"Smoke pH": A Review*

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CONTENTS

Summary	117
Zusammenfassung	118
Resume	118
I. Introduction	119
II. Development of methods to determine "smoke pH"	120
III. "Smoke pH" and biological activity of mainstream smoke	124
IV. "Smoke pH" and interaction with the smoker	124
V. Attempts to relate "smoke pH" to cigarette and smoke parameters	125
VI. "Smoke pH" and some aspects of mainstream smoke chemistry	126
VII. Effects of ammoniation of tobacco on "smoke pH" and other mainstream smoke properties	129
VIII. Conclusions	134
IX. References	135

SUMMARY

The analytical methods developed since the 1950s to determine the "smoke pH" of cigarette mainstream smoke (MSS) are reviewed. Most of the methods involve averaging the values obtained with all the puffs from a cigarette or averaging values from the total number of puffs from several cigarettes plus solution of the MSS in various quantities of water prior to pH determination. "Smoke pH" values thus obtained have little relevance to the situation involving a smoker who smokes a cigarette one puff at a time. In the human biological situation, the smoke components must traverse a layer of buffered fluid separating the smoke-filled respiratory tract cavity and the underlying tissue. Seldom is the effect of either the

volume or the pH of the buffered fluid taken into account in determining the "smoke pH" of cigarette MSS taken one puff at a time.

While numerous recent discussions have dealt with the effect of pH on the nature (degree of protonation) of nicotine in cigarette MSS and its rate of absorption by the smoker, seldom is the volume and/or pH of oral cavity saliva or of the fluid coating the lung surface considered in the assessment of either the nature or absorption of nicotine by the smoker. If the degree of protonation of nicotine be pH dependent, then the degree of protonation of nicotine as it traverses the film of fluid separating the respiratory tract cavity and the underlying tissue must be dependent on the pH of the buffered fluid and not on the "smoke pH" *per se*. Statements that adjustment of the "smoke pH" by ammoniation of one or more tobacco blend components increases both the level of MSS nicotine and its rate of absorption, thus resulting in greater consumer acceptance and continuation of smoking, fail to take into account the other changes that occur in the MSS composition to enhance its consumer acceptability. Inclusion of modest percentages of ammoniated tobacco in the blend increases the "smoke pH" of the MSS but does not necessarily increase MSS nicotine level. Not only are the MSS levels of several low molecular acids, aldehydes, and ketones known to be respiratory tract irritants substantially reduced but also the MSS levels of several highly flavorful pyrazines are substantially increased. These MSS composition changes yield an MSS classified as milder and more flavorful and whose consumer acceptability is considerably enhanced.

Until the pH of MSS is determined on a per puff basis in a system simulating that in the oral cavity or the lung of the smoker, the nature of specific smoke components at the time of contact and their reactivity with respiratory tract tissue remain highly speculative.

"Smoke pH" value for MSS, like the "tar" value for MSS,

provides little, if any, useful information about the chemical composition of the source of the MSS or about its chemical and biological properties. [Beitr. Tabakforsch. Int. 19 (2000) 117–139]

ZUSAMMENFASSUNG

Es wird eine Übersicht über die analytischen Methoden gegeben, die seit 1950 entwickelt wurden, um den „Rauch-pH“ des Hauptstromrauchs (HSR) von Zigaretten zu bestimmen. Die meisten Methoden beinhalten Durchschnittswerte für den pH-Wert, die sich aus der gesamten Zugzahl beim Abrauchen einer Zigarette oder aus der gesamten Zugzahl beim Rauchen mehrerer Zigaretten ergeben, einschließlich der Lösung des HSR in verschiedenen Wassermengen vor der Bestimmung des pH-Wertes. Die auf diese Weise ermittelten „Rauch-pH“-Werte lassen nur wenig Rückschlüsse auf das Rauchverhalten eines Rauchers zu, der eine Zigarette zugweise raucht. Beim Raucher müssen die Rauchkomponenten durch eine gepufferte Flüssigkeitsschicht diffundieren, die die rauchgefüllten Atemwege und das darunterliegende Gewebe voneinander trennt. Die Wirkung des Volumens oder der pH des gepufferten Mediums wird bei der Bestimmung des „Rauch-pHs“ des HSR von Zigaretten, die zugweise geraucht wurden, selten berücksichtigt.

Viele aktuelle Diskussionen haben sich mit der Auswirkung des pHs auf den Protonierungsgrad des Nikotins im HSR von Zigaretten und der Geschwindigkeit der Nikotinaufnahme durch den Raucher beschäftigt, nur selten aber wurde die Menge und/oder der pH des Speichels in der Mundhöhle oder die Flüssigkeit, die die Oberfläche der Lunge umgibt, bei der Bestimmung des Protonierungsgrades oder der Aufnahmegeschwindigkeit des Nikotins durch den Raucher berücksichtigt. Wenn das Ausmaß der Protonierung des Nikotins vom pH-Wert abhängt, dann muß das Ausmaß der Protonierung des Nikotins, wenn es durch das Flüssigmedium tritt, das den Atemtrakt und das darunterliegende Gewebe voneinander trennt, vom pH der Pufferlösung und nicht vom „Rauch-pH“ *per se* abhängig sein. Darstellungen, dass eine Veränderung des „Rauch-pHs“ durch die Zugabe von Ammonium zu einer oder mehrerer Komponenten des Tabakgemisches sowohl den Nikotingehalt des HSR als auch die Aufnahmegeschwindigkeit des Nikotins erhöht und daraus eine bessere Akzeptanz durch den Konsumenten und die Aufrechterhaltung des Rauchens resultiert, entbehren der Information über die anderen Veränderungen, die in der Zusammensetzung des HSR stattfinden, um eine bessere Akzeptanz durch den Konsumenten zu erreichen. Die Zugabe geringer Mengen ammoniumhaltigen Tabaks zur Blend erhöht den „Rauch-pH“ des HSR, jedoch nicht notwendigerweise den Nikotingehalt des HSR. Nicht nur der Gehalt mehrerer niedermolekularer Säuren, Aldehyde und Ketone, die bekanntermaßen die Atemwege reizen, wird substantiell reduziert, sondern der Gehalt mehrerer höchst geschmackintensiver Pyrazine im

HSR wird auch deutlich erhöht. Diese Veränderungen in der Zusammensetzung des HSR ergeben einen Tabakrauch, der als milder und wohlschmeckender klassifiziert wird und dessen Akzeptanz durch den Konsumenten beträchtlich verbessert ist.

Solange der pH-Wert des HSR auf der Basis eines Zuges in einem System bestimmt wird, das den Zustand in der Mundhöhle oder der Lunge eines Rauchers simuliert, bleibt die chemische Natur spezifischer Rauchkomponenten zum Zeitpunkt des Kontakts und ihre Reaktivität mit dem Gewebe des Atemtrakts höchst spekulativ.

Der „Rauch-pH“ ebenso wie der Kondensatwert des HSR gibt, wenn überhaupt, nur wenig nützliche Informationen über die chemische Zusammensetzung der Quelle des HSR oder über deren chemischen und biologischen Eigenschaften. [Beitr. Tabakforsch. Int. 19 (2000) 117–139]

RESUME

Une revue de la littérature depuis les années 1950, sur les méthodes analytiques pour déterminer le «pH de la fumée» du courant principal (CP) d'une cigarette, est présentée. La plupart des méthodes impliquent l'établissement des valeurs moyennes obtenues pour toutes les bouffées prises d'une seule cigarette, ou par l'ensemble des bouffées prises de plusieurs cigarettes, comprenant la solution du CP dans différentes quantités d'eau avant la détermination du pH. Les valeurs du «pH de la fumée» ainsi obtenues, ont peu de rapport avec le comportement des fumeurs qui fument la cigarette bouffée par bouffée. Chez les fumeurs, les composants de la fumée doivent traverser une couche d'un milieu tamponné qui sépare la cavité oro-pharyngée et le tissu sous-jacent. Les effets du volume ou du pH du milieu tamponné ne sont que rarement pris en compte lors de la détermination du «pH de la fumée» du CP des cigarettes fumées bouffée par bouffée.

De nombreuses discussions récentes ont porté sur l'effet du pH sur la nature (degré de protonation) de la nicotine dans le CP des cigarettes, et le taux d'absorption par le fumeur. Cependant, le volume et/ou le pH de la salive dans la cavité oro-pharyngée ou du milieu entourant la surface des poumons, ne sont que rarement pris en compte dans l'évaluation de la nature ou l'absorption de la nicotine par le fumeur. Si le degré de protonation de la nicotine dépend du pH, le degré de protonation de la nicotine, en traversant le milieu qui sépare la cavité oro-pharyngée et le tissu sous-jacent, doit dépendre du pH du milieu et non pas du «pH de la fumée» *per se*. Il est constaté que la modification du «pH de la fumée» par l'apport d'ammoniac à un ou plusieurs composants du mélange de tabac, augmente la teneur en nicotine dans le CP et le taux d'absorption de la nicotine par le fumeur, ce qui induit une plus grande acceptabilité par le consommateur et la poursuite du fumage; ces constatations évitent d'évoquer les autres changements qui ont lieu dans la composition du CP, et qui stimulent l'acceptabilité du consommateur. L'apport de faibles quantités de tabac

"ammoniaqué" dans le mélange, augmente le «pH de la fumée» du CP, mais n'augmente pas nécessairement la teneur en nicotine dans le CP. Non seulement la teneur en plusieurs acides, aldéhydes et cétones de faible poids moléculaire, qui sont notoirement des irritants du système respiratoire, est substantiellement réduite, mais la teneur en plusieurs pyrazines particulièrement aromatiques est substantiellement augmentée. Ces modifications de la composition du CP engendrent un CP caractérisé comme plus léger et plus aromatique, et dont l'acceptabilité par les consommateurs est considérablement augmentée.

Tant que le pH du CP est déterminé sur la base d'une bouffée, dans un système simulant les conditions de la cavité oro-pharyngée ou les poumons du fumeur, la nature des composants spécifiques de la fumée lors du contact et leur réactivité avec le tissu du système respiratoire reste hautement spéculative.

Le «pH de la fumée» du CP de même que la teneur en goudrons du CP fournissent peu, voire aucune, information utile sur la composition chimique de la source du CP ou sur ses propriétés chimiques et biologiques.

I. INTRODUCTION

During the past five years numerous statements have been made about "smoke pH", i.e., the pH of cigarette mainstream smoke (MSS), its alteration by such treatments as ammoniation of tobacco or reconstituted tobacco sheet, and the effect "smoke pH" has on the nature of nicotine in MSS and the perception by the smoker of nicotine and other MSS components. Seldom discussed has been the relationship of the "smoke pH" determined for individual puffs in the cigarette MSS, for the MSS from an individual cigarette, or for the combined MSSs from a number of cigarettes to the classical definition of pH. None of the methods used to determine the "smoke pH" of MSS is equivalent to the classical method used to determine pH.

Many previous publications on cigarette "smoke pH" suffer from the problem that the definition of pH, initially proposed in simultaneously published German and French articles by SØRENSEN in 1909 (1) and modified by SØRENSEN and LIEBERSTRØM-LANG in 1924 (2), has been either misinterpreted or ignored. SØRENSEN was the first to suggest the possible benefits to be derived from the use of pH measurements in biochemical studies involving enzymes.

To put the "smoke pH" of tobacco smoke or cigarette MSS pH in perspective, one should recall SØRENSEN's original definition of pH (1) in which pH was defined in terms of the hydrogen ion concentration, c_{H^+} , an entity nonexistent in solution but considered to be present as the hydronium ion which is either a monohydrated or multihydrated entity. Subsequently, the definition of pH was revised by SØRENSEN and LIEBERSTRØM-LANG (2) to encompass hydrogen ion activity a_{H^+} , rather than the

hydrogen ion concentration c_{H^+} , as shown in the following equation: $pH = \log \{1/a_{H^+}\} = -\log a_{H^+}$. Since this definition involves a single ion activity that is immeasurable, the activity has to be attained through a non-thermodynamic assumption. Alternatively, the above equation may be expressed as $a_{H^+} = 10^{-pH}$.

The importance of this equation is the entity in it – hydrogen-ion activity, a_{H^+} – an entity related to the effective concentration of the solute, i.e., the *availability* of the ion in solution. Activity is a function of many variables of which concentration is one. The effect of concentration is obvious from examination of the pH values for successively diluted aqueous solutions of a typical acid or base. For example, successive dilutions of 1.00 N hydrochloric acid to 0.10 N and 0.01 N result in substantial changes in the values from pH 0.10 to pH 1.07 to pH 2.02, respectively. Similar dilutions of 1.00 N sodium hydroxide to 0.10 N and 0.01 N result in changes from pH 14.05 to pH 13.07 to pH 12.12, respectively (3). These data suggest that, to be meaningful, the "smoke pH" of cigarette MSS should be determined under conditions simulating or approximating those encountered during the smoking of a cigarette by the smoker. The Brønsted and Lowry concept of acids and bases (an acid consists of a base in combination with a proton) and/or the Lewis theory of acids and bases (an acid is capable of accepting an electron pair to form a coordinate covalent bond, a base is capable of furnishing the pair) became integral parts of the understanding of pH (4).

The difficulty in accurately measuring a_{H^+} for most solutions led the International Union of Pure and Applied Chemistry and the US Natural Bureau of Standards to define pH as the reading on a pH meter standardized against a standard buffer solution. While on the surface, pH appears to be a relatively simple concept capable of ready determination, its complexity is outlined in the treatise by RICCI (5). Even in cases of the effect of a few simple ionic species on pH, literally hundreds of equations were needed to define the various examples discussed. None of the examples noted by RICCI approached the compositional complexity of cigarette MSS, a two-phase dynamic system involving thousands of chemical entities, most of which are not ionic. In 1965, BATES (6) outlined the limitations (simple solutes, temperature uniformity) of the determination of pH for relatively simple cases. He also stressed that the pH determined at one temperature has no quantitative meaning relative to the pH determined at another temperature. This is obvious from the equation used to define pH: Since activity is a temperature dependent function, then pH is obviously a temperature dependent function.

Even in the earliest studies on the "smoke pH" of cigarette MSS and its determination, several important factors were recognized. In addition to the dilution factor, it was recognized that the determination of "smoke pH" of cigarette MSS, whether obtained as a per cigarette value or a per puff value, was not comparable to the classical determination of pH.

Much has been written about “smoke pH” as well as “tobacco pH”, but in actuality neither value exists. Comparison of the terms “tar” and “smoke pH” reveals similarities and differences between the two concepts. “Tar” is a defined quantity, not a uniform chemical mixture. The laboratory conditions and procedures for the determination of “tar” have been precisely defined in several much used standard protocols, e.g., Federal Trade Commission of the United States (FTC), International Organization for Standardization (ISO), and CORESTA, as have the parameters for conditioning the smoking article. “Smoke pH” is also a defined quantity whose value depends not on the quantification of some inherent chemical property of MSS but on how the determination is conducted. “Tar” delivery and “smoke pH” precisely determined in the laboratory may have some value in the comparison of the MSSs from different cigarettes but they have little relevance to the “tar” and “smoke pH” values to which the cigarette smoker is exposed. The laboratory findings and human smoking data on “tar” and “smoke pH” provide no meaningful information on the source of the MSS or its chemical composition or biological properties.

II. DEVELOPMENT OF METHODS TO DETERMINE “SMOKE pH”

Over the past seventy years, the methodology to determine the “smoke pH” of the MSS from a cigarette, cigar, or pipe has varied considerably. Equally varied has been the interpretation of the “smoke pH” values obtained and their relationship to the smoker’s response to inspired and/or inhaled MSS. Occasionally, investigators in their reports of “smoke pH” mention the need to know the pH value of the smoke as it contacts the fluids coating the oral cavity and/or the respiratory tract tissue and how the pH of the smoke in conjunction with the pH of the coating fluid influences the perception and impact of the smoke and its components. The determination of the pH of such fluids presents other problems since the fluids usually contain complex proteinaceous material and are highly buffered (7). Thus, instead of a case of a simple acidic system contacting a simple basic system or *vice versa*, the contact between MSS and saliva or other tissue-coating fluid usually involves contact between two highly complex and buffered systems with different pH values.

- ▶ In 1931, WENUSCH (8) measured the pH of the water extract of an Oriental tobacco smoke condensate collected on cotton wool. The same year, SHMUK and KOLESNIK (9) reported pH values ranging from 5.6 to 8.5 for the MSS from various types of tobacco. Subsequent determinations of “smoke pH” involved diverse methodologies.
- ▶ Several investigators (10) reported attempts to determine “smoke pH” by measuring the pH of tobacco smoke solutions with pH indicator paper.
- ▶ In an attempt to confirm the statements of LICKINT (11) on the relationships among the “smoke pH” of the

MSSs from cigarettes, cigars, and pipes, their inhalability, and respiratory tract cancer incidence, KUKOWKA and RACKOW (12) determined the pH of the MSS generated from a specified weight (6.5 g) of tobacco by intermittent oral puffing of the tobacco product (cigarette, cigar, pipe), drawing the MSS through distilled water (100 mL), shaking the system to capture the smoke above the water surface, and determining the pH of the resulting “colloidal solution” with a pH meter as well as with two types of pH indicator paper. For cigarettes, the range was pH 4.5 to pH 5.3; for cigars, pH 5.8 to pH 6.9; for pipe, pH 5.7 to pH 6.6.

- ▶ PYRIKI and HOMANN (13) determined the pH of solutions of the MSS condensates from different tobaccos and attempted to relate the pH values to the smoking quality of the different tobaccos as defined by smokers.
- ▶ From cigarettes made from individual tobacco types (Oriental, flue-cured, Burley, and native Japan tobacco), KOBASHI *et al.* (14) generated MSSs and determined the pH values of their aqueous solutions.
- ▶ In 1961, GROB (15) passed cigarette MSS through a tube loosely packed with cotton wool, extracted the MSS particulate phase from the cotton plug with CO₂-free water, and determined the pH of the aqueous extract with a pH meter.
- ▶ In a study presented in 1963 and published in 1964, ARTHO and GROB (16) described some of the earliest experiments in which an attempt was made to determine the nicotine absorption from cigarette MSS by simulating the conditions in a smoker’s mouth. The absorption medium was a small quantity (0.6 mL) of highly buffered surrogate saliva (pH 6.5) whose quantity and pH value approximated those of the saliva in the mouth of a smoker. A deficiency of the study was the fact that the nicotine absorption from the MSS by the surrogate saliva was not determined on a per puff basis but on a per cigarette basis, i.e., 0.6 mL of the surrogate saliva was subjected to the MSS in all the puffs from the cigarette. This use of surrogate saliva in the pH determination was similar to the use of a surrogate “mucus” in the determination of *in vitro* ciliastatic activity of various MSS components (17, 18).
- ▶ In their 1965 cigarette MS pH study, ARTHO and GROB (19) used the Cambridge filter pad to collect cigarette MSS particulate phase from four cigarettes, extracted the pad with 50 mL of salt-free water, and determined the pH of the solution. The pH of the particulate phase collected on a Cambridge pad and that of the particulate phase collected on a cotton plug used previously by GROB (15) showed good agreement. ARTHO and GROB also noted the increasing interest in the relationship between the “smoke pH” of MSS and its physiological action on mucous membranes, an interest possibly triggered by their earlier study with surrogate saliva (16). However, they disregarded the admonition of CUNDIFF *et al.* (20) that the Cambridge pad retained only about 90%

of the weak and very weak acids in the particulate phase. How this would affect the “smoke pH” values determined by ARTHO and GROB is uncertain. In 1970, ARTHO and GROB described additional studies on nicotine absorption from cigarette MSS (21).

- ▶ Whether the filter tip was paper or cellulose acetate, AYRES and EVELYN (22) found that the filtration of nicotine from flue-cured MSS paralleled the filtration of “tar.” This was also the case for “tar” and nicotine filtration from Burley MSS by a paper filter tip. However, they reported that a cellulose acetate filter tip selectively removed more nicotine than “tar” from Burley MSS. The difference between nicotine filtration by paper *vs* cellulose acetate was attributed to the higher “smoke pH” of Burley tobacco MSS.
- ▶ FORDYCE and HORSEWELL (23), extending the study of AYRES and EVELYN, reported that selective filtration of nicotine (and other smoke components) depended on the distribution of the component between the vapor and particulate phases, the influence of “smoke pH” in determining such a distribution, and the equilibration of the vapor phase–particulate phase distribution following removal of a smoke component from the vapor phase by filtration.
- ▶ ARTHO and GROB (24) examined the effect of various variables on cigarette “smoke pH.” These included: buffered solutions (pH 4.6 and pH 7.2), wetting agents, contact time between Cambridge pad and solvent, number of cigarettes smoked, butt length, filter-tip material. Based on the results, their eventual analytical procedure involved the smoking of four cigarettes per determination; smoking parameters of 35-mL puff volume, 2-sec puff duration, one puff/min, 20 °C, 60% RH; trapping the MSS on a Cambridge pad (no blank puffs taken through pad prior to analysis); immediately after smoking the last cigarette, the pad was placed in a flask with 40 mL of water, shaken, then shaken 10 min and 20 min later; pad removed; pH determined electrometrically. ARTHO and GROB also noted:

Subject to the reservations dictated by the logarithmic character of the pH scale we would like to mention that during standard use of this method in multiple determinations over an extended period of time, a standard deviation of usually less than 0.3 pH units could be observed.

- ▶ The determination of the “smoke pH” of successive single puffs of MSS impinging on and being absorbed by an aqueous film coating the pH electrode was described by SENSABAUGH and CUNDIFF (25). Despite the sophistication of their analytical methodology, they noted:

The procedure is an empirical one and the results will depend upon the conditions under which the measurements are made. It should find utility in comparative work.

Even in this early study, the significance of dilution of cigarette MSS and its effect on the “smoke pH” value was recognized. Also recognized was the need to absorb the cigarette MSS in a medium that simulated the respiratory tract fluids to which the smoke would be exposed. About the dilution effect and the use of a saliva surrogate (a buffered solution rather than distilled water), SENSABAUGH and CUNDIFF wrote:

The electrode can be buffered to any desired pH by use of the proper buffer solution. Unless most of the buffer solution is removed from the electrode, the shape of the [pH] curve as well as the reproducibility will be considerably affected. A small piece of chamois skin, dampened with the buffer solution, has been used with good results for leaving a uniform film on the electrode.

For some years, this procedure or a minor modification of it was used in various studies where knowledge of “smoke pH” of cigarette MSS was pertinent or where various MSS pH comparisons were made. For example, in their study of cigarette and cigar MSSs, BRUNNEMANN and HOFFMANN (26) reported drawing the MSS over a highly sensitive electrode covered with a thin film of a buffered solution, a situation which they stated compared more favorably with the moist surfaces of the upper respiratory tract than did situations in which the smoke was drawn through CO₂-free water. They wrote:

We reason that the pH obtained by suspending the Cambridge filter in CO₂-free water can be misleading since it excludes the gaseous phase of the smoke and cannot be applied to individual puffs [Grob (15)]. A more realistic approach appears to be the determination of the pH of the total smoke, since this is comparable with smoke that passes over the mucous membranes of the respiratory tract.

In a 1970 review article on the analysis of various components in and factors for tobacco and tobacco smoke, DOBBINS (27) discussed “smoke pH” as follows:

workers have gravitated toward a very loose concept of pH. Many times the measurement given is the pH of an aqueous solution through which smoke has been bubbled and not the pH of the smoke itself. It is difficult to see how there could be a pH of smoke, if the classical definition [of pH] is observed. Nevertheless, Sensabaugh and Cundiff [25] describe an empirical method for determining the acid-base effect of whole smoke on an aqueous film. The method provides a puff-by-puff picture of phenomena which, though not pH, are at least pH-related. It is used in the evaluation and comparison of blends, though considerable experience must be gained before the resultant data can be properly interpreted . . .

Accompanying the graphical figures showing tracings of the pH-related instrument responses was the following comment by DOBBINS:

The general shape of the maxima, the minima, and the pH ranges should be considered in the interpretation of curves for comparative purposes.

Examination of the “smoke pH” literature issued since the late 1960s indicates that this recommendation by DOBBINS has seldom been followed.

As pointed out by ARTHO and GROB in 1965, one of the major problems with the determination of the pH of cigarette MSS was to ensure that the value obtained by measurement in the laboratory had some relevance to the pH of MSS at the time it came in contact with the mucous membranes of the smoker.

- ▶ Several procedures were used in the National Cancer Institute (NCI) decade-long program on the “less hazardous” cigarette to determine the pH of the CSCs from the many experimental, standard, and reference cigarette samples. PATEL (28) used the following method to determine the pH of the CSCs: A sample (1.0 g) of the CSC was suspended in 100 mL of CO₂-free water, shaken thoroughly, and the pH of the suspension measured directly with a pH meter. However, GUERIN and his colleagues at Oak Ridge National Laboratory (29) used the following procedure: A 200-mg sample of the CSC was weighed into a beaker and the beaker transferred to a nitrogen atmosphere. A known volume of CO₂-free water was added to form a 1% CSC slurry; the pH was immediately measured. For the first set of experimental cigarettes only, the pH of the vapor phase of the MSSs from the various cigarette samples was also determined (30) by the SENSABAUGH-CUNDIFF method (25). The relevance of the pH of a multi-cigarette CSC slurry to that of a smoker-inhaled puff of whole MSS is obscure, particularly when the range of per cigarette CSC deliveries (from 6 to 43 mg/cig) is considered. For example, at the 1.0-g CSC level, the number of cigarettes represented vary from about 23 to more than 160; at the 200-mg CSC level, the number of cigarettes represented vary from about 5 to 40! In the NCI study dealing with filter cigarettes (31), pH was not a parameter considered. Despite the various procedures used to determine CSC pH for the various cigarettes in the NCI study, the pH values obtained were not discussed in either the four monographs (28, 29) or the summary (32).
- ▶ HARRIS and HAYES (33) described the determination of the pH of whole MSS in the combined first puffs from 20 cigarettes from a single pack, the combined second puffs from the same 20 cigarettes, the combined third puffs from the 20 cigarettes, etc. Distilled water (50 mL) at pH 6.0 was used to extract each set of puffs during smoking. Subsequently the smoke extract was diluted with water (50 mL, pH 6.0) and the “smoke pH” determined at 25 °C. Since the

“smoke pH” varied with time, pH readings at 3.0 min after sample preparation were selected.

- ▶ In 1981, KLUS *et al.* (34) described a method for the determination of the “smoke pH” of whole MSS in which the MSS was passed directly onto the surface of the pH electrode. The following year, KRUSZYNSKI (35) criticized the KLUS *et al.* method because it gave a value which he claimed differed significantly from the definition of pH because it did not involve a water extraction or aqueous solution of the MSS.
- ▶ In his own so-called method of measurement of the “smoke pH” of whole cigarette MSS, KRUSZYNSKI (35) separated the MS particulate phase from the vapor phase. The particulate phase, collected on a Cambridge-type filter, was extracted with water and the pH of the aqueous extract determined. The vapor phase passing through the filter was collected in water, the pH of the aqueous extract determined. The two pH values differed significantly. No explanation was given of how these two pH values were related to the pH of whole MSS.
- ▶ At the USDA, LAKRITZ *et al.* (36) and STEDMAN *et al.* (36) reported that the MSS pH could be altered from pH 5.6 to pH 4.1 by addition of formic acid (33 mg/cig) and from pH 5.6 to pH 8.2 by addition of dipropylamine (100 mg/cig) to the cigarette tobacco. Examination of the pH 4.1 MSS indicated higher levels of nicotine and lower levels of pyridine than in the pH 5.6 MSS from the control cigarette. The pH 8.2 MSS from dipropylamine-treated cigarette showed no significant differences in pyridine and nicotine levels from those in the control cigarette MSS. This absence of significant difference was also noted with charcoal-filtered or cellulose acetate-filtered dipropylamine-treated cigarettes.
- ▶ In 1989, BRAUMANN and ELMENHORST (38) reported that the pH of CSC was strongly dependent on the amount of CSC trapped on the Cambridge pad. They also reported that (i) the “smoke pH” for whole MSS correlated well with the pH of the CSC, (ii) the range for whole “smoke pH” was narrower than that for CSC. This was attributed to the carbon dioxide in the vapor phase of whole MSS, other pH-significant components being present in the vapor phase in small quantities because of their failure to pass through the Cambridge pad. BRAUMANN and ELMENHORST suggested that the CSC pH represents the best measure of the acid-base balance of MSS. They also noted that the pH of CSC is readily predicted from its nicotine and total organic acid content.
- ▶ At the 50th Tobacco Chemists’ Research Conference (TCRC) in 1996, GREEN and RODGMAN (39) summarized the various presentations in which “smoke pH” was the major topic during the preceding 49 TCRCs.
- ▶ Two years later at the 52nd Tobacco Science Research Conference (TSRC), there was a spate of presentations on “smoke pH.” WINGATE *et al.* (40) stressed the significant problems involved among the

Table 1.
Variations in analytical methodologies used in determination of "smoke pH" for MSS

Year	Sample analyzed	Solvent used	Reference
1959	Whole MSS in all puffs from 6.5 g tobacco smoked in cigarette form	Collected in 100 mL water for pH determination	KUKOWKA and RACKOW (12)
1963/1964	Whole MSS in all puffs from a single cigarette	Collected in 0.6 mL of buffered surrogate saliva (pH 6.5) for pH determination	ARTHO and GROB (16)
1966/1971	Whole MSS in all puffs from 4 cigarettes	MSS treated with 40 mL water for pH determination	ARTHO and GROB (24)
1966/1967	Whole MSS in an individual puff	pH electrode coated uniformly with thin film of solution buffered to simulate pH of buffered oral cavity-respiratory tract fluids; pH determined on each puff	SENSABAUGH and CUNDIFF (25)
1976/1980	MSS CSC (1.00 g)	CSC converted to 1% aqueous slurry with CO ₂ -free water for pH determination; MSS vapor phase ignored with regard to pH	PATEL (28)
1976/1980	MSS CSC (200 mg)	CSC converted to 1% aqueous slurry CO ₂ -free water for pH determination; MSS vapor phase ignored with regard to pH	GUERIN <i>et al.</i> (29)
1976/1977	Whole MSS in 1st puffs from 20 cigarettes combined; 2nd puffs from 20 cigarettes combined, etc.	50 mL water (pH 6.0) used as extractant then 50 mL water as diluent for each puff set prior to pH determination	HARRIS and HAYES (33)
1981	Whole MSS impinged directly on surface of pH electrode	None. Method criticized (35) because MSS was neither extracted nor suspended in water	KLUS <i>et al.</i> (34)
1982	MSS particulate phase and MS vapor phase analyzed separately	Aqueous suspension of MSS particulate phase (Cambridge pad) for pH determination; aqueous solution of MSS vapor phase for pH determination; two values never reconciled	KRUSZYNSKI (35)
1998	MSS in all puffs from 10 cigarettes	MSS suspended in 300 mL of 1% (w/v) aqueous sodium chloride prior to pH determination	DONG <i>et al.</i> (41)

historically defined pH, the early "smoke pH" measurement techniques, and the current attempts by some investigators and federal and state government agencies to use "smoke pH" values obtained by these or similar techniques as if "smoke pH" values were absolute. WINGATE *et al.* stressed many of the points noted in the present report, i.e., the dependence of "smoke pH"

on the analytical methodology, the smoke collection method, the number of cigarettes smoked, and whether the "smoke pH" for MSS was determined on a per cigarette basis, on an average per cigarette basis when more than one cigarette was used, or on a per puff basis. WINGATE *et al.* made an excellent point in their comparison of the terms "tar" and "smoke pH":

Much like the concept of cigarette smoke "tar" which is a defined quantity rather than a precise and uniform chemical mixture, "smoke pH" values primarily reflect how the test was conducted instead of quantifying some inherent chemical property of cigarette smoke.

- ▶ DONG *et al.* (41) described a new and simple technique for the determination of the "smoke pH" of the MSS from 10 cigarettes smoked under "modified" FTC conditions. The MSS was trapped as an aqueous suspension in 300 mL of aqueous saline (1% w/v). DONG *et al.* asserted that the effect of the extreme dilution on the "smoke pH" value demonstrated the buffering properties of aqueous smoke solutions. They also asserted that their procedure accounted for the contribution of the MSS vapor and particulate phases to "smoke pH."
- ▶ CALLICUTT *et al.* (42) reported the determination of cigarette "smoke pH" in three related studies with the following smoking parameters: 45-mL puff, 2-sec puff duration, 2 puff/min. MSSs collected in impingers filled with water, 0.1 *N* sodium chloride, or 0.1 *N* potassium chloride gave similar "smoke pH" values with the water-collected MSS showing a slightly higher "smoke pH" than the two solutions. A comparison of the clearing puffs on "smoke pH" showed the number of puffs (0, 1, 2, or 3 puffs) only slightly influenced the "smoke pH" value. Puff-by-puff pH values were compared not only among themselves (puffs 1 through 10) but also with the "smoke pH" of the whole cigarette MSS and the average "pH" of the individual puffs: No differences were found. This result was somewhat surprising considering the numerous studies that have shown that the pH for individual puffs varies from puff to puff and this variation, although different, is observed for flue-cured cigarette puffs, Burley cigarette puffs, and cigar puffs.
- ▶ Walker *et al.* (43) examined the effect of smoking procedure on "smoke pH" by comparing puff-by-puff "smoke pH" analysis to whole smoke "smoke pH" analysis. The particulate phase collected on a Cambridge pad was extracted with 50 mL of degassed, de-ionized water, and the pH of the solution determined. The particulate-phase pH was reported to be strongly correlated to the total particulate matter (TPM) weight. WALKER *et al.* also reported that the average puff-by-puff "smoke pH" value was similar to whole cigarette "smoke pH" and the vapor phase lowered the "smoke pH" for the puff-by-puff determination and the whole cigarette MSS determination.

Table 1 summarizes the variations in several of the analytical methodologies described above to determine the "smoke pH" of cigarette MSS. How does one reconcile a "smoke pH" value obtained on a single puff contacting a thin film of a buffered solution, a "smoke pH" value obtained on many milliliters of an aqueous solution/ sus-

pension of the MSS from one or more cigarettes, and the pH of an MSS puff at the moment it contacts the oral cavity of the smoker? Omitted from the tabulated summary is any consideration of the diverse smoking parameters used to generate the MSS for the "smoke pH" determination. It is obvious from critical examination of the analytical procedures listed in Table 1 that most of the "smoke pH" values obtained bear no relationship to the classical definition of pH presented by SØRENSEN (1) or SØRENSEN and LINDERSTRØM-LANG (2) or to the pH of an MSS puff at the moment it contacts the tissue lining the oral cavity and/or lower respiratory tract of the smoker. Numerous investigators have criticized the meaningfulness of "smoke pH", e.g., FROST *et al.* (44) quite bluntly stated that the concept of "smoke pH" is scientifically invalid. In a review of methods developed in attempts to measure "smoke pH", BEVAN (45) noted:

These different methods have been shown to yield different values of "smoke pH", and it is in any case questionable as to how far the concept of pH can be meaningfully applied to an entity such as tobacco smoke, which is multicomponent, heterogeneous and dynamic. The use of "smoke pH" as a tool to attempt to quantify the amount of nicotine present in smoke as the unprotonated ("free base") form is therefore open to question.

The latter statement will be discussed in more detail below.

III. "SMOKE pH" AND BIOLOGICAL ACTIVITY OF MAINSTREAM SMOKE

In 1963, WYNDER and HOFFMANN (46) speculated whether the pH of cigarette smoke condensate (CSC) would affect tumor induction in laboratory animals skin-painted with CSC. Although no pH data were provided, WYNDER and HOFFMANN modified the acid level of the CSC by adding enough CSC acid fraction to double its level in the CSC. No significant difference was noted between the tumor response of the animals painted with normal CSC *vs* those painted with the acid fraction-enhanced CSC. Later, WYNDER and HOFFMANN (47) discussed the reported pH dependence of ciliary movement and the ciliastatic action of organic acids. They also noted that the laboratory ciliastasis assay did not take into account the possible buffering effect of mucus.

IV. "SMOKE pH" AND INTERACTION WITH THE SMOKER

Over the years, attempts were made to relate "smoke pH" to (i) the perception and consumer acceptability of the MSS, (ii) the composition of the MSS, (iii) the overall effect of the MSS on the smoker, (iv) the intake of MSS by the smoker, and (v) the intake of certain individual MSS components.

Table 2.
Effect of "CSC pH" on its tumorigenicity and mutagenicity

"CSC pH" and biological activity			Reference
{Tumorigenicity} ^a _{CSC, high-sugar-tobacco} { "CSC pH" } _{CSC, high-sugar-tobacco}	>	{Tumorigenicity} _{CSC, low-sugar-tobacco}	56
	<	{ "CSC pH" } _{CSC, low-sugar-tobacco}	56
{Tumorigenicity} _{CSC, normal acid fraction level} { "CSC pH" } _{CSC, normal acid fraction level}	=	{Tumorigenicity} _{CSC, acid fraction level doubled}	46
	>	{ "CSC pH" } _{CSC, acid fraction level doubled}	46
{Tumorigenicity} _{CSC, design technologies A} { "CSC pH" } _{CSC, design technologies A}	= varied =	{Tumorigenicity} _{CSC, design technologies B}	95
	= constant =	{ "CSC pH" } _{CSC, design technologies B}	95
{Mutagenicity} ^b _{CSC, high-sugar-tobacco} { "CSC pH" } _{CSC, high-sugar-tobacco}	<	{Mutagenicity} _{CSC, low-sugar-tobacco}	57, 58
	>	{ "CSC pH" } _{CSC, low-sugar-tobacco}	56

^aTumorigenicity is "specific tumorigenicity"

^bMutagenicity is "specific mutagenicity"

Initially, the purpose of the early research on the development of methods to determine "smoke pH" was to relate the "smoke pH" values obtained to the acceptability to the consumer of the taste and flavor of the smoke. More recently, LEFFINGWELL and LEFFINGWELL (48) noted the probable impact of "smoke pH" on the perception of flavors in tobacco smoke. They also mentioned the effect that ammonia, known to modify "smoke pH" value, has on the flavor of cigarette MSS because of the enhanced levels of several flavorful pyrazines in the smoke from ammonia-treated tobacco materials. Considerable effort was spent on the study of the effect of the alteration of "smoke pH" on MSS composition (36, 37).

V. ATTEMPTS TO RELATE "SMOKE pH" TO CIGARETTE AND SMOKE PARAMETERS

In the late 1960s and early 1970s, emphasis shifted to the relationship between lowering "smoke pH" by use of high-sugar tobaccos in or addition of sugars to the cigarette tobacco blend, the increased inhalation of the MSS by the smoker as the "smoke pH" decreased, and the incidence of lung cancer in cigarette smokers (49).

PASSEY and co-workers (50, 51) reported that MSSs from cigar tobacco and low-sugar cigarette tobacco were much less harmful to the respiratory system of rats than the MSSs from high-sugar flue-cured cigarette tobaccos. PASSEY and ELSON (52) emphasized that flue-cured tobaccos with high sugar content, as much as 25%, yielded an acidic smoke whereas air-cured tobaccos with low sugar content (<1%) yielded an alkaline smoke. ELSON and BETTS (53) further emphasized the sugar content of the tobacco and the cigarette MSS pH *vs* cigar MSS pH and pipe MSS pH in relation to lung cancer. ELSON *et al.* (54) reported that the MSS pH decreased as the sugar level in the cigarette tobacco blend was increased. MSS pH also decreased puff-by-puff as the

cigarette was smoked toward its butt. The lower sugar content of cigar tobacco *vs* cigarette tobacco was reported to yield cigar MSS with a "smoke pH" greater than that of cigarette MSS and the cigar MSS pH progressively increased puff-by-puff during the smoking of the cigar. Emphasis on this relationship among "smoke pH", sugar content of the tobacco blend, and the incidence of lung cancer in smokers continued into the early 1980s (55).

Paradoxically, reported tumorigenicity and mutagenicity studies appeared to differ significantly with regard to the effect of tobacco sugars, either inherent or added, on the biological properties of the CSCs. WYNDER and HOFFMANN (56) reported that the specific tumorigenicities of the CSCs from high-sugar tobaccos (flue-cured, Oriental) were much greater than those from low-sugar tobaccos (Burley, Maryland). Normally, the "smoke pH" of the MSS from a low-sugar tobacco would exceed the "smoke pH" of the MSS from a high-sugar tobacco. WYNDER and HOFFMANN also reported that the specific tumorigenicities of CSCs did not appear to be dependent on the acidity of the CSC (16). MIZUSAKI *et al.* (57) subsequently reported that the specific mutagenicities (Ames test, *Salmonella typhimurium* TA98) of the MSS CSCs from high-sugar (20–30%) tobaccos were significantly lower than those from low-sugar (5%) tobaccos. In their studies of the effect of sugars added to tobacco on the biological properties of MSS CSC, SATO *et al.* (58) reported that several sugars (sucrose, glucose, fructose, galactose, or lactose) significantly reduced the specific mutagenicities (Ames tests, *Salmonella typhimurium* TA98 and TA 100 with metabolic activation) of the CSCs. In Table 2 are shown the diverse situations existing among the various CSCs, their "CSC pHs", and their biological activities [specific tumorigenicity (mouse-skin bioassay), specific mutagenicity (Ames test)].

From the PASSEY-ELSON studies, it was suggested that the lower lung cancer incidence in cigar and pipe smokers was related to the fact that nicotine is more readily

absorbed in the form of the free base, under alkaline conditions pH >7.0, than in the form of a stable salt, under acidic conditions pH <7.0. To obtain the same degree of “nicotine satisfaction” as in smoking a pipe or a cigar, the smoker of cigarettes generating an acidic smoke would tend to smoke more, and to encourage more prolonged and extensive contact of the smoke with the mouth and bronchus, and to take the smoke into the lungs, which would thus suffer greater exposure to the “carcinogenic” effects of the smoke than would be the case with a cigar or pipe smoker.

Interestingly, MALHOTRA (59) expressed an entirely different view of the relationship between “smoke pH” and respiratory tract cancer. He considered cigarette smoke to be hazardous to the smoker not because of any carcinogenic agent in the particulate phase of the MSS but because of the hydrogen-ion concentration of the MSS. Coincident with several of these studies were those emphasizing the relationship between MSS “inhalability” and MSS pH. According to BRUNNEMANN and HOFFMANN (26), HOFFMANN *et al.* (60), and BRUNNEMANN *et al.* (61), the “inhalability” of MSS decreased as it became more alkaline, i.e., as the pH of the MSS increased above 6.0, its “inhalability” decreased. They also noted the caveat that an MSS pH increase induced by ammoniation of tobacco resulted in an increased delivery of ammonia in the MSS and the increased ammonia delivery caused the smoker to breathe more rapidly (61, 72).

VI. “SMOKE pH” AND SOME ASPECTS OF MAINSTREAM SMOKE CHEMISTRY

Lastly, “smoke pH” was much discussed when it was altered by the inclusion of treated tobaccos in the blend, particular tobaccos treated in some way with ammonia. It was asserted that such tobaccos delivered higher MSS levels of nicotine, delivered more of the overall nicotine in a form more readily and more rapidly absorbed by the smoker, and these conditions ensured that the cigarette smoker would continue to smoke.

Various investigators used different analytical methods to determine “smoke pH”. HOFFMANN and colleagues employed a modified SENSABAUGH–CUNDIFF procedure in their study of MSS “inhalability” (26, 60, 61) and the relationship between stalk position of tobacco leaves on the plant and MSS composition (62). Surprisingly, “smoke pH” did not appear in their multiple regression equations as a variable showing either a positive or negative correlation with the generation of TPM, benzo[*a*]pyrene, hydrogen cyanide, acrolein, phenol, or the cresols.

In comparison of the MSSs from cigarettes containing Cytrel®, flue-cured tobacco, or blends of the two, ALLEN and VICKROY (63) determined the “smoke pH” of each MSS sample with the ARTHO and GROB method (24). Their data showed that “smoke pH” correlated somewhat with the MSS ammonia content.

MSS analysis	100% Tob. ^a	10% Cyt. ^{®b}	20% Cyt. ^{®b}	50% Cyt. ^{®b}	100% Cyt. [®]
“Smoke pH” ^c	5.7	5.8	5.9	6.4	8.1
Ammonia (μg/cig)	22	22	20	21	50
Nicotine (mg/cig)	1.1	0.9	0.9	0.4	0

^aFlue-cured tobacco typical of that used in UK cigarettes.

^bBalance of cigarette filler blend was the flue-cured tobacco.

^cpH procedure of ARTHO and GROB (24).

In 1975, SLOAN and MORIE (64) described a method for the determination of unprotonated ammonia in cigarette smoke, a method not adaptable to the determination of unprotonated nicotine in tobacco smoke.

Other concerns were expressed about the effect of “smoke pH” on the formation of specific components in tobacco smoke and the effect of “smoke pH” on the absorption of specific MSS components by the smoker. For example, WYNDER and HOFFMANN (65) stated that *N*-nitrosamines formation in MSS was influenced by “smoke pH”, i.e., the MSS pH. They postulated, without providing any confirmatory data, that the formation of *N*-nitrosamines during the smoking process would be reduced under acidic conditions because of the effect of such conditions on the reaction equilibria. Unfortunately, one equilibrium they proposed, the reaction involving methyl nitrite and a secondary amine in *N*-nitrosamine formation, was subsequently shown to be essentially absent because initially the level of methyl nitrite in MSS is extremely low and the several hundred micrograms of methyl nitrite reported in a cigarette MSS (66) were subsequently shown to be formed during MSS aging (67). Since the early 1970s, much has been written about “smoke pH” and the absorption by the smoker of specific MSS components, particularly nicotine. From their study of absorption of nicotine in cigarette and cigar MSS, ARMITAGE and TURNER (68) asserted that the absorption of nicotine, a weak base, across a biological membrane such as oral mucosal membranes was dependent on its pH or state of acid-base dissociation. Later, ARMITAGE *et al.* (69) reported that, depending on inhalation patterns, retention times, and related factors, smokers may retain 30% to 90% of the nicotine generated and delivered via the inhaled MSS. ARMITAGE *et al.* (70) also wrote that when the tobacco product pH exceeded pH 7.0, as in the case of snuff and chewing tobaccos, nicotine was more readily absorbed from the mouth-held tobacco product. In discussions of nicotine absorption by cigarette, cigar, and pipe smokers, many investigators have used the calculation described by MORIE (71). He calculated the relationship between the level of protonated nicotine in tobacco smoke and “smoke pH” determined by the SENSABAUGH–CUNDIFF method (25). MORIE assumed:

that as soon as the nicotine contacted any biological tissue, it was in an aqueous medium and the acidity constants^a were valid.

^a Dissociation constants for nicotine from the LANGE *Handbook of Chemistry*

However, completely ignored not only by MORIE in his calculations based on a pristine nicotine–water situation but also by those who use his graphical representation were the following facts: (i) To contact a biological tissue, nicotine (and other smoke components) must traverse a film of a highly buffered fluid coating the tissue. (ii) The fluid, while aqueous in nature, is not pure water but a mixture whose composition ranges from simple to highly complex chemical entities. (iii) The pH of the fluid usually equals or exceeds pH 7. (iv) The approximate temperature of most respiratory tract tissues exposed to tobacco smoke and nicotine is 37 °C not 25 °C, the temperature used by MORIE in his calculations. Since it is based on an aqueous system, the graphical representation presented by MORIE is meaningless when dealing with the complex biological system involved in respiratory tract fluids.

In their effort to define “smoke inhalability”, HOFFMANN and WYNDER (72) presented chemical data from a comparison of the MSSs from cigarettes, little cigars, and cigars. They not only discussed the relationship between the sugar level in cigar *vs* cigarette tobaccos but also the relationship among the tobacco sugar levels, the levels of acids in tobacco, the acids generated during the smoking process, and the “smoke pH” of the MSS. They wrote:

At hydrogen ion concentrations below 10^{-6} ($>$ pH 6), tobacco contains increasing amounts of unprotonated nicotine (and other pyridines), the most toxic form of nicotine in tobacco smoke.

They also assumed that the pyridines contributed to the harshness of the taste of cigar smoke and thus strongly influenced its inhalability, i.e., its “uninhalability.” Citing their previous studies, BRUNNEMANN and HOFFMANN (73) wrote that, in addition to TPM, nicotine, “smoke pH”, and carbon monoxide, ammonia was a determining factor for the degree of “inhalability” of tobacco MSS. They also noted that inhalation of ammonia led to acceleration of breathing.

In 1978, RUSSELL and FEYERABEND (74) reported the important finding of their detection of nicotine in saliva of tobacco product users. Later, GORI *et al.* (75) reported that, because the “smoke pH” of cigarette MSS is less than pH 7.0, very little nicotine was absorbed across the oral mucous membranes, even if the smoke was held in the mouth for relatively long periods.

Some of the factors affecting “smoke pH” and its possible relationship to lung cancer induction were mentioned previously. In 1965, WYNDER and HOFFMANN (76) wrote:

As far as human smoking habits are concerned, it remains also to be estimated to which extent volatile smoke components reach the bronchial tree. Preliminary studies indicate a significant proportion of the gaseous components is being retained within the oral cavity. Furthermore, one must be aware that by selective removal of volatile acids, one might change the pH of cigarette smoke and thereby perhaps increase the toxicity of nicotine and other smoke alkaloids. It is important, therefore, in evaluating the effects of ciliotoxic and mucus-affecting components to consider both the gaseous and particulate phase.

Because they obviously did not consider it, the authors made no comment on the fact that ammonia, a vapor-phase component, is highly soluble in aqueous media and its removal from the smoke stream by retention in the oral cavity might produce an effect opposite to the effect of retention of the volatile acids.

HUBER (77), citing the results of studies by GORI *et al.* (75), discussed in some detail the influence of the buffered pH of the fluid coating the internal surface of the lung:

almost no nicotine from cigarette smoke is absorbed in the mouth, pharynx, or upper respiratory passageways [75]. . . . in its nonprotonated form, inhaled nicotine has an acute toxicity for man. The unique “advantage” of tobacco cigarette smoke, then, is that in an acidic state it can deliver the nicotine-containing microdroplets in a nontoxic form that will bypass the otherwise operative defenses of the upper respiratory system. When the cigarette smoke microdroplets reach the alveolar spaces and deposit on the vast internal surface of the lung, they are immediately buffered to a physiologic pH of nearly 7.4.

While the highly buffered saliva in the oral cavity may be affected by a variety of factors (diet, time since previous meal, etc.), it generally is at pH 7.0. Thus if the demonstrated absorption of nicotine in the oral cavity from cigarette MSS is negligible, will a minor difference in the “smoke pH” of MSS, e.g., pH 6.2 *vs* pH 6.7, equivalent to the difference observed when ammoniated tobacco is included in the cigarette blend, produce any significant increase in the nicotine absorption in the oral cavity? Similarly, when the same two MSSs reach the lungs, assuming no significant changes in their “smoke pHs” enroute, then will the controlling factor in the absorption of nicotine in the lungs be the buffered pH 7.4 of the fluid coating the lung surface? KOZLOWSKI and KLEIMAN (78) studied the effect of manipulation of the pH of buffered oral cavity fluid (from pH 5 to pH 8) on the perception of the MSS from a single cigarette brand whose “smoke pH” was reported to be “about pH 5.5.” They reported that the smoker’s perception of the MSS taken in 2-sec puffs at 20-sec intervals did vary with induced oral cavity pH. Their results might have been more informative if the research had also included the perception of the MSS from a second cigarette brand whose “smoke pH” was somewhat greater than pH 5.5, e.g., pH 6.5.

In their study of the absorption of volatile cigarette MSS components by saliva, THOME *et al.* (79) detected over 200 volatile organic components in the saliva (pH 6.5) of a human smoker who held the cigarette MSS puffs in the mouth for 10 seconds. The cigarette was smoked at 1 puff/min, the MSS puff held in the mouth for 10 sec, and the saliva spit into an impinger after each puff. The saliva eventually totaled about 8 mL. The volatile organic components, desorbed from the saliva at 40 °C by helium flow for 40 min, were trapped on Tenax®. Glass capillary gas chromatography/mass spectrometry (GC/MS) examination of the Tenax®-trapped material yielded 212 components, 121 of which were characterized completely, 63 characterized partially. None of the 212 components detected was a volatile carboxylic acid. Comparison of the absorption by the smoker's saliva of the volatile organic components in the vapor phase of the MSSs from two commercial cigarettes, one with and one without an ammoniated tobacco component, with "smoke pH" 6.2 and 6.7, respectively, showed no qualitative differences but did show a few quantitative differences. A few vapor-phase components in the MSS with "smoke pH" 6.2 were absorbed to a greater extent than those in the vapor phase of the MSS with "smoke pH" 6.7 and *vice versa*. Of the 212 components, only about 20 exhibited this behavior. No logical "smoke pH"-related explanations were apparent for these quantitative differences in the volatile organic component absorption by the saliva. Absorption of the volatile organic components by water in an oral cavity surrogate was qualitatively the same as the saliva absorption. Quantitative differences – less absorption of volatile hydrocarbons – were attributed to the lipophilic properties of the saliva.

In his 1999 comments on "smoke pH", BAKER (80) also referred to the effect of the buffered pH of respiratory tract fluids on nicotine absorption:

Reference is often made in smoke chemistry papers to the 'pH of smoke' (e.g. [15; 25; 71; 81]) and this has sometimes been interpreted in quantitative terms as to its effect on the form of nicotine in smoke. Although there is an undoubted relationship between smoke acidity and form of nicotine in smoke, this relationship is imprecise and caution should be applied when attributing quantitative significance to 'smoke pH' . . .

BAKER then continued with a brief description of the different methods used to measure "smoke pH":

Smoke pH is measured in different ways in different studies, either as the pH of an aqueous extract of the total particulate matter collected from smoke or as the pH of an aqueous solution from whole smoke, or when whole smoke is passed over an electrode covered with a thin film of a buffer solution and connected to a pH meter. Thus quoted ranges of smoke pH depend on the exact measuring technique and differ somewhat from study to study. However, typically quoted ranges of smoke pH together with the percentage of the unprotonated (free base) form of nicotine in the smoke, calculated from the acid-base equilibrium data in aqueous solution [71], are:

Smoke	"Smoke pH"	% Unprot. nicotine, calcul.
MSS: flue-cured cig.	5.0–6.0	0–1
MSS: US-blended cig.	5.5–6.5	0.3–3
MSS: dark-air cured cig.	7.0–7.5	9–25
MSS: cigar	8.0–8.5	50–80
Sidestream: cigarette	6.5–8.0	3–50

However, BAKER attempted to put in perspective many of the interpretative problems involved in the "smoke pH"-nicotine absorption issue and the use of the % unprotonated nicotine obtained solely by calculation:

However, in using the concept of pH, care has to be exercised in interpreting its exact relevance to smoke – at best smoke has only an indirect relationship, not quantifiable, to the form of nicotine in smoke. pH refers to the hydrogen ion concentration in an aqueous solution. Because nicotine is dibasic, it will be protonated by acids in any medium and the extent of the protonation will depend on the strength of the acids and their concentration. The pH of an aqueous suspension of smoke is a measure of the acidity of the smoke in terms of its ability to protonate a particular base (i.e. water) in a particular medium (i.e. an aqueous solution). The acidity measured in this way can only give an approximate indication of its ability to protonate a different base (i.e. nicotine) in a different medium (i.e. smoke particulate phase). The calculated 'unprotonated nicotine' figures quoted above are, therefore, likely to be, at best, highly inaccurate. . . .

It has been speculated [82] that as the smoke pH increases then the proportion of nicotine in the vapor phase will increase because of the volatility of the unprotonated nicotine. This is true in a general sense, but nicotine in mainstream smoke is predominantly in the particulate phase. For example, direct measurements [83] show that only 0.0007% of the mainstream smoke nicotine from a flue-cured cigarette (smoke pH ~6) is in the vapor phase while the equivalent figure is 0.01% for mainstream nicotine from a fermented air-cured cigarette (smoke pH ~7.5). The equilibrium between vapor and particulate phases will be established very rapidly. Therefore, when smoke is in contact with a surface that has an affinity for nicotine, a concentration gradient becomes established in which the nicotine is transferred by isothermal distillation. The extent to which this occurs depends on the equilibrium concentration in the vapor phase, hence the concentration of free base nicotine in the particulate phase, hence on the acidity of the particulate phase and hence the pH of an aqueous suspension of the smoke (smoke pH). Thus nicotine in basic solution (from cigar smoke, for example) is absorbed more rapidly through the mucous membranes of the mouth than in more acidic solution (from cigarette smoke) because of the higher concentration of unprotonated nicotine [68; 75]. The question of whether sensory changes in smoke are ultimately related to changes in nicotine vapor-particulate equilibrium or pH-driven changes in the kinetics of transport out of deposited smoke particles is open to speculation.

Once smoke is dissolved in the aqueous fluids within the human body, the form of nicotine (protonated versus unprotonated) will be determined by the buffering capacity of the body fluid itself.

Why are tobacco scientists interested in the pH of cigarette MSS? Do they desire information such as the following: What is the effect, if any, of the pH of cigarette MSS taken in by the smoker on its biological properties, e.g., the perception of tobacco smoke flavor (taste and aroma) by the smoker (48), the absorption of tobacco smoke components by cells of the tissue in the oral cavity or other respiratory tract tissues (68, 69, 70)?

VII. EFFECTS OF AMMONIATION OF TOBACCO ON “SMOKE pH” AND OTHER MAINSTREAM SMOKE PROPERTIES

Initially, the “smoke pH” of the MSSs from cigarettes and other smoking products was determined in attempts to define their acceptability to the consumer. Interest then shifted to the effect of MSS pH on its inhalability. More recently, interest has revolved around the inclusion in the cigarette blend of tobaccos treated with ammonia *per se*, with ammonium salts, or with aqueous solutions of ammonia, the increase in mainstream “smoke pH” induced by the ammonia-treated tobacco, the supposed effect of the increased “smoke pH” on the form of nicotine (nonprotonated *vs* protonated) in the MSS, and the subsequent absorption of the nicotine forms by the smoker. The latter effect, the more rapid absorption of nonprotonated nicotine by the smoker, has resulted in various companies within the Tobacco Industry being accused of “manipulating” nicotine in order to retain their customers (84). If, as discussed previously, the absorption of nicotine does not depend on “smoke pH” but on the buffered pH of the fluids coating the respiratory tract tissue, then what other MSS factors might be responsible for the increased consumer acceptability of cigarettes containing ammonia-treated tobaccos? From 1969 through 1976, nearly two dozen investigations¹ at R.J. Reynolds Tobacco Company of the MSSs from cigarettes containing ammonia-treated tobacco types and blends revealed that the tobacco compositions were changed significantly with slight to modest decreases in MSS “tar” delivery and changes in the levels of other components of the MSS. In these studies, ammonia was introduced into a tobacco type or blend in various ways to accomplish specific goals: (i) Ammonia/steam treatment to denicotinize high-nicotine tobaccos; (ii) to produce an ammoniated reconstituted tobacco sheet such as that described by Philip Morris Incorporated in its patents; (iii) to produce expanded tobacco laminae with ammonia and carbon dioxide as the expansion agents as described by R.J. Reynolds Tobacco Company in its

patent (85) and by Philip Morris Incorporated in its patent (86) and the NCI study of the “less hazardous” cigarette (87); (iv) to simply add ammonia to the tobacco blend or one of its components.

In almost every instance of ammoniation of tobacco, followed by reordering, the treated tobacco contained less nicotine than the untreated tobacco, the decrease ranging from slight to substantial. This was, of course, reflected in the level of nicotine delivered to the cigarette MSS during smoking. Examples of results from analyses of several ammonia-treated tobacco products and the MSSs from cigarettes containing such tobaccos are presented below. From the results of their comparison of the MSSs from cigarettes, little cigars, and large cigars, SCHMELTZ *et al.* (88) discussed the relationship between mainstream “smoke pH” and the level of ammonia in MSS. They also took into account the formation of ammonia from tobacco nitrate during the smoking process (89):

Like pH, ammonia levels in smoke almost seem to be a function of tobacco type and are characteristically high in the smoke from cigars (*vs* cigarettes). According to Johnson *et al.*, during the smoking part of the nitrate in tobacco is reduced to ammonia [89], and since most Burley and cigar tobaccos are relatively high in nitrate. This fact may partially explain the elevated ammonia levels in the smoke of little cigars and large cigars [73]. Little cigars, for example, whether wrapped in cigar wrapper or cigarette paper, give significantly higher values for ammonia than are obtained from a cigarette (593 and 680 $\mu\text{g}/\text{cigar}$ *vs*. 134 $\mu\text{g}/\text{cigarette}$).

ELLIS *et al.* (90) studied the effect of addition of modest amounts (0.12–0.31%) of ammonium compounds to a commercial cigarette blend. No significant difference was found in either the MS “smoke pH” or MSS nicotine delivery between the cigarettes with and without the added ammonium compounds, a result the investigators interpreted as suggesting that ammonium compound addition to a commercial cigarette increases neither “smoke pH” nor FTC nicotine yield.

Resolution of the question of whether the acceptability to the consumer of MSS with a “smoke pH” modified by an ammonia treatment of a component of the tobacco blend is primarily due to the effect of such treatment on the delivery or nature of the MSS nicotine or whether the acceptability is due to other MSS factors may be achieved by examination of other aspects of the MSS chemistry. Examination of the MSSs from cigarettes containing tobacco expanded by the ammonia–carbon dioxide process (85, 86) revealed much about the effect of the process on MSS composition.

Table 3 summarizes analytical data on control and ammonia–carbon dioxide expanded flue-cured tobacco and the MSSs from cigarettes fabricated from such tobaccos (91, 92). Also included are comparable analytical tobacco and MSS data for a flue-cured blend that comprised 10% expanded flue-cured tobacco and 90% control flue-cured tobacco. Examination of the data in Table 3 reveals the following: (i) The % nicotine and % sugars in

¹ Principal investigators at R.J. Reynolds Tobacco Co. R&D included T.H. Edwards, C.R. Green, R.A. Heckman, J.M. Martin, C.D. Mays, C.W. Miller, M.P. Newell, J.H. Reynolds *iv*, A. Rodgman, and J.B. Wilson. The analytical method for the determination of pyrazines and other bases in MSS was developed by Martin who conducted the pyrazines and pyridines analyses on the MSSs from a variety of control and test cigarettes.

Table 3.
Ammonia/carbon dioxide expansion of flue-cured tobacco: Effect on tobacco and MSS properties (91, 92)

Analyte	100% Contr. tob.	Blend of 10% exp.: 90% std.	100% Exp. tob.
Tobacco analysis			
Nicotine (%)	2.26		1.56
Sugars (%)	15.10		8.61
Ammonia (%)	0.14		0.82
Total N (%)	1.90		3.19
pH	4.75		6.48
MSS analysis^a			
TPM (mg)	40.8	36.7	25.6
Nicotine (mg)	2.75	2.34	1.18
FTC "tar" (mg)	32.9	28.9	19.9
Nicotine: "tar" ratio	0.084	0.081	0.059
Benzo[a]pyrene (ng)	28.5	26.8	10.2
Formaldehyde (µg)	31.2	28.0	15.2
Acetaldehyde (µg)	970	875	645
Acrolein (µg)	117	108	99
Acids, total (meq) ^b	0.114	0.104	0.089
Ammonia (µg)	48	55	188
pH, minimum ^c	5.67	5.84	6.98
pH, maximum ^c	5.90	6.08	7.42
Pyrazines and pyridines			
	% Increase over level in control tobacco MSS		
Pyrazine	236		
Pyrazine, 2-methyl-	345		
Pyrazine, 2-ethyl-	103 ^d		
Pyrazine, 2,3-dimethyl-	436		
Pyrazine, 2,5-dimethyl-	412		
Pyrazine, 2,6-dimethyl-	918		
Pyrazine, 2,3,5-trimethyl-	361		
Pyrazine, 2-ethyl-5-methyl-	229		
Pyridine	<10		
2-Picoline	14		
3-Picoline	<10		
4-Picoline	42		
Pyridine, 2-ethyl-	51		
Pyridine, 3-ethyl-	-26		
2,3-Lutidine	34		
2,4-Lutidine	58		
2,5-Lutidine	103 ^d		

^aPer cigarette delivery.

^bmeq = milliequivalents.

^cSENSABAUGH-CUNDIFF method (25).

^dMixture of 2-ethylpyrazine and 2,5-lutidine.

the tobacco decreased as a result of the ammonia-carbon dioxide expansion. (ii) Correspondingly, the ammonia level in and the pH of the tobacco increased. (iii) The "smoke pH" of the MSS, whether considered as the average minimum or average maximum pH, increased as the level of ammonia-carbon dioxide expanded flue-cured

Table 4.
Ammonia/carbon dioxide expansion of Burley tobacco: Effect on tobacco and MSS properties (91,92)

Analyte	100% Control tobacco	100% Expanded tobacco
Tobacco analysis		
Nicotine (%)	3.50	2.82
Sugars (%)	0.99	0.70
Ammonia (%)	0.50	0.89
Total N (%)	3.8	4.2
pH	5.90	6.32
MSS analysis^a		
TPM (mg)	27.7	21.5
Nicotine (mg)	1.92	1.28
FTC "tar" (mg)	22.3	17.4
Nicotine: "tar" ratio	0.086	0.074
Ammonia (µg)	78	223
pH, minimum ^b	5.75	7.51
pH, maximum ^b	6.29	8.43
Pyrazines and pyridines		
	% Increase over level in control	
Pyrazine	148	
Pyrazine, 2-methyl-	139	
Pyrazine, 2-ethyl-	98	
Pyrazine, 2,3-dimethyl-	84	
Pyrazine, 2,5-dimethyl-	142	
Pyrazine, 2,6-dimethyl-	102	
Pyrazine, 2,3,5-trimethyl-	208	
Pyrazine, 2-ethyl-5-methyl-	121	
Pyridine	0	
2-Picoline	58	
3-Picoline	-12	
4-Picoline	19	
Pyridine, 2-ethyl-	-18	
Pyridine, 3-ethyl-	-19	
2,3-Lutidine	21	
2,4-Lutidine	ND ^c	
2,5-Lutidine	25	

^aPer cigarette delivery.

^cND = not determined

^bSENSABAUGH-CUNDIFF method (25).

in the tobacco rod increased from 0% to 10% to 100%. (iv) The per cigarette MSS nicotine delivery decreased. (v) The per cigarette MSS levels of acids decreased as the level of ammonia-carbon dioxide expanded flue-cured in the tobacco rod increased. (vi) Similarly, the per cigarette MSS delivery of the three aldehydes – formaldehyde, acetaldehyde, and acrolein – decreased. (vii) The per cigarette levels of eight pyrazines increased substantially as the level of ammonia-carbon dioxide expanded flue-cured in the tobacco rod increased. (viii) The per cigarette MSS levels of nine pyridines varied from modest increases to slight decreases.

What do these data reveal? The MSS from a cigarette

Table 5.
Ammonia/carbon dioxide expansion of an experimental tobacco blend: Effect on tobacco and MSS properties (29, 94)

Analyte	100% Control tobacco	100% Expanded tobacco
Tobacco analysis^a		
Nicotine (%)	1.73	1.03
Sugars (%)	15.10	8.61
Ammonia (mM)	23.0	77.2
Ammonia (mg)	0.391	1.312
Total N (%)	2.57	3.24
MSS analysis^b		
TPM (mg)	32.8	22.3
Nicotine (mg)	1.79	0.74
FTC "tar" (mg)	27.1	18.2
Nicotine:"tar" ratio	0.066	0.041
Formaldehyde (μg)	31.2	15.2
Acetaldehyde (μg)	985	720
Acrolein (μg)	101	88
pH ^c	5.34	6.40

^aFiller was standard experimental blend II (SEB II).

^bPer cigarette delivery.

^cpH determined was that of a slurry of CSC (29).

containing ammonia–carbon dioxide expanded tobacco is perceived as milder not only because of the reduced levels of acids, several of which (formic, acetic) are irritating to the respiratory tract tissue, but also because of the reduced MSS levels of carbonyl components (formaldehyde, acetaldehyde, acrolein) also known to be irritating to the respiratory tract. In addition, smokers classify the MSS from such cigarettes as more flavorful, a classification most likely attributable to the increased level of the pyrazines. While tobacco smoke contains over 50 pyrazines, Tables 3, 4, and 6 list analytical data for only eight pyrazines in cigarette MSS. These and other pyrazines contribute to the highly acceptable taste and aroma of tea, coffee, cocoa, roasted nuts, cooked meats, etc. (48, 93). Analytical data for nine of the more than 200 pyridines in MSS are listed in Tables 3, 4, and 6. Despite the increase in MSS levels of the pyridines, the MSSs were acceptable to the panelists, a finding that appeared to be at odds with the suggestion by HOFFMANN and WYNDER (72) that the “uninhalability” of cigar MSS was due in part to its high content of pyridines, contributors to the unpleasant, harsh taste of cigar MSS (see Table 7). Since it is unlikely that a cigarette containing 100% expanded tobacco would be commercially viable, the cigarette with 10% expanded tobacco plus 90% control tobacco might approximate the situation in a commercial cigarette (Table 3). It is doubtful that the relatively small difference between the “smoke pH” of the MSS of this cigarette (pH min 5.84, pH max 6.08) and the “smoke

Table 6.
Ammoniation of reconstituted tobacco sheet (RTS): Effect on tobacco and MSS properties (92)

Analyte	Tobacco blend		
	RTS	Amm. RTS	DAHP- treated RTS ^c
Tobacco analysis			
Nicotine (%)	1.79	1.87	1.53
Sugars (%)	11.7	10.0	8.5
MSS analysis^a			
TPM (mg)	23.2	23.4	20.9
Nicotine (mg)	1.29	1.35	0.99
FTC "tar" (mg)	18.2	18.2	16.1
Nicotine:"tar" ratio	0.071	0.074	0.061
Ammonia (μg)	29	37	38
pH, minimum ^b	5.90	5.98	6.00
pH, maximum ^b	6.20	6.36	6.53
Pyrazines and pyridines			
	% Increase over level in control tobacco MSS		
Pyrazine	11	71	
Pyrazine, 2-methyl-	11	62	
Pyrazine, 2-ethyl-	11	57	
Pyrazine, 2,3-dimethyl-	15	62	
Pyrazine, 2,5-dimethyl-	18	67	
Pyrazine, 2,6-dimethyl-	23	71	
Pyrazine, 2,3,5-trimethyl-	19	63	
Pyrazine, 2-ethyl-5-methyl-	22	64	
Pyridine	–3	44	
2-Picoline	13	38	
3-Picoline	3	30	
4-Picoline	0	22	
Pyridine, 2-ethyl-	8	29	
Pyridine, 3-ethyl-	0	15	
2,3-Lutidine	16	59	
2,4-Lutidine	12	29	
2,5-Lutidine	8	23	

^aPer cigarette delivery.

^bSENSABAUGH-CUNDIFF method (25).

^cDAHP = diammonium hydrogen phosphate.

pH” of the MSS of the control cigarette (pH min 5.67, pH max 5.90) would contribute significantly to the calculated value for nonprotonated nicotine in the MSS? Table 4 summarizes analytical data on control and ammonia–carbon dioxide expanded Burley tobacco and the MSSs from cigarettes fabricated from such tobaccos (91, 92). Here again, a similar pattern but to a different degree is indicated for the ammonia–carbon dioxide expanded Burley tobacco and its MSS *vs* the control tobacco and its MSS.

Table 7.
Comparison of mainstream smokes from cigarettes, little cigars, a small cigar, and a cigar

Parameter measured	Cigarette		Little cigar		Small cigar C	Cigar D
	NF ^a	F ^b	A	B		
pH, last puff	5.94	5.76	7.73	7.25	7.11	7.96
No. of puffs, average	11	10	7.7	9.8	8.6	45
Total pyridines						
µg/smoking article	82.8	27.3	58.0	85.3	80.3	536.1
µg/puff	7.6	2.7	7.3	8.7	7.3	11.9
Carbon dioxide						
mg/smoking article	71.6	66.6	45.4	89.7	102.2	
mg/puff	6.51	6.66	5.9	9.15	8.81	
Nicotine						
mg/puff	0.26	0.14	0.08	0.16	0.27	

^aNF = nonfilter cigarette

^bF = filter-tipped cigarette.

Table 8.
Variations in cigarette smoke condensate composition at "CSC pH" 5.00 ± 0.10 (95)

Code no.	Cigarette design ^a	pH ^b	Level per gram of cigarette smoke condensate ^c						TBA (%) ^d 25 mg/day
			Phenol (mg)	o-Cresol (mg)	BaP (μg)	BaA (μg)	Acids (meq) ^c	Nicotine (mg)	
Standard experimental blend I (SEB-I)									
2	Regular paper	5.03	4.35	0.78	0.72	1.20	2.17	95.4	41
3	High-porosity paper	5.04	4.48	0.67	0.80	1.09	2.26	99.2	32
4	Low-porosity paper	5.02	3.87	0.72	0.92	1.37	2.32	88.4	44
5	Added nitrate	5.07	3.90	0.58	0.89	0.99	2.50	92.1	34
7	Fine cut (60 cpi)	4.99	4.17	0.63	0.86	1.31	2.58	98.4	39
Standard experimental blend II (SEB-II)									
48	RJR-expanded	5.09	2.56	0.36	0.76	0.88	—	75.6	37
55	Normal N fertilizer ^e	5.11	3.26	0.57	0.54	0.87	—	25.3	25
56	High N fertilizer ^e	5.03	3.93	0.59	0.43	0.73	—	18.2	31
Standard experimental blend III (SEB-III)									
81	No glycerol, cocoa	5.05	4.22	0.72	1.08	1.50	2.33	85.9	41
84	L&M additive	5.07	3.51	0.52	1.21	1.43	2.12	76.6	35
95	30:70 ATS:SEB-III ^f	5.06	4.06	0.84	1.40	2.17	2.17	84.7	55
Standard experimental blend IV (SEB-IV)									
10	RTS, slurry	5.08	3.42	0.41	0.80	1.07	2.44	80.5	60
21	Homogenized leaf	5.04	1.72	0.40	0.67	0.74	2.51	77.9	45
29	SEB-IV, 1.72% nic.	5.07	3.95	0.54	0.71	0.96	2.31	87.0	55
31	SEB-IV, 1.0% nic.	5.06	2.89	0.53	0.77	0.94	2.13	58.6	37
32	SEB-IV, 1.72% nic.	5.05	3.19	0.57	0.60	1.55	2.29	97.0	55

^aCigarette designs are described in detail by GORI (95).

^bPATEL (28).

^cmeq = milliequivalents.

^dTBA = tumor-bearing animals.

^eFlue-cured component of SEB-II only.

^fATS = artificial tobacco substitute.

Table 9.
Puff-by-puff pH of MSSs from two commercial cigarettes

Puff no.	Cigarette A			Cigarette B		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum
9	5.90	6.00	6.10	—	—	—
8	6.05	6.15	6.25	6.48	6.70	6.93
7	6.22	6.31	6.40	6.45	6.67	6.90
6	6.25	6.35	6.45	6.35	6.52	6.69
5	6.27	6.38	6.50	6.33	6.50	6.66
4	6.25	6.37	6.50	6.35	6.50	6.65
3	6.24	6.36	6.48	6.30	6.43	6.56
2	6.13	6.22	6.32	6.33	6.45	6.57
1	6.30	6.40	6.50	6.35	6.45	6.55
Average	6.18	6.28	6.40	6.37	6.53	6.69
pH range in puffs	0.40	0.40	0.40	0.18	0.27	0.38

In 1976, GORI (94) summarized various analytical data obtained in the NCI “less hazardous” cigarette study on a control (SEB II) and ammonia–carbon dioxide expanded experimental blend of tobaccos and the MSSs from cigarettes fabricated from such tobaccos (Table 5). No MSS pyrazine, pyridine, or ammonia data were generated. However, patterns in Table 5 for MSS nicotine, formaldehyde, acetaldehyde, and acrolein deliveries as well as “smoke pH” of the MSSs are similar to those summarized in Tables 3 and 4 for the expanded flue-cured and Burley tobacco MSSs, respectively.

Analytical data generated in the NCI “less hazardous” study (95) on the pH and compositions of the CSCs from several experimental cigarettes indicate how meaningless “CSC pH” and “smoke pH” may be. From examination of data reported in the NCI study on “less hazardous” cigarettes, RODGMAN (96) noted that the MSSs from different cigarette samples that delivered the same weight of FTC “tar” were significantly different compositionally because entirely different technologies were used in the design of the samples. The 16 CSCs from the various cigarette designs listed in Table 8 were selected because of the uniformity of the “CSC pH” reported by PATEL (28) for each of them at $\text{pH } 5.05 \pm 0.07$. They showed significant compositional differences. Examination of the analytical data for several selected CSC components reveals significant variations despite the uniformity of the “CSC pH” among the samples, e.g., the phenol and *o*-cresol levels varied from 1.72 to 4.48 mg/g and from 0.36 to 0.84 mg/g of CSC, respectively; the benzo[*a*]pyrene (BaP) and benz[*a*]anthracene (BaA) levels varied from 0.43 to 1.40 $\mu\text{g/g}$ and from 0.73 to 2.17 $\mu\text{g/g}$ of CSC, respectively; the levels of acids varied from 2.12 to 2.58 milliequivalent/g of CSC; and the nicotine levels varied from 18.2 to 99.2 mg/g of CSC. The specific tumorigenicities (% tumor-bearing animals) of the CSCs in the

mouse skin-painting bioassay (25 mg/day) ranged from 25 to 60, suggesting that “CSC pH” *per se* has no particular relationship to CSC specific tumorigenicity. Similar variations in MSS composition and biological properties may be found in comparisons of other experimental cigarette samples in the NCI study, e.g., those with “CSC pH” 5.35 ± 0.05 (4 samples) or “CSC pH” 5.75 ± 0.10 (8 samples) (95). These findings support the premise advanced by WINGATE *et al.* (40) that the FTC “tar” value and the “smoke pH” value have much in common: Neither value provides the consumer with any information about the composition or biological properties of the MSS to which he/she is exposed.

Table 6 summarizes analytical data from a control cigarette and from two cigarettes fabricated from the same blend but containing reconstituted tobacco sheet (RTS) treated with ammonia in two different ways. One contained RTS ammoniated with ammonia and steam (ammoniated RTS), the other contained RTS treated with diammonium hydrogen phosphate (DAHP-treated RTS). The analytical data in general exhibit the same patterns as those summarized in Tables 3 to 5. From the increase in levels of the MSS pyrazines, it is obvious that the cigarette containing the DAHP-treated reconstituted tobacco sheet would have the greater flavor enhancement.

An interesting inconsistency exists between the data in Tables 3 to 6 for various ammoniated tobacco systems and the data reported by the USDA team (36, 37) on dipropylamine-treated tobacco. Inclusion of 100 mg/cig of dipropylamine in the tobacco rod increased the MSS “smoke pH” from pH 5.6 for the control cigarette to pH 8.2 for the treated cigarette with no significant change in the MSS pyridine and nicotine levels from the two cigarettes. Despite this observation and the fact that not only is the $\text{p}K_i$ for ammonia (9.25) less than that for dipropylamine (11.0) but also its level in the blend never

Figure 1.
Puff-by-puff pH of mainstream smoke from two commercial cigarettes

approaches the 100 mg/cig level, it is often claimed that inclusion of ammonia in the blend will modify the MSS nicotine delivery.

When investigators use average “smoke pH” for cigarette MSS, whether it is the average of the “smoke pH” from the puffs from a cigarette or from several cigarettes or the average of the minimum, mean, or maximum pH per puff, they miss a crucial point in the assessment of cigarette mainstream “smoke pH.” **The smoker responds to cigarette smoke on a per puff basis.** The data in Table 9 and portrayed graphically in Figure 1 demonstrate the point. With the SENSABAUGH–CUNDIFF “smoke pH” method (25), the MSSs from two different cigarettes gave the per puff pH values depicted. One contained no ammoniated tobacco component, the other did. Despite the apparent differences in the average minimum, mean, or maximum pH values, examination of the plotted data in Figure 1 indicates that considerable overlap in the pH range occurs in Puff 1 and Puffs 3 through 6. It is highly unlikely that the delivery level and nature of nicotine in these puffs from the two cigarettes would differ significantly in their effect on the smoker or induce the smoker to adjust his/her puffing parameters.

VIII. CONCLUSIONS

Most analytical methods employed to determine the pH of cigarette MSS involve the averaging of the values obtained with all the puffs from a cigarette or the averag-

ing of the total number of puffs from several cigarettes plus solution of the MSS in various quantities of water prior to pH determination. Therefore, the relevance of these “smoke pH” values to the situation involving a smoker who smokes a cigarette one puff at a time is highly questionable. While many investigators have commented on the biological situation where the smoke components must traverse a layer of buffered fluid separating the smoke-filled respiratory tract cavity and the underlying tissue, seldom is the effect of either volume or the pH of the buffered fluid taken into account in determining the “smoke pH” of cigarette MSS taken one puff at a time. While numerous discussions, particularly during the past decade, have dealt with the effect of pH on the nature (degree of protonation) of nicotine in cigarette MSS and its rate of absorption by the smoker, seldom is the volume and/or pH of oral cavity saliva or the volume and/or pH of the fluid coating the lung surface taken into account in assessing either the nature or absorption of nicotine by the smoker. If it is accepted that the degree of protonation of nicotine is pH dependent, then logic dictates that the degree of protonation of nicotine as it traverses the film of fluid separating the respiratory tract cavity and the underlying tissue will be dependent on the pH of the buffered fluid and not on the “smoke pH” *per se*. The often repeated argument that adjustment of the “smoke pH” by a technique such as ammoniation of one or more of the tobacco blend components increases both the level of MSS nicotine and its rate of absorption, thus resulting in greater consumer

ERRATUM NOTICE

Issue no. 3, Volume 19, "Smoke pH: A Review" by Alan Rodgman (pp. 117–39):

p. 122, right hand column, lines 22–23: For "LAKRITZ *et al.* (36) and STEDMAN *et al.* (36) reported" read "LAKRITZ *et al.* (36) and STEDMAN *et al.* (37) reported".

p. 125, right hand column, lines 21–22: For "on the acidity of the CSC (16)" read "on the acidity of the CSC (46)".

An error was inadvertently introduced in the References Section during the editing process. Therefore, pages 135–39 of the article are completely reproduced and corrected on the following pages and can be replaced. The numbers in square brackets indicate the page numbers of the original manuscript.

The editors of the journal apologize for the error and the inconvenience it has produced.

acceptance and continuation of smoking, fails to take into account what other changes occur in the smoke to increase its consumer acceptability. Inclusion of modest percentages of ammoniated tobacco in the blend does indeed increase the "smoke pH" of the MSS, but it does not necessarily increase the level of MSS nicotine. Coincidentally, not only are the MSS levels substantially reduced of several low molecular acids, aldehydes, and ketones known to be respiratory tract irritants but also the MSS levels of several highly flavorful pyrazines are substantially increased. These MSS composition modifications result in an MSS classified as milder and more flavorful and whose consumer acceptability is considerably enhanced.

Until the pH of MSS is determined on a per puff basis in a system simulating that in the oral cavity or the lung of the smoker, the nature of specific smoke components at the time of contact and their reactivity with respiratory tract tissue will remain highly speculative.

Even though procedures to determine the MSS "tar" value are precisely defined whereas those for the determination of "smoke pH" value are not, "tar" and "smoke pH" have much in common: Neither value provides the consumer with any significant information about the composition or biological properties of the MSS to which he/she is exposed.

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