Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 21 · No. 2 · July 2004

DOI: 10.2478/cttr-2013-0771

Some Studies of the Effects of Additives on Cigarette Mainstream Smoke Properties. III. Ingredients Reportedly Used in Various Commercial Cigarette Products in the USA and Elsewhere*

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SUMMARY

In the mid-1980s, each major US cigarette manufacturer prepared a list of those ingredients added at that time to its cigarette products. The lists were combined into one and submitted to the US Office of Smoking and Health in 1986. It comprised 599 entities. On the basis of extensive literature survey and examination of much unpublished data from the Tobacco Industry members on the chemistry and toxicology of the ingredients, a panel of eminent toxicologists assessed the safety of each listed ingredient with regard to its pyrolysate components and its possible effect when added to cigarette tobacco on the chemical and biological properties of the cigarette mainstream smoke. Subsequently, DOULL *et al.* listed the 599 ingredients and summarized the conclusions of the panel on their effect on the chemical and biological properties of cigarette smoke. In addition to the panel and DOULL *et al.*, other investigators have noted that many of the compounds used as ingredients in cigarette tobacco blends are identical with or similar to identified components of tobacco and/or tobacco smoke. The validity of this statement is obvious when the compounds in the DOULL *et al.* list are cataloged as in Table 1. Those tobacco ingredients that are not individual compounds but are naturally-occurring oils, resins, etc. or extracts of naturally-occurring materials not only contain many of the compounds listed by DOULL *et al.* as tobacco additives but also contain many of the same compounds present in tobacco.

Detailed examination of the literature on the chemical and biological properties of the recently used tobacco ingredients listed by DOULL *et al.* plus a massive amount of chemical and biological data generated during the past several decades indicates that not only does none of the DOULL *et al.* listed ingredients contribute any significant adverse chemical properties to cigarette mainstream smoke (MSS) but also none affects adversely the biological properties of the MSS.

The chemical factors examined included: a) The effect on MSS composition of the ingredients added to cigarette tobacco at the usual use level or several times that. In two major series of studies, one by CARMINES *et al.* and one by BAKER *et al.*, the effect of the added ingredient on the concentration in mainstream smoke of specific components defined as toxicants was determined. The CARMINES *et al.* study involved analysis of the smoke components suggested by the US Consumer Product Safety Commission and of concern to the International Agency for Research on Cancer (IARC). The BAKER *et al.* study involved analysis of the so-called "Hoffmann analytes" in cigarette smoke. b) The nature of the pyrolysis products generated during the smoking process or during pyrolysis of an individual ingredient under conditions approximating those in the cigarette pyrolysis zone. In many instances when the added ingredient is a compound, a significant percentage of it is transferred unchanged to the MSS and sidestream smoke

*Received: 5th August 2003 – accepted: 23rd December 2003

(SSS). The small percentage not transferred intact to the smoke is seldom converted to an MSS component possessing significant toxic properties.
The extensive biological studies that showed no significant adverse effect of the MSS from ingredient-containing cigarettes included: a) The specific tumorigenicity to laboratory animal skin of the mainstream cigarette smoke condensate (CSC) from ingredient-containing cigarettes vs. the mainstream CSC from ingredient-free cigarettes. b) Exposure of laboratory animals via inhalation to the MSS from ingredient-containing cigarettes vs. the MSS from ingredient-free cigarettes. c) Determination in a variety of tests of the *in vitro* genotoxicity of the mainstream particulate phase and/or vapor phase.
In addition, the results of non-tobacco-related studies are available in which many individual compounds on the DOULL *et al*. list were assayed for mutagenicity in the Ames test with several strains of *Salmonella typhimurium.* An excellent example is the 1984 study by ISHIDATE *et al*. who examined the mutagenicity of many compounds included as additives in Japanese foods. Over 40 of the compounds exhibiting non-mutagenicity also occur on the DOULL *et al.* tobacco ingredient list.
Assessment of the total chemical and biological data cited herein provides a noteworthy contradiction to the much repeated assertions – with no data supporting them - that the ingredients added to cigarette tobacco result in significant adverse changes in the chemical and biological properties of the cigarette MSS. [Beitr. Tabakforsch. Int. 21 (2004) 47–104]

ZUSAMMENFASSUNG

Mitte der 1980er Jahre erstellte jeder US Zigarettenhersteller eine Liste der Substanzen, die zur damaligen Zeit den Zigaretten zugesetzt wurden. Diese Listen wurden in einer einzigen zusammengefasst und im Jahre 1986 der US Gesundheitsbehörde „Office of Smoking and Health“ vorgelegt. Diese Liste umfasste 599 Einträge. Auf der Basis einer umfassenden Literaturübersicht und unter Heranziehung einer Vielzahl unveröffentlichter Daten der Tabakindustrie über die chemischen und toxikologischen Eigenschaften der Zusatzstoffe bestimmte ein Gremium aus bekannten Toxikologen die Sicherheit jeder einzelnen aufgeführten Substanz im Hinblick auf die bei der Pyrolyse entstehenden Substanzen und die möglichen Auswirkungen auf die chemischen und biologischen Eigenschaften des Hauptstromrauchs von Zigaretten. Anschließend stellten DOULL *et al*. diese 599 Substanzen in einer Liste zusammen und fassten die Schlussfolgerungen der Kommission über die Auswirkung dieser Substanzen auf die chemischen und biologischen Eigenschaften des Zigarettenrauchs zusammen.
Zusätzlich zu diesem Gremium und der Arbeit von DOULL *et al*. wurde in anderen Untersuchungen festgestellt, dass viele Substanzen, die Tabakmischungen zugesetzt werden, mit bekannten Tabak- und/oder Tabakrauchbestandteilen identisch oder diesen ähnlich sind. Die Gültigkeit dieser Feststellung wird deutlich, wenn die von DOULL *et al*. aufgeführten Substanzen wie in Tabelle 1 aufgelistet werden. Die Zusatzstoffe, bei denen es sich nicht um Einzelsubstanzen sondern um natürlich vorkommende Öle, Harze usw. oder Extrakte natürlich vorkommender Stoffe handelt, enthalten nicht nur viele der von DOULL *et al.* als Tabakadditive aufgeführten Substanzen sondern auch viele der Substanzen, die im Tabak enthalten sind.
Eine umfassende Übersicht der Literatur zu den chemischen und biologischen Eigenschaften der gegenwärtig verwendeten und von DOULL *et al.* aufgeführten Tabakzusatzstoffe und eine große Anzahl chemischer und biologischer Daten der letzten Jahrzehnte weist darauf hin, dass keine der von DOULL *et al.* gelisteten Substanzen signifikant nachteilige chemische und biologische Wirkungen auf den Hauptstromrauch (MSS) dieser Zigaretten ausübt.
Die untersuchten chemischen Faktoren beinhalten: a) Die Auswirkung der Tabakzusatzstoffe auf die Zusammensetzung des MSS bei Hinzufügen zum Zigarettentabak in üblicher oder mehrfach erhöhter Menge. In zwei umfassenden Untersuchungsreihen, einer von CARMINES *et al.* und einer weiteren von BAKER *et al.*, wurde die Auswirkung von Zusatzstoffen auf das mengenmäßige Vorkommen spezifischer, als toxisch definierter Substanzen im Hauptstromrauch bestimmt. Bei der Studie von CARMINES *et al.* wurden jene Rauchkomponenten bestimmt, die von der US Verbraucherschutzorganisation Consumer Product Safety Commission vorgeschlagen wurden und denen von der International Agency for Research on Cancer (IARC) Bedeutung zugeschrieben wird. In der Untersuchung von BAKER *et al*. wurden die Rauchinhaltsstoffe der sogenannten „Hoffmann“-Liste untersucht. b) Die Natur der Pyrolyseprodukte, die während des Rauchvorgangs oder während der thermischen Zersetzung von Einzelsubstanzen unter Bedingungen, die denen in der Pyrolysezone der Zigarette ähneln, entstehen. Wenn es sich bei dem Zusatzstoff um eine Einzelsubstanz handelt, geht häufig ein signifikanter Anteil unverändert in den MSS und Nebenstromrauch (SSS) über. Der geringe Anteil, der nicht intakt in den MSS übergeht, wird selten zu einem MSS Inhaltsstoff mit signifikant toxischen Eigenschaften zersetzt.
Die umfassenden biologischen Studien, in denen sich bei Zigaretten mit Zusatzstoffen keine signifikant nachteiligen Wirkungen auf den Hauptstromrauch zeigten, beinhalten: a) Die spezifische tumorigene Wirkung des Rauchkondensats von Zigaretten mit Zusatzstoffen im Vergleich zum Kondensat von Zigaretten ohne Zusatzstoffe auf der Haut von Versuchstieren. b) Inhalative Tierversuche mit dem MSS von Zigaretten mit beziehungsweise ohne Zusatzstoffen. c) Bestimmung der *in vitro* Genotoxizität der Partikel- und/oder Gasphase des MSS in einer Vielzahl von Untersuchungen.
Außerdem stehen die Ergebnisse von nicht tabakbezogenen Studien zur Verfügung, bei denen viele Einzelsubstanzen der Liste von DOULL *et al*. in Bezug auf ihre Mutagenität im Ames *Salmonella typhimurium* Test untersucht wurden. Ein exzellentes Beispiel ist die Studie von ISHIDATE *et al.* aus dem Jahre 1984, in der die Mutagenität vieler Substanzen untersucht wurde, die in Japan als Zusatzstoffe in Lebensmitteln enthalten sind. Mehr als 40 dieser Substanzen, die keine Mutagenität aufwiesen, sind ebenfalls in der von DOULL *et al*. zusammengestellten Liste der Tabakzusatzstoffe aufgeführt.
Die Bewertung der gesamten hier zitierten chemischen und biologischen Daten stellt einen bemerkenswerten Widerspruch zu den häufig zitierten – ohne Daten belegten –

Behauptungen dar, dass die zum Zigarettentabak hinzugefügten Zusatzstoffe signifikant nachteilige Veränderungen auf die chemischen und biologischen Eigenschaften des MSS der Zigaretten hervorrufen. [Beitr. Tabakforsch. Int. 21 (2004) 47–104]

RESUME

Au milieu des années 1980, chaque producteur de cigarettes aux Etats Unis a préparé une liste d'additifs apportés aux cigarettes. Ces listes ont été regroupées en une seule et soumis à l'autorité compétente, US Office of Smoking and Health, en 1986. Cette liste comporte 599 entités. Basé sur une revue approfondie de la littérature et de l'examen des données non publiées de l'industrie du tabac sur la chimie et la toxicologie des ingrédients, un panel d'éminents toxicologistes a évalué la sécurité de chacun de ces ingrédients par rapport aux produits de pyrolyse et, dans le cas de l'apport au tabac, l'effet possible sur les propriétés chimiques et biologiques de la fumée du courant principal (CP). Par la suite, DOULL *et al.* ont compilé une liste des 599 ingrédients et présenté les conclusions du panel sur les effets de ces ingrédients sur les propriétés chimiques et biologiques de la fumée de cigarette.
En plus du panel d'experts et de l'analyse de DOULL *et al*., d'autres chercheurs ont montré que beaucoup des composants utilisés comme ingrédients dans des mélanges de tabac sont identiques, ou similaires, aux composants identifiés dans le tabac et/ou la fumée du tabac. La validité de cette constatation devient évidente si les composants de la liste de DOULL *et al.* sont catalogués comme c'est le cas dans le tableau 1. Les ingrédients du tabac, qui ne sont pas des composants uniques mais des huiles naturellement présentes, des résines etc. ou des extraits de matières naturellement présentes, ne contiennent pas seulement beaucoup des composants catalogués par DOULL *et al*. comme additifs du tabac, mais contiennent également beaucoup des mêmes composants présents dans le tabac.
L'examen approfondi de la littérature sur les propriétés chimiques et biologiques des ingrédients du tabac récemment utilisés et compilés par DOULL *et al.* ainsi qu'une quantité considérable de données biologiques obtenues au cours des dernières décennies indiquent qu'aucun des composants compilés par DOULL *et al.* n'a d'effets chimiques ou biologiques significativement défavorables sur les propriétés de la fumée du CP de cigarette.
Les facteurs chimiques examinés comprennent: a) Les effets sur la composition du CP des ingrédients apportés au tabac de cigarette à un niveau habituel ou plusieurs fois supérieur. Dans deux séries d'études principales, une de CARMINES *et al.* et l'autre de BAKER *et al.*, les effets des ingrédients apportés au tabac sur la teneur en composants spécifiques considérés comme toxiques dans la fumée du CP ont été déterminés. L'étude de CARMINES *et al.* comprend l'analyse des composants suggérés par l'organisation de la protection des consommateurs aux Etats Unis, Consumer Product Safety Commission, et ceux d'intérêt pour l'Agence Internationale de la Recherche sur le Cancer (IARC). L'étude de BAKER *et al.* comprend l'analyse des composants de la fumée de cigarette, appelés « analytes Hoffmann ». b) La nature des produits de pyrolyse générés au cours du fumage ou au cours de la pyrolyse d'un ingrédient individuel dans des conditions proches de celles de la zone de pyrolyse. Si l'ingrédient apporté est un composé, un pourcentage significatif est transféré sans modification dans le CP et le courant secondaire (CS). Le faible pourcentage qui n'est pas transféré de façon intacte est rarement converti en un composant du CP ayant des propriétés toxiques.
Les études biologiques approfondies qui n'ont pas montré d'effets significativement défavorables du CP de cigarettes avec ingrédients comprennent : a) La tumorigénicité spécifique du condensat du CP de cigarettes avec ou sans ingrédients dans des tests biologiques. b) Des études de l'inhalation chez des animaux de laboratoire en utilisant le CP de cigarettes avec ou sans ingrédients. c) Détermination de la génotoxicité *in vitro* des phases particulaires et/ou gazeuses du CP dans un grand nombre d'essais.
De plus, des résultats d'études non liées au tabac existent, dans lesquelles la mutagénicité de beaucoup de composants individuels de la liste de DOULL *et al.* a été déterminée par le test d'Ames avec *Salmonella typhimurium*. Un excellent exemple est l'étude d'ISHIDATE *et al.* en 1984 dans laquelle la mutagénicité d'un grand nombre de composants utilisés au Japon comme additifs dans la nourriture a été déterminée. Plus de 40 de ces composants non mutagènes sont aussi catalogués dans la liste de DOULL *et al.*
L'évaluation des données chimiques et biologiques présentée ici est en contradiction notable avec les allégations souvent répétées – et sans être confirmées par des données – que les ingrédients apportés au tabac de cigarette ont des effets significativement défavorables sur les propriétés chimiques et biologiques du CP des cigarettes. [Beitr. Tabakforsch. Int. 21 (2004) 47–104]

INTRODUCTION

For nearly four decades after the early 1950s an exceptional amount of information has been generated on the composition of the various types of tobacco, the smoke from many of the types, and the relationship between the two. Although much of the information has been published, much has not. Exemplary in this regard were the research personnel not only at the R.J. Reynolds Tobacco Company but also at other tobacco companies. Much information has been published in peer-reviewed journals and the remainder is available on the Internet. In the early tobacco and tobacco smoke studies, the chemical nature of one or two components was defined by means of classical chemical procedures, e.g., the identification of the terpenoid alcohol solanesol in flue-cured tobacco (1), the phenols eugenol and isoeugenol in the mainstream smoke (MSS) from Oriental tobacco (2), and maltol in the MSS from an ingredient-free German tobacco blend (3). However, as analytical methodology became more sophisticated and precise, many more components – sometimes several hundred newly identified in tobacco or smoke – were reported in a single publication. Examples of such publications are cited in subsequent paragraphs.
Involvement from the early 1950s to the late 1980s in in-house tobacco and tobacco smoke composition studies either in the laboratory or as a supervisor plus continual

cataloging of similar published literature from the early 1950s presented the author an excellent opportunity to utilize the information collected to validate statements made in the last decade by several investigators on the relationship between many of the ingredients added to cigarette tobacco blends and the components of tobacco and/or smoke. The monumental catalog by PASCHKE *et al*. (4) of the effect of materials added to tobacco on cigarette smoke composition and biological activity was published partway through the writing of the current report. While there is some overlap between this and the PASCHKE *et al*. report, there are numerous differences.

In 1986, each major US cigarette manufacturer listed the ingredients used at that time in its cigarette products. A combined list was submitted to the US Office of Smoking and Health. That list, comprising 599 additives, was subjected by a panel of eminent toxicologists not only to an extensive literature survey but also to an examination of unpublished data provided by the Tobacco Industry members on the chemistry and toxicology of the ingredients. The panel assessed the safety of each listed ingredient with regard to its pyrolysate components and its possible effect when added to cigarette tobacco on the chemical and biological properties of the cigarette MSS. The results were summarized in 1994 by DOULL *et al*. (5). Of the 599 ingredients, 460 (approximately 77%) are individual compounds. The remaining items are mixtures such as natural oils, plant extracts, oleoresins, etc. Many investigators have noted in their publications that numerous compounds on the list of ingredients are tobacco and/or cigarette MSS components. The following pages are an attempt to chronicle such a relationship between individual added components and their presence in untreated tobacco and/or its smoke. While PASCHKE *et al*. attempted to catalog every material ever added to tobacco and its effect on MSS chemical and/or biological properties, the present article deals only with those materials in the list by DOULL *et al*. While some of the additives cataloged by PASCHKE *et al*. did reduce the responses in specific bioassays and the levels of some MSS components considered toxic, they also rendered the MSS unacceptable to the consumer. Obviously, the ingredients listed by DOULL *et al*. did not suffer from such a problem since their addition was specifically designed to enhance the consumer acceptability of the MSS from the product.

As a beginning, DOULL *et al*. (5) in their report noted:

> . . . many of the ingredients added to cigarettes are identical or essentially similar in composition to natural leaf tobacco components.

In their 1998 report of the effect on rats of inhalation of MSS from ingredient-treated tobacco cigarettes, GAWORSKI *et al*. (6) expressed a similar view:

> . . . the addition of flavoring ingredients to the cigarette prior to smoking did not significantly alter the type or extent of biologic changes normally seen in smoke-exposed rodents. Given the fact that many of the added flavoring ingredients are structurally similar or identical to [*sic*] natural constituents of tobacco leaf or of tobacco smoke itself [LLOYD *et al*. (7)], these results are not totally unexpected.

Later, RUSTEMEIER *et al*. (8) in their description of the chemistry of MSS from ingredient-treated tobacco cigarettes noted:

> Many of these compounds or mixtures are also natural constituents of the tobacco leaf.

RODGMAN (9) concurred with the preceding statements when he wrote:

> Many flavorful tobacco additives listed by DOULL *et al*. are structurally identical with or similar to highly polar, volatile components identified in the aqueous alcohol-soluble portion of cigarette MSS and tobacco.

And recently RODGMAN and GREEN (10) wrote:

> With the capability to isolate and identify highly polar and volatile components of tobacco and its MSS, it was obvious that many were identical with or similar to ingredients of flavor formulations added to specific tobacco blends to impart unique smoking characteristics . . .
>
> Many "top-dressing" components are structurally identical with or similar to identified tobacco components. With no evidence to the contrary, it is assumed that such an individual added flavorant would behave during the smoking process (in terms of direct transfer to smoke or degradation, reaction, etc.) much in the same manner as the naturally occurring tobacco component.

While many authors consider a number of the individual compounds added to cigarette tobacco filler to be tobacco and/or tobacco smoke ingredients, it seems worthwhile to catalog the extent to which this view is true. Obviously, if a specific flavorful compound is already a tobacco component, then its addition to tobacco is an attempt to enhance its flavorful effect. If it is a compound generated during the smoking process, then its addition to tobacco enhances the level in the smoke by tobacco-to-smoke transfer.

The compounds added as ingredients to cigarette tobacco may fall into one of the following categories:

- It is a component of one or more of the tobacco types (flue-cured, Oriental, burley, Maryland) commonly used in cigarette blends.
- It is a component of cigarette MSS.
- It is a component of both tobacco and tobacco smoke.
- It is not a component of either the tobaccos or their smoke.

An ingredient compositionally similar to but not identical with a tobacco leaf or smoke component may be categorized in two ways: It is either an isomer or an homolog of a compound identified in natural tobacco leaf and/or its smoke. As noted, there are compounds used as cigarette ingredients that do not fall into any of the first three categories listed.

In the broad spectrum of chemistry, biochemistry, and biology, cases exist where the properties of one homolog vary significantly from those of another or where the properties of one isomer differ significantly from those of another. For example, whether classified as a "Group 2A carcinogen" by the International Agency for Research on Cancer (IARC) (11), or a significant carcinogen in cigarette MSS (12), or overall as a borderline carcinogen by others (13), the specific tumorigenicity of mouse-skin painted or subcutaneously injected benz[*a*]anthracene (B[*a*]A) is insignificant compared to that of its homolog, 7,12-dimethylbenz[*a*]anthracene (DMBA). The isomeric $C_{20}H_{12}$ polycyclic aromatic hydrocarbons (PAHs), benzo[*a*]pyrene (B[*a*]P), and benzo[*e*]pyrene (B[*e*]P) differ markedly in their specific tumorigenicities in studies involving mouse-skin painting or subcutaneous injection (13). B[*a*]P under appropriate laboratory conditions is one of the most potent tumorigens known whereas the isomeric B[*e*]P under the same conditions is essentially nontumorigenic.

In the 1950s, the organic solvent extraction of tobacco was studied extensively with the purpose of removing PAH precursors from the tobacco. Incorporated into one process was an aqueous alcohol-hexane partition to separate the polar, more flavorful tobacco components from the lipophilic PAH precursors. At that time, almost nothing was known about the nature of the polar tobacco components although it was apparent they made a considerable positive contribution to the flavor and aroma of cigarette MSS. Despite the lack of knowledge about the precise nature of the polar components, it was demonstrated they were not significant PAH precursors (14). The lack of knowledge about the polar components in tobacco was due to our inability at that time to separate highly polar compounds in a complex mixture. This situation continued during years of intensive effort on cigarette MSS composition but was finally resolved and utilized by SCHUMACHER *et al.* (15) in the 1970s. Of the over 800 MSS components identified by SCHUMACHER *et al.* (15), by NEWELL *et al.* (16), and by HECKMAN and BEST (17), many were highly polar components new to the tobacco smoke literature.

In his pioneer research on glass capillary gas chromatography, GROB (18) also succeeded in identifying a number of polar components in the MSS from cigarettes containing additive-free tobacco. Later, it will be shown that some of the polar components GROB identified in MSS are also in the DOULL *et al*. list.

With regard to tobacco components, LLOYD *et al.* (7) identified 275 previously unidentified components of additive-free flue-cured tobacco, 132 new to all tobacco types. Many of these compounds were highly polar and considered significant contributors to MSS flavor and aroma. Similar detailed studies were conducted on the composition of burley tobacco (ROBERTS and ROHDE, 19), Oriental tobacco (SCHUMACHER and VESTAL, 20), and Maryland tobacco (SCHUMACHER, 21). Years later, it became apparent that many of the highly polar components of tobacco and tobacco smoke were identical with or similar to many of the components used in the flavor additive formulations, i.e., the "top dressing", added to a specific tobacco blend to impart its unique smoking characteristics (5).

In the mid-1980s, each major US cigarette manufacturer listed the ingredients added to its cigarette products at that time. A combined list, comprising 599 entities, was submitted to the US Office of Smoking and Health in 1986. From an extensive literature survey and examination of much unpublished data from the cigarette manufacturers on the chemistry and toxicology of the ingredients, a panel of eminent toxicologists assessed the safety of each listed ingredient with regard to its pyrolysis products and its possible effect when added to cigarette tobacco on the chemical and biological properties of cigarette mainstream smoke. Subsequently, DOULL *et al.* (5) listed the ingredients assessed and summarized the conclusions of the panel on their effect on the chemical and biological properties of cigarette smoke.

In their assessment of available information on these ingredients variously used as cigarette tobacco additives, DOULL *et al*. concluded that none of the materials used as flavorants on smoking tobacco products, particularly cigarettes marketed by a US manufacturer, imparted any significant adverse chemical or biological properties to the MSS from the ingredient-treated tobacco. However, DOULL *et al*. did not publish an overview of the studies and reports they had examined or provide any details on their analysis. In their detailed assessment of reported chemical and biological properties of the MSS from cigarettes fabricated with tobacco with or without one or more additives, PASCHKE *et al*. (22) reached a similar conclusion; namely, that in general, no significant increase in the biological activity of tobacco was reported from cigarettes containing specifically described added ingredients. In his examination of extensive laboratory data generated from additives and additive-treated cigarettes between the mid-1950s and the late 1970s, RODGMAN (9,23) reached a conclusion similar to that of DOULL *et al*. and PASCHKE *et al*.

Discussed below are the studies reported since 1997 by GAWORSKI *et al*., CARMINES *et al*., and BAKER *et al*. on the effect or lack thereof of hundreds of ingredients added to cigarette tobacco on the chemical and biological properties of the MSS from such cigarettes. Many of the ingredients studied are used in commercially available products.

In the mid-1970s a somewhat similar but much less sophisticated study was conducted in an attempt to determine the effect of added cigarette ingredients on a specific biological property, namely mutagenicity in the Ames test, of its MSS. For many years, considerable thought was given to development of an accurate analytical method to determine the contribution of trace levels (a few μg/g of tobacco blend) of a flavorant added to cigarette tobacco to the levels of toxicants in MSS. Limitations in analytical methodology precluded the design of an experiment whose results would be meaningful. Even studies with radiolabeled compounds had their limitations in the study of the pyrogenesis of MSS components.

However, with the advent of the Ames *Salmonella typhimurium* test, an alternate experiment was devised in an attempt to show the effect of additives in commercial cigarette brands on total particulate matter (TPM) specific mutagenicity. Such ingredient formulations are qualitatively and quantitatively unique for each commercial brand and comprise many different individual ingredients, some of which are individual compounds, others are naturally occurring oils. Among the five commercial brands studied, a total of more than 150 different ingredients was involved. At that time, the total amount of flavorants added ranged from 1.0 to 1.5 mg/g of tobacco blend; the amounts of casing materials and menthol were obviously greater. Four sets of cigarettes for each of five commercial brands were fabricated. The levels of flavorants, casing materials, and humectants were varied as follows:

Cigarette variation [a]	Flavorant formulation level	Casing materials [b] and humectants [c] level
A	usual level used on brand	usual level used on brand
B	ten times the usual level used on brand	0
C	0	usual level used on brand
D	0	0

[a] Five cigarette brands included four commercial filter-tipped brands ranging from high- to ultralow-FTC "tar" deliveries plus a commercial mentholated filter-tipped cigarette. All cigarettes were manufactured in 1977. Cigarette A was the brand commercially available at that time.

[b] Licorice, cocoa, and sugars.

[c] Glycerol and propylene glycol.

A contract laboratory determined the mutagenicity of the various TPMs (24). Because the response of the *Salmonella typhimurium* was linear from 0 to 500 μg/plate of added wet total particulate matter (WTPM), mutagenicity in terms of revertant/plate was tabulated for the WTPM dose level of μg/plate. This permitted comparison of the four cigarette variations for each *Salmonella typhimurium* strain and for each of five commercial brands. The results of this study were presented in detail previously (9,10,23).

The flavorants added to the commercial brands did not increase its MSS specific mutagenicity. In fact, flavorant removal increased slightly the observed mutagenicity of the WTPM. The findings from this study indicated that the additives in the flavorant formulations for the five commercial products did not contribute toxic components to the MSS whose levels and potency were such that they produced increases in the intrinsic specific mutagenicity as measured in the Ames test system.

For proprietary reasons, neither the nature of a specific flavorful compound or natural oil nor the amount added per gram of tobacco blend is indicated for any of the five marketed brands used as a control cigarette. Logic dictates that each of the control samples (Sample A in each case) as marketed contained the usual casing materials and humectants, i.e., glycerol, propylene glycol, sugar, cocoa, and licorice. Here again, for proprietary reasons, the levels added to each control brand are not specified. Obviously, the one mentholated brand does contain added menthol but the level is not specified. In some instances, a specific compound was added not only individually but also as a component of a natural flavorful oil such as nutmeg or a casing material ingredient such as licorice.

Omission of the casing materials and humectants increased the specific mutagenicity of the various TPMs. This is not surprising when the transfer of added humectants from the tobacco filler to MSS is taken into account. Significant amounts of humectants (glycerol, propylene glycol) added to these particular tobacco blends are transferred to MSS TPM and sidestream smoke (SSS) TPM (15). Analysis of humectants in MSS indicated that the FTC "tar" from all commercial cigarettes contains significant amounts of humectants (25). These nonmutagenic humectants act as diluents for the MSS TPM mutagens produced pyrogenetically or transferred directly from tobacco to smoke during smoking. In a more recent study, HECK *et al*. (26) reported that inhalation of MSS from cigarettes with glycerol and propylene glycol, added either individually or in combination, had no significant adverse biological effects on rats.

In their study of added ingredients on the biological effect of inhaled cigarette MSS, GAWORSKI *et al*. (6) administered to rats via inhalation the MSS from cigarettes to which 172 specified ingredients (129 individual compounds, 43 mixtures) had been added. Most of the ingredients are included in the DOULL *et al.* list. From the results of their inhalation experiment, GAWORSKI *et al*. concluded that the addition of the flavoring ingredients to the cigarette tobacco had no discernible effect on the character or extent of the biological responses normally associated with inhalation of cigarette MSS in rats.

In a similar biological study, GAWORSKI *et al.* (27) investigated the effect on the specific tumorigenicity of skin-painted CSC from cigarettes to which 150 specified ingredients (109 individual compounds, 41 mixtures) had been added. Here again, most ingredients are included in the DOULL *et al.* list. In their skin-painting study, GAWORSKI *et al*. observed occasional differences between test and control CSCs in tumor incidence, latency, and multiplicity. Since the differences appeared to be within normal variation for the bioassay system, GAWORSKI *et al*. concluded that none of them was substantial enough to indicate that the tumor promotion capacity of CSC from cigarettes containing ingredient-treated tobacco was discernibly different from the CSC obtained from control cigarettes containing ingredient-free tobacco.

Early in 2002, CARMINES and his colleagues at INBIFO published a series of four reports (8,28,29,30) on their detailed study of the effects on the chemical and biological properties of the MSSs from a cigarette to which a group of ingredients had been added. A total of 333 specified ingredients commonly used in cigarette manufacture was added to a test cigarette, representative of a commercial blended cigarette. Ingredients were added not only at approximately the levels normally used in commercial cigarettes but also at levels several times those normally used. The MSS data vs. those from a control cigarette with no added ingredients indicated an increase in the TPM. Normalizing the yields of individual MSS ingredients to the TPM yields indicated a reduction in the majority of them. An increase in the amount relative to TPM was observed for only a few MSS components (RUSTEMEIER *et al*., 8). Their smoke component analysis was concentrated on 51 components suggested by the US Consumer Product Safety Commission and which were of concern to IARC.

These chemical results on the MSSs are consistent with the results obtained not only in *in vitro* mutagenicity and cytotoxicity studies with the TPMs from the ingredient-treated and control cigarettes (ROEMER *et al*., 29) but also in *in vivo* studies with rats exposed via inhalation to the MSSs from the treated and control cigarettes (VANSCHEEUWIJCK *et al*., 30): The ingredient addition did not increase the *in vitro* mutagenicity or cytotoxicity of the TPMs from the ingredient-treated cigarettes or the inhalation toxicity to rats of their MSSs even at the exaggerated exposure level used.

Even more recently, the effect of addition of mixtures of flavor ingredients to cigarette tobacco on its MSS chemistry and genotoxicity was studied. As BAKER and SMITH noted, in most instances no statistically significant effect on smoke yields relative to the untreated control was observed (31). The data reported by MASSEY *et al.* (32) and BAKER *et al.* (33) from the genotoxicity study (Ames test, chromosome aberration, mammalian cell mutation) on nearly 500 ingredients added in various groups indicated no additional activity of the MSS condensate from the ingredient-treated cigarette vs. the activity from the control cigarette. These findings not only bolster the observations reported by RODGMAN (9,23) and RODGMAN and GREEN (10) but also the conclusions reached by DOULL *et al.* (5), PASCHKE *et al.* (22), and GAWORSKI *et al.* (6,27,34,35) on the effect of the added ingredients listed by DOULL *et al*. on the chemical and biological properties of cigarette MSS. Many of the results and conclusions on the chemical and biological studies mentioned previously (4,5,6,8,9,26,27,28,29,30,31,32,34,35) have been summarized and excellently evaluated by BAKER and SMITH (36).

In addition to the evaluations noted above, BAKER *et al*. have described the results of a mammoth study on the effect of added ingredients on the chemical composition of cigarette MSS, particularly with regard to the effects on the so-called "Hoffmann analytes". In a two-part study, they determined the effect of a) 431 flavorants plus 19 other ingredients (37) and b) 29 casing ingredients plus 3 humectants (38) on MSS composition. These 482 ingredients, used in manufacture by

British American Tobacco, were added in various groupings. Of the total of 482 ingredients studied, 350 were also on the DOULL *et al*. list (5) of tobacco ingredients used in US cigarette brands. BAKER *et al.* reported the following from the results of their flavorant study (37):

> It was found that, in most cases, the mixtures of flavouring ingredients (generally added in parts per million levels) had no statistically significant effect on the analyte smoke yields relative to the control cigarette. Occasionally with some of the mixtures, both increases and decreases were observed for some smoke analyte levels relative to the control cigarette. These differences were generally up to about 15% with the mixtures containing flavouring ingredients. The significance of many of the differences was not present when the long-term variability of the analytical methodology was taken into account.

Based on the results from their study of casing ingredients, they reported (38):

> Their effects on smoke constituents were generally larger than the effects of flavouring ingredients, which were added at parts per million levels. Many of the casing ingredient mixtures either had no statistically significant effect on the level of the analytes investigated in smoke relative to a control cigarette, or they produced decreases of up to 44% in some cases . . . The largest increases were for formaldehyde levels, up to 73% in one case, observed from all casing mixtures containing sugar. This is most likely due to the generation of formaldehyde by pyrolysis of sugars.
>
> Occasional small increases were also observed for other analytes. However, the statistical significance of many of these increases was not present when the long-term variability of the analytical method was taken into account. The significance and possible reasons for the increases are discussed.

Considerable data have been reported from studies in which various materials, subsequently listed by DOULL *et al.* as added tobacco ingredients, were examined for mutagenicity in the Ames *Salmonella typhimurium* test. One such study was that of ISHIDATE *et al*. (39) who screened many of the ingredients added to foods commonly used in Japan (*Salmonella typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, TA98). Over 40 of the individual compounds examined by ISHIDATE *et al*. are also components in the tobacco ingredient list of DOULL *et al.* A few of the additives common to both lists were studied at 0.1, 0.5, or 1.0 mg/plate levels, e.g., cinnamaldehyde (CAS RN 104-44-2), citral (CAS RN 5392-40-5), geraniol (CAS RN 106-24-1), linalool (CAS RN 78-70-6). Only cinnamaldehyde showed borderline mutagenicity. These levels substantially exceed the per cigarette levels used in tobacco flavor formulations. The remainder of the materials common to both lists was studied at 5, 10, 20, or 25 mg/plate levels. Even at these highly excessive levels, none gave a positive mutagenic response.

2 STUDIES ON COMPOUNDS LISTED BY DOULL *et al*. (5)

In the present report, the ingredients listed by DOULL *et al*. are divided into two groups, a) ingredients that are individual compounds and b) those that are naturally occurring mixtures such as oils, resins, etc. or extracts of such materials. Table 1 catalogs the individual compounds listed by DOULL *et al*. as added cigarette ingredients and their effect on the chemical and biological properties of cigarette MSS. Table 2 lists the mixtures used as cigarette ingredients. To avoid confusion and to permit comparisons, the ingredients in Tables 1 and 2 are listed in the same order as they appear in the DOULL *et al*. list.

To simplify the understanding of Table 1 and to maintain its manageability, it should be noted that the following information is contained therein:

- Under *Ingredient* are listed the name used in the DOULL *et al*. report, the Chemical Abstract name, the Chemical Abstract Registry Number (CAS RN), and superscript designation (**F**) whether the ingredient is generally regarded as safe (GRAS) by the Flavor and Extract Manufacturers Association (FEMA) or is a Food and Drug Administration-approved (**FDA**) food additive or an FDA GRAS ingredient (**G**).

Ingredient		
As listed by DOULL *et al.*	CAS RN	CA nomenclature
Acetanisole [F]	100-06-1	ethanone, 1-(4-methoxy-phenyl)-

- Under *Chemistry* are listed references to studies where the individual ingredient was examined for its pyrolysis products (designated with superscript **P**), its effect on cigarette MSS composition, and its effect when added in a mixture of other ingredients on MSS composition. In an exceptional example of experimentation involving pyrolysis conditions approximating those occurring in the pyrolysis region of a burning cigarette, BAKER and BISHOP recently presented data on as many as ten of the major pyrolysis products from 291 compounds used as tobacco ingredients in commercial cigarette products (40). In many instances, the major pyrolysis product (>90%) of the ingredient studied was a result of its intact transfer to the pyrolysate. Over 240 of the 291 compounds studied by BAKER and BISHOP were also listed by DOULL *et al.* (5).
  It must be remembered, however, that it is highly improbable that the fate of a compound on pyrolysis will be equivalent to its fate during the cigarette smoking process when the compound is a component of a complex mixture such as tobacco that comprises thousands of other identified compounds, each of which may generate reactive fragments during the pyrolysis occurring in a burning cigarette (9,41).
- Under *Bioassay* are listed studies where the effect of the added individual ingredient was determined by results from mouse skin-painting studies with cigarette CSC, inhalation studies with cigarette MSS, and mutagenesis and/or genotoxicity studies plus the effect of that ingredient in a mixture of ingredients on the results from the same types of bioassays. Several instances are included in which the mutagenicity and/or genotoxicity were determined with the individual compound.
- Under Tobacco and/or Smoke are listed references to articles in which the identification of a) the ingredient or b) a homolog of the ingredient [reference designated][H] or c) an isomer of the ingredient [reference designated][I] in tobacco and/or cigarette MSS is described.

Table 1. Compounds in the DOULL *et al*. list (5): Studies on (a) their pyrolysis products, (b) their effect on the chemical and biological properties of cigarette MSS, and (c) their identification in untreated cigarette tobacco and/or its MSS

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
1	Acetanisole [F]	100-06-1	ethanone, 1-(4-methoxyphenyl)-; acetophenone, 4-methoxy-	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	29, 32, 33	7, 42	42, 43, 44, 45
2	Acetic acid [F]	64-19-7	acetic acid	8, 28, 31, 38, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33, 39	7, 21, 42, 44, 46,	15, 42, 44, 46, 47, 48, 49, 50
3	Acetoin [F]	513-86-0	2-butanone, 3-hydroxy-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42, 51	42, 52
4	Acetophenone [F]	98-86-2	ethanone, 1-phenyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 19, 42, 46, 53	19, 42, 52, 54
5	6-Acetoxydihydrotheaspirane [F]	57893-27-3		—	—	—	—	—	—
6	2-Acetyl-3-ethylpyrazine [F]	32974-92-8	ethanone, 1-(5-ethylpyrazinyl)-; homolog of ethanone, 1-pyrazinyl- [22047-25-2] and ethanone, 1-(5-methylpyrazinyl)- [22047-27-4]	—	—	—	—	—	[42, 46] [H]
7	2-Acetyl-5-methylfuran [F]	1193-79-9	ethanone, 1-(2-furanyl-5-methyl)-	—	—	—	—	7, 20, 42	42, 54, 55
8	Acetylpyrazine [F]	22047-25-2	ethanone, 1-pyrazinyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	19, 21, 42, 46, 56, 57	—
9	2-Acetylpyridine [F]	1122-62-9	ethanone, 1-(2-pyridinyl)-	—	—	—	—	42, 46, 56	17, 42, 58
10	3-Acetylpyridine [F]	350-03-8	ethanone, 1-(3-pyridinyl)-	—	—	—	24	7, 46, 44, 59, 152	48
11	2-Acetylthiazole [F]	24295-03-2	ethanone, 1-(2-thiazolyl)-; isomer of ethanone, 1-(4-thiazolyl)- [38205-66-2]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	[17, 42, 47, 48] [I]
12	Aconitic acid [F, G]	499-12-7	1-propene, 1,2,3-tricarboxylic acid	8, 28	—	30	29	—	42
13	*dl*-Alanine [FDA]	107-95-9	β-alanine	—	—	6	24, 39, 60 [P]	42, 44, 61, 62, 63, 64, 65, 66, 67	42, 44, 45, 48, 68, 69
		6898-94-8	alanine	60 [P]	—	—	60 [P]	61, 62, 63, 64, 65, 66, 67, 70	68, 69
14	Allyl hexanoate [F]	123-68-2	hexanoic acid, 2-propenyl ester	—	—	—	—	—	—
15	Allylionone [F]		homolog of 3-buten-2-one, 4-(2,6,6-trimethyl-1 (or 2)-cyclohexen-1-yl)-	—	—	—	—	[7, 20, 46] [H]	—
16	Ammonia	7664-41-7	ammonia	71	—	—	—	42	42, 47, 48, 57, 72
17	Ammonium bicarbonate [G]	1066-33-7	carbonic acid, mono-ammonium salt	73, 74, 75	76	—	39	42	42
18	Ammonium hydroxide [G]	1336-21-6		31, 40 [P]	—	—	32, 33	—	—
19	Ammonium phosphate dibasic [G]	7783-28-0		8, 28, 37, 31, 38, 71	—	30, 33	29, 32, 33, 77, 78	—	—
20	Ammonium sulfide [F]	12135-76-1		—	—	—	—	—	—
21	Amyl alcohol [F, FDA]	71-41-0	1-pentanol; homolog of 1-butanol	—	—	—	24	46, 79	[15, 42] [H]
22	Amyl butyrate [F, FDA]	540-18-1	butanoic acid, pentyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	—	—
23	Amyl formate [F, FDA]	638-49-3	formic acid, pentyl ester	8, 28	—	30	29	—	—
24	Amyl octanoate [F, FDA]	638-25-5	octanoic acid, pentyl ester	—	27, 35	6, 30	29	—	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
25	α-Amylcinnamaldehyde [F, FDA]	122-40-7		31, 37, 40 [P]	—	33	32, 33	—	—
26	Anethole [F, G] *trans*-	104-46-1 4180-23-8	benzene, 1-methoxy-4-(1-propenyl)-	80	27, 35	6	24	42, 53	42, 47, 80
27	Anisyl acetate [F, FDA]	104-21-2	acetic acid, 4-methoxybenzenemethyl- benzenemethanol, 4-methoxy-, acetate	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	42
28	Anisyl alcohol [F, FDA]	105-13-5	benzenemethanol, 4-methoxy-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	81	—
29	Anisyl formate [F, FDA]	122-91-8	benzenemethanol, 4-methoxy-, formate	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
30	Anisyl phenylacetate [F, FDA]	102-17-0	benzenemethanol, 4-methoxy-, phenylacetate	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
31	*l*-Arginine [F]	74-79-3	arginine	60 [P]	—	6, 30	24, 29, 60 [P]	42, 44, 48, 61, 62, 63, 70	—
32	Ascorbic acid [F, G]	50-81-7	L-gulofuranolactone, 3-oxo-	31, 37, 40 [P]	—	—	24, 32, 33, 39, 82	42, 44, 67, 83, 84	42
33	*l*-Asparagine monohydrate [FDA]	5794-13-8	asparagine	60 [P]	—	—	24, 60 [P]	42, 44, 48, 61, 63, 64, 65, 66, 67, 85, 86	42, 68, 69
34	*l*-Aspartic acid [F, FDA]	56-84-8	aspartic acid	60 [P]	—	—	24	42, 44, 61, 63, 64, 65, 66, 67, 70, 85, 86	42, 68, 69
35	Benzaldehyde [F, G]	100-52-7	benzaldehyde	8, 28, 31, 37, 40 [P], 87 [P], 88 [P], 89 [P]	27, 35	6, 30, 33	24, 29, 32, 33	7, 20, 21, 42, 44, 46, 90, 91	42, 47, 48, 52, 67, 91, 92
36	Benzaldehyde glyceryl acetal [F, FDA]	1319-88-6		31, 37, 40 [P]	—	33	32, 33	—	—
37	Benzoic acid [F, G]	65-85-0	benzoic acid	31, 37, 40 [P]	—	—	24, 32, 33, 39	7, 20, 42, 44, 90	15, 42, 44, 47, 50, 55, 93, 94, 95
38	Benzoin [F, FDA]	119-53-9	ethanone, 1,2-diphenyl-2-hydroxy-	—	—	6	—	—	—
39	Benzophenone [F, FDA]	119-61-9	methanone, diphenyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	42, 96
40	Benzyl alcohol [F, FDA]	100-51-6	benzenemethanol	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33, 39	7, 19, 20, 21, 42, 44, 48, 79, 90	42, 44, 47, 48, 52, 95
41	Benzyl benzoate [F, FDA]	120-51-4	benzoic acid, phenylmethyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 48	9, 42, 48, 97, 98, 99
42	Benzyl butyrate [F, FDA]	103-37-7	butanoic acid, phenylmethyl ester	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 20, 42	42, 54
43	Benzyl cinnamate [F, FDA]	103-41-3	2-propenoic acid, 3-phenyl-, phenylmethyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	—	9, 42, 48, 98, 100
44	Benzyl propionate [F, FDA]	122-63-4	propanoic acid, phenylmethyl ester	8, 28	—	30	29	—	—
45	Benzyl salicylate [F, FDA]	118-58-1	benzoic acid, 2-hydroxy-, phenylmethyl ester	8, 28	—	30	29	42	—
46	Bisabolene [F]	495-62-5		8, 28	—	30	29	—	—
47	Borneol [F, FDA]	507-70-0	bicyclo[2,2,1]heptan-2-ol, *endo*-1,7,7-trimethyl-	8, 28	—	30	24, 29	42, 44, 67, 101	42

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
48	Bornyl acetate [F, FDA]	76-49-3	acetic acid, *endo*-1,7,7-trimethylbicyclo[2,2,1]heptan-2-yl ester	8, 28	—	30	24, 29	—	—
49	1,3-Butanediol [FDA]	107-88-0	1,3-butanediol	—	27, 35	6	—	42	15, 42
50	2,3-Butanedione [F, G]	431-03-8	2,3-butanedione {diacetyl}	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	20	17, 42, 44, 47, 102, 103
51	1-Butanol [F, FDA]	71-36-3	1-butanol {butyl alcohol}	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 79	18, 42
52	2-Butanone [F, FDA]	78-93-3	2-butanone	—	—	—	24	42, 44	42, 44, 102, 103, 104
53	4-(2-Butylidene-3,5,5-trimethyl)-2-cyclohexen-1-one,	13215-88-8	2-cyclohexen-1-one, 4-(2-butenylidene)-3,5,5-trimethyl-	—	—	—	—	42, 105, 106	106
54	Butyl acetate [F, FDA]	123-86-4	acetic acid, butyl ester	31, 37, 40 [P]	—	—	32, 33, 39	42, 79	42, 48, 107
55	Butyl butyrate [F, FDA]	109-21-7	butanoic acid, butyl ester; homolog of butanoic acid, ethyl ester [105-54-4]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	[42, 48] [H]	[42, 44, 45, 48] [H]
56	Butyl butyryl lactate [F, FDA]	7492-70-8	butyl butyrolactate	8, 28	—	30	29	—	—
57	Butyl isovalerate [F, FDA]	109-19-3	butanoic acid, 3-methyl-, butyl ester; homolog of butanoic acid, 3-methyl-, ethyl ester [108-64-5]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	[7, 42] [H]	[42, 77, 78] [H]
58	Butyl phenylacetate [F, FDA]	122-43-0	benzeneacetic acid, butyl ester; homolog of benzeneacetic acid, methyl ester	8, 28	—	30	29	[7, 42, 53] [H]	[42, 44, 45, 108] [H]
59	Butyl undecylenate [F, FDA]		undecanoic acid, butyl ester; homolog of undecanoic acid, methyl ester	—	—	—	—	[109] [H]	—
60	3-Butylidenephthalide [F]	551-08-6	phthalide, 3-butylidene-	8, 28	—	30	29	—	—
61	Butyric acid [F, G]	107-92-6	butanoic acid	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33, 39	110	47, 50, 93, 94, 95
62	Cadinene [FDA]	29350-19-3	naphthalene, 1,6-dimethyl-1α,4α,4α,6α,8α,8β-hexahydro-4-(1-methylethyl)-	—	—	—	—	—	—
63	Caffeine [F, G]	58-08-2	1*H*-purine, 3,7-dihydro-1,3,7-trimethyl-	—	—	—	24	42	15, 42
64	Calcium carbonate [G]	471-34-1		37	—	—	—	—	—
65	Camphene [F, FDA]	79-92-5	bicyclo[2,2,1]heptane, 2,2-dimethyl-3-methylene-	8, 28	—	30	29	—	42
66	Carbon dioxide [G]	124-38-9	carbon dioxide	—	—	—	—	—	45
67	β-Carotene *trans*-	7235-40-7	β-carotene, *trans*-	—	—	—	24, 39, 82	42, 111	—
	cis-	6811-73-0	β-carotene, *cis*-	—	—	—	—	42	—
68	Carvacrol [F, FDA]	499-75-2	phenol, 2-methyl-5-(1-methylethyl)-	31, 37, 40 [P]	—	—	24, 32, 33	—	112
69	4-Carvomenthenol [F, FDA]	562-74-3	3-cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 113	42
70	*l*-Carvone [F, G]	99-49-0 6485-40-1	*l*-2-cyclohexen-1-one, 2-methyl-5-(1-methylethyl)-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 42, 53	42, 54, 114
71	β-Caryophyllene [F, FDA]	87-44-5	bicyclo[7,2,0]undec-4-ene, 8-methylene-4,11,11-trimethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
72	β-Caryophyllene oxide [FDA]	1139-30-6	5-oxatricyclo[8,2,0,0(4,6)]dodecane, 9-methylene-4,12,12-trimethyl-	31, 37, 40 [P]	27, 35	6	32, 33	42	—
73	Cellulose	9004-34-6 65996-61-4	cellulose	37, 38, 115 [P], 116, 117 [P], 118 [P], 119 [P], 120	—	33	24, 77	42, 44, 70, 121, 122	—
74	Cinnamaldehyde [F, G]	104-55-2	2-propenal, 3-phenyl-	8, 28, 80	—	—	29, 39, 123	7, 42	42
75	Cinnamic acid [F, FDA]	621-82-9	2-propenoic acid, 3-phenyl-	8, 28, 31, 37, 40 [P], 124 [P]	—	30, 33	24, 29, 32, 33	7, 42	42, 125
	Cinnamic acid	140-10-3	2-propenoic acid, 3-phenyl- (*E*)	—	—	—	—	7, 42, 110	15, 42
	Cinnamic acid	102-94-3	2-propenoic acid, 3-phenyl- (*Z*)	—	—	—	—	7, 42, 110	15, 42
76	Cinnamyl acetate [F, FDA]	103-54-8	acetic acid, 3-phenyl-2-propenyl ester	31, 37, 40 [P]	27, 35	6	32, 33	—	—
77	Cinnamyl alcohol [F, FDA]	104-54-1	2-propen-1-ol, 3-phenyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42, 53	—
78	Cinnamyl cinnamate [F, FDA]	122-69-0	2-propenoic acid, 3-phenyl-, 3-phenyl-2-propenyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	—	42, 45, 99
79	Cinnamyl isovalerate [F, FDA]	140-27-2	butanoic acid, 3-methyl-, 3-phenyl-2-propenyl ester	8, 28	—	30	29	—	—
80	Cinnamyl propionate [F, FDA]	103-56-0	propanoic acid, 3-phenyl-2-propenyl ester	—	—	—	—	—	—
81	Citral [F, G]	5392-40-5	2,6-octadienal, 3,7-dimethyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33, 39	—	42, 126
82	Citric acid [F, G]	77-92-9	1,2,3-propanetricarboxylic acid, 2-hydroxy-	8, 28, 31, 38, 40 [P], 115 [P], 127, 128, 129, 130	27, 35, 131, 132	6, 30, 33	24, 29, 32, 39	42, 133	—
83	*dl*-Citronellol [F, FDA]	106-22-9	6-octen-1-ol, 3,7-dimethyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	42, 53	42, 134
84	Citronellyl butyrate [F]	141-16-2	butanoic acid, 3,7-dimethyl-6-octenyl ester	—	—	—	—	—	—
85	Citronellyl isobutyrate [F, FDA]	97-89-2	propanoic acid, 2-methyl-, 3,7-dimethyl-6-octenyl ester	8, 28	—	30	29	—	—
86	Cuminaldehyde [F, FDA]	122-03-2	benzaldehyde, 4-(1-methylethyl)-	31, 37, 40 [P]	—	—	32, 33	42, 46	42
87	*p*-Cymene [F, FDA]	99-87-6	benzene, 1-methyl-4-(1-methylethyl)-	8, 28	—	30	24, 29	—	42, 45, 135
88	*l*-Cysteine [F, G]	52-90-4	*l*-cysteine	60 [P], 136 [P]	—	—	39, 60 [P]	42, 61,63	42, 137
89	*trans, trans*-2,4-Decadienal [F, FDA]	25152-84-5	2,4-decadienal	—	—	—	—	42, 79	15
90	δ-Decalactone [F, FDA]	705-86-2	2*H*-pyran-2-one, 6-pentyltetrahydro-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	42, 53	—
91	γ-Decalactone [F, FDA]	706-14-9	2(3*H*)-furanone, dihydro-5-hexyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	42, 138	—
92	Decanal [F, G]	112-31-2	decanal {capraldehyde}, homolog of hexanal [66-25-1]	8, 28, 31, 37, 40 [P]	—	30, 33	24, 29, 32, 33	7, 42	[18, 42] [H]
93	Decanoic acid [F, FDA]	334-48-5	decanoic acid {capric acid}	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33	7, 42	11, 42, 44, 47, 48, 93
94	1-Decanol [F, FDA]	112-30-1	1-decanol {capric alcohol}	8, 28	—	30	29	42, 109	—
95	3-Decenal [F, FDA]	58474-80-9	3-decenal; isomer of 2-decenal [2497-25-8]	—	—	—	—	[42] [I]	—
96	Dehydromenthofurolactone [F]			—	—	—	—	—	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
97	Diethyl malonate [F, FDA]	105-53-3	propanedioic acid, diethyl ester; homolog of propanedioic acid, dimethyl ester [108-59-8]	31, 37, 40 [P]	—	33	32, 33	[42, 139] [H]	[42] [H]
98	Diethyl sebacate [F, FDA]	110-40-7	decanedioic acid, diethyl ester	8, 28	—	30	29	—	—
99	Diethylpyrazine [F]	15707-24-1	pyrazine, 2,3-diethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	42, 46, 56, 71	47, 56, 125, 140, 152
	Diethylpyrazine	13238-84-1	pyrazine, 2,5-diethyl-	—	—	—	—	42, 56, 57, 71, 152	47, 56, 57, 125, 140, 141, 142
	Diethylpyrazine	13067-27-1	pyrazine, 2,6-diethyl-	—	—	—	—	7, 46, 56, 57, 71, 152	47, 56, 57, 140, 142, 143, 152
100	Dihydroanethole [F]	104-45-0	benzene, 1-methoxy-4-propyl-; homolog of benzene, 1-methoxy-4-methyl- [104-93-8]	—	—	—	—	—	[42, 144] [H]
101	5,7-Dihydro-2-methylthieno[3,4-*d*]pyrimidine [F]	36267-71-7		—	—	—	—	—	—
102	*m*-Dimethoxybenzene [F, FDA]	151-10-0	benzene, 1,3-dimethoxy-; isomer of benzene, 1,4-dimethoxy- [150-78-7]	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	[42, 145] [I]	[42, 146] [I]
103	*p*-Dimethoxybenzene [F, FDA]	150-78-7	benzene, 1,4-dimethoxy-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	42, 145	42, 146
104	2,6-Dimethoxyphenol [F]	91-10-1	phenol, 2,6-dimethoxy-	31, 37, 40 [P]	—	—	32, 33	42, 51, 147, 148	15, 42, 48, 54, 149, 150
105	Dimethyl succinate [F, FDA]	106-65-0	butanedioic acid, dimethyl ester	—	—	—	—	—	151
106	3,4-Dimethyl-1,2-cyclopentanedione [F]	13494-06-9	1,2-cyclopentanedione, 3,4-dimethyl-	31, 37, 40 [P]	—	6	32, 33	—	42, 54, 55, 125
107	3,5-Dimethyl-1,2-cyclopentanedione [F]	13494-07-0	1,2-cyclopentanedione, 3,5-dimethyl-	—	—	—	—	—	15, 42, 54, 125, 150
108	3,7-Dimethyl-1,3,6-octatriene [F, FDA]	13877-91-3	1,3,6-octatriene, 3,7-dimethyl- {ocimene}	8, 28	—	30	29	—	42
109	4,5-Dimethyl-3-hydroxy-2,5-dihydrofuran-2-one [F]	28664-35-9	isomer of 2(3*H*)-furanone, dihydro-4-hydroxy-2,5-dimethyl- [3658-77-3]	31, 37, 40 [P]	27, 35	6	32, 33	42	—
	Note: The CAS RN 28664-35-9 listed by Gaworski et al. (6, 27, 35) is for 4,5-dimethyl-3-hydroxyfuran-2-one not 4,5-dimethyl-3-hydroxy-2,5-dihydrofuran-2-one!								
110	6,10-Dimethyl-5,9-undecadien-2-one [F, FDA]	3796-70-1	5,9-undecadien-2-one, 6,10-dimethyl- [geranylacetone]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	42	42
111	3,7-Dimethyl-6-octenoic acid [F]	502-47-6	6-octenoic acid, 3,7-dimethyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
112	2,4-Dimethylacetophenone [F, FDA]	89-74-7	ethanone, 1-(2,4-dimethylphenyl)-; isomer of ethanone, 1-(3,4-dimethylphenyl)- [3637-01-2]	8, 28	—	30	29	—	[42, 54] [I]
113	α,*p*-Dimethylbenzyl alcohol [F]	536-50-5	ethanol, 1-(4-methylphenyl)-	—	—	—	—	—	—
114	α,α-Dimethylphenethyl acetate [F, FDA]	151-05-3	acetic acid, 1,1-dimethyl-2-phenylethyl ester	8, 28	—	30	29	—	—
115	α,α-Dimethylphenethyl butyrate [F, FDA]	10094-34-5	butanoic acid, 1,1-dimethyl-2-phenylethyl ester	8, 28	—	30	29	—	—
116	2,3-Dimethylpyrazine [F]	5910-89-4	pyrazine, 2,3-dimethyl-	31, 37, 40 [P]	27, 35	6	24, 32, 33	42, 46, 57, 71, 152	42, 47, 57, 71, 125, 140, 142, 152, 153, 154

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
117	2,5-Dimethylpyrazine [F]	123-32-0	pyrazine, 2,5-dimethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42, 57, 71, 79, 152	42, 47, 57, 71, 125, 140, 142, 143, 152, 154
118	2,6-Dimethylpyrazine [F]	108-50-9	pyrazine, 2,6-dimethyl-	31, 37, 40 [P]	27, 35	—	24, 32, 33	7, 42, 46, 57, 71, 152, 155, 156	42, 47, 57, 71, 125, 140, 142, 143, 152, 154, 157
119	Dimethyltetrahydrobenzofuranone [F]	13341-72-5	benzofuranone, dimethyltetrahydro-	8, 28	—	30	29	—	—
120	δ-Dodecalactone [F, FDA]	713-95-1	2*H*-pyran-2-one, 6-heptyltetrahydro-; homolog of 2*H*-pyran-2-one, 6-pentyltetrahydro- [705-82-6]	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	[42, 54] [H]	—
121	γ-Dodecalactone [F, FDA]	2305-05-7	2(*3H*)-furanone, dihydro-5-octyl-; homolog of 2(*3H*)-furanone, dihydro-5-pentyl- [104-61-0]	8, 28, 31, 37, 40 [P]	—	—	32, 33	[7, 15, 42] [H]	—
122	*p*-Ethoxybenzaldehyde [F, FDA]	10031-82-0	benzaldehyde, 4-ethoxy-; homolog of benzaldehyde, 4-methoxy- [123-11-5]	31, 37, 40 [P]	—	30	29, 32, 33	[42, 48] [H]	[42, 96] [H]
123	Ethyl 10-undecenoate [F, FDA]	692-86-4	10-undecenoic acid, ethyl ester	—	—	—	—	—	—
124	Ethyl 2-methylbutyrate [F, FDA]	7452-79-1	butanoic acid, 2-methyl-, ethyl ester; isomer of butanoic acid, 3-methyl-, ethyl ester [108-64-5]	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	[7, 42] [I]	[42, 44, 93, 95] [I]
125	Ethyl acetate [F, G]	141-78-6	acetic acid, ethyl ester	8, 28, 31, 37, 40 [P], 158	27, 35	6, 30	24, 29, 32, 33, 39	7, 42, 44, 48	15, 18, 42, 93, 95
126	Ethyl acetoacetate [F, FDA]	141-97-9	acetoacetic acid, ethyl ester	31, 37, 40 [P]	27, 35	6	32, 33	—	—
127	Ethyl alcohol [F, G]	64-17-5	ethanol	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33, 39	42, 44, 48	18, 42, 44, 45, 48
128	Ethyl benzoate [F, FDA]	93-89-0	benzoic acid, ethyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 42	42, 159
129	Ethyl butyrate [F, G]	105-54-4	butanoic acid, ethyl ester	8, 28, 31, 37, 40 [P]	—	6, 30	29, 32, 32, 33, 39	42, 48	42, 48, 93, 95
130	Ethyl cinnamate [F, FDA]	103-36-6	2-propenoic acid, 3-phenyl-, ethyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33, 39	—	42, 160
131	Ethyl decanoate [F, FDA]	110-38-3	decanoic acid, ethyl ester {ethyl caprate}	8, 28, 31, 37, 40 [P]	—	6, 30, 33	24, 29, 32, 33	7, 42	—
132	Ethyl fenchol [F]			—	—	—	—	—	—
133	Ethyl furoate	614-99-3	2-furancarboxylic acid, ethyl ester; homolog of 2-furancarboxylic acid, methyl ester [611-13-2]	—	—	—	24	—	[42, 47] [H]
134	Ethyl heptanoate [F, FDA]	106-30-9	heptanoic acid, ethyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 161	—
135	Ethyl hexanoate [F, FDA]	123-66-0	hexanoic acid, ethyl ester {ethyl caproate}	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	7, 42	18, 42, 44, 93, 95
136	Ethyl isovalerate [F, FDA]	108-64-5	butanoic acid, 3-methyl-, ethyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33, 39	7, 42	42, 44, 93, 95
137	Ethyl lactate [F, FDA]	97-64-3	propanoic acid, 2-hydroxy-, ethyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33	—	15, 42, 47
138	Ethyl laurate [F, FDA]	106-33-2	dodecanoic acid, ethyl ester	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7	—
139	Ethyl levulinate [F, FDA]	539-88-8	pentanoic acid, 4-oxo-, ethyl ester; homolog of pentanoic acid, 4-oxo-, methyl ester [624-45-3]	—	27, 35	6	24	[42, 162] [H]	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
140	Ethylmaltol [F, FDA]	4940-11-8	4*H*-pyran-4-one, 3-hydroxy-2-ethyl-	8, 28, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	42
141	Ethyl methylphenylglycidate [F, G]	77-83-8		—	—	—	—	—	—
142	Ethyl myristate [F, FDA]	124-06-1	tetradecanoic acid, ethyl ester	31, 37, 40 [P]	—	—	24, 32, 33	7, 42, 163	—
143	Ethyl nonanoate [F, FDA]	123-29-5	nonanoic acid, ethyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	7, 42	—
144	Ethyl octadecanoate [F]	111-61-5	octadecanoic acid, ethyl ester {ethyl stearate}	—	—	—	—	42	—
145	Ethyl octanoate [F, FDA]	106-32-1	octanoic acid, ethyl ester {ethyl caprylate}	8, 28, 31, 37, 40 [P]	—	33	24, 32, 33	7, 42	—
146	Ethyl oleate [F, FDA]	111-62-6	9-octadecenoic acid, ethyl ester	—	—	—	—	42	—
147	Ethyl palmitate [F]	628-97-7	hexadecanoic acid, ethyl ester	31, 37, 40 [P]	—	—	24, 32, 33	42, 109	42, 134, 164
148	Ethyl phenylacetate [F, FDA]	101-97-3	benzeneacetic acid, ethyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33, 39	7, 42	—
149	Ethyl propionate [F, FDA]	105-37-3	propanoic acid, ethyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33, 39	42, 48	42, 44, 48, 93, 95
150	Ethyl salicylate [F, FDA]	118-61-6	benzoic acid, 2-hydroxy-, ethyl ester	31, 37, 40 [P]	—	33	32, 33	42, 51	—
151	Ethyl *trans*-2-butenoate [F, FDA]	10544-63-5	2-butenoic acid, ethyl ester; {ethyl crotonate}; homolog of 2-butenoic acid, methyl ester	31, 37, 40 [P]	—	—	32, 33	[42, 79] [H]	—
152	Ethyl valerate [F, FDA]	539-82-2	pentanoic acid, ethyl ester	31, 37, 40 [P]	—	—	32, 33	42	42, 93, 95
153	Ethylvanillin [F, G]	121-32-4	benzaldehyde, 3-ethoxy-4-hydroxy-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33, 39, 123	42, 165, 166	42, 141, 167
154	2-Ethyl-3-methoxypyrazine [F]	25680-58-4	pyrazine, 2-ethyl-3-methoxy-; homolog of pyrazine, 3-methoxy-2-methyl-	—	—	6	—	—	—
155	2-Ethyl-5-methoxypyrazine [F]		pyrazine, 2-ethyl-5-methoxy-	—	—	6	—	—	—
156	2-Ethyl-6-methoxypyrazine [F]		pyrazine, 2-ethyl-6-methoxy-	—	—	6	—	—	—
157	2-Methyl-3-methoxypyrazine [F]	2847-30-5 [68378-13-2]	pyrazine, 2-methoxy-3-methyl- {pyrazine, 3-methoxy-2-methyl-}	8, 28, 31, 37, 40 [P]	—	6, 30	29, 32, 33	—	—
158	2-Methyl-5-methoxypyrazine [F]	2882-22-6 [68378-13-2]	pyrazine, 2-methoxy-5-methyl- {pyrazine, 5-methoxy-2-methyl-}	31, 37, 40 [P]	—	6	32, 33	—	—
159	2-Methyl-6-methoxypyrazine [F]	2882-21-5 [68378-13-2]	pyrazine, 2-methoxy-6-methyl- {pyrazine, 6-methoxy-2-methyl-}	31, 37, 40 [P]	—	6	32, 33	—	—
160	2-Ethyl-1-hexanol [F]	104-76-7	1-hexanol, 2-ethyl-	—	—	—	—	42	42
161	3-Ethyl-2-hydroxy-2-cyclopenten-1-one [F]	21835-01-8	2-cyclopenten-1-one, 3-ethyl-2-hydroxy-	31, 37, 40 [P]	—	—	32, 33	—	42
162	2-Ethyl-3,5-dimethylpyrazine [F]	13925-07-0 55031-15-7	pyrazine, 3,5-dimethyl-2-ethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	51, 57, 168	17, 42, 47, 71, 140, 142, 143
163	2-Ethyl-3,6-dimethylpyrazine [F]	13360-65-1 55031-15-7	pyrazine, 3,6-dimethyl-2-ethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	42, 46, 57	42, 47, 71, 125, 140, 141, 142, 154
164	5-Ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone [F]	698-10-2	2(5*H*)-furanone, 5-ethyl-3-hydroxy-4-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	29, 32, 33	—	—
165	2-Ethyl-3-methylpyrazine [F]	15707-23-0	pyrazine, 2-ethyl-3-methyl-	31, 37, 40 [P]	—	6	24, 32, 33	42, 46, 51, 152, 155	42, 125, 141, 142, 152, 169
166	4-Ethylbenzaldehyde [F]	4748-78-1	benzaldehyde, 4-ethyl-	31, 37, 40 [P]	—	—	32, 33	—	42, 164

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
167	4-Ethylguaiacol [F, FDA]	2785-89-9	phenol, 4-ethyl-2-methoxy-	31, 37, 40 [P]	—	—	32, 33	42	17, 42, 170
168	*p*-Ethylphenol [F]	123-07-9	phenol, 4-ethyl-	31, 37, 40 [P]	—	—	24, 32, 33	7, 42, 147, 148	42, 52, 170, 171, 172
169	3-Ethylpyridine [F]	536-78-7	pyridine, 3-ethyl-	—	27, 35	6	—	42, 109, 173, 174, 175, 176	42, 71, 152, 177, 178
170	Eucalyptol [F, FDA]	470-82-6	2-oxabicyclo[2,2,2]octane, 1,3,3-trimethyl- {1,8-cineole}	8, 28, 31, 37, 40 [P]	—	30, 33	24, 29, 32, 33	7, 42, 53, 179	42, 80
171	Farnesol [F, FDA]	4602-84-0	2,6,10-dodecatrien-1-ol, 3,7,11-trimethyl-	31, 37, 40 [P]	27, 35	6	32, 33	51, 180, 181	42, 45, 54, 182
172	*d*-Fenchone [F, FDA]	4695-62-9	bicyclo[2,2,1]heptanone, 1,3,3-trimethyl-	—	—	—	—	—	—
173	Furfurylmercaptan [F]	98-02-2	furan, 2-methanethiol	—	—	—	—	—	—
174	4-(2-Furyl)-3-buten-2-one [F]	623-15-4	3-buten-2-one, 4-(2-furanyl)-	—	27, 35	6	—	42, 81	17, 42
175	Geraniol [F, G]	106-24-1	2,6-octadien-1-ol, 3,7-dimethyl-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33, 39	7, 42, 46, 53	42, 45, 54
176	Geranyl acetate [F, G]	105-87-3	acetic acid, 3,7-dimethyl-2,6-octadien-1-yl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	—	—
177	Geranyl butyrate [F, FDA]	106-29-6	butanoic acid, 3,7-dimethyl-2,6-octadien-1-yl ester	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
178	Geranyl formate [F, FDA]	105-86-2	formic acid, 3,7-dimethyl-2,6-octadien-1-yl ester	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
179	Geranyl isovalerate [F, FDA]	1009-20-6	butanoic acid, 3-methyl-, 3,7-dimethyl-2,6-octadien-1-yl ester	—	—	—	—	—	—
180	Geranyl phenylacetate [F, FDA]	102-22-7		8, 28	—	30	29	—	—
181	*l*-Glutamic acid [F, G]	6899-05-4	*l*-glutamic acid	60 [P], 183 [P], 184 [P], 185 [P], 186 [P], 187 [P]	—	—	24, 60 [P]	42, 61,62, 63, 64, 65, 66, 67, 85, 86	42, 68, 69, 188
182	*l*-Glutamine [F, FDA]	6899-04-3	*l*-glutamine	—	—	—	60 [P]	42, 61, 62, 63, 65, 67, 85, 86	42, 68, 69, 188
183	Glycerol [F, G]	56-81-5	1,2,3-propanetriol {glycerol}	8, 28, 31, 37, 38, 40 [P], 189, 190, 191, 192, 193, 194, 195 [P], 196, 197, 198, 199, 200, 201, 202	27, 35, 191	6, 26, 30, 33	9, 10, 23, 24, 29, 32, 33, 39, 203	42, 204	15, 25, 42, 205
184	Glycyrrhizin, ammoniated [F, G]			—	—	—	—	—	—
185	Guaiacol [F, FDA]	90-05-1	phenol, 2-methoxy-	31, 37, 40 [P], 200	27, 35	6	24, 32, 33	42, 44, 48	42, 44, 47, 48, 206
186	2,4-Heptadienal [F]	4313-03-5	2,4-heptadienal (E,E)	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 42	—
187	γ-Heptalactone [F, FDA]	105-21-5	2(3*H*)-furanone, dihydro-5-propyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42, 207	—
188	Heptanoic acid [F, FDA]	111-14-8	heptanoic acid {enanthic acid}	31, 37, 40 [P]	27, 35	6, 33	24, 32, 33	7, 42, 208	42, 50, 93, 208, 215
189	2-Heptanone [F]	110-43-0	2-heptanone	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	7, 42, 79	42, 58, 209
190	3-Hepten-2-one [F]	1119-44-4	3-hepten-2-one	8, 28	—	30	29	—	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
191	2-Hepten-4-one [F]		2-hepten-4-one	—	—	—	—	—	—
192	4-Heptenal [F, FDA]	6728-31-0	4-heptenal; isomer of 2-heptenal [2463-63-0]	31, 37, 40 [P]	—	—	32, 33	—	—
193	2-Heptenal [F]	2463-63-0	2-heptenal; homolog of 2-hexenal [6728-6-3]	—	—	—	—	[42, 109] [H]	[42, 210] [H]
194	Heptyl acetate [F]	112-06-1	acetic acid, heptyl ester; homolog of acetic acid, butyl ester [123-86-4]	—	—	—	—	[42, 79] [H]	[42, 48, 107] [H]
195	ω-6-Hexadecenlactone [F, FDA]	7779-50-2		8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	—
196	γ-Hexalactone [F, FDA]	695-06-7	*2*(*3H*)-furanone, dihydro-5-ethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42	—
197	Hexanal [F, FDA]	66-25-1	hexanal {caproic aldehyde}	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32	42, 79	18, 42, 44, 48, 103
198	Hexanoic acid [F, FDA]	142-62-1	hexanoic acid {caproic acid}	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 42, 44, 208	42, 44, 50, 93, 95, 208
199	2-Hexen-1-ol [F, FDA]	928-95-0	2-hexen-1-ol; isomer of 3-hexen-1-ol [928-97-2]	31, 37, 40 [P]	—	—	32, 33	[7, 42] [I]	—
200	3-Hexen-1-ol [F, FDA]	544-12-7 928-97-2 928-96-1	3-hexen-1-ol 3-hexen-1-ol, (E) 3-hexen-1-ol, (Z)	8, 28, 211, 40 [P] 31, 37, 40 [P]	—	30	29, 32, 33	7, 42	—
201	*cis*-3-Hexen-1-yl acetate [F]	3681-71-8	acetic acid, 3-hexen-1-yl ester	31, 37, 40 [P]	—	—	32, 33	—	—
202	2-Hexenal [F, FDA]	6728-26-3 16635-54-4	2-hexenal, (E) 2-hexenal, (Z)	8, 28, 31, 40 [P]	—	30	24, 29, 32, 33	42, 109	42, 210
203	2-Hexenoic acid [F]	1289-40-3	2-hexenoic acid	—	—	—	—	—	42, 110
	trans-2-Hexenoic acid	13419-69-7	*trans*-2-hexenoic acid	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	—	—
204	3-Hexenoic acid [F, FDA]	4219-24-3	3-hexenoic acid	31, 37, 40 [P]	—	—	32, 33	42, 110, 145	16, 42, 55, 79
205	3-Hexenyl formate [F]	33467-73-1	formic acid, 3-hexenyl ester	31, 37, 40 [P]	—	—	32, 33	42	—
206	Hexyl 2-methylbutyrate [F, FDA]	10032-15-2	butanoic acid, 2-methyl-, hexyl ester	8, 28	—	30	29	—	—
207	Hexyl acetate [F, FDA]	142-92-7	acetic acid, hexyl ester	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	42, 109	—
208	Hexyl alcohol [F, FDA]	111-27-3	1-hexanol {caproyl alcohol}	31, 37, 40 [P]	—	—	24, 32, 33	42, 46	—
209	Hexyl phenylacetate [F, FDA]	5421-17-0	benzeneacetic acid, hexyl ester	8, 28	—	30	29	—	—
210	*l*-Histidine [F]	71-00-1	*l*-histidine	60 [P], 212 [P]	—	—	24, 60 [P]	42, 61, 62, 63, 64, 65, 66, 67, 70	—
211	5-Hydroxy-2,4-decadienoic acid δ-lactone [F]	27593-23-3	6-amyl-α-pyrone	—	—	—	—	—	—
212	2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone [F]	3658-77-3	3(2*H*)-furanone, 2,5-dimethyl-4-hydroxy- {furaneol}	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	29, 32, 33	—	42
213	2-Hydroxy-3,5,5-trimethyl-2-cyclohex-1-one [F]			—	—	—	—	—	—
214	4-Hydroxy-3-pentenoic acid lactone [F]	591-12-8	2(3*H*)-furanone, 5-methyl-	—	—	—	—	42	16
215	2-Hydroxy-4-methylbenzaldehyde [F]	698-27-1	benzaldehyde, 2-hydroxy-4-methyl-	31, 37, 40 [P]	—	—	24, 32, 33	—	—
216	4-Hydroxybutanoic acid lactone [F]	96-48-0	2(3*H*)-furanone, dihydro- {butyrolactone}	—	—	—	24	7, 42	15, 42, 55, 213
217	Hydroxycitronellal [F, FDA]	107-75-5	octanal, 3,7-dimethyl-7-hydroxy-	31, 37, 40 [P]	—	—	32, 33	42	—
218	6-Hydroxydihydrotheaspirane [F]	65620-50-0		—	—	—	—	—	—
219	4-(*p*-Hydroxyphenyl)-2-butanone [F, FDA]	5471-51-2	2-butanone, 4-(4-hydroxyphenyl)-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	42

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
220	α-Ionone [F, FDA]	127-41-3	3-buten-2-one, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	7, 42	42
221	β-Ionone [F, FDA]	14901-07-6	3-buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 42	42, 146, 160
222	α-Irone [F, FDA]	79-69-6	3-buten-2-one, 4-(2,5,6,6-tetramethyl-2-cyclohexen-1-yl)-	31, 37, 40 [P]	—	—	32, 33	—	—
223	Isoamyl acetate [F, FDA]	123-92-2	acetic acid, 3-methylbutyl ester	8, 28, 31, 37, 40 [P], 158	—	30	24, 29, 32, 33, 39	—	—
224	Isoamyl benzoate [F, FDA]	94-46-2	benzoic acid, 3-methylbutyl ester	8, 28	—	30	24, 29	42	—
225	Isoamyl butyrate [F, FDA]	106-27-4	butanoic acid, 3-methylbutyl ester {isopentyl butanoate}	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33, 39	—	—
226	Isoamyl cinnamate [F, FDA]	7779-65-9	homolog of 2-propenoic acid, 3-phenyl-, ethyl ester [103-36-6]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	[42, 160] [H]
227	Isoamyl formate [F, FDA]	110-45-2	formic acid, 3-methylbutyl ester	8, 28	—	30	29, 39	—	—
228	Isoamyl hexanoate [F, FDA]	2198-61-0	hexanoic acid, 3-methylbutyl ester	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	—	—
229	Isoamyl isovalerate [F, FDA]	659-70-1	butanoic acid, 3-methyl-, 3-methylbutyl ester	8, 28, 31, 37, 40 [P], 87 [P], 88 [P], 89 [P]	—	30	29, 32, 33, 39	—	—
230	Isoamyl octanoate [F, FDA]	2035-99-6	octanoic acid, 3-methylbutyl ester	31, 37, 40 [P]	—	—	32, 33	—	—
231	Isoamyl phenylacetate [F, FDA]	102-19-2	phenylacetic acid, 3-methylbutyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	—
232	Isobornyl acetate [F, FDA]	125-12-2	bicyclo[2,2,1]heptan-2-ol, 1,7,7-trimethyl-, acetate	31, 37, 40 [P]	—	—	32, 33	—	—
233	Isobutyl acetate [F, FDA]	110-19-0	acetic acid, 2-methylpropyl ester	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	—	—
234	Isobutyl alcohol [F, FDA]	78-83-1	1-propanol, 2-methyl-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32	42, 165	18, 42
235	Isobutyl cinnamate [F, FDA]	122-67-8	homolog of 2-propenoic acid, 3-phenyl-, ethyl ester [103-36-6]	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	[42, 160] [H]
236	Isobutyl phenylacetate [F, FDA]	102-13-6		8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	29, 32, 33	—	—
237	Isobutyl salicylate [F, FDA]	87-19-4		8, 28	—	30	29	—	—
238	2-Isobutyl-3-methoxypyrazine [F]	24683-00-9	pyrazine, 2-methoxy-3-methylpropyl-	—	27, 35	6	—	—	—
239	α-Isobutylphenethyl alcohol [F, FDA]	7779-78-4		—	27, 35	6	—	—	—
240	Isobutyraldehyde [F, FDA]	78-84-2	propanal, 2-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33	42, 48, 79, 109	42, 44, 54, 102, 150
241	Isobutyric acid [F, FDA]	79-31-2	propanoic acid, 2-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 20, 42, 214	15, 42, 45, 93, 215, 216
242	*dl*-Isoleucine [F]	73-32-5	*dl*-isoleucine	60 [P]	—	—	24, 39	42, 61, 63, 64, 65, 66, 67, 70	—
243	α-Isomethylionone [F, FDA]	125-51-5	3-buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	—	—	—	—	—	—
244	2-Isopropylphenol [F]	88-69-7	phenol, 2-(l-methylethyl)-	—	—	—	—	—	42, 47, 170
245	Isovaleric acid [F, FDA]	503-74-2	butanoic acid, 3-methyl-	31, 37, 40 [P]	27, 35	6, 30	24, 32, 33	7, 42	42, 45, 50, 54, 93, 215

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
246	Lactic acid [F, G]	50-21-5 598-82-3	propanoic acid, 2-hydroxy-	31, 37, 38, 40 [P]	27, 35	6, 33	24, 32, 33, 39	42, 48	42, 217, 218, 219
247	Lauric acid [F, G]	143-07-7	dodecanoic acid	8, 28, 31, 37, 40 [P]	—	30	24, 32, 29	42	42, 50
248	Lauric aldehyde [F, FDA]	112-54-9	dodecanal; homolog of hexanal [66-25-1]	—	—	—	—	[42, 79] [H]	[18, 42, 45, 48] [H]
249	*l*-Leucine [F, FDA]	7005-03-0	*l*-leucine	60 [P], 220 [P]	—	—	24	42, 61, 63, 64, 65, 66, 67, 70	42, 68, 69,
250	Levulinic acid [F, FDA]	123-76-2	pentanoic acid, 4-oxo-	221 [P], 222, 223	—	—	224	42, 225	15, 42, 45, 54, 215, 217, 218, 219
251	Linalool [F, G]	78-70-6	1,6-octadien-6-ol, 3,7-dimethyl-	8, 28, 31, 37, 40 [P], 226	—	6, 30	24, 29, 32, 33	7, 19, 42, 46, 48, 90, 101	—
252	Linalool oxide [F, FDA]	5989-33-3 60047-17-8	2-furanmethanol, *cis*-5-ethenyltetrahydro-α,α,5-trimethyl-	31, 37, 40 [P]	—	33	24, 32, 33	—	—
253	Linalyl acetate [FG]	115-95-7	acetic acid, 3,7-dimethyl-1,6-octadien-6-yl ester; 1,6-octadien-6-ol, 3,7-dimethyl-, acetate	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33, 39	42	—
254	*l*-Lysine [FDA]	56-87-1	*l*-lysine	60 [P], 220 [P], 227 [P]	—	6	24, 60 [P]	42, 61, 62, 63, 64, 65, 66, 67, 70	—
255	Malic acid [F, G]	6915-15-7	butanedioic acid, hydroxy-	31, 38, 40 [P], 115 [P], 228	—	6, 33	24, 32, 33, 39	42, 48, 133	45, 215, 217
256	Maltol [F, FDA]	118-71-8	4*H*-pyran-4-one, 3-hydroxy-2-methyl-	31, 37, 40 [P]	—	30, 33	29, 32, 33	7	3, 15, 42, 47, 213
257	Maltyl isobutyrate [F]	65416-14-0	propanoic acid, 2-methyl-, 2-methyl-4-oxo-4*H*-pyran-3-yl ester	8, 28	—	—	—	—	—
258	*p*-Mentha-8-thiol-3-one [F]	38462-22-5		31, 37, 40 [P]	—	33	32, 33	—	—
259	*l*-Menthol [F, FDA] *l*-Menthol (synthetic)	89-78-1 2216-51-5	cyclohexanol, 5-methyl-2-(1-methylethyl)-	8, 28, 31, 37, 40 [P], 229, 230, 231, 232, 233, 234, 235, 236 [P], 237, 238, 239, 240	27, 35, 241, 242	6, 30, 33, 34	24, 29, 32, 33, 39, 243	42	42, 52
260	*l*-Menthone [F, FDA]	89-80-5	cyclohexanone, 5-methyl-2-(1-methylethyl)-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	42, 244	42
261	Menthyl acetate [F] *l*-isomer	89-48-5 16409-45-3	acetic acid, 5-methyl-2-(1-methylethyl)-cyclohexanyl ester	31, 37, 40 [P]	—	—	32, 33	—	—
262	*dl*-Methionine [F, FDA]	63-68-3		60 [P], 136 [P], 245	—	—	60 [P]	42, 62, 63, 64, 70	—
263	Methoprene	41205-06-5	2,4-dodecadienoic acid, 11-methoxy-3,7,11-trimethyl-, 1-methylethyl ester	246	—	—	—	—	—
264	2-Methoxy-4-methylphenol [F, FDA]	93-51-6	phenol, 2-methoxy-4-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	42, 147	15, 42, 150
265	2-Methoxy-4-vinylphenol [F, FDA]	7786-61-0	phenol, 4-ethenyl-2-methoxy-	31, 37, 40 [P]	—	—	32, 33	7, 42	42, 247
266	*p*-Methoxybenzaldehyde [F, FDA]	123-11-5	benzaldehyde, 4-methoxy- {*p*-anisaldehyde}	8, 28, 31, 37, 40 [P], 87 [P], 88 [P], 89	27, 35	6, 30	29, 32, 33	42, 45	42, 44, 47, 96
267	1-(*p*-Methoxyphenyl)-1-penten-3-one [F, FDA]		1-penten-3-one, 1-(4-methoxyphenyl)-	—	—	—	—	—	—

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268	4-(*p*-Methoxyphenyl)-2-butanone [F, FDA]	104-20-1	2-butanone, 4-(4-methyoxyphenyl)-	31, 37, 40 [P]	—	—	32, 33	—	—
269	1-(*p*-Methoxyphenyl)-2-propanone [F, FDA]	122-84-9	2-propanone, 1-(4-methoxyphenyl)-; isomer of 2-propanone, 1-(2-methoxyphenyl)- [5211-62-1]	31, 37, 40 [P]	—	—	32, 33	—	[42, 55] [I]
270	Methoxypyrazine [F]	3149-28-8	pyrazine, methoxy-	—	27, 35	6	—	—	—
271	Methyl 2-furoate [F]	611-13-2	2-furancarboxylic acid, methyl ester	—	—	—	—	42, 248	42, 47
272	Methyl 2-octynoate [F, FDA]	111-12-6	2-octynoic acid, methyl ester	—	—	—	—	—	—
273	Methyl 2-pyrrolyl ketone [F]	1072-83-9	ethanone, 1-(1*H*-pyrrol-2-yl)-	31, 37, 40 [P]	—	—	32, 33	7, 20, 42, 46, 48, 90	15, 42, 54, 125, 150
274	Methyl anisate [F, FDA]	121-98-2	benzoic acid, 4-methoxy-, methyl ester	31, 37, 40 [P]	—	—	32, 33	—	—
275	Methyl anthranilate [F, G]	134-20-3	benzoic acid, 2-amino-, methyl ester	8, 28	—	30	29	42, 249	—
276	Methyl benzoate [F, FDA]	93-58-3	benzoic acid, methyl ester	31, 37, 40 [P]	—	—	32, 33	7, 42, 46	42, 250
277	Methyl cinnamate [F, FDA]	103-26-4	2-propenoic acid, 3-phenyl-, methyl ester; homolog of 2-propenoic acid, 3-phenyl-, ethyl ester [103-36-6]	8, 28, 31, 37, 40 [P], 87 [P], 88, 89	—	30	24, 29, 32, 33	—	[42] [H]
278	Methyl dihydrojasmonate [F]	24851-98-7	acetic acid, 2-pentyl-3-oxo-1-cyclopentyl-, methyl ester	31, 37, 40 [P]	—	—	32, 33	—	—
279	Methyl isovalerate [F, FDA]	556-24-1	butanoic acid, 3-methyl-, methyl ester	8, 28	—	30	29	7, 42	—
280	Methyl linoleate [F]	112-63-0	9,12-octadecadienoic acid (*Z,Z*), methyl ester	—	—	—	—	7, 19, 42, 251	42, 45, 251
281	Methyl linolenate [F]	301-00-8	9,12,15-octadecatrienoic acid, methyl ester	—	—	—	—	42, 214	42, 58, 252
	Methyl linoleate (48%) + methyl linolenate (52%) [F]		9,12-octadecadienoic acid (*Z,Z*), methyl ester 48%) + 9,12,15-octadecatrienoic acid, methyl ester (52%)	8, 28	—	30	29	—	—
282	Methyl naphthyl ketone [F]	1333-52-4	ethanone, 1-(naphthalenyl)-	—	—	—	—	—	42, 48, 108
283	Methyl nicotinate [F]	93-60-7	3-pyridinecarboxylic acid, methyl ester	—	—	—	—	42, 53	42, 96
284	Methyl phenylacetate [F, FDA]	101-41-7	benzeneacetic acid, methyl ester	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 42, 53, 79	42, 108
285	Methyl salicylate [F, FDA]	119-36-8	benzoic acid, 2-hydroxy-, methyl ester	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33, 39	7, 42	—
286	Methyl sulfide [F, FDA]	75-18-3	dimethyl sulfide	—	—	—	—	—	42
287	3-Methylcyclopentadecanone [F]	541-91-3	cyclopentadecanone, 3-methyl-	—	—	—	—	—	—
288	4-Methyl-1-phenyl-2-pentanone [F, FDA]	5349-62-2	2-pentanone, 4-methyl-1-phenyl-	—	—	—	—	—	—
289	5-Methyl-2-phenyl-2-hexenal [F]	21834-92-4	2-hexenal, 5-methyl-2-phenyl-	8, 28	—	30	29	—	—
290	5-Methyl-2-thiophenecarboxaldehyde [F]	13679-70-4	2-thiophenecarboxaldehyde, 5-methyl-	—	—	—	—	42	42
291	6-Methyl-3,5-heptadien-2-one [F]	1604-28-0	3,5-heptadien-2-one, 6-methyl-	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	7, 42, 79	—
292	2-Methyl-(*p*-isopropylphenyl)-propionaldehyde [F, FDA]			—	—	—	—	—	—
293	5-Methyl-3-hexen-2-one [F]	5166-53-0	3-hexen-2-one, 5-methyl-	—	—	—	—	59, 79	108
294	4-Isopropyl-3-methoxy-1-methylbenzene [F]	1076-56-8	benzene, 3-methoxy-1-methyl-4-(1-methylethyl)- = benzene, 2-methoxy-4-methyl-1-(1-methylethyl)-	31, 36, 37	—	33	32, 33	42	—

Table 1 (*cont.*)

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295	4-Methyl-3-penten-2-one [F]	141-79-7	3-penten-2-one, 4-methyl- {mesityl oxide}	—	—	—	—	42, 90	42
296	2-Methyl-4-phenylbutyraldehyde [F]		butanal, 2-methyl-4-phenyl-	—	—	—	—	—	—
297	6-Methyl-5-hepten-2-one [F]	110-93-0	5-hepten-2-one, 6-methyl-	8, 28, 31, 40 [P]	—	30	29, 32, 33	7, 42	—
298	4-Methyl-5-thiazoleethanol [F]	137-00-8		—	—	—	—	—	—
299	4-Methyl-5-vinylthiazole [F]	1759-28-0	thiazole, 5-ethenyl-4-methyl-	—	—	—	—	—	—
300	Methyl-α-ionone [F, FDA]	127-42-4		31, 37, 40 [P]	—	—	32, 33	—	—
301	Methyl-2-butenoic acid [F]	13201-46-2	2-butenoic acid, 2-methyl-	—	—	—	—	42, 46, 214	15, 42, 54, 55, 215
		80-59-1	2-butenoic acid, *trans*-2-methyl-	31, 37, 40 [P]	—	33	32, 33	—	—
		541-47-9	2-butenoic acid, 3-methyl-	—	—	—	—	42, 214	42, 79, 125
302	4-Methylacetophenone [F, FDA]	122-00-9	ethanone, 1-(4-methylphenyl)-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	7, 42	42, 52
303	*p*-Methylanisole [F, FDA]	104-93-8	benzene, 1-methoxy-4-methyl-	31, 37, 40 [P]	—	—	32, 33	—	42, 52
304	α-Methylbenzyl acetate [F, FDA]	93-92-5	acetic acid, 1-phenethyl ester	31, 37, 40 [P]	—	—	32, 33	42	—
305	α-Methylbenzyl alcohol [F]	98-85-1	ethanol, 1-phenyl-	—	—	—	—	42	—
306	2-Methylbutyraldehyde [F, FDA]	96-17-3	butanal, 2-methyl-	31, 37, 40 [P]	—	—	24, 32, 33	—	42, 103, 253
307	3-Methylbutyraldehyde [F, FDA]	590-86-3	butanal, 3-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	42, 46, 48, 109	42, 47, 103, 254, 255, 102
308	2-Methylbutyric acid [F, FDA]	116-53-0	butanoic acid, 2-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 42	42, 44, 48, 253
309	α-Methylcinnamaldehyde [F, FDA]	101-39-3	2-propenal, 2-methyl-3-phenyl-	—	—	—	—	—	—
310	Methylcyclopentenolone [F, FDA]	80-71-7	2-cyclopenten-1-one, 2-hydroxy-3-methyl-	8, 28, 37	27, 35	6, 30	24, 29	7, 42	15, 42, 54, 150, 155
311	2-Methylheptanoic acid [F, FDA]	1188-02-9	heptanoic acid, 2-methyl-; isomer of heptanoic acid, 5-methyl-	—	—	—	—	[42, 256] [I]	—
312	2-Methylhexanoic acid [F]	4536-23-6	hexanoic acid, 2-methyl-	8, 28	—	30	29	7	15, 42, 47, 48, 50
313	3-Methylpentanoic acid [F]	105-43-1	pentanoic acid, 3-methyl-	31, 37, 40 [P]	—	—	32, 33	7, 19, 20, 42, 110, 257	15, 42, 45, 47, 54, 55, 213, 215, 253
314	4-Methylpentanoic acid [F]	646-07-1	pentanoic acid, 4-methyl-	—	—	—	24	42, 110, 214	42, 47, 48, 50, 247
315	2-Methylpyrazine [F]	109-08-0	pyrazine, methyl-	31, 37, 40 [P]	27, 35	6	24, 32, 33	7, 42, 46, 57, 71, 152, 156	42, 47, 57, 71, 125, 140, 142, 152, 213
316	5-Methylquinoxaline [F]	13708-12-8	quinoxaline, 5-methyl-; isomer of quinoxaline, 2-methyl- [7251-61-8]	31, 37, 40 [P]	—	—	32, 33	—	[42, 17] [I]
317	2-Methyltetrahydrofuran-3-one [F]	3188-00-9	furan-3-one, 2-methyltetrahydro-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	7, 42	42
318	Methyl methylthiopyrazine [F]			—	—	—	—	—	—
319	3-Methylthiopropionaldehyde [F]	3268-49-3	propionaldehyde, 3-(methylthio)-	—	—	—	—	—	—
320	Methyl 3-methylthiopropionate [F, FDA]	13532-18-8		31, 37, 40 [P]	—	—	32, 33	—	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
321	2-Methylvaleric acid [F, FDA]	97-61-0	pentanoic acid, 2-methyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	42, 257	42, 93, 95, 108, 258
322	Myristaldehyde [F, FDA]	124-25-4	tetradecanal	—	—	—	—	42, 259	42, 260
323	Myristic acid [F, FDA]	544-63-8	tetradecanoic acid	—	—	—	—	7, 42	42, 47, 48, 50
324	β-Naphthyl ethyl ether [F]	93-18-5	naphthalene, 2-ethoxy-	—	—	—	—	42, 261	—
325	Nerol [F, FDA]	106-25-2	2,6-octadien-1-ol, 3,7-dimethyl-, (Z)	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 42, 46, 53	—
326	Nerolidol [F, FDA]	7212-44-4	1,6,10-dodecatrien-1-ol, 3,7,11-trimethyl-	31, 37, 40 [P]	—	—	24, 32, 33	4, 42	45
327	2,6-Nonadienal [F]	557-48-2	2,6-nonadienal	8, 28	—	30	29	42, 214	—
328	2,6-Nonadien-1-ol [F, FDA]	7786-44-9	2,6-nonadien-1-ol	31, 37, 40 [P]	—	—	32, 33	—	—
329	γ-Nonalactone [F, FDA]	104-61-0	2(3*H*)-furanone, dihydro-5-pentyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 20, 42, 145	—
330	Nonanal [F, FDA]	124-19-6	nonanal	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 214	—
331	Nonanoic acid [F, FDA]	112-05-0	nonanoic acid	8, 28, 31, 37, 40 [P]	—	30, 33	24, 29, 32, 33	7, 42	42, 48, 253
332	2-Nonanone [F, FDA]	821-55-6	2-nonanone	31, 37, 40 [P]	—	—	32, 33	42, 59	42, 146
333	2-Nonen-1-ol [F]	31502-14-4	2-nonen-1-ol	8, 28	—	30	29	—	—
334	2-Nonenal [F]	2463-53-8 18829-56-6	2-nonenal 2-nonenal (E)	—	—	—	—	42, 214	—
335	Nonyl acetate [F, FDA]	143-13-5	acetic acid, nonyl ester; homolog of acetic acid, hexyl ester [142-92-7]	8, 28	—	30	29	[42, 109] [H]	—
336	9,12-Octadecadienoic acid [F, G]	506-21-8	9,12-octadecadienoic acid {linoleic acid}	—	—	—	—	7, 19, 42, 251	42, 54, 55, 251
337	9,12,15-Octadecatrienoic acid [F, G]	463-40-1	9,12,15-octadecatrienoic acid {linolenic acid}	—	—	—	—	7, 42, 110	42, 54, 55
338	δ-Octalactone [F]	698-76-0	2*H*-pyran-2-one, 6-propyltetrahydro-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 20, 42, 53	—
339	γ-Octalactone [F, FDA]	104-50-7	2(3*H*)-furanone, 5-butyldihydro-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 15, 19, 20, 42	—
340	Octanal [F, FDA]	124-13-0	octanal; homolog of hexanal [66-25-1]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	[18, 42] [H]	[18, 42] [H]
341	Octanoic acid [F, G]	124-07-2	octanoic acid {caprylic acid}	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33	7, 42	42, 44, 67, 93
342	1-Octanol [F, FDA]	111-87-5	1-octanol	31, 37, 40 [P]	—	33	24, 32, 33	7, 42	—
343	2-Octanone [F, FDA]	111-13-7	2-octanone	—	—	—	24	42, 262	42, 45
344	3-Octen-2-one [F]	1669-44-9	3-octen-2-one	—	—	—	24	—	—
345	1-Octen-3-ol [F, FDA]	3391-86-4	1-octen-3-ol	31, 37, 40 [P], 200	27, 35	6	24, 32, 33	42, 46	—
346	1-Octen-3-yl acetate [F, FDA]	2442-10-6	acetic acid, 1-octen-3-yl ester	8, 28	—	30	29	—	—
347	2-Octenal [F]		2-octenal; homolog of 2-hexenal [6728-26-3]	—	—	—	—	—	[42] [H]
348	Octyl isobutyrate [F, FDA]	109-15-9	propanoic acid, 2-methyl-, octyl ester	8, 28	—	30	29	—	—
349	Oleic acid [F, FDA]	26764-26-1 112-80-1	9-octadecenoic acid	—	—	—	24	7, 42, 110, 146	42, 44, 54, 55, 125
350	Palmitic acid [F]	57-10-3	hexadecanoic acid	31, 37, 40 [P]	—	33	32, 33	7, 42	42, 50
351	ω-Pentadecalactone [F]	106-02-5	oxacyclohexadecan-2-one	8, 28, 31, 37, 40 [P]	—	30, 33	32, 33	42, 263	—
352	2,3-Pentanedione [F, FDA]	600-14-6	2,3-pentanedione	31, 37, 40 [P]	27, 35	6	32, 33	—	42, 48, 54, 103, 155

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
353	2-Pentanone [F, FDA]	107-87-9	2-pentanone	31, 37, 40 [P]	—	—	24, 32, 33	7, 42	18, 42, 103
354	4-Pentenoic acid [F, FDA]	591-80-0	4-pentenoic acid	—	—	—	—	42, 256, 257	42, 108
355	2-Pentylpyridine [F]	2294-76-0	pyridine, 2-pentyl-	—	—	—	—	—	42
356	α-Phellandrene [F, FDA]	(*d*) 2243-33-6 (*l*) 4221-98-1 99-83-2	1,3-cyclohexadiene, 2-methy-5-(1-methylethyl)-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	—	42
357	2-Phenethyl acetate [F, FDA]	103-45-7	acetic acid, 2-phenethyl ester	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 20, 42, 46	42, 45, 264
358	Phenethyl alcohol [F, FDA]	60-12-8	benzeneethanol	8, 28, 31, 37, 40 [P], 265	27, 35	6, 30	24, 29, 32, 33	7, 19, 20, 42, 44, 48	15, 42, 45, 46, 95, 54, 155
359	Phenethyl butyrate [F, FDA]	103-52-6	butanoic acid, phenylethyl ester; homolog of butanoic acid, phenylmethyl ester [103-37-7]	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	[7, 20 42] [H]	[42, 54] [H]
360	Phenethyl cinnamate [F]	103-53-7	2-propenoic acid, 3-phenyl-, phenylethyl ester; homolog of 2-propenoic acid, 3-phenyl-, phenylmethyl ester [103-41-3]	31, 37, 40 [P]	—	—	32, 33	—	[42] [H]
361	Phenethyl isobutyrate [F, FDA]	103-48-0	propanoic acid, 2-methyl-, phenylethyl ester; homolog of butanoic acid, phenylmethyl ester [103-37-7]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	[7, 20 42] [H]	[42, 54] [H]
362	Phenethyl isovalerate [F, FDA]	140-26-1	butanoic acid, 3-methyl-, phenethyl ester	8, 28, 31, 37, 40 [P], 266	—	30	29, 32, 33	42	—
363	Phenethyl phenylacetate [F, FDA]	102-20-5	benzeneacetic acid, phenylethyl ester; homolog of benzeneacetic acid, phenylmethyl ester [102-16-9]	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	[42] [H]	—
364	Phenethyl salicylate [F, FDA]	118-55-8	benzoic acid, 2-hydroxy-, phenyl ester	—	—	—	—	—	—
365	1-Phenyl-1-propanol [F, FDA]	93-54-9	1-propanol, 1-phenyl-	—	—	—	—	—	—
366	3-Phenyl-1-propanol [F, FDA]	122-97-4	benzenepropanol	31, 37, 40 [P]	—	—	24, 32, 33	42	42
367	2-Phenyl-2-butenal [F]	4411-89-6	benzeneacetaldehyde, α-ethylidene- {butenal, 2-phenyl-}	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	7, 42	42
368	4-Phenyl-3-buten-2-ol [F, FDA]		3-buten-2-ol, 4-phenyl-	—	—	—	—	—	—
369	4-Phenyl-3-buten-2-one [F, FDA]	122-57-6	3-buten-2-one, 4-phenyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	7, 42	42
370	Phenylacetaldehyde [F, FDA]	122-78-1	ethanal, phenyl-	8, 28, 31, 37, 40 [P]	—	6, 30, 33	24, 29, 32, 33	7, 42	42
371	Phenylacetic acid [F, FDA]	103-82-2	benzeneacetic acid	8, 28, 31, 37, 40 [P], 267, 268	27, 35	6, 30	24, 29, 32, 33	7, 42	42, 50
372	*l*-Phenylalanine [F, FDA]	63-91-2	*l*-phenylalanine {benzenepropanoic acid, α-amino-}	60 [P], 269 [P], 270 [P], 271 [P]	—	—	24, 39, 60 [P]	42, 61, 62, 63, 64, 65, 66, 67, 70	42, 68, 69
373	3-Phenylpropionaldehyde [F, FDA]	104-53-0	2-propanal, 3-phenyl-	31, 37, 40 [P]	—	33	32, 33	—	—
374	3-Phenylpropionic acid [F, FDA]	501-52-0	propanoic acid, 3-phenyl-	31, 37, 40 [P]	—	—	24, 32, 33	42	42
375	3-Phenylpropyl acetate [F, FDA]	122-72-5		—	—	—	—	—	—
376	3-Phenylpropyl cinnamate [F, FDA]			—	—	—	24	—	—
377	2-(3-Phenylpropyl)tetrahydrofuran [F, FDA]			—	—	—	—	—	—
378	Phosphoric acid [F]	7664-38-2		—	—	—	—	42	—

Table 1 (*cont.*)

No.	Ingredient			Chemistry	Bioassay			Tobacco and/or Smoke	
					Tumorigenicity		Mutagenicity/ Genotoxicity		
	As listed by Doull *et al.* (5)	CAS RN	Chemical Abstracts Nomenclature		Skin	Inhalation		Tobacco	Smoke
379	α-Pinene [F, FDA]	80-56-8 7785-26-4	bicyclo[3,1,1]hept-2-ene, 2,6,6-trimethyl-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 109	42
380	β-Pinene [F, FDA]	127-91-3 18172-67-3	bicyclo[3,1,1]heptane, 6,6-dimethyl-2-methylene-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	42, 113	42, 45, 48
381	*d*-Piperitone [F, FDA]	89-81-6 6091-50-5	2-cyclohexen-1-one, 3-methyl-6-(1-methylethyl)-	8, 28	—	30	29	7, 42	—
382	Piperonal [F, G]	120-57-0	1,3-benzodioxole-5-carboxaldehyde	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	29, 32, 33	42, 53, 166	42, 59
383	Potassium sorbate [F, G]	590-00-1 24634-61-5		8, 28, 37	27, 35	6, 30, 33	29	—	—
384	*l*-Proline [F, FDA]	147-85-3	*l*-proline	60 [P], 119 [P], 272 [P], 273 [P], 274	—	—	24	42, 61, 62, 63, 64, 65, 66, 67, 70, 85	42, 68, 69
385	5-Propenylguaethol [F, FDA]	94-86-0		8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	—
386	Propionic acid [F, G]	79-09-4	propanoic acid	31, 37, 40 [P]	27, 35	6, 33	24, 32, 33	7, 42	42, 50, 93, 95
387	Propyl acetate [F, FDA]	109-60-4	acetic acid, propyl ester	31, 37, 40 [P]	—	—	32, 33	7, 42	—
388	Propyl *p*-hydroxybenzoate [F, FDA]	94-13-3	benzoic acid, 4-hydroxy-, propyl ester; homolog of benzoic acid, 4-hydroxy-, methyl ester [99-76-3]	8, 28	—	30	29	—	[15, 42] [H]
389	Propylene glycol [F, G]	57-55-6	1,2-propanediol	8, 28, 31, 37, 38, 40 [P], 191, 275, 276	27, 35	6, 26, 30, 33	9, 10, 23, 24, 29, 32, 33, 39	42, 48	15, 25, 42, 205
390	3-Propylidenephthalide [F, FDA]	17369-59-4		8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	—	—
391	Pyridine [F, FDA]	110-86-1	pyridine	—	—	—	—	7, 42, 48, 56, 277	42, 47, 48, 56, 277
392	Pyroligneous acid [F, FDA]	8030-97-5	solution of 6-10% acetic acid	—	27, 35	6	—	—	—
393	Pyrrole [F]	109-97-7	1*H*-pyrrole	278 [P]	—	—	24	42, 45, 48, 125, 152	15, 42, 103, 279
394	Pyruvic acid [F, FDA]	127-17-3	propanoic acid, 2-oxo-	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	7, 42	15, 42, 44, 45
395	Rhodinol [F, FDA]	6812-78-8 141-25-3	7-octen-1-ol, 3,7-dimethyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
396	Salicylaldehyde [F, FDA]	90-02-8	benzaldehyde, 2-hydroxy-	8, 28, 37, 31, 40 [P]	—	6, 30	29, 32, 33	42, 44, 32	42, 44, 280, 281
397	Sclareolide [F, FDA]	564-20-5	naphtho[2,1-*b*]furan-2(1*H*)-one, decahydro-3a,6,6,9a-tetramethyl-	8, 9, 28, 245, 282	—	30	29	42, 283	42, 284
398	Skatole [F, FDA]	83-34-1	1*H*-indole, 3-methyl-	—	—	—	—	—	42, 52, 285
399	Sodium acetate [F, G]	127-09-3	acetic acid, sodium salt	37, 286 [P], 287 [P]	—	33	39	—	—
400	Sodium benzoate [F, G]	532-32-1	benzoic acid, sodium salt	37, 288 [P]	27, 35	6, 33	39	—	—
401	Sodium bicarbonate [G]	144-55-8		—	—	—	39	—	—
402	Sodium carbonate [G]	497-19-8		37	—	33	39	—	—
403	Sodium chloride [G]	7647-14-5		37	—	33	—	42	—
404	Sodium citrate [F, G]	68-04-2	1,2,3-propanetricarboxylic acid, 2-hydroxy-, sodium salt	37	27, 35	6, 33	39	—	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
405	Sodium hydroxide [G]	1310-73-2		—	—	—	—	—	—
406	Solanone	1937-54-8	6,8-nonadien-2-one, 8-methyl-5-(1-methylethyl)-	—	—	—	—	7, 19, 20, 42, 53	42, 45, 54, 149
407	Sucrose octaacetate [F, FDA]	126-14-7	α-D-glucopyranoside, 1,3,4,6-tetra-*O*-acetyl-	289	27, 35	6, 30	29	—	—
408	Sugar alcohols [F, G]	68425-17-2		—	27, 35	6, 30	29	—	—
409	Sugars [F, G]			146	—	33	—	—	—
	Sugars [F, G]	50-99-7 9055-00-9	glucose	37, 115 [P], 119 [P], 290, 291, 292, 293	27, 35	6, 30	24, 29, 290, 291	42, 48	42, 48, 292, 294, 295
		57-48-7	fructose	115 [P], 119 [P], 290, 291	—	—	290, 291	42, 48	42, 48, 294
		59-23-4	galactose	290, 291	—	—	290, 291	42, 48	42
		3458-28-4	mannose	—	—	—	—	42, 48	42
		57-50-1	sucrose	8, 28, 115 [P], 290, 291, 292, 293, 296 [P]	—	30	9, 10, 23, 24, 29, 290, 291, 297	42	42, 292
		8013-17-0	invert sugars	8, 28, 38, 191	27, 35, 191	30	29	—	—
		8029-43-4	corn syrup	38	—	30, 33	29	—	—
410	Tannic acid [F, G]	1401-55-4		—	—	—	—	42	—
411	*d*-Tartaric acid [F, G]	147-71-7	butanedioic acid, 2,3-dihydroxy-	—	27, 35	6, 30	39	298	—
	l-Tartaric acid	87-69-4	butanedioic acid, 2,3-dihydroxy-	31, 38, 40 [P]	—	33	32, 33	—	42
	dl-Tartaric acid	133-37-9	butanedioic acid, 2,3-dihydroxy-	—	—	—	—	—	—
	meso-Tartaric acid	147-73-9	butanedioic acid, 2,3-dihydroxy-	—	—	—	—	—	—
412	α-Terpineol [F, FDA]	98-55-5 10482-56-1	3-cyclohexene-1-methanol, α,α,4-trimethyl-	8, 28, 31, 37, 40 [P], 200	—	30	24, 29, 32, 33	7, 42	42
413	Terpinolene [F, FDA]	586-62-9	cyclohexene, 1-methyl-4-(methylethylidene)-	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	—	—
414	α-Terpinyl acetate [F, FDA]	80-26-2	2-(4-methyl-3-cyclohex-1-yl)-2-propyl acetate	8, 28, 31, 37, 40 [P], 200	—	30	24, 29, 32, 33	7, 42	42
415	5,6,7,8-Tetrahydroquinoxaline [F]	34413-35-9	quinoxaline, 5,6,7,8-tetrahydro-	31, 37, 40 [P]	—	—	32, 33	—	—
416	1,5,5,9-Tetramethyl-13-oxatricyclo[8,3,0,0(4,9)]tridecane [F]	6790-58-5		—	27, 35	6	—	—	—
417	2,3,4,5-Tetramethylethylcyclohexanone [F, FDA]			—	—	—	—	—	—
418	3,4,5,6-Tetramethylethylcyclohexanone [F, FDA]			—	—	—	—	—	—
419	2,3,5,6-Tetramethylpyrazine [F]	1124-11-4	pyrazine, tetramethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	24, 29, 32, 33	7, 42, 56, 57, 152, 156	42, 47, 56, 57, 140, 142, 143, 152
420	Thiamine hydrochloride [F, G]	67-03-8		—	—	—	—	42	—

Table 1 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Skin	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
421	Thiazole [F]	288-47-1	thiazole	—	—	—	—	—	42
422	*l*-Threonine [FDA]	72-19-5	*l*-threonine	60 [P]	—	—	24, 29, 39, 60 [P]	42, 62, 63, 65, 67, 85	42, 68, 69
423	Thymol [F, FDA]	89-83-8	phenol, 5-methyl-2-(1-methylethyl)-	31, 37, 40 [P]	—	33	24, 32, 33	42	42, 47, 299
424	α-Tocopherol [G]	59-02-9	2*H*-1-benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-	37	—	—	39, 82	42, 300, 301	42, 301, 302
	Tocopherol mixture	119-13-1		8, 28	—	30, 33	29	—	—
425	*o*-Tolualdehyde [F, FDA]	529-20-4	benzaldehyde, 2-methyl-	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	42, 46, 48	42, 48
426	*m*-Tolualdehyde [F, FDA]	620-23-5	benzaldehyde, 3-methyl-	8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	7, 42, 44, 48	47
427	*p*-Tolualdehyde [F, FDA]	104-87-0	benzaldehyde, 4-methyl-	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	42, 214, 303	42, 52
428	*p*-Tolyl 3-methylbutyrate [F]	55066-56-3	isovaleric acid, *p*-tolyl ester	—	—	—	—	—	—
429	*p*-Tolylacetaldehyde [F]			—	—	—	—	—	—
430	*p*-Tolyl acetate [F, FDA]	140-39-6		8, 28, 31, 37, 40 [P]	—	30, 33	29, 32, 33	—	—
431	*p*-Tolyl isobutyrate [F, FDA]	103-93-5		8, 28, 31, 37, 40 [P]	27, 35	6, 30, 33	29, 32, 33	—	—
432	*p*-Tolyl phenylacetate [F, FDA]	101-94-0		8, 28	27, 35	6, 30	29	—	—
433	Triacetin [F, G]	102-76-1	1,2,3-propanetriol, triacetate	8, 28, 31, 37, 40 [P], 304 [P]	27, 35	6, 30, 33	24, 29, 32, 33	—	42, 205, 305
434	2-Tridecanone [F]	593-08-8	2-tridecanone	—	—	—	—	42, 306	—
435	2-Tridecenal [F, FDA]	7774-82-5	2-tridecenal	—	—	—	—	—	—
436	Triethyl citrate [F, G]	77-93-0		31, 37, 40 [P]	—	6, 33	32, 33	42	—
437	3,5,5-Trimethyl-1-hexanol [FDA]	3452-97-9	1-hexanol, 3,5,5,-trimethyl-	31, 37, 40 [P]	—	—	32, 33	—	—
438	*p*,α,α-Trimethylbenzyl alcohol [F]	1197-01-9	benzene, 1-methyl-4-(1-hydroxy-1-methylethyl)-	—	—	—	—	42	42
439	4-(2,6,6-Trimethylcyclohex-2-enyl)-but-2-en-4-one [F]	35044-68-9 23776-92-3	2-buten-1-one, 1-(2,6,6-trimethyl-cyclohex-1-enyl)- {β-damascone}	8, 28, 31, 37, 40 [P]	27, 35	6, 30	29, 32, 33	7, 42, 46, 53	42, 307
440	2,6,6-Trimethylcyclohex-2-ene-1,4-dione [F]	1125-21-9	2-cyclohexene-1,4-dione, 2,6,6-trimethyl-	—	—	—	—	7, 20, 42, 46	42, 108
441	2,6,6-Trimethylcyclohexa-1,3-dienyl-methane [F]			—	—	—	—	—	—
442	4-(2,6,6-Trimethylcyclohexa-1,3-dienyl)-but-2-en-4-one [F]	23696-85-7	but-2-en-4-one, 4-(2,6,6-trimethyl cyclohexa-1,3-dienyl)- {β-damascenone}	8, 28, 31, 37, 40 [P]	—	30	29, 32, 33	—	—
443	2,6,6-Trimethylcyclohexanone [F]	2408-37-9	cyclohexanone, 2,2,6-trimethyl-	—	—	—	—	42	—
444	2,3,5-Trimethylpyrazine [F]	14667-55-1	pyrazine, trimethyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 42, 56, 57, 71, 152, 155, 156	42, 47, 56, 57, 71, 125, 140, 142, 143, 152, 154, 213, 308
445	*l*-Tyrosine [F, FDA]	60-18-4	*l*-tyrosine	60 [P]	—	—	24, 29, 60 [P]	42, 61, 62, 63, 64, 65, 66, 67, 70	—
446	δ-Undecalactone [F]	710-04-3	2*H*-pyran-2-one, 6-hexyltetrahydro-; homolog of 2*H*-pyran-2-one, 6-pentyltetrahydro- [705-86-2]	31, 37, 40 [P]	—	—	32, 33, 39	[53, 42] [H]	—

Table 1 (*cont.*)

No.	Ingredient			Chemistry	Bioassay			Tobacco and/or Smoke	
					Tumorigenicity		Mutagenicity/ Genotoxicity		
	As listed by Doull *et al.* (5)	CAS RN	Chemical Abstracts Nomenclature		Skin	Inhalation		Tobacco	Smoke
447	γ-Undecalactone [F, FDA]	104-67-6	2(3*H*)-furanone, dihydro-5-heptyl-; homolog of 2(3*H*)-furanone, dihydro-5-pentyl- [104-61-0]	8, 28, 31, 37, 40 [P]	—	30, 33	24, 29, 32, 33	[7, 20, 42, 214] [H]	—
448	Undecanal [F, FDA]	112-44-7	undecanal; homolog of hexanal [66-25-1]	—	—	—	—	—	[18, 42] [H]
449	2-Undecanone [F, FDA]	112-12-9	2-undecanone	31, 37, 40 [P]	—	33	32, 33	42, 46, 146	42
450	10-Undecenal [F, FDA]	112-45-8	10-undecenal	—	—	—	—	—	—
451	Urea [F]	57-13-6	urea	8, 28, 31, 37, 40 [P], 309 [P]	—	30, 33	29, 32, 33	310	42
452	Valencene [F]	4630-07-3	naphthalene, 1,2,3,6,7,8,8a-octahydro-1,8a-dimethyl-7-(1-methylethenyl)-	—	—	—	—	—	—
453	Valeraldehyde [F, FDA]	110-62-3	pentanal	8, 28, 31, 37, 40 [P]	—	30, 33	24, 29, 32, 33	42, 79	42, 102, 103
454	Valeric acid [F, FDA]	109-52-4	pentanoic acid	8, 28, 31, 37, 40 [P]	—	30	24, 29, 32, 33	7, 42, 208	42, 93, 95, 208
455	γ-Valerolactone [F]	108-29-2	2(3*H*)-furanone, dihydro-5-methyl-	8, 28, 31, 37, 40 [P]	27, 35	6, 30	24, 29, 32, 33	7, 19, 42	42, 295
456	Valine [F, FDA]	7004-03-7	valine	60 [P]	—	—	24, 29, 39, 60 [P]	42, 62, 63, 64, 66, 67, 70	42, 68, 69
457	Vanillin [F, G]	121-33-5	benzaldehyde, 4-hydroxy-3-methoxy-	8, 28, 31, 37, 40 [P], 87 [P], 311, 312, 313, 314	27, 35	6, 30, 33	24, 29, 32, 33, 39, 123	7, 19, 42, 48, 315	15, 42, 45, 48, 54, 150
458	Veratraldehyde [F, FDA]	120-14-9	benzaldehyde, 3,4-dimethoxy-; isomer of benzaldehyde, 2,6-dimethoxy- [3392-97-0]	8, 28, 31, 37, 40 [P]	27, 35	6	32, 33	42, 53, 316	[42, 54] [I]
459	Water	7732-18-5	water	8, 28, 37, 38	—	30, 33	29	42, 48	42, 44, 45, 317
460	3,4-Xylenol [F]	95-65-8	phenol, 3,4-dimethyl-	—	—	—	—	42	42, 45, 52, 171, 247

In 2002, RODGMAN and GREEN noted (10):

> Over the years it has been repeatedly asserted [see (9)] that cigarette ingredients added at normal levels to pre-1980 cigarettes or at slightly increased levels to more recent lower "tar" cigarettes might adversely modify the chemistry and biology of the MSSs from such cigarettes. However, no chemical or biological evidence has been presented in support of such assertions.

Examination of the data presented in Table 1 permits verification of the statements by numerous investigators that many of the ingredients in the DOULL *et al*. list have been identified as components in untreated tobacco types and/or the MSS from cigarettes containing such tobaccos. Such an examination also permits an assessment of the effect of a number of the listed ingredients that have been reported in a variety of studies to not adversely affect the chemical or biological properties of the MSS from cigarettes containing such ingredients or the chemical properties of the pyrolysates from individual ingredients.

3 STUDIES ON MIXTURES LISTED BY DOULL *et al.* (5)

Table 2 catalogs various mixtures (oils, extracts, resins, etc.) listed in the DOULL *et al*. report as ingredients added to cigarette tobacco and their effect on the chemical and biological properties of cigarette MSS.

Some of the ingredients listed in Tables 1 and 2 are not only used as additives to the tobacco blend but also several are used as filter-tip flavorants. Obviously, those included in the filter tip are not subjected to the range of high temperatures encountered during the smoking process by those ingredients added to the tobacco rod. Seldom is any part of the filter tip subjected to temperatures significantly greater than 100 ˚C.

To simplify the understanding of Table 2 and to maintain its manageability, it should be noted that the following information is contained therein:

- Under *Ingredient* are listed the name used in the DOULL *et al*. report, the Chemical Abstract Registry Number (CAS RN), and designation (**F**) whether the ingredient is generally regarded as safe (GRAS) by the Flavor and Extract Manufacturers Association (FEMA) or is a Food and Drug Administration-approved (**FDA**) food additive or an FDA GRAS ingredient (**G**).
- Under *Chemistry* are listed references to studies where the composition of the mixture was determined (designated with superscript **C**), the ingredient was examined for its pyrolysis products (designated with superscript **P**), its effect on cigarette MSS composition, and its effect when added in a mixture of other ingredients on MSS composition.
- Under *Bioassay* are listed studies where the effect of the added mixture ingredient was determined by results from mouse skin-painting studies with cigarette CSC, inhalation studies with cigarette MSS, and mutagenic and/or genotoxic studies plus the effect of that ingredient in a mixture of ingredients on the results from the same types of bioassays.

Examination of the data in Table 2 permits an assessment of the effect of a number of the listed mixture ingredients that have been reported in a variety of studies to not adversely affect the chemical or biological properties of the MSS from cigarettes containing such ingredients or the chemical properties of the pyrolysates from individual ingredients.

4 COMPOUNDS LISTED BY DOULL *et al*. THAT ARE COMPONENTS OF MIXTURES LISTED BY DOULL *et al.*

In the mid-1960s, considerable analytical information was available on the components of coffee, cocoa, and licorice. The latter two materials had a long history of use as components of the casing materials formulation added to tobacco smoking products, including cigarettes. As such, their level of addition to cigarette filler is much greater than that of the flavorful naturally occurring oils as part of the flavor formulation or "top dressing", the total of which is less than a few mg/g of tobacco filler. From a comparison of the coffee, cocoa, and licorice components with tobacco and/or smoke components reported at that time, it was obvious that many of the components of the major casing materials were identical with or similar to many of the tobacco and/or smoke components.

This finding plus the analytical methodologies improved during the previous decade plus the amount of ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS) analytical data generated on the components from different ingredient-free tobacco types (flue-cured, burley, Oriental) and their cigarette MSSs prompted detailed examination of the composition of several naturally occurring flavorful oils used in many cigarette "top dressing" formulations. These included cardamom oil, coriander oil, davana oil, nutmeg oil, and styrax oil. For an entirely different reason, the composition of maple syrup was also determined. Subsequently, all of these compositionally defined flavor mixtures were included in the DOULL *et al.* list (5).

More recently, the numbers of identified components in coffee (322), cocoa (320), and licorice (335, 337) have been greatly expanded over the numbers known in the late 1960s. Many of the components of the highly complex materials coffee, cocoa, and licorice are also components of tobacco containing no added ingredients. Many are also found to be components of the MSS from untreated tobaccos. Although many of the findings on the naturally occurring flavor oils were previously unpublished, they are summarized in Table 3. The Table 3 compilation reveals that nearly 250 of the components of the flavorful oils and casing materials are identical with or similar to the individual chemical compounds listed by DOULL *et al.* Thus, the use of such flavorful oils does not constitute the addition of a series of totally unknown components to tobacco but actually represents an enhancement of the levels of many flavorful components already present in the tobacco.

While the definition of the composition of several of the naturally occurring oil ingredients was accomplished in the late 1960s (see Table 3), it is now possible to download the reported general compositions of many of the others through various Internet addresses. A limited selection of examples is shown in Table 4. Many of the components of these naturally occurring materials are also components of

Table 2. Mixtures in the DOULL *et al*. list (5): Studies on their effect on the chemical and biological properties of cigarette MSS

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Chemistry	Bioassays: Tumorigenicity: Skin	Bioassays: Tumorigenicity: Inhalation	Bioassays: Mutagenicity/ Genotoxicity
1	Alfalfa extract [F, G]	84082-36-0	8, 38	—	30, 33	29, 32, 33
2	Allspice extract, oleoresin and oil [F, G]	8006-77-7	—	—	—	—
3	Almond bitter oil [F, G]		—	—	—	—
4	Ambergris tincture [F, G]	8038-65-1	8	—	30	29
5	Amyris oil [FDA]	8015-65-4	8, 37	—	30, 33	29, 32, 33
6	Angelica root, oil and seed oil [F, G]	8015-64-3	8, 37	—	30	29, 32, 33
7	Anise, anise star, extract and oils [F, G]		—	—	—	—
8	Apple juice concentrate, extract, skins	85251-63-4	8, 37	27, 35	6, 30, 33	29, 32, 33
9	Apricot extract and juice concentrate	68650-44-2	8, 38	—	30, 33	29, 32, 33
10	Asafetida fluid extract and oil [F, G]		—	—	—	—
11	Balsam Peru and oil [F, G]	8007-00-9	8, 37	—	30	29, 32, 33
	Balsam Peru	8007-00-9	8	27, 35	6, 30	29
12	Basil oil [F, G]		—	—	—	—
13	Bay leaf, oil and sweet oil [F, G]		—	—	—	—
14	Beeswax white [F, G]	8006-40-4	—	27, 35	6	—
15	Beet juice concentrate	89957-90-4	—	27, 35	6	—
16	Benzoin resin [F, FDA]	9000-05-9	—	27, 35	—	—
17	Bergamot oil [F, G]	8007-75-8	8	—	30	29
18	Black currant buds absolute [F, FDA]	68650-46-4	37	—	—	—
19	Buchu leaf oil [F, FDA]	68650-46-4	8, 37	—	30	29, 32, 33
20	Butter, butter esters, and butter oil [F, FDA]		—	—	—	—
	Butter	91745-88-9	—	27, 35	6	
21	Cananga oil [F, G]	68606-83-7	8, 37	—	30, 33	29, 32, 33
22	Capsicum oleoresin		—	—	—	—
23	Caramel color [F, G]	8028-95-5	8, 37	27, 35	6, 30, 33	29, 32, 33
24	Caraway oil [F, G]	8000-42-8	8, 37	—	30	29, 32, 33
25	Cardamom oleoresin, extract, seed oil, and powder [F, G]	977090-82-6 8000-66-6	—	—	33	—
	Cardamom seed oil	8000-66-6	8, 37, 318 [C]	27, 35	30	29, 32, 33
26	Carob bean and extract [F, G]	84961-45-5	8, 37	27, 35	6, 30, 33	29, 32, 33
	Carob bean extract	84961-45-5	8, 38	—	30, 33	29, 32, 33
27	Carrot oil [F, G]	8015-88-1	8	—	30	29
28	Cascarilla oil and bark extract [F, G]	8007-06-5	8, 37	—	30	29, 32, 33
29	Cassia bark oil [F, G]	8007-80-5	37	27, 35	6, 33	33
30	Cassia absolute and oil [F, FDA]	89958-31-6	8, 37	—	30	29, 32, 33
31	Castoreum extract, tincture and absolute [F, G]		—	—	—	—
	Castoreum extract	8023-83-4	8	27, 35	6, 30	29
32	Cedar leaf oil [F, FDA]		—	—	—	—
33	Cedarwood oil terpenes and Virginiana [FDA]		—	—	—	—
34	Cedrol [FDA]		—	—	—	—
35	Celery seed extract, solid, oil, and oleoresin [F, G]	8015-90-5	8, 37	—	—	32, 33
	Celery oleoresin	8015-90-5	8	—	33	29
	Celery seed oil	8015-90-5	8	—	30	29
36	Chamomile flower oil and extract [F, G]		—	—	—	—
	Chamomile oil	8002-66-2	37	27, 35	6	32, 33
	Chamomile flower, Hungarian, oil	8002-66-2	8	—	30, 33	29
	Chamomile flower, Roman, extract	8015-92-7	8, 37	—	30, 33	29, 32, 33
	Chamomile flower, Roman, oil	8015-92-7	8	—	30	29
	Chamomile oil, German	8002-66-2	8	—	30	29
37	Chicory extract [F, G]	68650-43-1	38	—	30, 33	29, 32, 33
38	Chocolate [G]		38	—	30, 33	29, 32, 33
39	Cinnamon leaf oil, bark oil, and extract [F, G]	8015-91-6	—	—	—	—
	Cinnamon bark oil	8015-91-6	8, 37	—	30, 33	29
	Cinnamon leaf oil	8015-91-6	8	—	30	29
40	Citronella oil [F, G]	8000-29-1	37	—	30	24, 29, 32, 33
41	Civet absolute [F, G]	68916-26-7	8	—	30	29
42	Clary oil [F, G]	8016-63-5	8, 37	—	30	29, 32, 33
43	Clover tops, red solid extract [F, G]		—	—	—	—

Table 2 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Chemistry	Bioassays: Tumorigenicity: Skin	Bioassays: Tumorigenicity: Inhalation	Bioassays: Mutagenicity/ Genotoxicity
44	Cocoa, cocoa shells, extract, distillate and powder [G]		—	—	—	—
	Cocoa		8	—	30	29
	Cocoa powder	84649-99-0	38, 191, 319 [P], 320	27, 35, 191, 321	6, 33	9, 10, 23, 24, 32, 33
	Cocoa extract	84649-99-3	8, 38	—	6, 30, 33	24, 29, 32, 33
	Cocoa shells		8	—	30	29
	Cocoa shell extract	8002-31-1	8, 37	—	30, 33	29, 32, 33
45	Coconut oil		—	—	—	—
46	Coffee [G]	8001-67-0	322 [C]	27, 35	6	—
	Coffee extract	84650-00-0 93348-12-0	8, 37, 38	—	30, 33	29, 32, 33, 323, 324
47	Cognac white and green oil [F, G]	8016-21-5 977050-49-9	37	27, 35	6	32, 33
	Cognac, green oil	8016-21-5	8, 37	—	30	29, 32, 33
48	Copaiba oil [FDA]	8013-97-6	8	—	30	29
49	Coriander extract and oil [F, G]		—	—	33	—
	Coriander oil	8008-52-4	8, 37, 325 [C]	—	30	24, 29, 32, 33
50	Corn oil		—	—	—	—
51	Corn silk [F, G]		8	—	30	29
52	Costus root oil [F, FDA]	8023-88-9	8	—	30	29
53	Cubeb oil [F, FDA]	8007-87-2	8	—	30	29
54	Dandelion root solid extract [F, G]	68990-74-9	8	—	30	29
55	Davana oil [F, FDA]	8016-03-3	8, 37, 326 [C]	—	30	29, 32, 33
56	Dill seed oil and extract [F, G]	8016-06-6	38	—	—	32, 33
	Dill oil	8006-75-5	8, 38	—	30	29, 32, 33
57	Fennel sweet oil [F, G]		—	—	—	—
58	Fenugreek, extract, resin and absolute [F, G]	68990-15-8 84625-40-1	37, 38	27, 35	6, 33	32, 33
	Fenugreek extract,	68990-15-8	8	—	30, 33	29
59	Fig juice concentrate	90028-74-3	8, 37, 38	27, 35	6, 30, 33	29, 32, 33
60	Food starch modified	9005-25-8	37, 115 [P], 327, 328 [P]	27, 35	6	—
61	Galbanum oil [F, FDA]	8023-91-4	8, 37	—	30, 33	29, 32, 33
62	Genet absolute [F, FDA]	8023-80-1	8	—	30	29
63	Gentian root extract [F]		—	—	—	—
64	Geranium rose oil [F, G]	8000-46-2	8, 37, 38	—	30	29, 32, 33
65	Ginger oil and oleoresin [F, G]	8007-08-7 84696-15-1	37	—	33	32, 33
	Ginger oil	8007-08-7	8, 37	27, 35	6, 30	29, 32, 33
66	Grape juice concentrate		—	—	—	—
67	Guaiac wood oil [F]	8016-23-7	8, 37	27, 35	6, 30	29, 32, 33
68	Guar gum [F]	9000-30-0	37	—	33	32, 33
69	Honey	8028-66-8	37, 38, 329 [P], 330	27, 35	6, 33, 329	32, 33, 329, 331
70	Hops oil		—	—	—	—
71	Hydrolyzed milk solids		—	—	—	—
72	Hydrolyzed plant proteins [G]		—	—	—	—
73	Hyssop oil [F, G]	8006-83-5	8	—	30	29
74	Immortelle absolute and extract [F, FDA]		—	—	—	—
	Immortelle extract	8023-95-8	8, 37	27, 35	6, 30	29, 32, 33
75	Jasmine absolute, concrete and oil [F, G]	8031-01-4 8022-96-6	37	—	33	32, 33
	Jasmine absolute	8031-01-4	8, 37	—	30	29, 32, 33
76	Kola nut extract [F, G]	68916-19-8	8, 38	—	30, 33	29, 32, 33
77	Labdanum absolute and oleoresin [F, FDA]	977092-72-0	—	—	33	—
	Labdanum absolute	8016-26-0	8, 37	27, 35	6, 30, 33	29, 32, 33
78	Lavandin oil [F, G]		—	—	—	—
79	Lavender oil [F, G]	8000-28-0	8, 37	—	30, 33	29, 32, 33
80	Lemon oil and extract [F, G]		—	—	33	—
	Lemon oil	8008-56-8	—	—	—	—
81	Lemongrass oil [F, G]	8007-02-1	8	—	30	29

Table 2 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Chemistry	Bioassays: Tumorigenicity: Skin	Bioassays: Tumorigenicity: Inhalation	Bioassays: Mutagenicity/ Genotoxicity
82	Licorice root, fluid extract and powder [F, G]		332	—	33	—
	Licorice		38, 333 [P], 334 [P a], 335 [C], 336, 337 [C]	—	6	9, 10, 23, 24, 32, 33
	Licorice extract	68916-91-6	8, 38	27, 35	30, 33	29, 32, 33
83	Lime oil [F, G]	8008-26-2	8, 37	—	30	29, 32, 33
84	Linden flowers [F, G]		—	—	—	—
85	Lovage oil and extract [F, FDA]	8016-31-7	—	—	—	—
	Lovage oil	8016-31-7	37	27, 35	6	32, 33
	Lovage extract	8016-31-7	8, 37	—	30, 33	29, 32, 33
86	Mace powder, extract and oil [F, G]		—	—	33	—
	Mace oil	8007-12-3	8, 37	—	30, 33	29, 32, 33
87	Malt and malt extract [F]		—	—	—	—
	Malt	8002-48-0	—	27, 35	—	—
	Malt extract	8002-48-0	8, 37	—	30, 33	29, 32, 33
88	Maltodextrin [G]		—	—	—	—
89	Mandarin oil [F, G]	8008-31-9	8, 37	—	30, 33	29, 32, 33
90	Maple syrup and concentrate	8029-81-0 91770-22-8	37, 38	—	33	32, 33
	Maple syrup	8029-81-0	8, 338 [C]	—	30, 33	29
91	Mate leaf, absolute and oil [F]	68916-96-1	38	—	—	32, 33
	Mate leaf, absolute	68916-96-1	8, 37	—	6, 30, 33	29, 32, 33
92	Mimosa absolute and extract [F, FDA]		—	—	—	—
	Mimosa absolute	93685-96-2	8, 37	—	30	29, 32, 33
93	Molasses extract and tincture [F]		—	—	—	—
	Molasses, blackstrap	8052-35-5	8, 38	—	30	29, 32, 33
94	Mountain maple solid extract [F, FDA]	91770-23-9	—	27, 35	6	—
95	Mullein flowers [FDA]		—	—	—	—
96	Myrrh oil [F, FDA]	8016-37-3	37	27, 35	6	32, 33
97	Neroli bigarde oil [F, G]	8016-38-4	8, 37	—	30, 33	29, 32, 33
98	Nutmeg powder and oil [F, G]		—	—	—	—
	Nutmeg oil	8008-45-5	8, 37, 339 [C]	—	30, 33	29, 32, 33
99	Oak chips extract and oil [F, FDA]	68917-11-3	38	—	33	32, 33
100	Oak moss absolute [F, FDA]	9000-50-4	8, 37	27, 35	6, 30	29, 32, 33
101	Olibanum oil [F, FDA]	8016-36-2	37	—	—	32, 33
102	Opoponax oil and gum [FDA]	8021-36-1	37	—	—	32, 33
	Opoponax gum	9000-78-6	8	—	30	29
	Opoponax oil	8021-36-1	8, 37	—	30, 33	29, 32, 33
103	Orange blossoms water, absolute and leaf absolute [F, G]		—	—	—	—
	Orange blossom absolute	8016-38-4	37	—	33	32, 33
104	Orange oil and extract [F, G]		—	—	—	—
	Orange oil distilled	68606-94-0	8, 38	—	30	29, 32, 33
	Orange oil terpenes	68917-57-7	8	—	30	24, 29
	Orange oil, bitter	68916-04-1	8, 37	—	30, 33	29, 32, 33
	Orange oil, sweet	8008-57-9	8, 37	27, 35	6, 30, 33	29, 32, 33
	Orange oil, terpeneless	68606-94-0	8, 37	—	30, 33	29, 32, 33
105	Origanum oil [F, G]	8007-11-2	8	—	30	29
106	Orris concrete oil and root extract [F, FDA]		37	—	33	32, 33
	Orris root extract	8002-73-1	8, 38	—	—	29, 32, 33
107	Palmarosa oil [F, G]	8014-19-5	8, 37	—	30	29, 32, 33
108	Parsley seed oil [F, G]	8000-68-8	8, 37	—	30	29, 32, 33
109	Patchouli oil [F, FDA]	8014-09-3	37	—	—	32, 33
110	Pepper oil, black and white [F, G]		—	—	—	—
	Pepper oil, black	8006-82-4	8, 37	—	30	29, 32, 33
111	Peppermint oil [F, G]	8006-90-4	8, 37	27, 35	6, 30	29, 32, 33
112	Peruvian (bois de rose) oil [F, G b]		—	—	30	29
113	Petitgrain absolute, mandarin oil and terpeneless oil [F, G]	8014-17-3	37	—	—	32, 33
	Petitgrain oil, terpeneless	68915-85-5	8	—	30	29
114	Pimenta leaf oil		8	—	30	29
115	Pine needle oil [F, FDA]	8021-29-2	8, 37	—	30, 33	29, 32, 33
116	Pine oil, Scotch [F, FDA]	8023-99-2	8	—	30	29
117	Pineapple juice concentrate	9001-00-7	37	27, 35	6	32, 33

Table 2 (*cont.*)

No.	Ingredient: As listed by Doull *et al.* (5)	Ingredient: CAS RN	Chemistry	Bioassays: Tumorigenicity: Skin	Bioassays: Tumorigenicity: Inhalation	Bioassays: Mutagenicity/ Genotoxicity
118	Pipsissewa leaf extract [F, G]	89997-56-8	37	—	33	32, 33
119	Plum juice	90082-87-4	37, 38	—	33	32, 33
120	Prune juice and concentrate	85594-37-2	37	27, 35	6, 33	32, 33
121	Raisin juice concentrate	68915-86-6	8, 38	—	30, 33	29, 32, 33
122	Rose absolute and oil [F, G]		—	—	—	—
	Rose absolute	8007-01-0	8, 37	—	30, 33	29, 32, 33
	Rose oil, Bulgarian, true otto	8007-01-0	8	—	30	29
123	Rosemary oil [F, G]	8000-25-7	37	—	—	—
124	Rum	90604-30-1	8, 37	—	6, 30, 33	29, 32, 33
125	Rum ether [F, FDA]	8030-89-5	—	27, 35	6	—
126	Rye extract	91770-60-4	38	—	33	32, 33
127	Sage, sage oil, and sage oleoresin [F, G]	8022-56-8	37	—	33	32, 33
	Sage oleoresin	84082-79-1	8	—	30	29
128	Sandalwood oil, yellow [F]	8006-87-9	8, 37	—	6, 30	29
129	Smoke flavor		—	—	—	—
130	Snakeroot oil [F, FDA]		—	—	—	—
131	Spearmint oil [F, G]	8008-79-5	37	27, 35	6	—
132	Styrax extract, gum, and oil [F, FDA]		340 [C]	—	—	—
	Styrax extract	8024-01-9	8, 37	—	30, 33	29, 32, 33
	Styrax gum	8046-19-3	—	27, 35	—	—
	Styrax	8024-01-9	8	—	6, 30	29
133	Tagetes oil [F, FDA]	8016-84-0	8	—	30	29
134	Tea leaf and absolute [FDA]	84650-60-2	37, 38	—	33	32, 33
135	Thyme oil, white and red [F, G]		—	—	—	—
	Thyme oil, white	8007-46-3	8, 37	—	30	29, 32, 33
136	Tolu balsam gum and extract [F, FDA]	9000-64-0	—	27, 35	6	—
137	Valerian root extract, oil, and powder [F, FDA]	8057-49-6	—	27, 35	—	—
	Valerian root extract		8	—	30, 33	29
	Valerian root oil	8008-88-6	8, 37, 38	—	30, 33	29, 32, 33
138	Vanilla extract and oleoresin [F, G]	8024-06-4	37	—	—	32, 33
	Vanilla extract	8024-06-4	8	27, 35	6, 30, 33	29
	Vanilla oleoresin	8023-78-7	8, 37	—	30	29, 32, 33
139	Vetiver oil [FDA]	8016-96-4	8, 37	—	30	29, 32, 33
140	Violet leaf absolute [F, G]	90147-36-7	37	—	...	32, 33
141	Walnut hull extract [F, FDA]	481-39-0	8	—	30	29
142	Wheat extract and flour		—	—	—	—
143	Wild cherry bark extract [F, G]		—	—	—	—
144	Wine and wine sherry	91082-91-6 8030-68-0	—	—	—	—
	Wine, sherry	8030-68-0	8, 37	—	30	29, 32, 33
145	Xanthan gum [FDA]	11138-66-2	37	—	—	32, 33
146	Yeast		—	—	—	—

[a] This study involved the pyrolysis of rutin, a major component of licorice.
[b] Peruvian (bois de rose) oil is listed in some studies as only bois de rose oil.
[C] See Table 3 for results of chemical composition study.

one or more types of additive-free tobacco. These naturally occurring materials account for only a small proportion of the few milligrams of the "top dressing" formulation applied to the tobacco blend.

5 DISCUSSION

As noted previously, the cataloging by PASCHKE *et al.* (4) of the effect of materials added to tobacco on cigarette smoke composition and biological activity was admittedly a monumental task despite the fact of several omissions some readers might consider significant. PASCHKE *et al.* included the 1970 study by JENKINS *et al.* (235) on the fate of ^{14}C-radiolabeled menthol during the smoking of a mentholated cigarette but did not take into account the fact that JENKINS *et al.* had noted their results confirmed those previously reported with radiolabeled menthol by NEWELL *et al.* (231) in 1968. Similarly, PASCHKE *et al.* included the 1962 study by KATO and SHIBAYAMA (313) who reported the conversion of vanillin added to tobacco to phenol in cigarette MSS but they did not include in their catalog the results of the study by GREEN *et al.* (311, 312) with radiolabeled vanillin in which no radiolabeled phenol was detected in the MSS from cigarettes containing added radiolabeled vanillin. The difference between the KATO and SHIBAYAMA and the GREEN *et al.* results is readily explained when the unorthodox smoking regime used by KATO and SHIBAYAMA is taken into account. Not included in the PASCHKE *et al.* catalog were the studies reported by

Table 3. Composition of several flavor and casing material ingredients; the numbers in square brackets designate the number of the respective ingredient in Table 2

No. in Tab. 1	Ingredient	CAS RN	Flavor ingredient							Casing material ingredient	
			Cardamom (318) [25] 8000-66-6	Coffee (322) [46] 84650-00-0	Coriander (325) [49] 8008-52-4	Davana (326) [55] 8016-03-3	Maple syrup (338) [90] 8029-81-0	Nutmeg (339) [98] 8008-45-5	Styrax (340) [132] 8024-01-9	Cocoa (319, 320) [44] 84649-99-0	Licorice (335, 337) [82] 68916-91-6
1	Acetanisole [F]	100-06-1	—	—	—	—	—	—	x {4}	—	—
2	Acetic acid [F]	64-19-7	—	x	—	—	x	—	—	x	x
3	Acetoin [F]	513-86-0	—	x	—	—	x	—	—	—	x
4	Acetophenone [F]	98-86-2	—	x	—	—	—	—	x	x	x
7	2-Acetyl-5-methylfuran [F]	1193-79-9	—	x	—	—	—	—	—	—	—
8	Acetylpyrazine [F]	22047-25-2	—	x	—	—	—	—	—	—	—
9	2-Acetylpyridine [F]	1122-62-9	—	x	—	—	—	—	—	x	—
10	3-Acetylpyridine [F]	350-31-7	—	x	—	—	—	—	—	x	—
11	2-Acetylthiazole [F]	24295-03-2	—	x	—	—	—	—	—	—	—
12	Aconitic acid [F, G]	499-12-7	—	x	—	—	—	—	—	—	—
13	*dl*-Alanine [FDA]	107-95-9	—	x	—	—	—	—	—	x	x
16	Ammonia	7664-41-7	—	x	—	—	—	—	—	—	—
21	Amyl alcohol [F, FDA]	71-41-0	—	x	—	—	—	—	—	x	x
22	Amyl butyrate [F, FDA]	540-18-1	—	—	—	—	—	—	—	x	—
23	Amyl formate [F, FDA]	638-49-3	—	x	—	—	—	—	—	—	—
26	Anethole [F, G]	104-46-1	—	—	x	—	—	—	—	—	—
	trans-	4180-23-8									
31	*l*-Arginine [F]	74-79-3	—	x	—	—	—	—	—	—	x
32	Ascorbic acid [F, G]	50-81-7	—	x	—	—	—	—	—	—	—
33	*l*-Asparagine monohydrate [FDA]	5794-13-8	—	x	—	—	—	—	—	—	—
34	*l*-Aspartic acid [F, FDA]	56-84-8	—	x	—	—	—	—	—	—	x
35	Benzaldehyde [F, G]	100-52-7	—	x	—	—	—	—	—	—	x
37	Benzoic acid [F, G]	65-85-0	—	x	—	—	—	—	—	x {12}	x
40	Benzyl alcohol [F, FDA]	100-51-6	—	x	—	—	—	—	—	x	x
41	Benzyl benzoate [F, FDA]	120-51-4	—	—	—	—	—	—	—	x	—
43	Benzyl cinnamate [F, FDA]	103-41-3	—	—	—	—	—	—	—	x	—
47	Borneol [F, FDA]	507-70-0	—	—	x	—	—	—	—	—	x
50	2,3-Butanedione [F, G]	431-03-8	—	x	—	—	—	—	—	—	x
51	1-Butanol [F, FDA]	71-36-3	—	x	—	—	—	—	—	—	x
52	2-Butanone [F, FDA]	78-93-3	—	x	—	—	—	—	—	—	x
54	Butyl acetate [F, FDA]	123-86-4	—	x	—	—	—	—	—	—	—
61	Butyric acid [F, G]	107-92-6	—	x	—	—	—	—	—	—	—
63	Caffeine [F, G]	58-08-2	—	x	—	—	—	—	—	—	x
67	β-Carotene										
	trans-	7235-40-7	—	x	—	—	—	—	—	—	—
	cis-	6811-73-0									
68	Carvacrol [F, FDA]	499-75-2	—	—	—	—	—	—	—	—	x

Table 3 (*cont.*)

No. in Tab. 1	Ingredient	CAS RN	Flavor ingredient							Casing material ingredient	
			Cardamom (318) [25] 8000-66-6	Coffee (322) [46] 84650-00-0	Coriander (325) [49] 8008-52-4	Davana (326) [55] 8016-03-3	Maple syrup (338) [90] 8029-81-0	Nutmeg (339) [98] 8008-45-5	Styrax (340) [132] 8024-01-9	Cocoa (319, 320) [44] 84649-99-0	Licorice (335, 337) [82] 68916-91-6
69	4-Carvomenthol [F, FDA]	562-74-3	—	—	—	x	—	—	—	—	—
70	*l*-Carvone [F, G]	99-49-0	—	x	—	—	—	—	—	—	—
71	β-Caryophyllene[F, FDA]	87-44-5	—	—	—	—	—	—	x {22}	x	—
73	Cellulose	9004-34-6	—	x	—	—	—	—	—	—	x
74	Cinnamaldehyde [F, G]	104-55-2	—	—	—	—	—	—	x	—	—
75	Cinnamic acid [F, FDA]	621-82-9	—	—	—	—	—	—	x	—	—
77	Cinnamyl alcohol [F, FDA]	104-54-1	—	—	—	—	—	—	x {17}	—	—
78	Cinnamyl cinnamate [F, FDA]	122-69-0	—	—	—	—	—	—	x	—	—
82	Citric acid [F, G]	77-92-9	—	x	—	—	x	—	...	—	x
87	*p*-Cymene [F, FDA]	99-87-6	—	x	x	—	—	x	x	x	x
88	*l*-Cysteine [F, G]	52-90-4	—	x	—	—	—	—	—	—	—
91	γ-Decalactone [F, FDA]	706-14-9	—	x	—	—	—	—	—	—	—
92	Decanal [F, G]	112-31-2	—	x	—	—	—	—	—	x	—
93	Decanoic acid [F, FDA]	334-48-5	—	x	—	—	—	—	—	x	x
99	2,3-Diethylpyrazine [F]	15707-24-1	—	x	—	—	—	—	—	—	—
	2.5-Diethylpyrazine	13238-84-1	—	x	—	—	—	—	—	—	—
	2.6-Diethylpyrazine	13067-27-1	—	x	—	—	—	—	—	—	—
102	*m*-Dimethoxybenzene [F, FDA]	151-10-0	—	x	—	—	—	—	—	—	—
103	*p*-Dimethoxybenzene [F, FDA]	150-78-7	—	x	—	—	—	—	—	—	—
104	2,6-Dimethoxyphenol[F]	91-10-1	—	x	—	—	x	—	—	—	—
109	4,5-Dimethyl-3-hydroxy-2,5-dihydrofuran-2-one[F]	28664-35-9	—	x	—	—	—	—	—	—	—
116	2,3-Dimethylpyrazine[F]	5910-89-4	—	x	—	—	—	—	—	x	—
117	2,5-Dimethylpyrazine[F]	123-32-0	—	x	—	—	—	—	—	x	—
118	2,6-Dimethylpyrazine[F]	108-50-9	—	x	—	—	—	—	—	x	x
124	Ethyl 2-methylbutyrate [F, FDA]	7452-79-1	—	x	—	—	—	—	—	—	—
125	Ethyl acetate [F, G]	141-78-6	—	x	—	—	—	—	—	x	—
126	Ethyl acetoacetate [F, FDA]	141-97-9	—	x	—	—	—	—	—	—	—
127	Ethyl alcohol [F, G]	64-17-5	—	x	—	—	—	—	—	x	—
128	Ethyl benzoate [F, FDA]	93-89-0	—	...	—	—	—	—	—	x	—
129	Ethyl butyrate [F, G]	105-54-4	—	x	—	—	—	—	—	—	—
130	Ethyl cinnamate [F, FDA]	103-36-6	—	x	—	x	—	—	x	x	—
131	Ethyl decanoate [F, FDA]	110-38-3	—	—	—	—	—	—	—	x	—
133	Ethyl furoate		—	—	—	—	—	—	—	x	—
134	Ethyl heptanoate [F, FDA]	106-30-9	—	—	—	—	—	—	—	x	—
135	Ethyl hexanoate [F, FDA]	123-66-0	—	x	—	—	—	—	—	x	—
136	Ethyl isovalerate [F, FDA]	108-64-5	—	x	—	—	—	—	—	x	—
137	Ethyl lactate [F, FDA]	97-64-3	—	—	—	—	—	—	—	x	—

Table 3 (*cont.*)

No. in Tab. 1	Ingredient	CAS RN	Flavor ingredient							Casing material ingredient	
			Cardamom (318) [25] 8000-66-6	Coffee (322) [46] 84650-00-0	Coriander (325) [49] 8008-52-4	Davana (326) [55] 8016-03-3	Maple syrup (338) [90] 8029-81-0	Nutmeg (339) [98] 8008-45-5	Styrax (340) [132] 8024-01-9	Cocoa (319, 320) [44] 84649-99-0	Licorice (335, 337) [82] 68916-91-6
139	Ethyl levulinate [F, FDA]	539-88-8	—	—	—	—	—	—	—	x	—
142	Ethyl myristate [F, FDA]	124-06-1	—	—	—	—	—	—	—	x	—
143	Ethyl nonanoate [F, FDA]	123-29-5	—	—	—	—	—	—	—	x	—
145	Ethyl octanoate [F, FDA]	106-32-1	—	—	—	—	—	—	—	x	—
147	Ethyl palmitate [F]	628-97-7	—	x	—	—	—	—	—	—	x
148	Ethyl phenylacetate [F, FDA]	101-97-3	—	x	—	—	—	—	—	x	x
149	Ethyl propionate [F, FDA]	105-37-3	—	—	—	—	—	—	—	x	—
150	Ethyl salicylate [F, FDA]	118-61-6	—	x	—	—	—	—	—	—	—
152	Ethyl valerate [F, FDA]	539-82-2	—	x	—	—	—	—	—	—	—
153	Ethylvanillin [F, G]	121-32-4	—	—	—	—	x	—	—	—	—
154	2-Ethyl-3-methoxypyrazine[F]	25680-58-4	—	x	—	—	—	—	—	—	—
157	2-Methyl-3-methoxypyrazine[F]	2847-30-5	—	x	—	—	—	—	—	—	—
160	2-Ethyl-1-hexanol[F]	104-76-7	—	x	—	—	—	—	—	—	—
161	3-Ethyl-2-hydroxy-2-cyclopenten-1-one[F]	21835-01-8	—	x	—	—	—	—	—	—	—
162	2-Ethyl-3,5-dimethylpyrazine[F]	13925-07-0	—	x	—	—	—	—	—	x	—
163	2-Ethyl-3,6-dimethylpyrazine[F]	13360-65-1	—	x	—	—	—	—	—	—	—
164	5-Ethyl-3-hydroxy-4-methyl-2(5*H*)-furanone [F]	698-10-2	—	x	—	—	—	—	—	—	—
165	2-Ethyl-3-methylpyrazine[F]	15707-23-0	—	x	—	—	—	—	—	x	—
	2-Ethyl-5-methylpyrazine	13360-64-0	—	x	—	—	—	—	—	x	—
	2-Ethyl-6-methylpyrazine[F]	13925-03-6	—	x	—	—	—	—	—	x	x
167	4-Ethylguaiacol [F, FDA]	2785-89-9	—	x	—	—	—	—	—	—	—
168	*p*-Ethylphenol [F]	123-07-9	—	x	—	—	—	—	x	x	x
169	3-Ethylpyridine [F]	536-78-7	—	x	—	—	—	—	—	—	—
170	Eucalyptol [F, FDA]	470-82-6	x {30}	—	—	—	—	—	—	—	—
175	Geraniol [F, G]	106-24-1	x	—	x	—	—	x	—	x	x
176	Geranyl acetate [F, G]	105-87-3	—	—	—	x	—	x	—	x	—
181	*l*-Glutamic acid [F, G]	6899-05-4	—	x	—	—	—	—	—	x	—
185	Guaiacol [F, FDA]	90-05-1	—	x	—	—	x	—	—	x	x
187	γ-Heptalactone [F, FDA]	105-21-5	—	—	—	—	—	—	—	—	x
188	Heptanoic acid [F, FDA]	111-14-8	—	x	—	—	—	—	—	x	x
189	2-Heptanone[F]	110-43-0	—	x	—	—	—	—	—	x	—
193	2-Heptenal[F]	2463-63-0	—	x	—	—	—	—	—	—	—
196	γ-Hexalactone [F, FDA]	695-06-7	—	x	—	—	—	—	—	x	x
197	Hexanal [F, FDA]	66-25-1	—	x	—	—	—	—	—	x	—
198	Hexanoic acid [F, FDA]	142-62-1	—	x	—	—	—	—	—	x	x
200	3-Hexen-1-ol [F, FDA]	544-12-7	—	x	—	—	—	—	—	—	—
202	2-Hexenal [F, FDA]	6728-26-3	—	x	—	—	—	—	—	—	x

Table 3 (*cont.*)

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206	Hexyl 2-methylbutyrate [F, FDA]	10032-15-2	—	x	—	—	—	—	—	—	—
208	Hexyl alcohol [F, FDA]	111-27-3	—	x	—	—	—	—	—	x	—
210	*l*-Histidine [F]	71-00-1	—	x	—	—	—	—	—	x	—
215	2-Hydroxy-4-methylbenzaldehyde [F]	698-27-1	—	...	—	—	—	—	—	—	x
216	4-Hydroxybutanoic acid lactone [F]	96-48-0	—	x	—	—	—	—	—	x	—
223	Isoamyl acetate [F, FDA]	123-92-2	—	x	—	—	—	—	—	x	—
224	Isoamyl benzoate [F, FDA]	94-46-2	—	...	—	—	—	—	—	x	—
233	Isobutyl acetate [F, FDA]	110-19-0	—	x	—	—	—	—	—	—	—
234	Isobutyl alcohol [F, FDA]	78-83-1	—	x	—	—	—	—	—	x	—
240	Isobutyraldehyde [F, FDA]	78-84-2	—	x	—	—	—	—	—	x	—
241	Isobutyric acid [F, FDA]	79-31-2	—	x	—	—	—	—	—	—	x
242	*dl*-Isoleucine [F]	73-32-5	—	x	—	—	—	—	—	x	x
245	Isovaleric acid [F, FDA]	503-74-2	—	x	—	—	—	—	—	x	—
246	Lactic acid [F, G]	50-21-5	—	x	—	—	—	—	—	x	—
247	Lauric acid [F, G]	143-07-7	—	x	—	—	—	—	—	x	x
249	*l*-Leucine [F, FDA]	7005-03-0	—	x	—	—	—	—	—	x	—
250	Levulinic acid [F, FDA]	123-76-2	—	x	—	—	—	—	—	—	—
251	Linalool [F, G]	78-70-6	x	x	x {75}	x	—	x	—	x	x
252	Linalool oxide [F, FDA]	5989-33-3	—	—	—	—	—	—	—	x	x
253	Linalyl acetate [F, G]	115-95-7	x	x	—	x	—	—	—	x	—
254	*l*-Lysine [FDA]	56-87-1	—	—	—	—	—	—	—	x	—
255	Malic acid [F, G]	6915-15-7	—	x	—	—	x	—	—	—	x
256	Maltol [F, FDA]	118-71-8	—	—	—	—	—	—	—	x	x
259	Menthol [F, FDA]	89-78-1	—	—	—	—	—	—	—	x	—
	Menthol (synthetic)	2216-51-5									
260	Menthone [F, FDA]	89-80-5	—	—	—	—	—	—	—	x	—
262	*dl*-Methionine [F, FDA]	63-68-3	—	x	—	—	—	—	—	x	—
264	2-Methoxy-4-methylphenol [F, FDA]	93-51-6	—	x	—	—	—	—	—	—	—
265	2-Methoxy-4-vinylphenol [F, FDA]	7786-61-0	—	x	—	—	—	—	—	—	—
266	*p*-Methoxybenzaldehyde [F, FDA]	123-11-5	—	x	—	—	—	—	—	—	—
271	Methyl 2-furoate [F]	611-13-2	—	x	—	—	—	—	—	—	—
273	Methyl 2-pyrrolyl ketone [F]	1072-83-9	—	x	—	—	—	—	—	—	—
275	Methyl anthranilate [F, G]	134-20-3	—	x	—	—	—	—	—	—	—
276	Methyl benzoate [F, FDA]	93-58-3	—	x	—	—	—	—	—	—	—
277	Methyl cinnamate [F, FDA]	103-26-4	—	—	—	x	—	—	x	—	—
283	Methyl nicotinate [F]	93-60-7	—	x	—	—	—	—	—	—	—
284	Methyl phenylacetate [F, FDA]	101-41-7	—	x	—	—	—	—	—	—	—
285	Methyl salicylate [F, FDA]	119-36-8	—	x	—	—	—	—	—	—	x

Table 3 (*cont.*)

No. in Tab. 1	Ingredient	CAS RN	Flavor ingredient							Casing material ingredient	
			Cardamom (318) [25] 8000-66-6	Coffee (322) [46] 84650-00-0	Coriander (325) [49] 8008-52-4	Davana (326) [55] 8016-03-3	Maple syrup (338) [90] 8029-81-0	Nutmeg (339) [98] 8008-45-5	Styrax (340) [132] 8024-01-9	Cocoa (319, 320) [44] 84649-99-0	Licorice (335, 337) [82] 68916-91-6
290	5-Methyl-2-thiophenecarboxaldehyde [F]	13679-70-4	—	x	—	—	—	—	—	—	—
295	4-Methyl-3-penten-2-one [F]	141-79-7	—	x	—	—	—	—	—	—	—
297	6-Methyl-5-hepten-2-one [F]	110-93-0	—	x	—	—	—	—	—	—	—
301	Methyl-2-butenoic acid [F]	13201-46-2	—	x	—	—	—	—	—	—	—
302	4-Methylacetophenone [F, FDA]	122-00-9	—	—	—	—	—	—	—	x	—
305	α-Methylbenzyl alcohol [F]	98-85-1	—	—	—	—	—	—	x	—	—
306	2-Methylbutyraldehyde [F, FDA]	96-17-3	—	x	—	—	—	—	—	x	—
307	3-Methylbutyraldehyde [F, FDA]	590-86-3	—	x	—	—	—	—	—	x	—
308	2-Methylbutyric acid [F, FDA]	116-53-0	—	x	—	—	—	—	—	x	—
310	Methylcyclopentenolone [F, FDA]	80-71-7	—	x	—	—	x	—	—	—	—
313	3-Methylpentanoic acid [F]	105-43-1	—	x	—	—	—	—	—	—	—
314	4-Methylpentanoic acid [F]	646-07-1	—	x	—	—	—	—	—	x	—
315	2-Methylpyrazine [F]	109-08-0	—	x	—	—	—	—	—	x	—
316	5-Methylquinoxaline [F]	13708-12-8	—	x	—	—	—	—	—	—	—
317	2-Methyltetrahydrofuran-3-one [F]	3188-00-9	—	—	—	—	—	—	—	x	—
321	2-Methylvaleric acid [F, FDA]	97-61-0	—	x	—	—	—	—	—	—	—
323	Myristic acid [F, FDA]	544-63-8	—	x	—	—	—	—	—	x	—
326	Nerolidol [F, FDA]	7212-44-4	x	—	—	—	—	—	—	—	—
327	2,6-Nonadienal [F]	557-48-2	—	x	—	—	—	—	—	—	—
329	γ-Nonalactone [F, FDA]	104-61-0	—	x	—	—	—	—	—	x	x
330	Nonanal [F, FDA]	124-19-6	—	x	—	—	—	—	—	x	—
331	Nonanoic acid [F, FDA]	112-05-0	—	x	—	—	x	—	—	x	x
332	2-Nonanone [F, FDA]	821-55-6	—	x	—	—	—	—	—	x	—
334	2-Nonenal [F]	2463-53-8 18829-56-6	—	x	—	—	—	—	—	—	—
339	γ-Octalactone [F, FDA]	104-50-7	—	—	—	—	—	—	—	—	x
340	Octanal [F, FDA]	124-13-0	—	x	—	—	—	—	—	x	—
341	Octanoic acid [F, G]	124-07-2	—	x	—	—	x	—	—	x	x
342	1-Octanol [F, FDA]	111-87-5	—	x	—	—	—	—	—	x	—
343	2-Octanone [F, FDA]	111-13-7	—	x	—	—	—	—	—	x	—
345	1-Octen-3-ol [F, FDA]	391-86-4	—	—	—	—	—	—	—	x	x
349	Oleic acid [F, FDA]	26764-26-1	—	x	—	—	—	—	—	—	x
350	Palmitic acid [F]	57-10-3	—	x	—	—	x	—	—	x	x
352	2,3-Pentanedione [F, FDA]	600-14-6	—	x	—	—	—	—	—	—	—
353	2-Pentanone [F, FDA]	107-87-9	—	x	—	—	—	—	—	x	—
356	α-Phellandrene	99-83-2	—	—	—	—	—	x	—	—	—
357	2-Phenethyl acetate [F, FDA]	103-45-7	—	—	—	—	—	—	—	—	x
358	Phenethyl alcohol [F, FDA]	60-12-8	—	x	—	—	—	—	—	x	x

Table 3 (*cont.*)

No. in Tab. 1	Ingredient	CAS RN	Flavor ingredient							Casing material ingredient	
			Cardamom (318) [25] 8000-66-6	Coffee (322) [46] 84650-00-0	Coriander (325) [49] 8008-52-4	Davana (326) [55] 8016-03-3	Maple syrup (338) [90] 8029-81-0	Nutmeg (339) [98] 8008-45-5	Styrax (340) [132] 8024-01-9	Cocoa (319, 320) [44] 84649-99-0	Licorice (335, 337) [82] 68916-91-6
366	3-Phenyl-1-propanol [F, FDA]	122-97-4	—	—	—	—	—	—	x {8}	—	—
367	2-Phenyl-2-butenal [F]	4411-89-6	—	x	—	—	—	—	—	—	—
370	Phenylacetaldehyde [F, FDA]	122-78-1	—	x	—	—	—	—	—	x	x
371	Phenylacetic acid [F, FDA]	103-82-2	—	x	—	—	—	—	—	x	—
372	*l*-Phenylalanine [F, FDA]	63-91-2	—	x	—	—	—	—	—	x	—
373	3-Phenylpropionaldehyde [F, FDA]	104-53-0	—	—	—	—	—	—	x	—	x
374	3-Phenylpropionic acid [F, FDA]	501-52-0	—	—	—	—	—	—	x	—	x
376	3-Phenylpropyl cinnamate [F, FDA]		—	—	—	—	—	—	x	—	—
379	α-Pinene [F, FDA]	80-56-8	x	—	x	—	—	x {22}	x {10}	—	—
380	β-Pinene [F, FDA]	127-91-3	—	—	—	—	—	x	x	x	—
384	*l*-Proline [F, FDA]	147-85-3	—	x	—	—	—	—	—	x	x
386	Propionic acid [F, G]	79-09-4	—	x	—	—	—	—	—	—	x
391	Pyridine [F, FDA]	110-86-1	—	x	—	—	—	—	—	—	—
393	Pyrrole [F]	109-97-7	—	x	—	—	—	—	—	—	x
394	Pyruvic acid [F, FDA]	127-17-3	—	x	—	—	—	—	—	—	—
396	Salicylaldehyde [F, FDA]	90-02-8	—	x	—	—	—	—	—	—	—
409	Sugars [F, G]									—	x
	glucose	50-99-7	—	x	—	—	—	—	—		
	fructose	57-48-7	—	—	—	—	—	—	—	—	x
	galactose	59-23-4	—	x	—	—	—	—	—	—	—
	mannose	3458-28-4	—	x	—	—	—	—	—	—	x
	sucrose	57-50-1	—	x	—	—	—	—	—	—	x
410	Tannic acid [F, G]	1401-55-4	—	x	—	—	—	—	—	—	—
411	*d*-Tartaric acid [F, G]	147-71-7	—	x	—	—	—	—	—	—	—
412	α-Terpineol [F, FDA]	98-55-5	x {8}	x	x	—	—	x	x	x	x
413	Terpinolene [F, FDA]	586-62-9	x	—	—	—	—	x	...	—	x
414	α-Terpinyl acetate [F, FDA]	80-26-2	x {25}	—	—	—	—	—	—	x	—
415	5,6,7,8-Tetrahydroquinoxaline [F]	34413-35-9	—	x	—	—	—	—	—	—	—
419	2,3,5,6-Tetramethylpyrazine [F]	1124-11-4	—	—	—	—	—	—	—	x	x
421	Thiazole [F]	288-47-1	—	x	—	—	—	—	—	—	—
422	*l*-Threonine [FDA]	72-19-5	—	x	—	—	—	—	—	x	x
423	Thymol [F, FDA]	89-83-8	—	—	—	—	—	—	—	—	x
424	Tocopherol [G]	59-02-9	—	x	—	—	—	—	—	—	—
425	*o*-Tolualdehyde [F, FDA]	529-20-4	—	x	—	—	—	—	—	—	—
426	*m*-Tolualdehyde [F, FDA]	620-23-5	—	x	—	—	—	—	—	—	—

Table 3 (*cont.*)

No. in Tab. 1	Ingredient	CAS RN	Flavor ingredient							Casing material ingredient	
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427	*p*-Tolualdehyde [F, FDA]	104-87-0	—	x	—	—	—	—	—	—	—
434	2-Tridecanone [F]	593-08-8	—	x	—	—	—	—	—	—	—
440	2,6,6-Trimethylcyclohex-2-ene-1,4-dione [F]	1125-21-9	—	x	—	—	—	—	—	—	—
444	2,3,5-Trimethylpyrazine [F]	14667-55-1	—	—	—	—	—	—	—	x	x
445	*l*-Tyrosine [F, FDA]	60-18-4	—	x	—	—	—	—	—	x	—
449	2-Undecanone [F, FDA]	112-12-9	—	x	—	—	—	—	—	—	—
453	Valeraldehyde [F, FDA]	110-62-3	—	x	—	—	—	—	—	x	—
454	Valeric acid [F, FDA]	109-52-4	—	x	—	—	—	—	—	x	—
455	γ-Valerolactone [F]	108-29-2	—	x	—	—	—	—	—	x	—
456	Valine [F, FDA]	7004-03-7	—	x	—	—	—	—	—	x	x
457	Vanillin [F, G]	121-33-5	—	x	—	—	x	—	—	—	—
458	Veratraldehyde [F, FDA]	120-14-9	—	x	—	—	—	—	—	—	—

Table 4. Composition of several naturally-occurring ingredients added to cigarettes

Internet address	Insert for xxx	Number in Table 2
www.iisr.org/spices/xxx.htm	Allspice	2
	Anise	7
	Basil	12
	Bayleaf	13
	Caraway	24
	Cassia	29
	Celery	35
	Cinnamon	39
	Fennel	57
	Fenugreek	58
	Ginger	65
	Rosemary	123
	Sage	127
	Thyme	135
	Vanilla	138
www.springboard4health.com/notebook/herbs_xxx.html	Thyme	135
	Valerian	137
	Insert for index	**Number in Table 2**
www.essentialoils.co.za/index.htm	Angelica	6
	Bergamot	17
	Chamomile	36
	Geranium	64
	Myrrh	96
	Neroli	97
	Oregano	105
	Patchouli	109
	Sage	127

LYNM (265) on the fate of radiolabeled phenethyl alcohol and by GREEN *et al*. (267) on the fate of radiolabeled phenylacetic acid. The reason for the omission of the references noted cannot be because they were only presentations at various Tobacco Chemists' Research Conferences and/or CORESTA Meetings/Congresses: In over a dozen instances, PASCHKE *et al*. did not cite published articles but cited the presentations at scientific functions such as those mentioned.

Subsequent to the development in the early 1970s of the Ames test with *Salmonella typhimurium*, the 1977 mutagenicity study (24) represents one of the earliest studies that demonstrated that ingredients added to tobacco – whether flavorants, humectants, or casing materials – do not significantly contribute adversely to the biological activity, namely its mutagenicity, of the resulting MSS. In fact, because of their level in the MSS particulate matter (25) and their lack of mutagenicity in the Ames test system, omission of the humectants (glycerol, propylene glycol) results in increases in the mutagenicity.

With technologies much improved over those used in 1977, more recent studies by ROEMER *et al*. (29) and MASSEY *et al*. (32) of the effect of ingredient addition to a tobacco blend on mutagenicity and/or genotoxicity have essentially confirmed the earlier findings. Additional support for these findings was provided by the demonstration that the effect produced by the MSS from ingredient-treated cigarette tobacco was not significantly different from that produced by control cigarette in classical skin painting or inhalation studies.

Since the 1977 study, the use of a few individual components in "top dressing" flavorant formulations has been discontinued because of reported possible concerns about their biological properties. Examples include the tobacco components eugenol, isoeugenol, and coumarin. Thus, these and other discontinued ingredients do not appear in the DOULL *et al*. list.

6 CONCLUSIONS

As noted by several investigators (5,6,8,9,10), a great number of the compounds added as ingredients to the cigarette tobacco blend are identical with or similar to components of tobacco and/or tobacco smoke. The validity of this statement is obvious from the catalog of compounds in the DOULL *et al*. list depicted in Table 1 and the summary presented in Table 5. Those tobacco ingredients that are not individual compounds but are naturally occurring oils, resins, etc. or extracts of naturally occurring materials not only contain many of the compounds on the DOULL *et al*. list but also contain many of the same compounds present in tobacco (see Table 3).

Detailed examination of the scientific literature (5,22) on the chemical and biological properties of the recently used tobacco ingredients listed by DOULL *et al*. plus a massive amount of chemical and biological data generated during the past several decades indicates that not only does none of the DOULL *et al.* listed ingredients contribute any significant adverse chemical properties to cigarette MSS but also

Table 5. Summary of studies reported in Tables 1 and 2

Of the 460 compounds and 146 mixtures listed in Tables 1 and 2, respectively	Number (%) in Table 1	Number (%) in Table 2
The number identified in untreated tobacco	245 (53.3)	NA
The number identified in MSS from cigarettes containing untreated tobaccos	212 (46.1)	NA
The number identified in both untreated tobacco and its smoke	168 (36.5)	NA
The number studied that did not contribute significant levels of toxicants to the MSS from ingredient-treated tobacco or to a pyrolysate from the individual ingredient	335 (72.8)	117 (80.1)
The number studied either individually and/or as added ingredients that did not enhance the specific tumorigenicity of MSS CSC as measured in the mouse skin-painting bioassay	104 (22.6)	39 (26.7)
The number studied either individually and/or as added ingredients that did not enhance the specific tumorigenicity of MSS as measured in a smoke inhalation bioassay	259 (56.3)	112 (76.7)
The number studied either individually and/or as added ingredients that did not enhance the mutagenicity and/or genotoxicity of MSS or did not exhibit mutagenicity or genotoxicity in themselves	343 (74.6)	112 (76.7)

none affects adversely the biological properties of the MSS. Table 5 summarizes the information on the number of individual compounds and mixtures studied in various ways and their percentages relative to the number of individual compounds and mixtures in the DOULL *et al.* list.

Among the chemical factors considered were:

- The effect on MSS composition of the ingredients added to cigarette tobacco at the usual use level or several times that (9,22,23,31,37,38).
- The nature of the pyrolysis products generated during the smoking process or during pyrolysis of an individual ingredient under conditions approximating the cigarette smoking process (40). In many instances when the added ingredient is a compound, a significant percentage of it is transferred unchanged to the MSS and SSS. The small percentage not transferred intact is seldom converted to an MSS component with significant toxic properties.

The biological studies that showed no significant adverse effect included:

- The specific tumorigenicity to laboratory animal skin of the mainstream CSC from ingredient-containing cigarettes vs. the mainstream CSC from ingredient-free cigarettes (8,27,35).
- Exposure of laboratory animals via inhalation to the MSS from ingredient-containing cigarettes vs. the MSS from ingredient free cigarettes (6,26,30,33,34).
- Determination in a variety of tests of the *in vitro* genotoxicity of the MSS particulate phase and/or vapor phase (9,23,24,29,32,33).

In addition, the results of non-tobacco-related studies are available in which many individual compounds on the DOULL *et al*. list were assayed for mutagenicity in the Ames test with several strains of *Salmonella typhimurium*. An excellent example is the 1984 study by ISHIDATE *et al*. (39) who examined the mutagenicity of many compounds included as additives in Japanese foods. Over 40 of the compounds exhibiting non-mutagenicity also occur on the DOULL *et al*. tobacco ingredient list.

Assessment of all the chemical and biological data cited herein provides a noteworthy contradiction to the much repeated assertions – with no data to support them - that the ingredients added to cigarette tobacco might result in significant adverse changes in the chemical and/or the biological properties of the cigarette MSS.

Those making the assertions about tobacco ingredients both before and after the advent of the low-"tar" cigarette have not replied over the past few years in any way to the wealth of data generated on tobacco ingredients. On occasion, the DOULL *et al*. list has been mentioned in articles by American Health Foundation personnel, e.g., see various articles by the HOFFMANNs issued between 1995 and 2001 (341, 342,343,344).

One might ask whether the assertions about the possible adverse effects of added tobacco ingredients on the chemical and biological properties of cigarette MSS fall into the same category as the numerous other assertions (41) made about MSS composition, the precursors of its components, etc. which have no or little evidence to support them. The assertions about individual tobacco ingredients such as licorice, cocoa, vanillin, glycerol, sugars, and flavor ingredients in general have been contradicted by an overwhelming catalog of data generated under the most arduous conditions.

Table 6 summarizes many of the recent large-scale laboratory studies involving literally hundreds of the tobacco ingredients but does not include many significant studies summarized elsewhere (9,23). Despite the publication of the DOULL *et al*. report in 1994, HOFFMANN *et al.* (341) wrote:

> Little is known about the fate of such additives during the smoking of cigarettes.

This statement was re-iterated in 1997 by HOFFMANN and HOFFMANN (342). The conclusions reached by DOULL *et al*. were never specifically mentioned in their 1995 and 1997 publications. In the latter publication, HOFFMANN and HOFFMANN did however note that the IARC had reversed its classification of coumarin as a carcinogen. Its original classification was primarily based on the studies in the early 1970s by GRIEPENTROG and his colleague (345). This reversal by the IARC is not surprising since the biological findings at the two high dose levels used by GRIEPENTROG in a feeding experiment were not confirmed in a similar FDA study conducted by HAGAN *et al*. (346). Also, numerous studies have shown that coumarin is not mutagenic in the Ames *Salmonella typhimurium* test (347).

Table 6. A summary of recent tobacco ingredient studies

Analysis	Date	No. of ingredients studied	Reported findings/conclusions	Reference
Detailed literature survey of ingredients added to US tobacco products	1994	599	". . . it was concluded that there was no evidence that any ingredient added to cigarette tobacco produces harmful effects under the conditions of use in cigarettes."	Doull *et al.* (5)
Effect of added tobacco ingredients on cigarette MSS chemistry	2002	333	"The smoke chemistry data revealed changes towards both higher and lower amounts of various smoke constituents . . . This suggests that the addition of 333 commonly used ingredients to cigarettes in three groups did not add to the toxicity of the smoke, even at the exaggerated levels tested . . .	Carmines (28); Rustemeier *et al.* (8)
			"An overall assessment of our data suggests that these ingredients, when added to the tobacco, do not add to the toxicity of smoke, even at the elevated levels used in this series of studies."	
	2002	482	"In most cases, the flavour mixtures had no statistically significant effect on the smoke yields relative to the control cigarette. In a few cases, the small increases or decreases were observed for some analytes relative to the control cigarette. The smoke yields of the experimental cigarettes were well within the ranges observed in the three reference cigarettes."	Baker and Smith (31)
	2003	482	"The significances of differences between the test and control cigarettes were determined using both the variability of the data on the specific occasion of the measurement, and also taking into account the long-term variability of the analytical measurements over the one-year period in which analyses were determined in the present study. This long-term variability was determined by measuring the levels of the 44 "Hoffmann analytes" in a reference cigarette on many occasions over the one-year period of this study.	Baker *et al*. (37)
			". . . It was found that, in most cases, the mixtures of flavouring ingredients (generally added in parts per million levels) had no statistically significant effect on the analyte smoke yields relative to the control cigarette."	
Effect of added tobacco ingredients on cigarette MSS biology	1997, 2002	≈152	"Although the mutagenic activities appeared to be similar, there were statistically significant differences in mutagenic activities among the sample."	Bioresearch [for RJRT] (24); Rodgman (9, 23)
			[The differences were primarily due to the increase in mutagenicity of the CSC when the humectants (glycerol, propylene glycol) were not added to the cigarette tobacco and thus were not present as diluents in the CSC].	
a) *in vitro* genotoxicity and cytotoxicity	2002	333	"Within the sensitivity and specificity of the test systems, the in vitro mutagenicity and cytotoxicity of the cigarette smoke were not increased by the addition of the ingredients."	Carmines (28); Roemer *et al.* (29)
	2002	482	"The data has been analyzed and demonstrates no additional activity from the flavoured cigarettes above that of the control products."	Massey *et al*. (32)
b) MSS smoke inhalation	1997, 2002	2 (glycerol, propylene glycol)	"It was concluded that addition of the tested humectants singly or in combination had no meaningful effect on the site, extent or frequency of respiratory tract changes associated with smoke exposure in rats."	Gaworski *et al.* (26)
	1997	1 (menthol)	"The results of this 13-week inhalation study indicated that the addition of 5000 ppm menthol to tobacco had no substantial effect on the character or extent of the biological responses normally associated with inhalation of mainstream cigarette smoke in rats."	Gaworski *et al.* (34)

Table 6 (*cont.*)

Analysis	Date	No. of ingredients studied	Reported findings/conclusions	Reference
b) MSS smoke inhalation (*cont.*)	1998	170	"The results indicate that the addition of flavoring ingredients to cigarette tobacco had no discernible effect on the character or extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats."	Gaworski *et al.* (6)
	2002	333	"The data indicate that the addition of these 333 commonly used ingredients, added to cigarette in three groups, did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used."	Carmines (28); Vanscheeuwijck *et al*. (30)
c) MS CSC and skin painting	1999	150	"While tumor incidence, latency and multiplicity data occasionally differed between test and comparative reference CSC groups, all effects appeared to be within normal variation for the model system. Furthermore, none of the changes appeared to be substantial enough to conclude that the tumor promotion capacity of CSC obtained from cigarettes containing cigarettes with ingredients was discernibly different from the CSC obtained from reference cigarettes containing tobacco processed without ingredients."	Gaworski *et al.* (35)
Pyrolysis of tobacco ingredients under conditions simulating those in the cigarette burning zone	2003	291	"The results are compatible with parallel studies in which the ingredients are added to tobacco and the effect on cigarette smoke constituents are measured. In general, the number of "Hoffmann analytes" detected among the pyrolysis products of the ingredients, and their levels, are low . . . Of the 291 tobacco ingredients pyrolysed, almost a third transfer out of the pyrolysis zone intact, and almost two thirds transfer at least 95% intact."	Baker and Bishop (40)

Citing the 1989 study by GREEN *et al*. (89) at British American Tobacco on the fate during pyrolysis of anisaldehyde (no. 266; 123-11-5), anisole (100-66-3), benzaldehyde (no. 35; 100-52-7), methyl cinnamate (no. 277; 103-26-4), isoamyl isovalerate (no. 229; 659-70-1), and vanillin (no. 457; 121-33-5), HOFFMANN and HOFFMANN (343) reported that *the latter two* did not appear on the list of 599 additives in use in 1994 by one or more of the six major American cigarette companies [DOULL *et al*. (5)]! Obviously, the authors misread the DOULL *et al*. report: From the numerical sequence in Table 1, one can see that anisaldehyde (no. 266; CAS RN 123-11-5), benzaldehyde (no. 35; CAS RN 100-52-7), methyl cinnamate (no. 277; CAS RN 103-26-4), isoamyl isovalerate (no. 229; CAS RN 659-70-1), and vanillin (no. 457; CAS RN 121-33-5) are listed by DOULL *et al*. Only anisole (methoxybenzene) (CAS RN 100-66-3) is not listed as a tobacco ingredient by DOULL *et al*! However, anisole was identified in tobacco smoke in 1958 by CARRUTHERS *et al*. (348) and in 1965 by GROB (18).

In 2001, HOFFMANN *et al*. (343) cited the DOULL *et al*. ingredients report and the 1998 report by GAWORSKI *et al*. (6) on inhalation of MSS from cigarettes containing ingredient-treated tobacco. They criticized the duration of exposure (13 weeks) in the study with the implication that a longer exposure time might have resulted in tumor development. They neglected to note the infrequency of induction of lung carcinomas in numerous studies from 1936 to date in which large numbers of laboratory rodents were exposed for their lifetime via inhalation to cigarette MSS with no induction of squamous cell carcinoma (cf. 349,350). Despite the fact that laboratory research personnel, previously at the Sloan Kettering Institute but currently at the American Health Foundation, had published a great number of articles over a four-decade span on mouse skin-painting studies with CSC and the generation of skin carcinoma [e.g., see pp. 268–295 in (49)], they failed to mention the skin painting studies reported in 1999 (27,35) in which laboratory animals skin-painted with CSC from cigarettes containing ingredient-treated tobacco were compared to laboratory animals skin-painted with the CSC from cigarettes containing control non-ingredient-treated tobacco. Their critical remarks on the inhalation study and their omission of any mention of the results in the skin-painting comparison were repeated in a second 2001 report (344).

7 INGREDIENTS USED OUTSIDE OF THE USA

The original aim of this study was to catalog the ingredients in the 1994 DOULL *et al*. list (5) with regard to a) their presence or absence in untreated tobacco and b) their effect when added to a cigarette on the chemical and biological properties of its MSS. The DOULL *et al*. list of 599 ingredients comprises the ingredients used by one or more US cigarette manufacturers on products. Because cigarette manufacturers outside of the US use not only many of the ingredients on the DOULL *et al*. list but also other flavorful and aromatic ingredients, it became apparent that additional information could accompany the assessment of the ingredients listed by DOULL *et al*. In Tables 7A and 7B are listed another 80 ingredients used by cigarette manufacturers in countries other than the US.

Table 7A. Compounds used as tobacco ingredients in products outside of the US: Studies of (a) their pyrolysis products, (b) their effect on the chemical and biological properties of cigarette MSS, and (c) their identification in untreated tobacco and/or its MSS

	Ingredient				Bioassay		Tobacco and/or Smoke	
No.	As listed by the investigators	CAS RN	Chemical Abstracts Nomenclature	Chemistry	Tumorigenicity: Inhalation	Mutagenicity/ Genotoxicity	Tobacco	Smoke
1A	Ambroxide	3738-00-9	13,14,15,16-tetranorlabdane, 8α-12-oxido-	31, 36, 37, 40 [P]	—	32, 33	—	—
2A	Ammonium glycyrrhizinate [a]	53956-04-0		31, 36, 37,	33	32, 33	—	—
3A	Amyl hexanoate	540-07-8	hexanoic acid, *n*-amyl ester	31, 36, 37, 40 [P]	—	32, 33	—	—
4A	Anisole	100-66-3	benzene, methoxy-	40 [P]	—	—	—	18, 42, 44, 107, 348
5A	Anisyl propionate	7549-33-9	propanoic acid, anisyl ester	31, 36, 37, 40 [P]	—	32, 33	—	—
6A	Benzyl formate	104-57-4	formic acid, phenylmethyl ester	31, 36, 37, 40 [P]	—	32, 33	7, 42	—
7A	Benzyl isobutyrate	103-28-6	propanoic acid, 2-methyl-, phenylmethyl ester	31, 36, 37, 40 [P]	—	32, 33	42	—
8A	Benzyl isovalerate	103-38-8	butanoic acid, 3-methyl-, phenylmethyl ester	31, 36, 37, 40 [P]	—	32, 33	7, 42	—
9A	Bornyl isovalerate	76-50-6	isovaleric acid, 2-bornyl ester	8, 28	28, 30	28, 29	42	—
10A	Butyl valerate	591-68-4	pentanoic acid, *n*-butyl ester	31, 36, 37	—	32, 33	—	—
11A	*d*-Carvone	2244-16-8	*d*-2-cyclohexen-1-one, 2-methyl-5-(1-methylethyl)-	37, 40 [P]	33	32, 33	—	—
12A	Cinnamyl isobutyrate	103-59-3	propanoic acid, 2-methyl-, 3-phenyl-2-propen-1-yl ester	31, 36, 37, 40 [P]	—	32, 33	—	—
13A	Citronellal	106-23-0	6-octenal, 3,7-dimethyl-	31, 36, 37, 40 [P]	—	32, 33	—	42, 45, 80
14A	Citronellyl acetate	150-84-5	acetic acid, 3,7-dimethyl-6-octen-1-yl ester	31, 36, 37, 40 [P]	—	32, 33	—	—
15A	Cyclamen aldehyde	103-95-7	propanaldehyde, α-methyl-*p*-isopropylphenyl-	31, 36, 37, 40 [P]	33	32, 33	—	—
16A	Dextrin	9004-53-9		31, 36, 37	33	32, 33	42, 44	—
17A	3-Ethyl-4-hydroxy-5-methyl-3(2*H*)-furanone	27538-09-6	3(2*H*)-furanone, 3-ethyl-4-hydroxy-5-methyl-	31, 36, 37, 40 [P]	—	32, 33	—	—
18A	Ethyl isobutyrate	97-62-1	propanoic acid, 2-methyl-, ethyl ester	31, 36, 37, 40 [P]	—	32, 33	—	—
19A	Hexen-2-al	505-57-7	2-hexenal	31, 36, 37	—	32, 33	42	42
20A	2-Hexenol	2305-21-7	2-hexenol	31, 36, 37	—	32, 33	—	—
21A	2-Hexenyl acetate	2497-18-9	acetic acid, 2-hexen-1-yl ester; 2-hexen-1-ol, acetate	31, 36, 37, 40 [P]	—	32, 33	42	—
22A	Ionone	14901-07-6	3-buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	8, 28	28, 30	28, 29	7, 20, 42	42, 146
23A	Isoamyl propionate	105-68-0		31, 36, 37, 40 [P]	33	32, 33	—	—
24A	Isoamyl salicylate	87-20-7		31, 36, 37, 40 [P]	—	32, 33	42	—
25A	Isobutyl butyrate	5398-90-2		31, 36, 37, 40 [P]	33	32, 33	—	—
26A	*dl*-Isomenthone	491-07-6		31, 36, 37, 40 [P]	—	32, 33	—	—
27A	Isopropyl myristate	110-27-0	tetradecanoic acid, 1-methylethyl ester	31, 36, 37, 40 [P]	—	32, 33	—	—
28A	Linalyl benzoate	126-64-7		31, 36, 37, 40 [P]	33	32, 33	—	—
29A	Linalyl isobutyrate	78-35-3		31, 36, 37, 40 [P]	33	32, 33	—	—
30A	Methional	3268-49-3	propanal, 3-(methylthio)-	31, 36, 37, 40 [P]	33	32, 33	—	42, 279
31A	5*H*-5-Methyl-6,7-dihydrocyclopenta-[*b*]-pyrazine	237747-48-0		31, 36, 37, 40 [P]	—	32, 33	—	—

Table 7A (*cont.*)

No.	Ingredient: As listed by the investigators	Ingredient: CAS RN	Ingredient: Chemical Abstracts Nomenclature	Chemistry	Bioassay: Tumorigenicity: Inhalation	Bioassay: Mutagenicity/ Genotoxicity	Tobacco and/or Smoke: Tobacco	Tobacco and/or Smoke: Smoke
32A	Menthyl isovalerate	16409-46-4		31, 36, 37, 40 [P]	—	32, 33	—	—
33A	Methyl anthranilate	134-20-3	benzoic acid, 2-amino-, methyl ester	8, 28	28, 30	28, 29	42	—
34A	1-Methyl-2,3-cyclohexadione	3008-43-3	2,3-cyclohexanedione, 1-methyl-	31, 36, 37, 40 [P]	—	32, 33	—	—
35A	Methylcyclopentenolone	765-70-8	1,2-cyclopentanedione, 3-methyl- {cyclotene}	40 [P]	—	—	7, 42	15, 42, 54, 150, 155
36A	6-Methyl-5-hepten-2-one	1335-09-7		31, 36, 37	—	32, 33	—	—
37A	Methyl 2-octynate	111-12-6		31, 36, 37, 40 [P]	—	32, 33	—	—
38A	4-Methyl-5-thiazole ethanol	137-00-8		31, 36, 37, 40 [P]	33	32, 33	—	—
39A	Neryl acetate	141-12-8		31, 36, 37, 40 [P]	33	32, 33	—	—
40A	δ-Nonalactone	3301-94-8	2*H*-pyran-2-one, 6-butyltetrahydro-	37	—	32, 33	—	—
41A	Pectin	9000-69-5		38	33	32, 33	42, 44, 48, 67, 351, 352	—
42A	Pent-4-en-4-olide	591-12-8	2(3*H*)-furanone, 5-methyl- {α-angelica lactone}	31, 36, 37, 40 [P]	33	32, 33	42	—
43A	Potassium citrate	866-84-2		31, 36, 37	33	32, 33	—	—
44A	Rose oxide	16409-43-1	pyran, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)-	31, 36, 37, 40 [P]	—	32, 33	—	—
45A	Sodium ethyl 4-hydroxybenzoate	35285-68-9		31, 36, 37	33	32, 33	—	—
46A	Sodium methyl 4-hydroxybenzoate	5026-62-0		31, 36, 37	33	32, 33	—	—
47A	Sodium propyl 4-hydroxybenzoate	35285-69-9		31, 36, 37	33	32, 33	—	—
48A	Sorbic acid	110-44-1	2,4-hexadienoic acid	31, 36, 37	—	32, 33	42, 110	42, 45, 353
49A	Sorbitol	50-70-4	D-glucitol	40 [P]	33	—	44, 67	—
50A	Tetradecalactone	2721-22-4	2*H*-pyran-2-one, 6-nonyltetrahydro-	31, 36, 37, 40 [P]	—	32, 33	—	—

[a] The Doull *et al.* list does not include this item *per se* but does include glycyrrhizin, ammoniated (see Table 1, item No. 184)

Table 7B. Mixtures used as tobacco ingredients in products outside of the US: Studies of their effect on the chemical and biological properties of cigarette MSS

No.	Ingredients as listed by the investigators	CAS RN	Chemistry	Bioassay	
				Tumorigenicity: Inhalation	Mutagenicity/ Genotoxicity
1B	Allspice oil	8006-77-7	8, 28	28, 30	28, 29
2B	Angelica root extract/tincture	84665-41-7	31, 36, 37	33	32, 33
3B	Banana extract	97281-11-3	31, 36, 37	33	32, 33
4B	Benzoin resinoid Sumatra	84929-79-3	37	—	32, 33
5B	Boronia absolute	91771-36-7	31, 36, 37	—	32, 33
6B	Brandy absolute		37	33	32, 33
7B	Caramel sugar syrup		37	33	32, 33
8B	Carob bean extract (roasted)	84961-45-5	37	—	32, 33
9B	Catechu powder	8001-76-1	31, 36, 37	33	32, 33
10B	Cherry juice	89997-53-5	31, 36, 37	33	32, 33
11B	Clary sage infusion	84775-83-7	31, 36, 37	33	32, 33
12B	Cocoa infusion	84649-99-0	31, 36, 37	33	32, 33
13B	Cumin seed oil	8014-13-9	31, 36, 37	33	32, 33
14B	Fig extract	68916-52-9	31, 36, 37	33	32, 33
15B	Grapefruit oil, terpeneless	90045-43-5	37	33	32, 33
16B	Lemon extract	84929-31-7	37	33	32, 33
17B	Lemon oil, expressed	8020-19-7	31, 36	—	32, 33
18B	Lemon oil terpenes		8, 28	28, 30	28, 29
19B	Lemon oil, terpeneless	68648-39-5	37	33	32, 33
20B	Lime oil, expressed	8008-26-2	37	33	32, 33
21B	Lime oil, terpeneless	68916-84-7	—	28, 30	28, 29
22B	Molasses, sugar cane	68476-78-8	31, 36, 37	33	32, 33
23B	Peppermint oil, terpeneless	68606-97-3	31, 36, 37	33	32, 33
24B	Pineapple extract	97676-27-2	31, 36, 37	33	32, 33
25B	Pineapple juice	97676-27-2	31, 36, 37	33	32, 33
26B	Prune extract	90082-87-4	31, 36, 37	33	32, 33
27B	Raspberry distillate	84929-76-0	31, 36, 37	33	32, 33
28B	Rose oil, red	90106-38-0	31, 36, 37	—	32, 33
29B	Rum dark	91450-09-8	31, 36, 37	33	32, 33
30B	Rum white	90604-31-1	31, 36, 37	33	32, 33
31B	Storax		8, 28	28, 30	28, 29
32B	Tangerine oil	8008-31-9	8, 28, 31, 36, 37	28, 30	28, 29
33B	Verbena oil	85116-63-8	31, 36, 37	33	32, 33
34B	Ylang-ylang oil	8006-81-3	37	—	32, 33

Here again, the compounds and mixtures are essentially cataloged with the formats used in Tables 1 and 2, respectively. Examination of the compounds listed in Table 7A indicates that some, like the compounds listed in Table 1, are components of tobacco and/or its smoke. The effect of many of the ingredients listed in Tables 7A and 7B has been studied in other bioassays but the data are not yet available.

Examination of the data from the various extensive chemical and biological studies on the effect of many of the ingredients listed in Tables 1 and 2 and those listed in Tables 7A and 7B on smoke properties indicates no significant chemical or biological problem with the 684 tobacco ingredients.

8 ACKNOWLEDGMENTS

I am deeply indebted to many colleagues whose research over the years provided me with considerable information to include in this article. Listing their individual names and findings here would result in an unusually lengthy ACKNOWLEDGMENTS. However, the reader may ascertain their names and noteworthy contributions from the many citations to their work included in REFERENCES (see 1, 2, 7, 10, 15, 16, 17, 19, 20, 25, 41, 58, 61, 71, 73, 75, 77, 79, 81, 82, 86, 90, 105, 108, 114, 116, 134, 139, 156, 164, 166, 169, 180, 198, 199, 200, 203, 204, 205, 207, 222, 231, 232, 238, 252, 254, 258, 260, 265, 267, 301, 303, 307, 312, 320, 329, 331, 335, 338, 340). I am extremely grateful to Dr. Charles R. Green, formerly of RJRT R&D, and Dr. Richard R. Baker of BAT R&D for several meaningful suggestions on an early draft of my manuscript. Lastly, I greatly appreciate the capable assistance of Ms. Helen S. Chung, Ms. Patricia C. Comer, and others at RJRT Science Information for their acquisition of numerous pertinent references for me.

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ERRATUM NOTICE

p. 59: item no 120, third column, the CAS RN following "pentyltetrahydro-" shold read "[705-86-2]" instead of "[705-82-6]"