURE 8.4.1-1

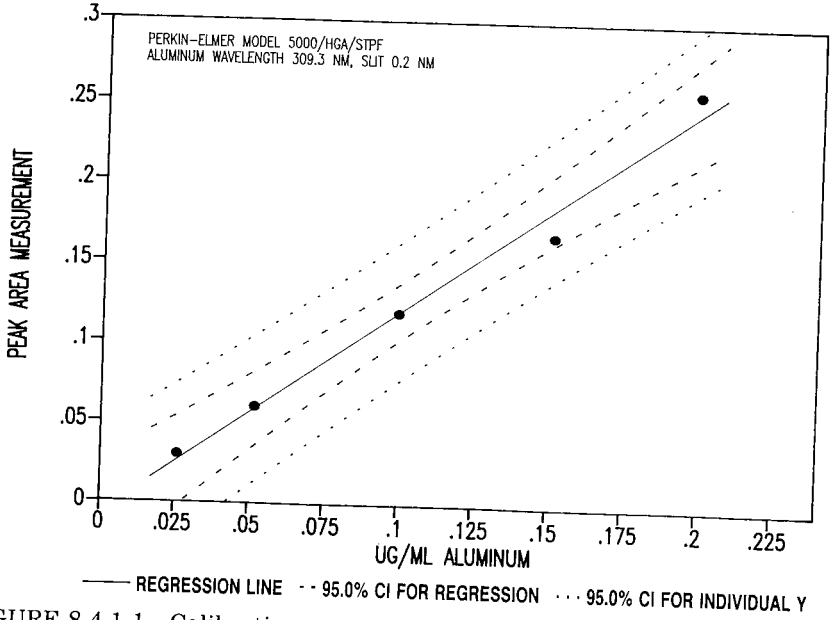

FIGURE 8.4.1-1 Calibration curve aluminum using NBS Certified Standard Reference Material 1412. The aluminum oxide standards were made up in a glycerol-meter matrix to mimic the smoke condensate from the NEW CIGARETTE. The standards were analyzed by graphite furnace atomization coupled with atomic absorption spectroscopy.

To analyze smoke condensates, cigarettes were smoked under different conditions, and the condensate was collected by electrostatic precipitation. To minimize background contamination, Teflon sleeves were used on all ground-glass joints in the apparatus, and plasticware was used to transfer the slurries. Results of a typical analysis are shown in Table 8.4.1-1.

TABLE 8.4.1-1 Aerosol Aluminum Analyses [a,b,c,d,e,f,g]

Study	Sample Description	Smoking Conditions	Amount Found (μg/cig)	Standard Deviation (μg/cig)	Limit of Detection [e] (Instrument) (μg/cig)	Limit of Detection [f,g] (Method) (μg/cig)	Limit of Quantitation [f,g] (μg/cig)	N
TM-5/1R4F	TM-5	FTC	n.d	—	0.113	—	—	6
Comparison	1R4F	FTC	n.d	—	0.113	—	—	7
	Blank	FTC	n.d	—	0.113	—	—	6
Prototype	Prototype A	FTC	0.008	0.002	0.002	0.006	0.013	6
Comparison	Prototype B	FTC	0.015	0.011	0.002	0.006	0.013	6
	Blank	FTC	0.003	0.001	0.002	0.006	0.013	5
	No Silica Gel	Stressed	0.025	0.007	0.002	0.011	0.025	5
Silica Gel	Silica Gel	Stressed	0.012	0.002	0.002	0.011	0.025	6
Comparison	Blank	Stressed	0.005	0.002	0.002	0.011	0.025	6

[a] n.d. = Not detected.
[b] Condensate from 100 cigarettes was collected for each sample.
[c] Quantitation was accomplished using the regression equation from the calibration curve.
[d] FTC smoking conditions consist of taking a 35-ml puff of 2-second duration every 60 seconds. Stressed smoking conditions consist of taking a 75-ml puff of 2-second duration every 35 seconds.
[e] Miller, J. C. and Miller, J. N., "Statistics for Analytical Chemistry," John Wiley & Sons: New York, 1984.
[f] Taylor, J. K., "Quality Assurance of Chemical Measurements," Lewis Publishers, Inc., 1987.
[g] American Chemical Society Committee Report, "Principles of Environmental Measurement," Anal. Chem. 55, 2210, 1983.

The data indicate that even with the improved methodology, little or no aluminum can be detected in the aerosol samples. In the study comparing NEW CIGARETTE prototype TM-5 with the 1R4F reference cigarette, no aluminum was detected. In the prototypes comparison study, the value of 0.015 μg/cig found for prototype B was slightly above the limit of detection for the method, but not above the limit of quantitation. In the silica gel comparison (see Section 8.11.1 for a discussion of the silica gel), the prototype without silica gel gave a value of 0.025 μg/cig. This value is slightly above the limit of detection of the method, but is equal to the limit of quantitation. Because these values are in the "gray area" of detectability and quantitation, there is a strong likelihood that no aluminum is present.

If one assumes that the determined aluminum values are real (a questionable assumption based on the data) and that they are due to alumina, it is possible to calculate the maximum amount of alumina that could be present in the aerosol. The highest value of aluminum measured was 0.025 μg/cig.; this corresponds to 0.047 μg/cig. of alumina. A 70 kg person smoking 60 cigarettes per day would receive 0.040 μg/kg/day of alumina. The ACGIH classifies alumina as a nuisance dust with a time-weighted average-threshold limit value (TWA-TLV) of 10 mg/m^3 of air. Therefore, a 70 kg worker transpiring 10 m^3 of air per day is allowed to be exposed to 1429 μg/day. This amount is approximately 35,700 times more than the maximum amount the same smoker would receive from smoking 60 of the NEW CIGARETTE prototypes in a day, assuming the presence of *alpha*-alumina in the aerosols. The limitations of using the TWA-TLV for such calculations have been previously discussed in Section 3.4.2.

8.4.2 *Overview of* Alpha-*Alumina as Substrate in the NEW CIGARETTE*

Review of the scientific literature associated with the toxicity of *alpha*-alumina, chemical analysis for aluminum in smoke condensates from the NEW CIGARETTE and lack of aluminum-specific biological activity in inhalation studies of the NEW CIGARETTE smoke aerosols indicates the use of *alpha*-alumina in the NEW CIGARETTE is consistent with the Product Development Objectives (see Section 1.5).

8.5 Spray-Dried Tobacco

The function, composition and production of spray-dried tobacco have been discussed in Section 2. Spray-dried tobacco was negative when tested in the Ames assay. In addition, it has been tested indirectly in the 14- and 90-day rat and hamster inhalation studies (Section 6). The use of spray-dried tobacco is considered consistent with meeting the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

8.5.1 *Stability of the Spray-Dried Tobacco*

Like other materials containing sugar and other substrates for microbial growth, the spray-dried tobacco has the potential to mold and support bacterial growth. Molding is minimized by the nicotine naturally present, the low moisture content, and by storing the tobacco in a clean, dry environment. Even though the spray-dried tobacco will not be stored for prolonged periods, studies have been done on stored spray-dried tobacco to monitor for bacteria, yeast and mold.

These studies monitored total sugar, pH, moisture, bacteria cells/gram of tobacco, and yeast and mold cells/gram. One study sampled the spray-dried tobacco 14 times during a six-month period, and another sampled once per month for six months. Neither study showed a significant change in total sugars, pH or moisture. Although the bacteria cells/gram and yeast cells and mold cells/gram were somewhat variable, the only evident trend was toward decreased cell counts. These data indicate that properly stored spray-dried tobacco is not a substrate conducive to the growth of bacteria, yeast and molds. Tobaccos with high moisture content stored in high humidity can support the growth of fungi. Welty and Weeks (1) reported that moisture contents of 16% and below inhibited mold growth. They found that high moisture content led to increases in mold counts and large reductions in sugar levels of tobacco. The 6-7% moisture content (by weight) of the spray-dried tobacco also apparently inhibits microbiological growth. Although these two studies used spray-dried tobacco stored for six months, when the NEW CIGARETTE is in full-scale commercial production the spray-dried tobacco will be stored for a much shorter time.

8.5.2 *Analysis for Mycotoxins in Spray-Dried Tobacco*

An independent laboratory qualified to analyze various materials for mycotoxins has analyzed spray-dried tobacco that had been stored for a prolonged period. No evidence of mycotoxin contamination was found. Specific analyses were done for the following mycotoxins: Aflatoxins B_1, B_2, G_1, and G_2; Ochratoxin A and B; T-2 toxin; Zearelenone, Zearalenone; sterigmatocystin, deoxynivalenol and diacetoxyscirpenol.

REFERENCE

1) Welty, D. E.; Weeks, W. W. Influence of Relative Humidity, Temperature, and Time of Fungal Growth and Chemical Composition of Flue-Cured Tobacco. Tob. Sci. 19: 71-74, 1975.

8.6 FLAVOR

The flavor ingredients used in the development of the NEW CIGARETTE are proprietary and cannot be disclosed. Although many flavor ingredients were considered and used in the prototypes described in this monograph, the current flavor consists of only two components: a simple saccharide found in many food products and an extract of a very common food. Throughout cigarette development, the flavor ingredients have been individually reviewed by assessing the available scientific literature. All flavor mixtures were tested in the Ames assay, as was the smoke from prototypes containing these flavors. In addition, flavors with use potential have been tested in an *in vitro* genetic toxicology battery, with negative results. Various flavor mixtures have also been assayed indirectly in the aerosol in 14- and 90-day rat and hamster inhalation studies. Although the flavor package changed for each Test Model, the assay results remained consistent from model to model. The literature reviews and the *in vitro* and *in vivo* studies indicate the flavor used in the NEW CIGARETTE is consistent with the Product Development Objectives (see Section 1.5).

8.6.1 *Assessment of Scientific Literature*

The potential for biological activity of the individual flavoring components considered in the development of the NEW CIGARETTE was reviewed by assessing the available scientific literature. At times during flavor development, this review

resulted in several ingredients being either removed or replaced.

8.6.2 In Vitro *Assays*

In addition to the literature reviews discussed above, the flavors have been tested for potential biological activity both by R.J. Reynolds and by independent contract laboratories. Biological testing has paralleled the development of the NEW CIGARETTE and has been done almost from the inception of the cigarette. Flavors were tested as mixtures rather than as individual flavor compounds, to allow the expression of the interaction of these components within the complex mixtures. This permitted observations of any enhancement or reduction of potential biological activity in each flavor mixture. During development, *in vitro* bacterial mutagenicity of the flavors was assessed using the Ames assay.

8.6.3 *Flavor Development*

Since there was no history of use for the NEW CIGARETTE, guidelines were set for the development of NEW CIGARETTE flavors. The flavor chemists were restricted to using the following:

1) Flavoring substances determined by the Flavor Extract Manufacturers Association (FEMA) or the FDA to be GRAS for use in food

2) Flavoring substances approved by the FDA for use in food

3) Flavoring substances that are natural food substances or extracts of natural food substances

4) Flavoring substances naturally found as cigarette smoke constituents, with no reported or suspected adverse health effects

5) Substances that were tested in genotoxicity assays and found to have no genotoxicity potential under the conditions of the assays.

In addition to providing the required flavor attributes, the flavors could not be mutagenic in the Ames assay nor could they contribute any potential mutagenicity to the NEW CIGARETTE smoke aerosol, as measured by the tests used to assess this potential in the smoke of the NEW CIGARETTE. More than

100 flavors or flavor components were tested in the Ames assay during product development.

An example of how R.J. Reynolds used the results from mutagenicity testing during the development of the NEW CIGARETTE can be shown using one of the prototype flavors. When this flavor was first tested in the Ames assay, it was mutagenic to strain TA-98 with metabolic activation, but negative with the other combinations. The individual flavor formulations constituting the total flavor were tested to determine which component was mutagenic. One component was mutagenic; the others were not. The flavor was reformulated without the mutagenic component and retested. This was done to ensure that the original mutagenicity was due to the suspected component alone and not to some other factor. The results of this test were negative. Once the mutagenic component was confirmed, it was replaced with one that was nonmutagenic. The new flavor containing the replacement component was then tested and found to be nonmutagenic.

In some instances, individual flavor components were tested in either the complete genetic toxicology battery or in selected assays from the battery. Decisions to test an individual flavor component were based upon the following:

1) A lack of history of use in tobacco products
2) A lack of occurrence in smoke from other cigarettes
3) A lack of history of use in other consumer products
4) Structure/activity considerations.

Components that tested positive in these assays were not used in the NEW CIGARETTE.

8.6.4 In Vivo *Assays*

In addition to the *in vitro* testing described above, various flavor packages have contributed to the aerosols in the Test Models tested in rat and hamster 14- and 90-day inhalation assays. Although there were differences in the components of the flavor for each Test Model, the results of the different assays were constant (Section 6).

8.7 GLYCEROL

In various forms, glycerol is a component of many complex physiological chemicals that are essential to plant and animal

life. Glycerol, like glucose, has a very low potential for adverse biological activity, as demonstrated by the review of the scientific literature and from scientific studies conducted at R.J. Reynolds and in independent contract laboratories (Section 8.14.4). The use of glycerol is, therefore, considered consistent with the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

8.8 Tobacco Roll

The tobacco roll is made from standard tobaccos commonly used in manufacturing cigarettes. The blend of tobaccos chosen depends on the organoleptic properties desired in the cigarette. Since the tobacco roll is not burned, many of the tobacco smoke compounds alleged to have adverse biological effects are not produced. Heating rather than burning tobacco is, therefore, assessed as significantly reducing the potential for biological activity from the smoke of the NEW CIGARETTE, and is consistent with meeting its Product Development Objectives (see Section 1.5).

8.9 Tobacco-Paper Filter

The tobacco-paper filter is composed of tobacco fiber and unbleached softwood kraft, both of which are cellulose-based materials. As with other components of the NEW CIGARETTE, the tobacco-paper filter has been tested indirectly in the *in vitro* and *in vivo* genetic toxicology battery as condensates and aerosol (Section 5), and the 14- and 90-day rat and hamster inhalation studies (Section 6). The test results indicate that the use of a tobacco-paper filter is consistent with the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

8.10 Polypropylene Filter

Polypropylene is approved by the FDA as a food-contact packaging material, and the recommended TWA-TLV is the one for nuisance dusts. Polypropylene has a high chemical inertness and is essentially nontoxic. Thermal degradation of polypropylene occurs only at temperatures above that of the NEW CIGARETTE aerosol temperature as it traverses the filter. The biological monitoring of polypropylene-manufacturing

workers has not produced evidence of adverse effects. In addition, polypropylene is used in many commodities, such as diaper liners, bed linens, surgical gowns, drapes, protective garments and many other products. The biological activity of polypropylene is reviewed in Section 8.14.5. The use of polypropylene as a cigarette filter in the NEW CIGARETTE is, therefore, considered consistent with the Product Development Objectives (see Section 1.5).

8.10.1 *R.J. Reynolds Studies Involving Polypropylene Filter*

NEW CIGARETTE prototypes containing the polypropylene filter were smoked under stressed conditions, and the resulting condensates were tested in the Ames assay with *Salmonella typhimurium* strains TA-98 and TA-100 with S-9. In this assay, the NEW CIGARETTE prototype configuration consisted of an open hole between the capsule and the polypropylene filter to allow the aerosol to be at exaggerated temperatures when it contacted the filter. There was no tobacco-paper filter. A smoking regimen of 100-cc puffs every 15 seconds resulted in severe polypropylene-filter melting on all six models smoked. The aerosol condensate was tested at 0, 250, 500 and 700 µg in 50 ul DMSO and at 950, 1200 and 1400 µg in 100 ul DMSO. There was no significant increase in revertant number with an increase in dose level with either strain.

Since it was a part of the developmental prototypes being evaluated, the polypropylene filter has been tested indirectly in numerous mutagenicity assays (Section 5), 14- and 90-day rat and hamster inhalation studies (Section 6) and in the human studies (Section 7). None of the results from any of these tests indicated any potential adverse biological effects from the polypropylene filter under the conditions of use in the NEW CIGARETTE.

8.11 Silica Gel

Amorphous silica gel is used as a manufacturing aid with the alumina substrate. The information reviewed indicates that the use of silica gel meets the Product Development Objectives of the NEW CIGARETTE (Section 1.5). Chemical analysis

of condensates from several NEW CIGARETTE prototypes indicates that little or no silicon is present in the mainstream smoke (Section 8.11.1).

The FDA has approved silicon dioxide for several food uses, and the Joint FAO/WHO Expert Committee on Food Additives has set no limit, within good manufacturing practice, for the acceptable daily intake of silicon dioxide. In addition, the ACGIH has recommended a TWA-TLV of 10 mg/m^3 for silica gel, the level recommended for a nuisance dust.

The silica gel is an amorphous silica with no crystalline structure present. Studies of human workers indicate that true amorphous silicas lacking crystalline structure have a low potential for biological activity. Although fibrosis has been produced in experimental animals with amorphous silicas, these silicas are different from the silica gel used as a manufacturing aid for the NEW CIGARETTE. In these studies, crystalline structure was present, the routes of administration were not relevant or the doses were unrealistically large. The biological activity of silica gel is reviewed in Section 8.14.6.

8.11.1 *Chemical Analysis of NEW CIGARETTE Aerosol for Silicon*

During the development of the NEW CIGARETTE, R.J. Reynolds' analytical chemists conducted studies using graphite furnace atomization, coupled with atomic absorption spectrometry, to access the potential for silicon delivery in the mainstream aerosol. NEW CIGARETTE prototypes with and without silica gel were smoked using the FTC standards of 35 cc puffs of two-second duration every 60 seconds. In addition, cigarettes with and without silica gel were smoked under stressed conditions of 75cc puffs of two-second duration every 35 seconds. An average of 0.2 µg silicon/cigarette was determined in all studies. Since the stressed conditions yield more condensate than the FTC conditions, a corresponding increase in the silicon content of the condensate would be expected if the silicon values were real. An increase in condensate silicon did not occur. This result is not surprising since the values determined are in the "gray area" near the limits of detection. Although the data cannot rule out a trace of silicon in the

smoke aerosol, chemical analysis of the condensates from several NEW CIGARETTE prototypes indicates there is no evidence of silicon present in mainstream smoke within the limits of quantitation. See Section 8.2.2.1 for details of the analysis.

8.12 PAPERS

The major component of all the papers is softwood kraft fiber, which is composed of naturally occurring cellulose-based materials. Other proprietary agents associated with paper manufacture to impart desired characteristics may occur in the NEW CIGARETTE papers. All of the components used in the NEW CIGARETTE papers have been evaluated by reviewing the available scientific literature, regulations by the FDA and Occupational Safety and Health Administration (OSHA), and recommendations by the ACGIH. Additionally, the papers in the NEW CIGARETTE have been indirectly tested in both the genetic toxicology battery (Section 5) and the animal inhalation studies (Section 6). The review and test results indicate that the various papers selected for use in the NEW CIGARETTE are consistent with Product Development Objectives (see Section 1.5).

8.12.1 *The Outer-Wrap Paper*

The outer-wrap paper has two important functions. The first is to connect the two main components, the front-end piece and the mouth-end piece, together. The second is to burn back for only a specified distance to simulate the ash of other cigarettes. This special, patented paper was developed by a supplier specifically for the NEW CIGARETTE. Two components of the outer-wrap paper assist in producing its special characteristics, glass fibers and attapulgite clay.

8.12.1.1 *Glass Fibers of the Outer-Wrap Paper*

The first component that gives the outer-wrap paper its unique characteristics is long glass fibers, which are added to the wood pulp and become an integral component with the fibrous cellulose strands to form the paper. These glass fibers add strength to the burnt paper and maintain an integral ash. As opposed to the cellulose fibers that are carbonized and lose strength, the glass fibers withstand the heat of paper combustion and maintain the strength of the ash.

The fibers have a nominal diameter of 1.0 μm. As noted in Section 8.2 and the review of glass fiber toxicology in Section 8.14.1, these fibers are, by definition, respirable because of their diameter. However, only 6-8 mm of the outer-wrap paper is burned. Any stray fiber that might become entrapped into the air flow of the cigarette would probably be filtered by the extensive filtration system of the NEW CIGARETTE as discussed in Section 8.2.1.1. As discussed in Sections 8.2.2 and 8.2.2.1, there is no evidence of the occurrence of glass fibers in the mainstream smoke aerosol of the NEW CIGARETTE. The biological activity of glass fibers is reviewed in Section 8.14.1. These data indicate that the use of glass fibers in the outer-wrap paper is consistent with the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

8.12.1.2 *Attapulgite Clay in the Outer-Wrap Paper*

Attapulgite clay is a hydrated aluminum-magnesium silicate added to the outer-wrap paper of the NEW CIGARETTE as a filler to control both paper and ash porosity. The review in Section 8.14.7 indicates that the use of attapulgite clay in the outer-wrap paper is consistent with the Product Development Objectives of the NEW CIGARETTE (see Section 1.5). The attapulgite clay is mined from a large deposit located in Georgia and northern Florida. Attapulgite fibers from this deposit range in length from 0.1 to 2.5 μm, with a mean of 0.52 μm. They range in diameter from 0.02 to 0.1 μm, with a mean of 0.06 μm. Aspect ratios (length:diameter) are generally greater than 10:1. Attapulgite is found in association with other clays, but purities up to 90% can be attained.

There are currently more than 80 specific uses for attapulgite clay including carriers for pesticides, pharmaceuticals and cosmetics; pet waste absorbents; oil and grease absorbents; drilling muds; thickeners for paints; fillers for paper; and as asbestos substitutes in plaster, joints, underseals, sealants and brake linings. American attapulgite is of low toxicity (see review in Section 8.14.7). The International Agency for Research on Cancer determined that there is limited evidence for the carcinogenicity of attapulgite in experimental animals, and inadequate evidence for such results in humans.

8.13 Adhesives

The adhesives used in the NEW CIGARETTE are proprietary, and their individual reviews cannot be presented here. However, all ingredients of the adhesives have been evaluated.

The adhesives used in the NEW CIGARETTE are either currently used by R.J. Reynolds or have been used in the past to manufacture the company's other cigarette brands. Since no more than the first 6-8 mm of the outer-wrap and insulator-mat inner-wrap papers of the NEW CIGARETTE are burned, only about 240 μg of adhesive per cigarette is pyrolyzed. Therefore, the number and quantity of pyrolysis products that could potentially occur in the smoke aerosol are limited.

As with the other components of the NEW CIGARETTE, the adhesives have been tested indirectly in the *in vitro* and *in vivo* genetic toxicology battery (Section 5) and in the 14- and 90-day rat and hamster inhalation studies (Section 6) in the form of the whole cigarette.

The results of these studies, as well as the individual literature reviews, indicate that the use of the various adhesives is consistent with the Product Development Objectives of the NEW CIGARETTE (see Section 1.5).

8.14 Literature Reviews of Components Used in the NEW CIGARETTE

8.14.1 *Review of the Toxicology of Glass Fibers*

Although this review should not be considered comprehensive, it does present representative studies using a number of routes of administration and various fiber sizes. Certain of these studies have been included even though they are neither representative of the potential route of exposure nor of the fiber size associated with the NEW CIGARETTE. A large number of scientific studies have been directed toward the determination of the potential adverse effects of man-made vitreous fibers (MMVF). When evaluating data from these studies, it is important to distinguish between studies designed to produce data on mechanisms associated with the biological activity of fibers by direct application to various tissues and those studies designed to determine potential adverse effects and hazard assessment by the inhalation route.

As is often the case, those studies directed toward an understanding of mechanisms use models that have little or no relationship to human exposure to MMVF. These studies use a number of dosing methodologies, which although possibly adequate for mechanistic studies, bear little relationship to actual human exposure. For instance, studies using implantation of MMVF into various body cavities have provided important information on the mechanisms associated with the potential biological activity of fibers, but cannot be extrapolated to human inhalation exposure. Other studies have employed intratracheal instillation of masses of fibers and do not reflect the circumstances associated with actual inhalation of fibers. Instillation delivers a massive quantity of fibers to very specific respiratory surfaces and bypasses many of the protective mechanisms of the respiratory tract.

Only carefully designed and performed inhalation studies of MMVF come close to the exposure characteristics associated with human exposure. However, these studies also have limitations. Most of them have been performed with laboratory animal species that differ both anatomically and physiologically from humans. Other limitations include extremely high exposure levels, lack of knowledge of inhalation dosimetry, and general nonuniformity of fiber size. However, even with these restrictions, inhalation studies are more useful in assessing the potential hazard associated with human exposure to MMVF than those using implantation and instillation.

The current data on the presence or absence of potential adverse effects associated with human exposure to MMVF are derived from epidemiological studies of individuals employed in fiber manufacture and use. The difficulties associated with the proper design, control and interpretation of epidemiological studies are generally well-known and beyond the scope of this discussion. It may be especially difficult to determine the precise nature of pulmonary exposures, since other dusts and materials may be involved concurrently and may complicate data interpretation. It should also be pointed out that studies with free-living human populations comprised of genetically, socially, nutritionally, environmentally, emotionally and constitutionally diverse individuals are extremely difficult to interpret. There are many complex interactions that may influence risk and thus the interpretation of data.

Two additional factors that are important in understanding the potential adverse effects associated with exposure to MMVF are the exposure level and the physical and chemical nature of the fibers under study. These are key points in every study and must be carefully evaluated to decrease confusion concerning what is actually being investigated.

A large database on the biological activity of fibrous materials has been generated through studies designed to determine the mechanisms of carcinogenicity associated with certain fibers in animals. Table 8.14.1-1 lists some of the natural and man-made fibers that have been shown to produce biological activity in animals.

TABLE 8.14.1-1 Man-Made and Natural Fibers with Biological Activity in Animals[a]

Aluminum Oxide
Aluminum Silicate Glass
Amosite
Anthopyllite
Attapulgite
Borosilicate Glass
Chrysotile
Crocidolite
Mineral Wool
Potassium Titanate
Silicon Carbide
Sodium Aluminum Carbonate
Tremolite
Wollastonite

[a]Adapted from Leineweber (1).

In recent years, there have been extensive reviews of fiber toxicology. Gross and Braun (2), Lee (3), Leineweber (1,4), and Lippmann *et al.* (5) have reviewed the chemistry and physics of mineral and vitreous fibers in relation to biological activity in the pulmonary tract.

Leineweber (1,4) has discussed the major physical and chemical characteristics associated with the biological activity of various fibers. He considers the major determinants of biological activity to be the following:

1) Exposure and dose response

2) Fiber dimension, structure and composition
3) Biological durability.

The level of exposure is a major determinant of biological activity since fibers exhibit classic dose-response behavior in biological studies. Due to the ubiquitous nature of mineral fibers, most humans are exposed to small quantities of these minerals in their environment and appear to suffer no adverse effect. The physical dimensions of the fiber in the environment contribute to actual exposure since only fibers below a certain size are respirable (6), *i.e.*, able to reach the alveolar area of the lung. Dimensions are also important since the nature of the fiber's biological activity appears to be primarily related to size rather than its composition. Durability within the lung is also important since the ability of a fiber to fragment, dissolve or leach can affect its ability to be cleared from the lung.

8.14.1.1 *Inhaled Fiber Dose*

Upon environmental exposure to a fiber, the actual intake level of an individual is a function of several factors. A major factor influencing both dose and deposition in the lung is the number of respirable fibers that occur in the breathing zone. Other major factors are associated with the fiber itself. Differentiation should be made between upper respiratory tract deposition and lower respiratory tract deposition. The latter involves the potential for deposition in the alveoli of the lung and possible retention, with potential adverse effects to lung tissue itself. Upper respiratory tract deposition may lead to irritation and inflammation of the tissues in the major airways, such as nasal and pharyngeal areas, the larynx, and the tracheal and bronchial airways.

Timbrell and colleagues (7,8) have studied alveolar fiber deposition from both a theoretical and experimental aspect. They found that fibers in an airstream orient their long axis in the direction of the flow and behave as spheres with equivalent aerodynamic diameters. However, deposition within the lung depends not only upon diameter but also upon length. For instance, a long fiber may be trapped by the mucus of the airways by interception. Fibers as long as 200 μm have a very small probability of reaching the alveolar portion of the lung. Timbrell found that the limiting factor for respirability, and thus deposition in the lung, was a diameter of 3 μm (9). A

fiber with a diameter of 3 μm and a length of 200 μm could be respired. Morgan *et al.* (10) found that as fiber diameter increases above 3 μm, the potential for alveolar access and deposition falls off markedly and at 6 μm in diameter, alveolar deposition approaches nil. Particles, as opposed to fibers, with diameters of 10 μm or less can be considered respirable. From these studies, it can be seen that the dose is a function of the concentration of the fiber at the breathing zone and the respirability of the fiber.

8.14.1.2 *Physics and Chemistry of Fibers*

The second major aspect that influences the biological activity of fibers is dimension, structure and chemical composition. It should be immediately noted that the specific chemical composition of the fiber itself does not appear to determine the fiber's biological activity. As will be discussed, most investigators believe that biological activity is generally associated with the physical nature of the fiber and not with its chemical composition. Chemical composition is important primarily in that it determines the physical nature and behavior of the fiber. Some fibers appear to be composed of predominately covalently bound atoms with little or no ionic bonds, while others are ionic in nature. Some fibrous materials have both covalent and ionic bonds. A quartz crystal is a typical covalently bonded material consisting of a continuous, three-dimensional structure of silicon-oxygen-silicon bonds. This structure results in a crystal with equal strength in all directions. Breakage is therefore random and unpredictable. Sodium chloride is an example of an ionic crystal with the atoms in a box-like structure. Breakage of such a crystal results in cleavage along specific planes and in the production of smaller cubic crystals. Impurities can occur in either type of crystal and can result in defects in the crystalline structure. These defects alter the fragmentation pattern of the crystals, with cleavage planes likely to occur at the defects.

An example of how crystal structure can affect biological activity can be seen with asbestos-type mineral fibers. When stressed, these structures not only break transversely to form shorter fibers, but also fracture longitudinally to form filaments with *smaller* diameters. The longitudinal fractures do not always break cleanly and often produce fibers with frayed

ends. Not only do asbestos-type fibers break longitudinally in the environment, they may also fragment *in vivo*. The long, thin fibers resulting from longitudinal fracture can have quite small diameters. These fibers can be respirable, resulting in deposition within the lung. They may also pierce the lung tissue and produce mesothelioma formation in the pleural cavity.

In direct contrast to asbestos-like fibers, MMVF have a more-or-less random structure, which results in an amorphous, as opposed to a crystalline, structure. Fracture of these materials occurs *only* in the transverse plane, resulting in the production of shorter fibers. Longitudinal fracture *does not* occur; therefore, the diameter of the fiber does not change (see Figure 8.2.1.2-1). For example, Assuncao and Corn (11) found that a variety of treatments, including ball milling, resulted in the transverse breakage of glass fibers producing shorter lengths, but there was *no* longitudinal splitting resulting in decreased fiber diameter. This is important since a glass fiber manufactured in a nonrespirable diameter will not break to produce fibers with respirable diameters.

8.14.1.3 *Pulmonary Clearance*

An additional factor influencing the biological activity of fibers is the ability of the upper and lower respiratory tract to remove the fibers from the pulmonary system. Materials that can be rapidly cleared behave toxicologically as if the apparent exposure was smaller than the actual exposure. Residence time in the respiratory tract after fiber deposition depends on two main processes:

1) The mucociliary escalator system
2) Alveolar macrophage activity.

The mucociliary escalator system consists of the mucous lining of the tracheobronchial system and the ciliated cells that sweep this mucus up and out of the respiratory system. It is effective in the rapid removal of fibers and particles from the bronchial system. Neither particle size nor shape appears important in the operation of this clearance mechanism, except that longer fibers appear to be more slowly cleared. An important aspect of lung clearance is that the mucociliary escalator occurs only in the bronchial system and not in the alveolar regions of the lung. Some alveolar clearance may take place via

8.14.8 *Review of the Toxicology of Propylene Glycol*

Propylene glycol (1,2-propanediol) is an aliphatic alcohol and is prepared commercially from propylene oxide or glycerol. Propylene glycol has many uses. It is Generally Recognized as Safe (GRAS) as a food ingredient. As such, it is used as an anticaking agent, antioxidant, dough strengthener, emulsifier, flavor agent, humectant, processing aid, solvent and vehicle, stabilizer, thickener, surface active agent and texturizer. Usage levels in various foods range from $< 0.001\%$ in soups and soup mixes to 5% in confections and 15% in seasonings and flavors (1-3). The Food and Drug Administration (FDA) (3) limits usage levels to 5% in alcoholic beverages, 24% in confections, 2.5% in frozen dairy products, 97% in seasonings and flavorings, 5% in nuts and nut products, and 2% in all other food categories.

Estimates of human intake of propylene glycol in foods vary considerably. A National Research Council Subcommittee (4) estimated the average daily intake to be 13 mg/kg body weight and the maximum daily intake to be 36 mg/kg. The Select Committee on GRAS Substances (1), on the other hand, estimated the actual daily intakes to range from 0.5 to 1.2 mg/kg body weight. The WHO/FAO Joint Expert Committee on Food Additives (5) set an acceptable daily intake of propylene glycol at 125 mg/kg. For a 70 kg person, the estimated average intake of propylene glycol ranges from 35-2500 mg/day, and the acceptable intake is approximately 9 g/day. Based upon NEW CIGARETTE prototype analytical data (Section 4.2.1), a smoker would potentially inhale approximately 0.4 mg propylene glycol/NEW CIGARETTE. This would result in a possible daily exposure of about 24 mg if a smoker smoked 60 NEW CIGARETTES/day. This value is 1.5-105 times less than the estimated intake and 375 times less than the acceptable intake of propylene glycol.

Propylene glycol has been used as a tobacco ingredient for over 30 years. It is used as a humectant and as a solvent/vehicle for adding flavors to tobacco.