Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 20 · No. 6 · July 2003

DOI: 10.2478/cttr-2013-0758

The Composition of Cigarette Smoke: Problems with Lists of Tumorigens*

by

Alan Rodgman

2828 Birchwood Drive, Winston-Salem, North Carolina, 27103-3410, USA

CONTENTS

SUMMARY

Since the mid-1960s, various investigators, agencies, and institutions have disseminated lists of cigarette mainstream smoke (MSS) components reported to be tumorigenic on the basis of laboratory bioassays conducted under conditions significantly different from those encountered by the smoker during exposure to the components in the cigarette MSS aerosol. Since 1990, numerous lists of cigarette MSS components, defined as significant tumorigens, have been compiled by American Health Foundation personnel, Occupational Safety and Health Administration (OSHA), FOWLES and BATES, and R.J. Reynolds R&D personnel. The purpose of most of the reports was to define human risk assessment and to dissuade smokers from smoking. Various investigators and agencies have frequently cited the earlier and/or the more recent lists of tumorigenic entities. The recent compilations, involving nearly 80 MSS components, suffer from serious deficiencies including: a) Use of per cigarette delivery ranges for specified components which often include analytical data from cigarettes manufactured in the 1950s and 1960s which are not comparable to lower-"tar" yield cigarettes manufactured since the mid-1970s. b) Absence of standard analytical procedures for most of the listed components. c) Methodological considerations regarding bioassays used to determine tumorigenicity of the listed MSS components. d) Difficulty in extrapolating *in vivo* bioassay data obtained by non-inhalation modes of administration of a single compound to the human smoking situation involving inhalation of a complex aerosol containing that compound. e) Inhalation data inadequacies regarding the tumorigenicity of many of the components. f) Several tobacco smoke components are listed despite the fact their presence has not been confirmed, their MSS level has not been defined, or their MSS level is no longer relevant. g) Insufficient consideration of inhibitors of tumorigenesis and mutagenesis found in MSS. h) Difficulty in extrapolation of inhibition/anticarcinogenesis/antimutagenesis observed in a one-on-one *in vivo* situation to the complex MSS aerosol situation. j) Alternate exposures to many of the listed smoke components. k) Discrepancies among the lists. l) Discrepancies within the lists.
A more appropriate use of the listing process is the identification of potential chemical targets for removal from, or inhibition in cigarette MSS. [Beitr. Tabakforsch. Int. 20 (2003) 402–437]

ZUSAMMENFASSUNG

Seit Mitte der sechziger Jahre wurden durch verschiedene Forscher, Ämter und Institutionen Listen über Inhaltsstoffe des Hauptstromrauchs (HSR) von Zigaretten verbreitet, die als Tumor verursachend gelten. Diese Listen beruhen auf Tierversuchen im Labor, bei denen Bedingungen herrschten, die sich signifikant von denen beim menschlichen Rauchen unterscheiden, wo die Exposition über die Inhalation der Substanzen des HSR-Aerosols von Zigaretten erfolgt. Seit 1990 wurden mehrere Listen über Inhaltsstoffe des HSR, die als signifikant Tumor verursachende Substanzen definiert wurden, von Mitarbeitern der American Health Foundation, Occupational Safety and Health Administration (OSHA), FOWLES und BATES und Mitarbeitern von R.J. Reynolds R&D zusammengestellt. Die meisten dieser Berichte wurden zum Zweck der Risikoabschätzung beim Menschen durchgeführt und um Raucher vom Rauchen abzubringen. Viele Forscher und Ämter haben die früheren und/oder neueren Listen über Tumor verursachen-

*Received: 8th November 2001 – accepted: 5th November 2002

de Substanzen häufig zitiert. Die neueren Zusammenstellungen, in denen annähernd 80 Inhaltsstoffe des HSR enthalten sind, weisen eine Reihe ernstzunehmender Schwächen auf, wie: a) Die angegebenen Spannbreiten für ermittelte Zigarettenabrauchwerte der einzelnen Substanzen beinhalten häufig analytische Daten von Zigaretten aus den 1950er und 1960er Jahren, die mit Zigaretten mit einem niedrigeren Kondensatgehalt, die seit Mitte der 1970er Jahre hergestellt werden, nicht zu vergleichen sind. b) Fehlen analytischer Standardmethoden für die meisten der aufgeführten Substanzen. c) Methodische Überlegungen bezüglich der Tierversuche, mit denen die Tumor verursachende Wirkung der aufgeführten Tabakrauchinhaltsstoffe nachgewiesen wurde. d) Schwierigkeiten bei der Extrapolation von nicht-inhalativen Tierversuchen mit Einzelstoffen auf die Situation beim menschlichen Rauchen, wo ein komplexes Aerosol, das diese Einzelstoffe enthält, inhaliert wird. e) Unzulänglichkeiten bei den Inhalationsdaten bezüglich der Tumor verursachenden Wirkung vieler Inhaltsstoffe. f) Mehrere Tabakrauchinhaltsstoffe sind in den Listen enthalten, obwohl ihre Existenz nicht als gesichert gilt, ihr mengenmäßiges Vorkommen im HSR nicht näher bestimmt wurde oder die ermittelte Konzentration nicht länger von Bedeutung ist. g) Unzulängliche Berücksichtigung von im HSR gefundenen Inhibitoren der Tumorigenität und Mutagenität. h) Schwierigkeiten, die *in vivo* von Einzelsubstanzen ermittelten inhibitorischen/antikanzerogenen/antimutagenen Wirkungen auf das komplexe Aerosol des HSR zu extrapolieren. j) Exposition mit vielen der gelisteten Tabakrauchinhaltsstoffen aus anderen Quellen. k) Widersprüchlichkeiten zwischen den Listen. l) Widersprüchlichkeiten innerhalb der Listen.
Eine geeignetere Nutzung der erstellten Listen ist die Identifikation potentiell schädlicher chemischer Substanzen, um diese aus dem HSR von Zigaretten zu entfernen oder deren Wirkung zu blockieren. [Beitr. Tabakforsch. Int. 20 (2003) 402–437]

RESUME

Au milieu des années 1960 des listes ont été diffusées par des chercheurs, des autorités et des institutions, sur les composants de la fumée du courant principal (CP) de la cigarette qui passent pour être tumorigènes dans des biotests de laboratoire effectués en conditions significativement différentes des conditions du fumage humain, quand le fumeur est exposé aux composants de l' aérosol de fumée du CP de cigarette. Depuis 1990, de nombreuses listes de composants de la fumée de cigarette, considérés comme significativement tumorigènes, ont été constituées par des équipes de l' American Health Foundation, Occupational Safety and Health Administration (OSHA), FOWLES et BATES, et par le personnel de R.J. Reynolds R&D. Le but de la plupart de ces études a été l' évaluation du risque et la dissuasion du fumeur. De nombreux chercheurs et autorités ont fréquemment cité les listes antérieures et/ou plus récentes de composants tumorigènes. Les compilations récentes, comprenant 80 composants du CP, font apparaître de graves déficiences, dont : a) La gamme utilisée de rendements par cigarette en composants spécifiques comprend souvent des données analytiques de cigarettes manufacturées dans les années 1950 et 1960, qui ne sont pas comparable aux cigarettes à rendements en goudron plus faibles manufacturées à partir du milieu des années 1970. b) Absence de procédures analytiques standard pour la plupart des composants compilés. c) Considérations méthodologiques par rapport aux biotests utilisés pour évaluer la tumorigénicité des composants du CP compris dans les listes. d) Difficultés d' extrapolation des données obtenues *in vivo* par des biotests, comprenant l' application d' un composant unique, sans mode d' inhalation, aux conditions du fumage humain, avec le fumeur inhalant un aérosol complexe contenant ce même composant. e) Données d' inhalation inadéquates par rapport à la tumorigénicité de plusieurs des composants. f) L' inclusion dans les listes de plusieurs composants de la fumée de cigarette, bien que leur présence ne soit pas assurée, leur rendement dans le CP n' a pas été établi où n' est plus pertinent. g) Les effets inhibiteurs de la tumorigénèse et la mutagénèse n' ont pas assez été pris en compte. h) Difficulté d' extrapolation des effets d' inhibition/anticarcinogénèse/antimutagénèse observés dans des situation *in vivo* après application d' une substance unique, à l' aérosol complexe du CP. j) Différences d' expositions à plusieurs des composants compris dans les listes. k) Divergences parmi les listes. l) Divergences dans les listes elles-mêmes.
L' identification de substances chimiques potentielles et leur élimination ou inhibition dans la fumée de cigarette paraît être une utilisation plus appropriée de ces listes. [Beitr. Tabakforsch. Int. 20 (2003) 402–437]

1 INTRODUCTION

In the 1970s and 1980s the writing and publishing of usually lengthy and often repetitive review articles on *N*-nitrosamines (NNAs) in tobacco and tobacco smoke appeared to be the trend (1). However, by the late 1980s this trend was replaced by a new one: The writing and publishing of lengthy and repetitive articles on the "changing cigarette". Such articles almost invariably include a listing of cigarette MSS components classified as significant tumorigens. Infrequently, the MSS components in a list are classified as biologically active with the implication that the activity is adverse.
In 1986, two reports on tumorigenic MSS components were issued: One by HOFFMANN and WYNDER (2), the other by the International Agency for Research on Cancer (IARC) (3). From the tobacco and MSS components cited by IARC as tumorigenic, HOFFMANN and HECHT (4) generated their notable "List of 43" components that they classified as significant tumorigens. Their MSS components, with one minor difference (the per cigarette delivery range for quinoline), were again listed in 1993 by HOFFMANN *et al*. (5). It is interesting to note that many of the per cigarette delivery ranges listed for tumorigenic MSS components in the IARC report are derived from pre-1986 WYNDER and HOFFMANN publications (6,7,8). While the HOFFMANN-HECHT list was essentially based on the list in the 1986 IARC report (3), its publication was followed by others. However, as noted in a recent interview with Dr. Hoffmann, the 1990 "List of 43" earned him the title of "Author of the List" (9). From 1986 to date in 2002, the published lists of tumorigenic MSS components include:

Year	Author(s)
1986	HOFFMANN and WYNDER (2)
1986	IARC (3)
1990	HOFFMANN and HECHT (4)
1993	HOFFMANN *et al.* (5)
1994	Occupational Safety and Health Administration (OSHA) (10)
1997	HOFFMANN and HOFFMANN (11)
1998	HOFFMANN and HOFFMANN (12)
1997	SMITH *et al.* (13)
2000	SMITH *et al.* (14)
2001	SMITH *et al.* (15)
2001	HOFFMANN and HOFFMANN (16)
2001	HOFFMANN *et al.* (17)
2001	FOWLES and BATES (18)
2002	RODGMAN and GREEN (19)

While more extensive than previous ones, the HOFFMANN-HECHT 1990 list was not the first to be published. In their 1964 review, WYNDER and HOFFMANN (20) listed 14 tumorigenic (tumor-initiating) polycyclic aromatic hydrocarbons (PAHs) plus three tumorigenic aza-arenes reported in MSS by VAN DUUREN *et al*. (21). WYNDER and HOFFMANN also included four NNAs, four peroxides, epoxides and lactones, and several metallic components (arsenic, nickel carbonyl, ^{40}K) as suspected tumorigens in MSS. In the chapter on tobacco and tobacco smoke in its report, the 1964 ADVISORY COMMITTEE (22) listed six possibly tumorigenic PAHs as well as the three aza-arenes. In their 1967 book, WYNDER and HOFFMANN (6) modified their 1964 list slightly, adding ^{210}Po as a metallic suspect. In 1968, HOFFMANN and WYNDER (23) in their listing of tumorigens in cigarette MSS acknowledged that the $C_{24}H_{14}$ PAH reported incorrectly as dibenzo[*a,l*]pyrene was not dibenzo[*a,l*]pyrene but the isomeric dibenz[*a,e*]aceanthrylene (dibenzo[*a,e*]fluoranthene). In 1979, the US SURGEON GENERAL (24) listed as tumorigens many of the same MSS components noted by WYNDER and HOFFMANN (6). Table 1 summarizes these early lists. In subsequent reports issued between 1979 and 1986, the US SURGEON GENERAL (25,26,27) again included abbreviated lists of cigarette MSS components reported to be tumorigenic in various laboratory bioassays.

In 2000, SMITH *et al*. completed an international literature survey of components reported in cigarette MSS which are classified by the IARC as either Group I (13), Group 2A (14) or Group 2B carcinogens (15). The purpose of this

Table 1. Tumorigens listed in tobacco smoke, 1964-1979

Component	Wynder and Hoffmann 1964 (20)	Advisory Committee 1964 (22)	Wynder and Hoffmann 1967 (6)	Hoffmann and Wynder 1968 (23)	Surgeon General 1979 (24)
Benz[*a*]anthracene	x	—	x	x	x
Benzo[*b*]fluoranthene	x	—	x	x	x
Benzo[*j*]fluoranthene	x	x	x	x	x
Benzo[*c*]phenanthrene	x	x	x	x	x
Benzo[*a*]pyrene	x	x	x	x	x
Benzo[*a*]pyrene, methyl-	x	—	x	—	—
Benzo[*e*]pyrene	x	—	x	—	x
Chrysene	x	—	x	x	x
Chrysene, methyl-	x	—	x	—	x [a]
Dibenz[*a,h*]anthracene	x	x	x	x	x
Dibenzo[*a,i*]pyrene	x	x	x	x	x
Dibenzo[*a,h*]pyrene	x	—	x	—	x
Dibenzo[*a,l*]pyrene [b]	x	x	x	x	—
Indeno[1,2,3-*cd*]pyrene	x	—	x	x	x
Dibenz[*a,h*]acridine	x	x	x	—	x
Dibenz[*a,j*]acridine	x	x	x	—	x
7*H*-dibenzo[*c,g*]carbazole	x	x	x	—	x
Sterol hydroperoxides	x	—	x	—	—
Epoxides	x	—	x	—	—
Lactones (3)	x	—	x	—	—
N-Nitrosodiethylamine	—	—	x	—	—
N-Nitroso-*n*-butylmethylamine	—	—	x	—	—
N-Nitrosopyrrolidine	—	—	x	—	—
Other *N*-nitrosamines	—	—	x	—	—
α-Emitters (^{226}Ra, ^{222}Rn)	x	—	x	—	x
^{210}Po	—	—	x	—	x
^{40}K	x	—	x	—	x
Arsenic	x	—	—	—	x
Nickel tetracarbonyl	x	—	x	—	x
Metal salts/oxides	x	—	—	—	x

[a] 5-Methylchrysene was listed specifically.

[b] The MSS component classified as dibenzo[*a,l*]pyrene was subsequently shown to be the isomer dibenz[*a,e*]aceanthrylene (dibenzo[*a,e*]fluoranthene) (143), a fact noted by Hoffmann and Wynder (23).

literature survey was threefold: a) To identify potential chemical targets for removal from or reduction in MSS; b) to better understand the biological properties of MSS by summarizing and analyzing the tobacco plant precursors and mechanisms of formation of IARC compounds in smoke; and c) to clarify misstatements in the literature.

IARC defines Group I chemical entities as those "known" to be carcinogenic in humans, Group 2A as "probable" human carcinogens and Group 2B as "possible" human carcinogens. The analysis by SMITH *et al*. indicated that ten Group I candidates had been reported in cigarette MSS [benzene, cadmium, arsenic, nickel, chromium, 2-naphthylamine, vinyl chloride, 4-aminobiphenyl, beryllium, ethylene oxide (13)]. Similarly, nine Group 2A compounds have been reported [formaldehyde, benzo[*a*]pyrene (B[*a*]P), dibenz[*a,h*]anthracene (DBA), benz[*a*]anthracene (B[*a*]A), *N*-nitrosodimethylamine, *N*-nitrosodiethylamine, acrylamide, 1,3-butadiene, 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (IQ) (14)] (Table 2). Forty-eight compounds from the Group 2B "possible" carcinogen category have also been reported in MSS (15).

In contrast to the threefold purpose of the SMITH *et al*. survey, the numerous lists of "tumorigenic" compounds reported in cigarette MSS were compiled for the purpose of human risk assessment. Herein, a number of serious limitations regarding the use of such lists for this purpose will be discussed. Presently, no particular component or class of components within the complex MSS aerosol has been definitively assigned a specific *in vivo* role in either DNA damage or increased cell proliferation rates.

In their response to a 1997 statement by the EDITORS (28) of *Beiträge zur Tabakforschung International* on the number of identified components in cigarette MSS plus a listing of biologically active agents in MSS, HOFFMANN and HOFFMANN (12) stated in a 1998 inaugural Letter to the Editors that the previous number of identified MSS components was incorrect and the listing of active agents deserved updating. Their estimate of the number of identified MSS components plus their own listing of biologically active agents in non-filtered cigarette MSS, according to them, "reflects our current knowledge more satisfactorily". Not only was the HOFFMANNs' account of the number of identified MSS components seriously out of date but also comparison of their listing of biologically active MSS agents with earlier lists revealed numerous inconsistencies in per cigarette MSS delivery levels (29). Other inconsistencies are also evident on examination of different tables in the various publications (2,3,4,5,10,11, 12,16,17,18). For example, authors of these articles repeatedly list dibenz[*a,h*]acridine, dibenz[*a,j*]acridine, and 7*H*-dibenzo[*c,g*]carbazole as tumorigenic or biologically active MSS components despite the fact that: a) In 1990, their presence in MSS had not been confirmed in several investigations conducted between 1963 and 1990 (29). b) Between 1990 and 2000, additional studies failed to confirm their presence in MSS (30,31). c) Several summaries of the attempts to confirm the findings of VAN DUUREN *et al*. have been published (32,33). In 2002, RUSTEMEIER *et al*. (34) did report the presence of dibenz[*a,j*]acridine. Other tumorigens in cigarette MSS, including several whose presence was and is suspect, have been listed since the early 1960s.

2 THE "LIST OF 43"

In the early 1990s, the US Environmental Protection Agency (EPA) issued several draft documents (35) and a final report (36) classifying environmental tobacco smoke (ETS) as a "Group A Carcinogen." In its final report, EPA summarized results of epidemiological studies on lung cancer incidence in ETS-exposed nonsmokers and interpreted them as indicating that ETS was causally related to lung cancer. In addition to epidemiological data, EPA relied on tobacco smoke composition data. Considered important were the many studies on cigarette MSS composition plus the fewer studies dealing with cigarette sidestream smoke (SSS) composition.

Quantitative data have been obtained on per cigarette deliveries on only a limited number of SSS components. Of those quantitatively determined, some are delivered at higher per cigarette levels in SSS than in MSS, others are delivered at lower levels in SSS than in MSS. Many of the quantified SSS components are considered as potential contributors to pathological responses based upon results from laboratory animals. EPA extrapolated these SSS (and MSS) qualitative and quantitative composition data directly to ETS without adequately considering profound quantitative differences between MSS and SSS composition, the high dilution of ETS, its constantly changing composition, and the biological implications of these differences (37,38,39). EPA also emphasized MSS and SSS components that had been described as tumorigenic at doses far in excess of those encountered in either MSS or SSS (35,36). Earlier, the US Surgeon General had discussed some of the same MSS and SSS components and their presence in ETS (27).

Of great concern to the EPA were the components in the 1990 HOFFMANN-HECHT "List of 43" compiled from data in two IARC monographs on tobacco and tobacco smoke (3,40).

In its attempt to relate MSS composition to ETS composition, EPA stated (35):

> Of the 99 compounds in tobacco smoke that have been studied in detail, at least 43 are complete carcinogens [a], each able on its own to cause the development of cancer in humans or animals.
>
> [a] The citation referred to the Surgeon General's 1989 report (USPHS, 41) that, in turn, reproduced the table eventually presented by HOFFMANN and HECHT (4).

As noted by RODGMAN (37), EPA's assessment of the 43 components in the HOFFMANN-HECHT list overstates the strength of the data as: a) Most of the 43 listed components have not been shown to be tumorigenic in humans. Only six of the compounds listed in Table 2 that were evaluated by IARC have sufficient evidence of tumorigenicity in humans. b) Thirty-nine have not been shown to produce lung tumors in laboratory animals.

In the text accompanying the "List of 43", several specific statements were provided that illustrate the difficulty of extrapolating available laboratory bioassay data on MSS components to the risk of developing pulmonary carcinoma in humans, e.g.:

- **4-(*N*-methyl-nitrosamino)-1-(3-pyridinyl)-1-butanone (NNK)**

  "It [NNK] has not been tested by inhalation" (HOFFMANN and HECHT, 4). "Relevant information not available [on this compound, NNK"] (OSHA, 10).

Table 2. Summary of lists of tumorigenic components in tobacco and tobacco smoke (MSS delivery/cig)

Component	1986 IARC (3)	American Health Foundation (1986–2001)						1994 OSHA (10)	1997–2001 Smith *et al.* (13,14,15)	2001 Fowles & Bates (18)	2002 Rodgman & Green (19)[b]
		1986 Hoffmann & Wynder (2)	1990, 1993 Hoffmann & Hecht (4); Hoffmann *et al.* (5)	1997 Hoffmann & Hoffmann (11)	1998 Hoffmann & Hoffmann (12)[a]	2001 Hoffmann & Hoffmann (16)	2001 Hoffmann *et al.* (17)				
Number of tumorigens	*52*	35	43	60	70	68	69	42	63	63	
Polycyclic aromatic hydrocarbons											
Benz[*a*]anthracene	*40-70 ng*	40–70 ng	20–70 ng	→ "[c]	→ "	→ "	→ "	→ "	tr–80 ng	45 ng	11.4 ng
Benzo[*b*]fluoranthene	*30 ng*	30 ng	4–22 ng	→ "	→ "	→ "	→ "	P, NDL	1.2–48 ng	**13 µg**	5.5 ng
Benzo[*j*]fluoranthene	*60 ng*	60 ng	6–21 ng	→ "	→ "	→ "	→ "	NL	5–40 ng	1.35 ng	{21 ng}
Benzo[*k*]fluoranthene	*6–12 ng*	NL	6–12 ng	→ "	→ "	→ "	→ "	P, NDL	1.8–25 ng	9 ng	1.3 ng
Benzo[*a*]pyrene	*10–50 ng*	10–50 ng	20–40 ng	→ "	→ "	→ "	→ "	→ "	4–108 ng	9.9 ng	5.2 ng
Chrysene	*40–60 ng*	40–60 ng	→ "	NL	NL	NL	NL	NL	NL	50 ng	14.0 ng
Chrysene, 5-methyl-	*0.6 ng*	0.6 ng	→ "	→ "	→ "	→ "	→ "	P, NDL	tr–2 ng	0.6 ng	7.6 ng
Dibenz[*a,h*]anthracene	*4 ng*	40 ng	4 ng	→ "	→ "	→ "	→ "	P, NDL	4–76 ng	4 ng	0.4 ng
Dibenzo[*a,e*]pyrene	*P, NDL*	NL[d]	NL	NL	P, NDL	P, NDL	P, NDL	P, NDL	P, NDL	NL	{P}
Dibenzo[*a,h*]pyrene	*P, NDL*	NL	NL	NL	NL	NL	NL	P, NDL	5–9.5 ng	NL	{P}
Dibenzo[*a,i*]pyrene	*2–3 ng*	NL	**1.7–3.2 ng**	**1.7–3.2 ng**	**NL**[e]	**NL**[e]	**NL**[e]	P, NDL	0.2–10 ng	2.5 ng	{3.2 ng}
Dibenzo[*a,l*]pyrene[f]	*P, NDL*[g]	P, NDL	**P, NDL**	**P, NDL**	**1.7–3.2 ng**[e]	**1.7–3.2 ng**[e]	**1.7–3.2 ng**[e]	P, NDL	P, NDL	NDL	{P}
Indeno[1,2,3-*cd*]pyrene	*4–20 ng*	4 ng	4–20 ng	→ "	→ "	→ "	→ "	P, NDL	1–20 ng	12 ng	3.1 ng
Aza-arenes											
Quinoline	*NL*	NL	1–2 µg 0.2–1.3 µg[i]	1–2 µg	**2–180 ng**	**1–2 ng**	**1–2 µg**	NL (0.5–2 µg)[j]	NL	356 ng	270 ng
Dibenz[*a,h*]acridine[h]	*0.1 ng*	0.1 ng	→ "	→ "	→ "	→ "	→ "	P, NDL	0.1 ng	0.1 ng	{0.1 ng}
Dibenz[*a,j*]acridine	*3–10 ng*	3–10 ng	→ "	→ "	→ "	→ "	→ "	P, NDL	2.7–10 ng	2.7 ng	{2.7 ng}
7*H*-dibenzo[*c,g*]carbazole	*0.7 ng*	0.7 ng	→ "	→ "	→ "	→ "	→ "	P, NDL	0.7 ng	0.7 ng	{0.7 ng}
N-Nitrosamines											
N-Nitrosodimethylamine	*1–200 ng*	1–180 ng	0.1–180 ng	→ "	2–180 ng	→ "	2–1000 ng	10–40 ng	ND–1620 ng	24.4 ng	11.8 ng
N-Nitrosoethylmethylamine	*0.1–10 ng*	1–40 ng	3–13 ng	→ "	→ "	→ "	→ "	NL	ND–200 ng	6.0 ng	{13 ng}
N-Nitrosodiethylamine	*ND–10 ng*	0.1–28 ng	ND–25 ng	ND–2.8 ng	→ "	→ "	→ "	ND–25 ng	0–7.6 ng	8.3 ng	2.8 ng
N-Nitrosodi-*n*-propylamine	*ND–1 ng*	NL	NL	NL	ND–1.0 ng	→ "	→ "	P, NDL	ND–42 ng	NL	{1.0 ng}
N-Nitrosodi-*n*-butylamine	*ND–3 ng*	NL	NL	NL	ND–30 ng	→ "	→ "	P, NDL	ND–19 ng	12 ng	{30 ng}
N-Nitrosopyrrolidine	*2–42 ng*	2–110 ng	**1.5–110 ng**	**3–60 ng**	**3–110 ng**	→ "	→ "	6–30 ng	1–270 ng	113 ng	10.6 ng
N-Nitrosopiperidine	*ND–9 ng*	ND–9 ng	NL	NL	ND–9 ng	→ "	→ "	P, NDL	ND–231 ng	NL	{9 ng}
***N*-Nitrosodiethanolamine**	*ND–90 ng*	ND–40 ng	ND–36 ng	ND–68 ng	→ "	→ "	→ "	20–70 ng	ND–290 ng	30 ng	4.3 ng
***N*-Nitrososarcosine**	*NL*	NL	NL	ND	ND	NL	NL	NL	NL	NL	NL

Table 2 (*cont.*)

Component	1986 IARC (3)	American Health Foundation (1986–2001)						1994 OSHA (10)	1997–2001 Smith *et al.* (13,14,15)	2001 Fowles & Bates (18)	2002 Rodgman & Green (19)[b]
		1986 Hoffmann & Wynder (2)	1990, 1993 Hoffmann & Hecht (4); Hoffmann *et al*. (5)	1997 Hoffmann & Hoffmann (11)	1998 Hoffmann & Hoffmann (12)[a]	2001 Hoffmann & Hoffmann (16)	2001 Hoffmann *et al*. (17)				
N-Nitrosamines (cont.)											
N'-Nitrosonornicotine	*0.13–2.5 µg*	**0.12–3.7 µg**	→ **"**	→ **"**	**120–3.7 ng**	**0.12–3.7 µg**	→ "	0.2–3.0 µg	0.004–5.32 µg	1.90 µg	115 ng
4-(*N*-Methylnitrosamino)-1-(3-pyridyl)-1-butanone	*0.08–0.77 µg*	0.12–0.95 µg	0.08–0.77 µg	→ "	→ "	→ "	→ "	0.1–1.0 µg	ND–1.75 µg	300 ng	102 ng
N'-Nitrosoanabasine	*ND–200*	**40–400 ng**	**0.14–4.6 µg**	→ "	ND–150 ng	NL	NL	NL	NL	19 ng	20.3 ng
N'-Nitrosoanatabine	*ND–3.7 µg*	NL	NL	NL	NL	NL	NL	NL	NL	**72.2 µg**	122 ng
***N*-Nitrosomorpholine**	*NL*	NL	ND in MSS	→ "	→ "	NL	NL	NL	NL	NDL	NL
Aromatic amines											
2-Toluidine	*30–200 ng*	30–160 ng	**30–200 ng**	→ "	**30–337 ng**	→ "	→ "	160 ng	23–938 ng	115 ng	{337 ng}
Aniline, 2,6-dimethyl-	*NL*	NL	NL	NL	NL	**4–50 µg**	**4–50 ng**	NL	3.6–18 ng	NL	{50 ng}
1-Naphthylamine	*3–4 ng*	NL	NL	NL	NL	NL	NL	NL	NL	9.6 ng	16.8 ng
2-Naphthylamine	*1–22 ng*	4.3–27 ng	**1–22 ng**	→ **"**	**1–334 ng**	→ "	→ "	1.7 ng	0.2–22 ng	7.0 ng	11.1 ng
Biphenyl, 4-amino-	*2–5 ng*	2.4–4.6 ng	2–5 ng	→ "	2–5.6 ng	→ "	→ "	4.6 ng	0.19–5 ng	1.2 ng	3.1 ng
N-Heterocyclic amines											
A*a*C [k]	*NL*	NL	NL	25–260 ng	→ "	→ "	→ "	NL	ND–258 ng	NL	{260 ng}
MeA*a*C	*NL*	NL	NL	2–37 ng	→ "	NL	2–37 ng	NL	1.6–37 ng	NL	{37 ng}
Glu-P-1	*NL*	NL	NL	**0.37–0.89 ng**	**6.37–0.89 ng**	0.37–0.89 ng	→ "	NL	ND–0.89 ng	NL	{0.89 ng}
Glu-P-2	*NL*	NL	NL	0.25–0.88 ng	→ "	→ "	→ "	NL	0.25–0.88 ng	NL	{0.88 ng}
PhIP	*NL*	NL	NL	11–23 ng	→ "	→ "	→ "	NL	ND–22.9 ng	NL	{23 ng}
IQ	*NL*	NL	NL	0.26 ng	0.3 ng	→ "	→ "	NL	0.26–0.49 ng	NL	{0.3 ng}
MeIQ	*NL*	NL	NL	NL	NL	NL	NL	NL	0.28–0.75 ng	NL	{0.75 ng}
Trp-P-1	*NL*	NL	NL	0.29–0.48 ng	0.3–0.5 ng	→ "	→ "	NL	0.19–0.3 ng	NL	{0.5 ng}
Trp-P-2	*NL*	NL	NL	0.82–1.1 ng	0.8–1.1 ng	→ "	→ "	NL	ND–0.2 ng	NL	{1.1 ng}
Aldehydes											
Formaldehyde	*20-88 µg*	5–100 µg	70–100 µg	70–100 µg [l]	→ "	→ "	→ "	→ "	3.4–283 µg	33 µg	18 µg
Acetaldehyde	*18–1400 µg*	500–1400 µg	18–1400 µg	**18–1400 µg** [l]	**500–1.400 µg**	→ "	→ "	P, NDL	8–2815 µg	680 µg	581 µg
Crotonaldehyde	*NL*	NL	10–20 µg	NL	10–20 µg	NL	NL	NL	NL	14.2 µg	17.3 µg
Acrolein	*25–140 µg*	NL		NL	60–140 µg	NL	NL	NL	NL	68.8 µg	54 µg

Table 2 (*cont.*)

Component	1986 IARC (3)	American Health Foundation (1986–2001)						1994 OSHA (10)	1997–2001 Smith *et al.* (13,14,15)	2001 Fowles & Bates (18)	2002 Rodgman & Green (19)[b]
		1986 Hoffmann & Wynder (2)	1990, 1993 Hoffmann & Hecht (4); Hoffmann *et al*. (5)	1997 Hoffmann & Hoffmann (11)	1998 Hoffmann & Hoffmann (12)[a]	2001 Hoffmann & Hoffmann (16)	2001 Hoffmann *et al*. (17)				
Volatile hydrocarbons, NL (5)											
1,3-Butadiene	*NL*	NL	NL	20–75 µg [l]	→ ”	→ ”	→ ”	NL (69.2 µg)[d]	16–77 µg	NL	40.3 µg
Isoprene	*NL*	NL	NL	**450–1000 µg**[l]	**450–1.00** µg	**450–1000 µg**	→ ”	NL	93–1065 µg	264 µg	370 µg
Benzene	*12–48 µg*	NL	12–48 µg	12–70 µg [l]	20–70 µg	→ ”	→ ”	12–48 µg	0.05–104 µg	46.3 µg	42.7 µg
Styrene	*10 µg*	NL	NL	10 µg	→ ”	→ ”	→ ”	P, NDL	<0.005–48 µg	5.71 µg	5.48 µg
Miscellaneous organic compounds											
Acetamide	*38–56 µg*	NL	NL	NL	38–56 µg	→ ”	→ ”	NL	2.2–111 µg	NL	3.97 µg
Acrylonitrile	*3.2–15 µg*	NL	3.2–15 µg	→ ”	3–15 µg	→ ”	→ ”	P, NDL	3.2–19.4 µg	8.9 µg	10.6 µg
Acrylamide	*NL*	NL	NL	P, NDL	P, NDL	P, NDL	P, NDL	NL	1.1–2.34 µg	NL	{P}
Hydrazine, 1,1-dimethyl-	*P, NDL*	NL	P, NDL	NDL	P, NDL	P, NDL	P, NDL	P, NDL	NL	NDL	{P}
Nitromethane	*NL*	NL	NL	NL	NL	0.3–0.6 µg	0.5–0.6 µg	NL	NL	NL	{0.6 µg}
2-Nitropropane	*0.73–1.21 µg*	0.2–2.2 µg	0.73–1.21 µg	→ ”	0.2–2.2 µg	0.7–1.2 µg	→ ”	P, NDL	0.22–2.42 µg	1 ng	{2.2 µg}
Nitrobenzene	*NL*	NL	NL	NL	25 µg	→ ”	→ ”	NL	25 ng	NL	(25 µg}
Vinyl chloride	*1–16 ng*	1.3–16 ng	1–16 ng	→ ”	11–15 ng	→ ”	→ ”	P, NDL	1.3–15.8 ng	8.6 ng	30 ng
Ethyl carbamate	*20–38 ng*	**20–38 ng**	→ ”	→ ”	→ ”	**20–38 µg**	**20–38 µg**	P, NDL	10–35 ng	29 ng	**{38 µg}**
Ethylene oxide	*NL*	NL	NL	7 µg	→ ”	→ ”	→ ”	NL	4.5[m]–105[n] µg	NL	{7 µg}
Propylene oxide	*NL*	NL	NL	NL	NL	12–100 ng	ND–100 ng	12–100 ng	NL	NL	{100 ng}
Di(2-ethylhexyl) phthalate	*NL*	NL	NL	20 µg	→ ”	NL [o]	NL	NL	NL	NL	NL [o]
Furan	*NL*	**NL**	**NL**	**18–30 µg** [l]	**18–30 ng**	**18–37 ng**	**18–37 µg**	NL	18–65 µg	NL	{37 µg }
Benzo[*b*]furan	*NL*	NL	NL	P, NDL	P, NDL	P, NDL	P, NDL	NL	P, NDL	NL	{P}
Phenols											
Catechol	*40–350 µg*	25–360 µg	NL	NL	200–400 µg	**100–360 µg**	**90–2000 µg**	NL	1–502 µg	88.2 µg	44.5 µg
Methyleugenol	*NL*	NL	NL	NL	20 ng	→ ”	→ ”	NL	NL	NL	{20 ng }
Caffeic acid	*NL*	NL	NL	NL	NL	< 3 µg	→ ”	NL	P, NDL	NL	{< 3 µg}
Chloroaromatic compounds											
DDT	*NL*	NL	NL	**0.8–1.2 µg**	**800–1.20** ng	**800–1200 µg**	→ ”	0.8–1.2 µg	NL	NL	{1.2 µg}
DDE	*NL*	NL	NL	**200–370 ng**	→ ”	**200–370 µg**	**200–370 µg**	NL	NL	NL	{370 ng}
Polychlorodibenzo-*p*-dioxins	*NL*	NL	NL	NL	NL	NL	NL	NL	NL	75 pg	{75 pg}
Polychlorodibenzofurans	*NL*	NL	NL	NL	NL	NL	NL	NL	NL	2.98 pg	{2.98 pg}

Table 2 (*cont.*)

Component	1986 IARC (3)	American Health Foundation (1986–2001)						1994 OSHA (10)	1997–2001 Smith *et al.* (13,14,15)	2001 Fowles & Bates (18)	2002 Rodgman & Green (19)[b]
		1986 Hoffmann & Wynder (2)	1990, 1993 Hoffmann & Hecht (4); Hoffmann *et al*. (5)	1997 Hoffmann & Hoffmann (11)	1998 Hoffmann & Hoffmann (12)[a]	2001 Hoffmann & Hoffmann (16)	2001 Hoffmann *et al*. (17)				
Inorganic compounds											
Hydrazine	*24–43 ng*	24–43 ng	→ ”	→ ”	**24–34 µg**	**24–43 ng**	→ ”	32 ng	24–56.7 ng	34 ng	{43 ng}
Arsenic	*1–25 µg*	NL	**40–120 ng**	→ ”	→ ”	**40–120 µg**	40–120 µg	P, NDL	0–1.4 µg	700 ng	4.43 ng
Beryllium	*NL*	NL	NL	NL	**0.3 µg**	**0.5 ng**	0.5 ng	NL	ND–0.5 ng	0.25 ng	{0.5 ng}
Cobalt	*0.2 ng*	NL	NL	NL	0.13–0.2 ng	→ ”	→ ”	NL	0.13–100 ng	NL	37.6 ng
Nickel	*ND–600 ng*	2–3000 ng	ND–600 ng	→ ”	→ ”	→ ”	→ ”	20–80 ng	ND–510 ng	11 ng	4.41 ng
Chromium vi	*4–70 ng*	NL	4–70 ng	→ ”	→ ”	→ ”	→ ”	P, NDL	0.2–500 ng	4.2 ng	1.32 ng
Cadmium	*9–70 ng*	NL	41–62 ng	→ ”	NL	7–350 ng	7–350 ng	110 ng	0–6.67 µg	103 ng	52.1 ng
Lead	*P, NDL*	NL	35–85 ng	→ ”	34–85 ng	→ ”	→ ”	P, NDL	ND–980 ng	12.8 ng	38.3 ng
Polonium-210	*0.03 pCi*	0.03–1.0 pCi	→ ”	→ ”	→ ”	→ ”	→ ”	NL (0.03–1.0 pCi)[g]	NL	NDL	0.03–1.0 pCi

[a] Hoffmann and Hoffmann (12) not only listed tumorigenic components of MSS but also “biologically active” components. Presumably the biological activity denoted was adverse since none of the biologically active inhibitors, anticarcinogens, or antimutagens was listed.

[b] Specific component data listed under Rodgman and Green are the averages of one or more analyses from various laboratories (INBIFO, RJRT, Omni, Rickert) on the MSS from the Kentucky reference 1R4F cigarette. Values in brackets {} are the highest value obtained by other investigators for a component determined in the MSS from a cigarette other than the 1R4F.

[c] The symbol → ” indicates that the range listed in the publication designated in the column is the same range as that indicated in the publication in the column to the immediate left.

[d] NL = not listed as a tumorigenic or carcinogenic component of cigarette MSS; in some instances the compound is listed in an alternate table in the article as an MSS component.

[e] The range is that of dibenzo[*a,i*]pyrene, not dibenzo[*a,l*]pyrene; a range listed in **bold** type contains a numerical error and/or a unit error (ng vs. µg).

[f] Components listed in **bold** are no longer relevant (19).

[g] P = present; ND = not detected; NDL = no delivery level listed for cigarette MSS; tr = trace.

[h] The controversy with regard to the presence of the three aza-arenes in MSS is described in detail in Table 4.

[i] The range listed for quinoline was different in Hoffmann *et al*. (5) than in Hoffmann and Hecht (4); all the other ranges were identical in the two publications.

[j] The components listed are from Table II-2 by OSHA (10); the per cigarette deliveries listed are from Tables III-6 and III-7 in OSHA (10). In several instances, the per cigarette delivery for a component not listed by OSHA as a “human or animal” tumorigen was listed in Tables III-6 and III-7.

[k] A*a*C = 2-amino-9*H*-pyrido[2,3-*b*]indole; MeA*a*C = 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole; Glu-P-1 = 2-amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole; Glu-P-2 = 2-aminodipyrido[1,2-*a*:3',2'-*d*]imidazole; PhIP = 2-amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine; IQ = 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoline; MeIQ = 2-amino-3,4-dimethyl-3*H*-imidazo[4,5-*f*]quinoline; Trp-P-1 = 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole; Trp-P-2 = 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole.

[l] In several instances in the 1997 article by Hoffmann and Hoffmann (11) the per cigarette delivery range listed for a specific component in their Tables 1 and 3 differ significantly.

Component	Range listed in Table 1	Range listed in Table 3	Component	Range listed in Table 1	Range listed in Table 3
Formaldehyde	20–100 µg	70–100 µg	1,3-Butadiene	25–40 µg	20–75 µg
Acetaldehyde	400–1400 µg	18–1400 µg	Isoprene	200–400 µg	450–1000 µg
Furan	20–40 µg	18–30 µg	Benzene	6–70 µg	12–70 µg

[m] See Binet (154).

[n] See Binet and Lindner (155).

[o] On reevaluation of di(2-ethylhexyl)phthalate, IARC removed it from the Group 2B carcinogen list [see Table 5-4, Footnote c in (16)]).

- **2-toluidine**
  "Recent studies have . . . shown that single ring aromatic amines, including the weak bladder carcinogen *o*-toluidine [2-toluidine], are present in human urine . . . The available data do not indicate that there are significant differences between smokers and nonsmokers" (HOFFMANN and HECHT, 4).
- **acrylonitrile**
  "Although it is present in cigarette MS, its role in tobacco carcinogenesis is difficult to evaluate due to lack of data" (HOFFMANN and HECHT, 4).
- **vinyl chloride**
  "Its low levels in cigarette MS do not support a major role in tobacco carcinogenesis" (HOFFMANN and HECHT, 4).
- **chromium, cadmium, lead**
  "The possible roles of chromium, cadmium, and lead in tobacco carcinogenesis are difficult to evaluate given the present data base. Taken together, the evidence for a major role of these materials as etiologic factors in tobacco carcinogenesis is not compelling" (HOFFMANN and HECHT, 4).
- **polonium-210**
  "The quantities of polonium-210 found in the lungs of smokers are generally about three times higher than those in nonsmokers. However, the significance of polonium-210 in tobacco-induced lung cancer has been questioned upon comparison of these data with those obtained in miners" (HARLEY *et al.*, 42) . . . (HOFFMANN and HECHT, 4).

In Tables 3 and 4, these and other limitations are addressed in a critique of the various lists summarized in Table 2.

In their 1990 list (Table 2), HOFFMANN and HECHT cataloged the tobacco and/or tobacco smoke components classified as "tumorigenic agents" and the per cigarette MSS deliveries of each. Prior to examining the individual components on the list, an important distinction between "tumorigenicity" and "carcinogenicity" should be noted. In the 27th edition (1988) of DORLAND's medical dictionary (43), the definition of carcinogenesis, first enunciated in 1923, is the same as that listed in the 13th edition issued in 1927 (44). Some investigators incorrectly use the term "carcinogenesis" for the production of any tumor type, not just for a carcinoma. The correct term, if used in this manner, is "tumorigenesis". The term "carcinogen" is often applied, again often incorrectly, to any factor that induces any type of tumor. Common in the past, but seldom used now, was the term "sarcogenesis" used to describe the production of sarcoma, the endpoint obtained in many investigations in which the mode of administration of the compound under test, e.g., a PAH, was by subcutaneous injection.

Additionally, terms such as *carcinogen*, *carcinogenicity*, and/or *carcinogenesis* or *sarcogen*, *sarcogenicity*, and/or *sarcogenesis* should not be considered as fixed properties of compounds. It should be noted that in several of their earlier publications, WYNDER and HOFFMANN (20,45,46, 47) carefully differentiated among the terms *carcinogenesis*, *sarcogenesis*, and *tumorigenesis* but eventually discontinued this practice. Carcinogenicity is a variable property, depending on a number of factors. It differs from other properties of a compound that are fixed; e.g., melting point, boiling point, refractive index, specific gravity, crystalline form. As noted by SHEAR and LEITER (48), by HARTWELL (49), and by many others, a substance or factor can show a range of effects from carcinogenicity to noncarcinogenicity to anticarcinogenicity and the response will differ in the laboratory depending on the animal used (species, strain, sex, age), route of administration [inhalation, ingestion, injection (subcutaneous, intravenous, intraperitoneal), skin painting, douching], mode of administration (single vs. multiple doses, neat, in solution, as an aerosol, as a vapor), diet supplied the animals, and cage care.

From the standpoint of human risk assessment, the inclusion of many of the MSS and/or tobacco components in the 1990 "List of 43" is not well supported on the basis of the literature on their tumorigenicity to laboratory animals at levels determined in MSS, their lack of tumorigenicity in most instances via the inhalation route of exposure, and the equivocal evidence showing their tumorigenicity in humans at levels in MSS. Specifically, all but five (B[*a*]P, *N*-nitrosodimethylamine, *N*-nitrosodiethylamine, cadmium, and ^{210}Po) of the 43 components have never produced respiratory tract tumors in laboratory animals exposed to the component via inhalation. Because of the level of exposure, far in excess of that in MSS, the Registry of Toxic Effects of Chemical Substances (RTECS) categorized the findings with B[*a*]P, *N*-nitrosodimethylamine, and *N*-nitrosodiethylamine as "equivocal". Many have never been tested by administration via inhalation (50). The data for MSS tumorigens are derived from bioassays on individual components. In line with the SHEAR-LEITER admonition, the prediction not only of complex mixture tumorigenicity from individual component data but also the tumorigenicity of an individual component in the mixture is extremely problematic.

In Tables 3 and 4, several of the components on the HOFFMANN-HECHT "List of 43" are discussed in terms of MSS level, the firmness of the data indicating their presence, their relevance to US cigarettes manufactured since 1980, and reasons why they are inappropriate for inclusion in a human risk assessment.

MSS levels determined between 1955 and 1975 for some of the listed components are not comparable with the MSS levels expected if the analyses for these components were conducted on more recent or current cigarettes. For example, dibenz[*a*,*h*]acridine and 7*H*-dibenzo[*c*,*g*]carbazole levels were obtained with 1959–1960 cigarettes. MSS values for dibenz[*a*,*j*]acridine are from 1959–1960 and from 1963 cigarettes, while the MSS value for DBA is also from 1963 cigarettes. The MSS data for 5-methylchrysene date from 1973 and the MSS value for *N*-nitrosodiethanolamine was determined from commercial cigarettes manufactured in or before 1981. Eight cigarette design technologies comprising tobacco blend, efficient filtration, processed tobacco materials (reconstituted tobacco sheet [RTS], expanded tobacco), air dilution (porous paper, filter-tip perforations), and filter-tip and paper additives have progressively reduced the FTC sales-weighted average MSS total particulate matter (TPM) by almost 70% from nearly 40 mg/cig in the early 1950s to less than 12 mg/cig in the late 1980s [see Figure 1 (SMITH *et al*., 15)]. These design technologies are considered significant in the design of a "less hazardous" cigarette [WYNDER and HOFFMANN (6,20), HOFFMANN and HOFFMANN (11), US SURGEON GENERAL (24,25), GORI (51)].

Table 3. Summary of lists of tumorigenic components in tobacco and/or tobacco smoke

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
		Polycyclic aromatic hydrocarbons	
Benz[*a*]anthracene {B[*a*]A}	2A	no	‣ Dipple *et al.* (79) classified the tumorigenicity of B[*a*]A in animals and humans as "disputed". ‣ OSHA [see pp. 15987–15988, Table III-7 in (10)] classified B[*a*]A as an animal carcinogen only. ‣ B[*a*]A is generally classified as an extremely weak tumorigen (79). Steiner and Falk (78) reported that B[*a*]A significantly inhibited the specific tumorigenicity of such potent tumorigens as DBA in laboratory animals.
Benzo[*b*]fluoranthene {benz[*e*]acephenanthrylene}	2B	no	‣ The tumorigenic potencies of these three benzofluoranthenes were reported by Deutsch-Wenzel *et al.* (156) to be much less than that of B[*a*]P. Their potencies relative to B[*a*]P were estimated at 11%, 3% and 3%, respectively, for benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, and benzo[*k*]fluoranthene.
Benzo[*j*]fluoranthene	2B	no	
Benzo[*k*]fluoranthene	2B	no	
Benzo[*a*]pyrene {B[*a*]P}	2A	yes	‣ The specific tumorigenicity of B[*a*]P is significantly inhibited by simultaneous administration (skin painting, subcutaneous injection) of B[*a*]P and a weakly tumorigenic PAH such as B[*a*]A or nontumorigenic PAHs such as anthracene, pyrene, perylene, or fluoranthene, all MSS components [*cf*. Kotin and Falk (100), Wynder and Hoffmann (101)]. The tobacco smoke components 2-naphthol as well as benz[*c*]acridine and benzo[*a*]carbazole inhibit the tumorigenicity of B[*a*]P. ‣ OSHA (10) listed B[*a*]P as a probable human carcinogen. ‣ IARC (3) lists B[*a*]P as a probable human carcinogen [*cf*. Hoffmann and Hecht (4)]. ‣ Lung tumor production with large doses of B[*a*]P via inhalation was categorized as "equivocal" by RTECS (50). ‣ The range reported for MSS delivery of B[*a*]P is unrealistic for current cigarettes. None of the cigarettes recently analyzed approached a MSS B[*a*]P delivery of 40 ng/cig. In the mid-1980s, Adams *et al.* (157) reported a high value of 20 ng/cig for the MSS B[*a*]P delivery from a marketed cigarette. ‣ A threshold limit value was demonstrated for B[*a*]P by Wynder *et al.* (158), confirming previously reported findings by Poel (159) and Poel and Kammer (160). ‣ Despite the fact that it has been repeatedly reported that only a small percentage of the tumorigenicity to mouse skin is attributed to B[*a*]P or B[*a*]P plus the other tumorigenic PAHs in MSS (22,24,103,110), some investigators attribute the lung cancer induction in smokers to the tumorigenic PAHs and NNK (148).
Chrysene	3	no	‣ Dipple *et al.* (79) listed the tumorigenicity of chrysene in animals as "disputed". ‣ IARC (3) characterized the degree of evidence for the tumorigenicity of chrysene in animals or man as "limited". ‣ Kotin and Falk (100) classified chrysene as an anticarcinogen vs. B[*a*]P and DBA. ‣ Hoffmann and Hoffmann (11, 12) deleted chrysene from their 1997 and 1998 revised listing, in agreement with the OSHA 1994 listing (10).
Chrysene, 5-methyl-	2B	no	‣ A single MSS delivery value reported by Hecht *et al.* (161) for 5-methylchrysene in MSS was based on a cigarette possibly manufactured in 1972–1973 and thus the MSS delivery will not be representative of its level in the MSS of post-1990 cigarettes. ‣ Because of the "thermodynamic instability" of several methylchrysenes described by Hecht *et al.* (161), it is highly probable that 5-methylchrysene in ETS may rapidly dissipate.
Dibenz[*a,h*]anthracene {DBA}	2A	no	‣ The value for cigarette MSS delivery of DBA is presumably based on only one determination, that reported by Wynder and Hoffmann (162) for a cigarette manufactured in 1962 or 1963. The Hoffmann reports in 1990 and 1997 did not include the value reported by Van Duuren (142) who listed a cigarette MSS delivery of 5 ng/cig for DBA. More recently manufactured cigarettes differ substantially in design, TPM delivery, and smoke component deliveries from those marketed more than three decades ago. ‣ An early example of a threshold limit value for PAH-induced tumorigenesis involved DBA and was described by Dobrowolskaïa-Zavadskaïa (163).

Table 3 (*cont.*)

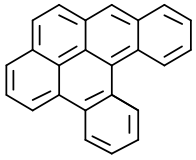
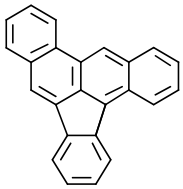
Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
Dibenz[*a,h*]anthracene {DBA} (*cont.*)			‣ The specific tumorigenicity of DBA is significantly inhibited by simultaneous administration (skin painting, subcutaneous injection) of DBA and a weakly tumorigenic PAH such as B[*a*]A or nontumorigenic PAHs such as anthracene, pyrene, perylene, or fluoranthene, all MSS components [cf. Kotin and Falk (100), Wynder and Hoffmann (101)]. The tobacco smoke components 2-naphthol as well as benz[*c*]acridine and benzo[*a*]carbazole inhibit the tumorigenicity of DBA.
Dibenzo[*a,e*]pyrene {naphtho[1,2,3,4-*def*]chrysene}	2B	no	
Dibenzo[*a,h*]pyrene {dibenzo[*b,def*]chrysene}	2B	no	
Dibenzo[*a,l*]pyrene {benzo[*rst*]pentaphene}	2B	no	
Dibenzo[*a,l*]pyrene {dibenzo[*def,p*]chrysene} (**I**)  (**I**)	2B	no	‣ In the late 1950s, the structure of a tobacco smoke isolate was reported as dibenzo[*a,l*]pyrene by Lyons and Johnston (164), Wynder and Wright (103), Van Duuren (142), Wynder *et al.* (107), Rodgman and Cook (84), and others. Subsequently, Lavit-Lamy and Buu-Hoï (143) reported that the compound originally thought to be dibenzo[*a,l*]pyrene was a different isomeric PAH. The reported tobacco smoke isolate was actually dibenz[*a,e*]aceanthrylene (**II**) (originally known as dibenzo[*a,e*]fluoranthene), an isomer of dibenzo[*a,l*]pyrene (**I**). ‣ This structure correction was noted and accepted by most tobacco smoke investigators (84,103,142,164), including Hoffmann and Wynder (23). ‣ IARC (3,144) characterized the degree of evidence for the tumorigenicity of dibenz[*a,e*]aceanthrylene in animals or man as "limited", the same classification it applied to styrene. For dibenzo[*a,l*]pyrene, IARC cites only the 1958 data reported in a footnote by Van Duuren (142), which are obviously data pertinent to dibenz[*a,e*]aceanthrylene. In 1983, IARC notes (144) that all articles published prior to 1966 on dibenzo[*a,l*]pyrene were reviewed under the assumption that the compound was, in fact, dibenzo[*a,e*]aceanthrylene.
Dibenz[*a,e*]aceanthrylene (**II**)  **(II)**	2B	no	‣ The authentic dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene) was subsequently reported in cigarette MSS by Snook *et al.* (82) at the USDA, but they provided no quantitative data on its per cigarette MSS delivery level. ‣ Most publications on dibenzo[*a,l*]pyrene in tobacco smoke unfortunately cite the reports of the incorrect compound. Hoffmann and Hecht (4) did not indicate which MSS isolate was included in their list – the isolate **II** reported in the 1950s (84,103,142,164) or the isolate **I** reported by Snook *et al.* (82) in 1977. ‣ In 1999, Hecht (148) noted that the presence of dibenzo[*a,l*]pyrene in MSS had not been confirmed.
Indeno[1,2,3-*cd*]pyrene	2B	no	
			Aza-Arenes
Quinoline		no	‣ In Hoffmann and Hoffmann (12), the cigarette MSS delivery range for quinoline is listed as 2–180 ng/cig, a range less than 10% of that listed in Hoffmann and Hecht (4) and Hoffmann and Hoffmann (11).
Dibenz[*a,h*]acridine	2B	no	‣ The single value (0.1 ng/cig) rather than a range indicates the MSS level is based on a single report, that of Van Duuren *et al.* (21). The value was determined with cigarettes marketed in 1959 or 1960. ‣ From 1961 through 2000, no investigators in the US [Candeli *et al.* (165); Schmeltz *et al.* (166,167); Snook (168); Snook *et al.* (116); Sasaki and Moldoveanu (31)], in Germany [Grimmer *et al.* (169)], or in Japan [Kaburaki *et al.* (170); Kamata *et al.* (30)] reported the confirmation of the presence and/or levels of these three aza-arenes (dibenz[*a,h*]acridine, dibenz[*a,j*]acridine, and 7*H*-dibenzo[*c,g*]carbazole) in cigarette MSS and/or nicotine pyrolysates. The results reported by these investigators are summarized in Table 4. ‣ In 2002, Rustemeier *et al.* (34) reported the presence of dibenz[*a,j*]acridine in cigarette MSS but no data or comment was provided on the identification of the compound.
Dibenz[*a,j*]acridine	2B	no	
7*H*-Dibenzo[*c,g*]carbazole	2B	no	

Table 3 (*cont.*)

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
		N-Nitrosamines	
None of the list compilers noted that the MSS levels listed for both volatile NNAs and TSNAs may be incorrectly high because of the artifactual formation of both types of these *N*-nitrosamines during MSS (and SSS) collection as reported by Caldwell and Conner (171). EPA (35,36) accepted the MSS volatile NNAs and TSNAs delivery levels reported by Hoffmann and Hecht (4). Presumably, OSHA did likewise in 1994 in preparation of its report (10).			
N-Nitrosodimethylamine {NDMA}	2A	yes	‣ Lung tumor production in laboratory animals exposed via inhalation to NDMA was classified as "equivocal" by RTECS (50). ‣ Lee *et al.* (135) reported that pyridine alkaloids (nicotine, nornicotine) as well as an aqueous extract of MSS "tar" inhibited the mutagenicity of NDMA in the Ames *Salmonella typhimurium* test and induction of sister chromatid exchange. ‣ OSHA (10) listed NDMA as a "probable human carcinogen".
N-Nitrosoethylmethylamine {NEMA}	2B	no	
N-Nitrosodiethylamine {NDEA}	2A	yes	‣ Lung tumor production in laboratory animals exposed via inhalation to NDEA was classified as "equivocal" by RTECS (50). ‣ OSHA (10) listed NDEA as a "probable human carcinogen".
N-Nitrosodi-*n*-propylamine {NDPA}	2B	no	‣ NDPA, omitted from lists by Hoffmann and Hecht (4) and Hoffmann and Hoffmann (11), was included in the 1998 list reported by Hoffmann and Hoffmann (12).
N-Nitrosodi-*n*-butylamine {NDBA}	2B	no	‣ NDBA, omitted from Hoffmann and Hecht (4) and Hoffmann and Hoffmann (11) listings, was included in 1998 listing by Hoffmann and Hoffmann (12).
N-Nitrosopyrrolidine {NPYR}	2B	no	‣ OSHA (10) listed NPYR as a "probable human carcinogen". ‣ In Hoffmann and Hoffmann (12), the MSS delivery range for NPYR is listed as 3–110 ng/cig, a range different from that reported earlier.
N-Nitrosopiperidine {NPIP}		no	
***N*-Nitrosodiethanolamine** {NDELA}	2B	no	‣ The only precursor in tobacco and/or tobacco smoke of NDELA is the diethanolamine salt of maleic hydrazide, often added to tobacco as a sucker control agent. However, it has been banned from use in USA tobacco agronomy since 1981 (172). The potassium salt of maleic hydrazide has been the reagent of choice since 1981. ‣ The diminution of levels of NDELA in tobacco should parallel the chronicled decrease in levels of arsenic and DDT in tobacco after these materials were no longer used in tobacco agronomy, e.g., between 1968 and 1974, the residual DDT level in USA flue-cured tobacco decreased from 52 µg/g in 1968 to 6 µg/g in 1970 to 0.23 µg/g in 1974 (3,24). ‣ Griffin *et al.* (173) reported similar decreases for arsenic residues in tobacco (3,24). ‣ In 1984, Hoffmann *et al.* (174) predicted that NDELA residues on tobacco (and in tobacco smoke) would gradually decrease because of the 1981 ban on the use of the diethanolamine salt of maleic acid. Despite the fact that this indeed occurred, many lists still contain NDELA as a tumorigen. ‣ In 1986, the IARC (3) noted: "Tobaccos grown in a [diethanolamine salt-free] environment and smoke generated from such tobaccos are devoid of *N*-nitrosodiethanolamine." ‣ OSHA (10) listed NDELA as a "probable human carcinogen". ‣ As noted by Rodgman and Green (19) NDELA no longer has any relevance as a tobacco smoke toxicant.
***N*-nitrososarcosine** {NSAR} {2-(methylnitrosamino)acetic acid}		no	‣ NSAR has been identified as a tobacco component but has not been identified to date as a tobacco smoke component.
N'-Nitrosonornicotine {NNN}	2B	no	‣ In contrast to NNK, NNN seldom induces lung tumors [when administered by non-inhalation routes] (4). ‣ OSHA (10) listed NNN as an "animal carcinogen". ‣ Nornicotine is an effective antimutagen vs. several NNAs (135,136).
4-(*N*-Methylnitrosamino)-1-(3-pyridinyl)-1-butanone {NNK}	2B	no	‣ In 1990, Hoffmann and Hecht (4) noted [NNK] "has not been tested by inhalation". ‣ OSHA (10) commented that "relevant information [is] not available" on this compound (NNK). ‣ Lee *et al.* (135) reported that pyridine alkaloids (nicotine, nornicotine, cotinine) as well as an aqueous extract of cigarette MSS "tar" inhibited the mutagenicity of NNK in the Ames *Salmonella typhimurium* test and induction of sister chromatid exchange. ‣ In 1991, with no new supporting evidence, Hecht and Hoffmann (175) listed the PAHs and NNK as the major carcinogens involved in lung cancer induction by cigarette smoke. Hecht reiterated this view in 1999 (148).

Table 3 (*cont.*)

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
N'-Nitrosoanabasine {NAB}	3	no	‣ In 1998, Hoffmann and Hoffmann (12) listed the MSS delivery range for NAB as ND–150 ng/cig whereas the range was reported earlier (4,5,11) as 0.14–4.6 µg. In subsequent lists NAB was no longer listed (16,17)
N'-Nitrosoanatabine {NAT}	3	no	
***N*-nitrosomorpholine** {NMOR}		no	‣ NMOR has been identified as a tobacco component but has not been identified to date as a tobacco smoke component.
		Aromatic amines	
2-Toluidine {aniline, 2-methyl-}	2B	no	‣ In 1986, IARC (3) considered the evidence to classify 2-toluidine as a human carcinogen to be "inadequate", cf. Hoffmann and Hecht (4). ‣ In 1998, Hoffmann and Hoffmann (12) listed the MSS delivery range for 2-toluidine as 30–337 ng/cig. This was a substantial difference from the range (30–200 ng/cig) listed in 1990 by Hoffmann and Hecht (4) and in 1997 by Hoffmann and Hoffmann (11). ‣ Hoffmann and Hecht (4) stated: "Recent studies have . . . shown that single ring aromatic amines, including the weak bladder carcinogen *o*-toluidine [2-toluidine], are present in human urine . . . The available data do not indicate that there are significant differences between smokers and nonsmokers". ‣ OSHA (10) listed 2-toluidine as an "irritant, cardiovascular system".
2-Naphthylamine	1	no	‣ In 1974, IARC (176) considered the evidence "sufficient" to classify 2-naphthylamine as a human carcinogen. ‣ In 1998 and 2001, Hoffmann and Hoffmann (12,16,17) listed the MSS delivery range for 2-naphthylamine as 1–334 ng/cig, a substantial difference from the range (1–22 ng/cig) listed in 1990 by Hoffmann and Hecht (4), in 1993 by Hoffmann *et al.* (5), and in 1997 by Hoffmann and Hoffmann (11). ‣ "An aromatic diamine . . . and 2-naphthylamine have also been reported in tobacco or tobacco smoke. The latter compound [2-naphthylamine] is a bladder carcinogen in man . . . , but is present in cigarette smoke in amounts . . . too low to be considered a health hazard" [Hoffmann *et al.* (177); Schmeltz and Hoffmann (178)]. ‣ In 1981, the US Surgeon General [see p. 25 in (25)] noted: "The presence of β-naphthylamine in cigarette smoke has been demonstrated . . . , along with other carcinogenic aromatic amines . . . The yield was so low that [the researchers] did not believe these agents contributed significantly to the risk of bladder cancer in smokers." ‣ In 1982, the US Surgeon General noted [see pp. 207–208 in (26)]: "On the basis of quantitative data for aromatic amines in cigarette smoke, an etiological significance of these traces of carcinogenic amines in bladder cancer is questionable, even if one were to consider the total of the aromatic amines and their metabolites." ‣ In the same publication, Hoffmann and Hecht (4) wrote two divergent statements: 1) "Because [its] concentration in cigarette smoke is relatively low, there is uncertainty about [its] role in human bladder cancer induced by smoke." 2) "2-Naphthylamine [is one of the two] most likely cigarette smoke components to be involved in bladder cancer induction in smokers, according to presently available data." ‣ OSHA (10) listed 2-naphthylamine as a known human carcinogen.
Biphenyl, 4-amino-	1	no	‣ IARC (179) considers the evidence "sufficient" to classify 4-aminobiphenyl as a human carcinogen. ‣ In 1982, the US Surgeon General [see pp. 207–208 in (26)] noted: "On the basis of quantitative data for aromatic amines in cigarette smoke, an etiological significance of these traces of carcinogenic amines in bladder cancer is questionable, even if one were to consider the total of the aromatic amines and their metabolites." ‣ In 1990, Hoffmann and Hecht (4) wrote: "Because [its] concentration in cigarette smoke is relatively low, there is uncertainty about [its] role in human bladder cancer induced by smoke." Compare this statement with another in the same publication: "4-Aminobiphenyl . . . [is one of the two] most likely cigarette smoke components to be involved in bladder cancer induction in smokers, according to presently available data." ‣ OSHA (10) listed 4-aminobiphenyl as a known human carcinogen.

Table 3 (*cont.*)

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
		N-Heterocyclic amines	
9*H*-Pyrido[2,3-*b*]indole, 2-amino- {A*a*C}	2B	no	
9*H*-Pyrido[2,3-*b*]indole, 2-amino-3-methyl {MeA*a*C}	2B	no	
1*H*-Imidazo[4,5-*b*]-pyridine, 2-amino-1-methyl-6-phenyl- {PhIP}	2B	no	
Dipyrido[1,2-*a*:3',2'-*d*]-imidazole, 2-amino-6-methyl- {Glu-P-1}	2B	no	‣ Lee *et al.* (137) reported that the mutagenicity (Ames test with *Salmonella typhimurium*) of Glu-P-1 was inhibited by cigarette MSS.
Dipyrido[1,2-*a*:3',2'-*d*]-imidazole, 2-amino- {Glu-P-2}	2B	no	‣ Lee *et al.* (137) reported that the mutagenicity (Ames test with *Salmonella typhimurium*) of Glu-P-2 was inhibited by cigarette MSS.
3*H*-Imidazo[4,5-*f*]quinoline, 2-amino-3-methyl- {IQ}	2A	no	‣ Lee *et al.* (137) reported that the mutagenicity (Ames test with *Salmonella typhimurium*) of IQ was inhibited by cigarette MSS.
3*H*-Imidazo[4,5-*f*]quinoline, 2-amino-3,4-dimethyl- {MeIQ}	2B	no	‣ Lee *et al.* (137) reported that the mutagenicity (Ames test with *Salmonella typhimurium*) of MeIQ was inhibited by cigarette MSS.
5*H*-Pyrido[4,3-*b*]indole, 3-amino-1,4-dimethyl- {Trp-P-1}	2B	no	‣ Lee *et al.* (137) reported that the mutagenicity (Ames test with *Salmonella typhimurium*) of Trp-P-1 was inhibited by cigarette MSS.
5*H*-Pyrido[4,3-*b*]indole, 3-amino-1-methyl- {Trp-P-2}	2B	no	‣ Lee *et al.* (137) reported that the mutagenicity (Ames test with *Salmonella typhimurium*) of Trp-P-2 was inhibited by cigarette MSS.
		Aldehydes	
Formaldehyde	2A	no	‣ In 1982, IARC (180) did not categorize formaldehyde as tumorigenic to humans. ‣ OSHA (10) listed formaldehyde as a "probable human carcinogen". ‣ In Tables 1 and 3 in Hoffmann and Hoffmann (11), two different MSS delivery ranges are listed for formaldehyde and acetaldehyde.
Acetaldehyde	2B	no	‣ Dalhamn *et al.* (181) reported that because of their water solubility, large proportions of formaldehyde, acetaldehyde, and crotonaldehyde do not reach the ciliated tissue of the lung because they are removed from orally-inhaled MSS and ETS by the scrubbing action of the fluids coating the oral cavity and laryngeal area and from nasally-inhaled ETS by *resorption.*
Crotonaldehyde	3	no	‣ Hoffmann and Hoffmann (11,16) and Hoffmann *et al.* (17) excluded crotonaldehyde from their 1997 and 2001 listings, respectively, but included it in their 1998 listing (12).
		Volatile hydrocarbons	
1,3-Butadiene	2A	no	
Isoprene	2B	no	
Styrene {benzene, ethenyl}	2B	no	
Benzene	1	no	‣ Benzene was listed by OSHA (10) as a known human carcinogen. ‣ IARC (182) classified benzene as an "A2 substance", i.e., a suspected human carcinogen, not because of any tumorigenic property but because it is leukemogenic. Epidemiological studies on smoking do not show a strong association between leukemia and cigarette smoking. ‣ Numerous attempts to induce skin carcinoma via skin-painting experiments with benzene in a variety of mammalian species were unsuccessful [e.g., see Hartwell (49) for pertinent studies by Lignac, Hess, Bernard, etc.]. ‣ In innumerable early studies [*cf*. Hartwell (49); Shubik and Hartwell (183); Thomas *et al.* (184)] on the carcinogenicity of compounds such as PAHs, benzene was used as the solvent in skin-painting studies where several control groups [cage controls(no treatment); solvent controls (painted with solvent only); positive controls (painted with solution of a known carcinogen in the solvent); the experimental group (painted with test material dissolved in the solvent)] were treated with benzene or benzene solutions. Tumor development at the painting site with benzene alone was rare; tumors at sites other than the painted area were rare. Later, acetone replaced benzene. ‣ In the mid-1940s, Crabtree (77) demonstrated that benzene, naphthalene, and anthracene were highly effective anticarcinogens for B[*a*]P and DBA. Naphthalene and anthracene, identified PAHs in cigarette MSS, are present in MSS at levels far in excess of those for B[*a*]P, DBA, and the other PAHs listed as tumorigens by Hoffmann and Hecht (4), OSHA (10), and Hoffmann and Hoffmann (11,12).

Table 3 (*cont.*)

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
Benzene (*cont.*)			‣ In Tables 1 and 3 in Hoffmann and Hoffmann (11), two different MSS delivery ranges are listed for benzene.
		Miscellaneous organic compounds	
Acetamide	2B	no	
Acrylonitrile	2A	no	‣ In 1979, IARC (185) considered the evidence "limited" to classify acrylonitrile as a human carcinogen. ‣ Hoffmann and Hecht (4) noted that the role of acrylonitrile in tobacco carcinogenesis is difficult to evaluate due to lack of data.
Acrylamide	2B	no	
Hydrazine, 1,1-dimethyl-	2B	no	
Nitromethane	2B	no	
2-Nitropropane	2B	no	‣ About 2-nitropropane, Hoffmann and Hecht (4) wrote: "Its organospecificity for liver suggests that it does not play a major role in tobacco carcinogenesis." The MSS delivery range listed for 2-nitropropane in (4,5,11,16,17) differs significantly from that listed in (2,12).
Nitrobenzene	2B	no	
Vinyl chloride	1	no	‣ In 1979, IARC (186) classified vinyl chloride as a human carcinogen. ‣ About vinyl chloride, Hoffmann and Hecht (4) wrote: "Its low levels in cigarette MSS do not support a major role in tobacco carcinogenesis." ‣ MSS delivery range listed for vinyl chloride in (12,16,17) differs from the range in (4,5,11).
Ethyl carbamate	1	no	‣ About ethyl carbamate (urethane), Hoffmann and Hecht (4) wrote: "Its potential role in tobacco carcinogenesis is difficult to evaluate." ‣ Because of its water-solubility, a large proportion of ethyl carbamate does not reach the lung because it is removed from orally-inhaled MSS and ETS by "scrubbing" in the oral cavity and laryngeal area and from nasally-inhaled ETS by "resorption".
Ethylene oxide	2B	no	
Propylene oxide	2B	no	
Di(2-ethylhexyl) phthalate		no	‣ In in-house studies at RJRT R&D on the composition of tobacco and tobacco smoke, di(2-ethylhexyl) phthalate (DEHP) was often found in tobacco extracts or smoke fractions. Study of this component revealed that its presence was artifactual, arising by use of extraction and/or chromatographic solvents introduced into the procedure via plasticized tubing and/or plasticized 55-gal drum faucets. The ester was not detected when the isolated fractions were obtained by use of highly purified solvents and no contact with plasticized equipment. ‣ The report of the presence of DEHP is reminiscent of the 1960 report by Schepartz *et al.* (187) of silicon-containing compounds in tobacco and the 1967 reports by Dymicky and his colleagues (188) of silicon-containing compounds in MSS. Subsequently, these silicon-containing tobacco and smoke components were shown to be artifactual and due to the silicone grease used on separatory funnel stopcocks. ‣ In its re-evaluation of di(2-ethylhexyl) phthalate in 2000, IARC classified di(2-ethylhexyl) phthalate as noncarcinogenic [see Footnote c, Table 5-4 in (16)].
Furan	2B	no	
Benzo[*b*]furan	2B	no	
		Phenols	
Catechol	2B	no	
Methyleugenol		no	
Caffeic acid	2B	no	
		Chloroaromatic compounds	
DDT	2B	no	‣ Between 1968 and 1974, the residual level of DDT in US flue-cured tobacco decreased from 52 µg/g in 1968 to 6 µg/g in 1970 to 0.23 µg/g in 1974 (3,24). Similar decreases were reported for arsenic residues (3,24,173) after arsenic use in US agronomy was discontinued (see below).

Table 3 (*cont.*)

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
DDT (*cont.*)			▸ Transfer rates of DDT from tobacco to cigarette MSS have been reported at 5% by Nesemann *et al.* (189) and at 12% by Hoffmann *et al.* (190). ▸ IARC (3) considered the evidence sufficient for DDT to be classified as carcinogenic to animals.
DDE		no	▸ DDT, a major precursor of DDE, is banned from use in US agronomy, including tobacco agronomy
Polychlorodibenzo-*p*-dioxins	1		
Polychlorodibenzofurans	3		
		Inorganic compounds	
Hydrazine	2B	no	▸ IARC (191) considered the evidence "inadequate" to classify hydrazine as a human carcinogen. ▸ In 1990, Hoffmann and Hecht (4) reported:" Data on hydrazine levels in cigarettes [*sic*] marketed in 1987 are not available." ▸ Because of its water-solubility, a large proportion of hydrazine does not reach the lung because it is removed from orally-inhaled MSS and ETS by "scrubbing" and from nasally-inhaled ETS by "resorption". ▸ OSHA (10) listed hydrazine as a probable human carcinogen.
Arsenic	1	no	▸ In 1952, arsenicals were removed from the list of permitted insecticides for tobacco. By 1968, the arsenic content of US tobacco had decreased from the 1951 level of about 50 µg/g to 0.5–1.0 µg/g (3,24). In 1975, Griffin *et al.* (173) reported tobacco arsenic levels in the range 0.5–0.9 µg/g. ▸ Cogbill and Hobbs (192) reported that a cigarette containing 7.1 µg of arsenic delivered 0.031 µg/puff (0.25 µg/cig) in its MSS, a transfer rate of 4.4%. ▸ A 2.5 pack-a-day smoker might inhale 12.5 µg/day of arsenic, cf. the report by Satterlee (193) that an urban area atmosphere (New York) over a 12-year period showed an arsenic level of 100–400 µg/10 m^3, the approximate daily intake of a resident. If the arsenic level in its tobacco were 0.9 µg/g as reported by Griffin *et al.* (173), a cigarette would deliver about 0.032 µg (32 ng) of arsenic in its MSS. ▸ In 1980, IARC (194) considered the evidence "sufficient" to classify arsenic as a human carcinogen. ▸ In 1999, Hecht noted that the arsenic level in MSS is substantially lower since discontinuance of its use in tobacco agronomy in 1952 (148). He also categorized the role of metals in MSS in tobacco smoke-induced lung cancer as "murky".
Beryllium	1		
Cobalt	2B		
Nickel	1	no	▸ IARC (195) considered the evidence "limited" to classify nickel as a human carcinogen. ▸ In 1979, the US Surgeon General (24) reported: "It is not likely that nickel plays a significant role in the etiology of lung cancer in smokers." This statement is repeated in the Surgeon General's 1982 report [see p. 211 in (26)]. ▸ OSHA (10) listed nickel as a known human carcinogen.
Chromium vi	1	no	▸ IARC (196) considered the evidence "sufficient" to classify chromium as a human carcinogen. ▸ In 1990, Hoffmann and Hecht (4) stated: "The possible [role] of chromium . . . in tobacco carcinogenesis [is] difficult to evaluate given the present data base."
Cadmium	1	yes	▸ IARC (3) considered the evidence "limited" to classify cadmium as a human carcinogen. ▸ Although lung tumors were induced in laboratory animals by inhalation of cadmium, in 1990, Hoffmann and Hecht (4) stated: "The possible [role] of cadmium in tobacco carcinogenesis [is] difficult to evaluate given the present data base . . . evidence for carcinogenicity [of cadmium] in humans is limited ." ▸ OSHA (10) listed cadmium as a probable human carcinogen.
Lead	2B	no	▸ IARC (197) considered the evidence "inadequate" to classify lead as a human carcinogen. ▸ In 1990, Hoffmann and Hecht (4) stated: "The possible [role] of . . . lead . . . in tobacco carcinogenesis [is] difficult to evaluate given the present database."

Component	IARC rating	Inhalation toxicology: SCC[a] production	Comments
Polonium-210	1	yes	‣ In 1981, the US Surgeon General [see p. 94 in (25)] stated: "In the case of polonium-210, a recent indepth [*sic*] study raises doubts on the significance of ^{210}Po as a factor contributing to lung cancer in smokers . . ." ‣ In 1982, the US Surgeon General [see p. 190 in (26)] wrote: "Polonium-210 (^{210}Po) is present in tobacco and cigarette smoke (0.03 to 1.0 pCi/cigarette); however, it is unlikely these traces represent a major risk for the smoker." From comparison of radon-daughter exposure of underground miners with their relative risk of lung cancer, Harley *et al.* (42) deduced that ^{210}Po is a questionable risk factor for lung cancer in cigarette smokers. ‣ In 1990, Hoffmann and Hecht (4) noted: "The quantities of polonium-210 found in the lungs of smokers are generally about three times higher than those in nonsmokers. However, the significance of polonium-210 in tobacco-induced lung cancer has been questioned upon comparison of these data with those obtained in miners" [Harley *et al.* (42)]. ‣ OSHA (10) listed ^{210}Po as a known human carcinogen.

[a]SCC = squamous cell carcinoma.

Coincident with the reduction in delivery of MSS TPM was a significant alteration in the composition of the MSS. For example, the B[*a*]P content for a commercial cigarette (expressed as ng B[*a*]P/mg TPM) decreased about 33%, i.e., from 1.2 ng/mg TPM to 0.8 ng/mg TPM during the same time period. In his 1979 report, the US SURGEON GENERAL summarizes these B[*a*]P data for a commercial cigarette sold in the US from 1954 to 1979 [see Chapt. 14, pp. 110–112 in (24)]. The decrease in cigarette tobacco blend nicotine content and MSS nicotine delivery over the same time period may also have influenced the pyrogenesis of the dibenzacridines and dibenzocarbazole during tobacco smoking. More recently, it was noted (16,17,52) that the MSS B[*a*]P delivery of a cigarette monitored since 1959 decreased by 62% whereas the MSS NNK delivery increased 78% between 1978 and 1997, the changes attributed to the increased nitrate content of the cigarette filler. For comparison purposes, listed in Table 2 are data from RODGMAN and GREEN (19) on the deliveries of various components in the MSS from the Kentucky reference 1R4F cigarette, a cigarette more closely related to currently marketed cigarettes than those whose MSSs were analyzed in the 1950s, 1960s, and 1970s. The delivery data listed are the averages of one or more analyses from various laboratories (INBIFO, RJRT, Omni, Labstat) on the MSS from the Kentucky reference 1R4F cigarette.

RODGMAN and GREEN (19) discussed at length the exposure of a pack-a-day smoker to MSS components classified as tumorigens or other types of toxicants. The exposures to all but a few MSS components are significantly less than the limits permitted by various industrial exposure rules, e.g., the American Conference of Governmental Industrial Hygienists' threshold limit value (TLV), OSHA's 8-hr time weighted average (TWA_8).

3 THE POST-1993 LISTS: AN ANALYSIS

In 1994, OSHA issued its indoor air quality report (10) that dealt at some length with ETS. In its report, OSHA listed 43 tobacco smoke components for which it stated "there is 'sufficient evidence' of carcinogenicity in humans or animals". These components are listed in Table 2. Since the "OSHA List of 43" includes only 42 items, polonium-210 may have been omitted inadvertently. The OSHA and HOFFMANN-HECHT lists share many components, but the OSHA list includes several components not listed by HOFFMANN and HECHT and *vice versa*. For example, OSHA (10) includes styrene and DDT but HOFFMANN and HECHT (4) do not.

The HOFFMANN and HOFFMANN 1997 list comprised 60 tobacco and/or tobacco smoke components classified as "carcinogens in tobacco and cigarette smoke" (11). Several components in the HOFFMANN-HECHT 1990 list but omitted from the OSHA 1994 list were also omitted from the HOFFMANN-HOFFMANN 1997 list. A major addition to the 1997 list that accounts for much of the increase to the 60 components in the HOFFMANN-HOFFMANN list is the inclusion of eight *N*-heterocyclic amines, many of which exhibit high mutagenicities in the Ames test (53). The HOFFMANN-HOFFMANN 1997 list also includes several additional vapor-phase components, ethylene oxide, 1,3-butadiene, and isoprene and the particulate-phase component DDE. This list is essentially duplicated in their 1998 Letter to the Editors of *Beiträge zur Tabakforschung International* (12).

Examination of the lists summarized in Table 2 reveals that a total of 83 different components are tabulated. In Tables 3 and 4, many of these components are examined in detail with comments as to why inclusion of many of them in a human risk assessment is problematic.

Of the components in the lists, the four classes of cigarette MSS components investigated in greatest detail during the past five decades are the PAHs, the aza-arenes, the NNAs and most recently the *N*-heterocyclic amines. They account for over 50% of the components tabulated as significant tumorigens in MSS. Because of the wealth of pre-1950 information available on PAHs and their demonstrated tumorigenicity in laboratory animals, extensive research (isolation, identification, quantitation, precursors, removal, prevention of formation, etc.) was conducted in the 1950s and 1960s on the PAHs in cigarette MSS.

The database on B[*a*]P stands out among the PAHs. Over almost five decades, an inordinate effort has been directed toward many aspects of B[*a*]P in tobacco smoke, whether in MSS, SSS, or ETS. This emphasis led COULTSON (54) in his 1980 discussion of the extensive research conducted on B[*a*]P in MSS to note:

Table 4. Dibenz[*a,h*]acridine (I), dibenz[*a,j*]acridine (II), and 7*H*-dibenzo[*c,g*]carbazole (III) in nicotine pyrolysates (Pyr) and mainstream cigarette smoke condensate[a]

	Dibenz[*a,h*]acridine[b]		Dibenz[*a,j*]acridine[b]		7*H*-Dibenzo[*c,g*]carbazole[b]	
Investigators	Pyr	CSC	Pyr	CSC	Pyr	CSC
Van Duuren *et al.* (21)	yes	yes	yes	yes	no	yes
Candeli *et al.* (165); Wynder and Hoffmann (162)	NE	no	NE	yes	NE	NE
Kaburaki *et al.* (170)	no	NE	no	NE	NE	NE
Schmeltz *et al.* (166)	no	NE	no	NE	no	NE
Schmeltz *et al.* (167)	no	no	no	no	no	no
Snook (168)	NE	no	NE	no	NE	no
Snook *et al.* (116)	NE	no	NE	no	NE	no
Grimmer *et al.* (169)	NE	no	NE	no	NE	no
Kamata *et al.* (30)	NE	no	NE	no	NE	NE
Sasaki and Moldoveanu (31)	NE	no	NE	no	NE	NE
Rustemeier *et al.* (34)	NE	no	NE	yes	NE	NE

[a] Examination of these results indicates that Van Duuren *et al.* (21) reported the identification of the three *N*-heterocyclic compounds (**I**, **II**, and **III**) in MS CSC and two of them (**I** and **II**) in a nicotine pyrolysate; whereas, Candeli *et al.* (165) failed to identify **I** but did identify **II** in MS CSC. The 1963 Candeli *et al.* findings on **II** in MS CSC were not confirmed in 1979 by investigators (167) from the same laboratory: Hoffmann was a participant in both the 1963 and 1979 studies. Two studies (166,167) confirmed the 1960 report by Van Duuren *et al.* that 7*H*-dibenzo[*c,g*]carbazole (**III**) was not present in a nicotine pyrolysate.

[b] yes = Compound identified; no = compound not found or identified; NE = substrate not examined for compound in question.

> Whether it's benzo[*a*]pyrene or not, nobody really knows. More work has been done on benzo[*a*]pyrene to prove it to be the causative agent in cigarette smoking than I think on any other chemical for any disease that I know. As yet the point is, you can't prove it.

This issue of differential research emphasis is relevant to the listing process. For example, except for the studies by SMITH *et al*., components such as DBA and 5-methylchrysene have only one MSS delivery level listed. Dibenzo[*a,l*]pyrene (benzo[*def,p*]chrysene), dibenzo[*a,e*]pyrene (naphtho[1,2,3,4-*def*]chrysene), and benzo[*b*]furan are listed only as "present". These less documented listings are awarded the same stature as B[*a*]P for which hundreds of MSS delivery determinations have been made and reported. Included in Table 2 are the data listed by FOWLES and BATES (18) on polychlorodibenzo-*p*-dioxins and polychlorodibenzofurans. Despite the fact that these tumorigens are known MSS components [see references in (19)], they have not appeared in any other list. Other biological properties of these compounds are discussed in Section 5.

4 ALTERNATE SOURCES OF EXPOSURE

Although the increased toxicologic potency of exposure via inhalation as compared with ingestion precludes direct quantitative comparison [ROZMAN and KLAASSEN, 55)], dietary exposures are notable. For many years prior to the identification of tumorigenic PAHs (mid- to late 1950s) and NNAs (mid-1960s) in cigarette MSS, it was known that these compound classes are present in a variety of beverages and foods, particularly cooked foodstuffs. Following the identification in the mid-1970s of several *N*-heterocyclic amines in cooked meats and several amino acid and protein pyrolysates [cf. SUGIMURA (53)], they too were identified in cigarette MSS. These compounds possess not only inordinately high mutagenicities when assayed in the Ames *Salmonella typhimurium* test but also are tumorigenic when administered via feeding to laboratory animals, including monkeys (13,14). Table 5 lists some references describing alternate exposures to PAHs, NNAs, and *N*-heterocyclic amines. Table 6 lists the B[*a*]P and B[*a*]A levels in a number of commonly consumed foodstuffs.

Since the late 1980s, several studies of daily exposures to B[*a*]P have provided much interesting data: a) MAGA (56) estimated the dietary intake of B[*a*]P to be 500 ng/day; b) WALDMAN *et al.* (57) found that the dietary intake of B[*a*]P ranged from 2 to 500 ng/day, much greater than the range found for inhalation, 10 to 50 ng/day; c) HATTEMEYER-FREY and TRAVIS (58) reported B[*a*]P exposure to be 2200 ng/day of which 97% resulted from dietary intake, 3% from inhalation; d) More recently, KAZEROUNI *et al*. (59) reported the B[*a*]P content of 200 commonly consumed food items and estimated that the daily dietary intake for 228 subjects ranged from less than 20 to 160 ng/day. However, none of these studies includes B[*a*]P exposure from beverages (coffee, tea) whose B[*a*]P content has been known since the 1950s, e.g., in 1957, FIESER (60) noted that the identification of B[*a*]P in roasted coffee beans preceded its identification in cigarette MSS by several years. Dietary and inhalation exposures to other PAHs probably parallel those of B[*a*]P, one of five PAHs most commonly found in food (61).

A reason often offered that PAHs such as B[*a*]P and DBA would have little effect on the host by ingestion in foodstuffs is their insolubility in aqueous media. Omitted from consideration is the fact that NEISE (62) demonstrated that such PAHs form water-soluble complexes with several purines and the PAHs may readily be recovered from the complex. The effective purines, present in beverages often consumed in conjunction with PAH-containing cooked foodstuffs, include caffeine (a component of coffee, tea, cocoa, and many carbonated beverages) and theobromine

Table 5. Alternate exposures to polycyclic aromatic hydrocarbons, *N*-nitrosamines , and *N*-heterocyclic amines listed as tobacco smoke tumorigens (2,3,4,5,10,11,12,16,17,18)

Cigarette MSS component	Alternate exposures	References
	Polycyclic aromatic hydrocarbons	
Benz[*a*]anthracene	broiled fish, broiled hamburger, barley malt, puffed cereals, common cooked and uncooked foods, coffee, tea	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
	gasoline and/or Diesel exhaust	Wynder and Hoffmann (91)
Benzo[*b*]fluoranthene	broiled fish, broiled hamburger, barley malt, common cooked and uncooked foods	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
Benzo[*j*]fluoranthene	common cooked and uncooked foods	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
	gasoline and/or Diesel exhaust	Wynder and Hoffmann (91)
Benzo[*k*]fluoranthene	broiled fish, broiled hamburger, puffed cereals, common cooked and uncooked foods	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
	gasoline and/or Diesel exhaust	Wynder and Hoffmann (91)
Benzo[*a*]pyrene	broiled fish, broiled hamburger, barley malt, puffed cereals, common cooked and uncooked foods, coffee, tea	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
	gasoline and/or Diesel exhaust, coal furnace emission	Wynder and Hoffmann (91), Grimmer *et al.* (198,199,200)
Chrysene	broiled hamburger, common cooked and uncooked foods	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
	gasoline and/or Diesel exhaust	Wynder and Hoffmann (91)
Chrysene, 5-methyl-	not identified in any foodstuff to date	
Dibenz[*a,h*]anthracene	broiled hamburger, barley malt, common cooked and uncooked foods	Grasso (61), Maga (56), Phillips (64)
	gasoline and/or Diesel exhaust	Wynder and Hoffmann (91)
Dibenzo[*a,e*]pyrene	common cooked and uncooked foods	Grasso (61), Maga (56)
Dibenzo[*a,h*]pyrene	common cooked and uncooked foods	Grasso (61), Maga (56)
Dibenzo[*a,i*]pyrene	common cooked and uncooked foods	Grasso (61), Maga (56)
Dibenzo[*a,l*]pyrene	common cooked and uncooked foods	Grasso (61), Maga (56)
Indeno[1,2,3-*cd*]pyrene	common cooked and uncooked foods	Grasso (61), Maga (56), Phillips (64), Kazerouni *et al.* (59)
	gasoline and/or Diesel exhaust, coal furnace emission	Wynder and Hoffmann (91), Grimmer *et al.* (200)
	N-Nitrosamines	
N-Nitrosodimethylamine	fried bacon, cured meats, fish, cheeses, alcoholic beverages (e.g. beer), water, rubber goods, tanned leather, pesticides, pharmaceuticals, cosmetics	Lijinsky (65), Tricker (201), Preussmann and Eisenbrand (202), Maga (56)
N-Nitrosodiethylamine	fried bacon, cured meats, fish, cheeses, alcoholic beverages, water, rubber goods, tanned leather	Lijinsky (65), Preussmann and Eisenbrand (202)
N-Nitrosodi-*n*-propylamine	pesticides	Preussmann and Eisenbrand (202)
N-Nitrosodi-*n*-butylamine	meat products, rubber goods	Lijinsky (65), Preussmann and Eisenbrand (202)
N-Nitrosopyrrolidine	fried bacon, cured meats, fish, water	Lijinsky (65), Tricker (201), Preussmann and Eisenbrand (202), Maga (56)
N-Nitrosodiethanolamine	beverages, cosmetics	Tricker (201), Preussmann and Eisenbrand (202)
N-Nitrososarcosine	diet, processed rubber	Tricker (201), Preussmann and Eisenbrand (202)
N-Nitrosomorpholine	beverages, cosmetics, rubber goods	Tricker (201), Preussmann and Eisenbrand (202), Maga (56)
N-Nitrosopiperidine	fried bacon, cured meats, cheeses, water, rubber goods	Lijinsky (65), Tricker (201), Preussmann and Eisenbrand (202), Maga (56)
	N-Heterocyclic amines	
A*a*C[a]	grilled meats, heated proteins (soya bean globulin)	Sugimura (53), Keating *et al.* (66)
MeA*a*C	grilled meats, heated proteins	Sugimura (53)
Glu-P-1	broiled squid, heated proteins, heated amino acid (glutamic acid)	Sugimura (53)
Glu-P-2	broiled squid, heated proteins, heated amino acid (glutamic acid)	Sugimura (53)
PhIP	heated proteins	Sugimura (53), Keating *et al.* (66)
IQ	broiled sardines, fried beef, heated proteins	Sugimura (53), Keating *et al.* (66)
Trp-P-1	broiled fish, heated proteins, heated amino acid (tryptophan)	Sugimura (53)
Trp-P-2	broiled fish, heated proteins, heated amino acid (tryptophan)	Sugimura (53)

[a] See Footnote, Table 2 for the complete chemical names of the *N*-heterocyclic amines.

Table 6. Level of benzo[*a*]pyrene (B[*a*]P) and benz[*a*]anthracene (B[*a*]A) in common foodstuffs

	(B[*a*]P)			(B[*a*]A)		
Foodstuff	ng/g	ng/serving[a]	cig/equiv[b]	ng/g	ng/serving[a]	cig/equiv[b]
Fresh vegetables	2.85–24.5	325–2800 (4)	32–280	0.3–43.6	34–4,970 (4)	3–400
Vegetable oils	0.4–1.4	46–160 (4)	5–16	0.8–1.1	91–125 (4)	7–10
Coconut oil	43.7	1245 (1)	125	98.0	2800 (1)	225
Margarine	0.4–0.5	11–14 (1)	1	1.4–3.0	40–85 (1)	3–7
Mayonnaise	0.4	23 (2)	2	2.2	125 (2)	10
Coffee	0.3–1.3	17–74 (2)	2–7	1.3–3.0	74–171 (2)	6–14
Tea	3.9	222 (2)	22	2.9–4.6	165–262 (4)	13–21
Grain	0.19–4.13	22–471 (4)	2–47	0.40–6.85	46–780 (4)	4–62
Oysters and mussels	1.5–9.0	171–1026 (4)	17–103	—	—	—
Smoked ham	3.2	370 (4)	37	2.8	319 (4)	25
Smoked fish	0.83	95 (4)	10	1.9	217 (4)	17
Smoked bonito	37	4218 (4)	422	189	21500 (4)	1720
Smoked whiting	6.9	787 (4)	79	—	—	—
Cooked sausage	12.5–18.8	1425–2143 (4)	143–214	17.5–26.2	2000–2900 (4)	160–232
Singed meat	35–99	3990–11290 (4)	400–1130	28–79	3200–9000 (4)	256–720
Broiled meat	0.17–0.63	19–72 (4)	2–7	0.2–0.4	23–46 (4)	2–4
Broiled hamburger, fatty	2.6	296 (4)	30	—	—	—
Broiled hamburger, lean	0	0 (4)	0	—	—	—
Charcoal-broiled steak	8.0	912 (4) 1824 (8)	9 (4) 182 (8)	4.5	513 (4) 1026 (8)	41 82
Charcoal-broiled T-bone	50	5700 (4) 11400 (8)	570 (4) 1140 (8)	—	—	—
Broiled mackerel	0.9	103 (4)	10	2.9	330 (4)	26
Barbecued beef	3.3	376 (4)	38	13.2	1500 (4)	120
Barbecued pork	4.5	513 (4)	51			
Barbecued ribs	10.5	1197 (4)	120	3.6	410 (4)	33
Bread, untoasted	0.23	20 (3)	2	—	—	—
Bread, light toast (3 min)	0.39	33 (3)	3	—	—	—
Bread, dark toast (5 min)	0.56	48 (3)	5	—	—	—
Cigarette MSS [c]	*20–25*			*20–35*		

[a] Number in parentheses indicate estimated number of ounces consumed. B[*a*]P and B[*a*]A content calculated at level in each ounce (28.35 g) consumed.

[b] Inhaled cigarette MSS particulate phase from one cigarette is assumed to deliver 10 ng of B[*a*]P and 12.5 ng of B[*a*]A to the smoker. It is also assumed, **contrary to experimental fact**, that "none of the MSS particulate phase, nor its B[*a*]*P* content, nor its B[*a*]A content is exhaled by the smoker".

[c] The total MSS (vapor phase + particulate phase) from an 85-mm filtered cigarette smoked under FTC conditions approximates 0.5 g.

(a cocoa component). This ability of PAHs to form water-soluble complexes with purines was the basis for an efficient method developed by ROTHWELL and WHITEHEAD to isolate PAHs from cigarette MSS (63).

Consumer exposures from food to many PAHs, NNAs, and *N*-heterocyclic amines are generally much greater than exposures to these compounds by inhalation of cigarette MSS or ETS. Examples of these exposures are summarized in Tables 5 and 6. Of course, a major exception is the exposure of smokers to tobacco-specific *N*-nitrosamines (TSNAs). In a recent series of reviews, relationships between cancer incidence and the dietary intakes of PAHs (64), NNAs (65), *N*-heterocyclic amines (66), metals (67), and man-made mutagens and carcinogens (68) were summarized.

5 INHIBITORS AND ANTICARCINOGENS IN MSS

As indicated previously, many investigators and agencies have repeatedly published lists of significant "tumorigens" or "carcinogens" in cigarette MSS despite numerous misinterpretations and misconceptions involved in assigning the term significant to some of the listed components. If it is considered appropriate to publish lists of MSS "tumorigens" with the various problems noted in Tables 3 and 4, is it not equally appropriate to list the anticarcinogens and/or inhibitors in MSS? However, only a few such lists have been published (37,38,39,69) that catalog MSS components that are either anticarcinogenic to or inhibit the tumorigenicity of some of the listed MSS components (4,10,11,12,16,17,18).

Proponents of the adverse effect of cigarette smoke and its components that they classify as "tumorigenic" or "carcinogenic" seldom discuss the details of the bioassays in which the specific component was demonstrated to be tumorigenic. Also seldom discussed is the fact that cigarette MSS (or SSS) contains many components reported, in the same types of bioassays used to demonstrate the "tumorigenicity" of the listed components, to inhibit the tumorigenicity of "tumorigenic" MSS components, or to be

anticarcinogens that nullify the "tumorigenicity"of one or more of the listed MSS "tumorigens."

Inhibitors of carcinogens or anticarcinogens are agents that prevent cancer development. WATTENBERG (70) placed them in three categories, based on the period in the carcinogenic process when they are effective. Category 1 comprises compounds that prevent formation of tumorigens from precursors, e.g., ascorbic acid (71), tocopherols (72), phenols (72,73). These compounds inhibit the formation of carcinogenic NNAs from precursor amines and nitrite both *in vivo* and *in vitro*. Category 2 comprises "blocking agents" which inhibit tumorigenesis by preventing tumorigens from reaching or reacting with critical target sites in the tissues, e.g., disulfiram (74), which inhibits the metabolism of symmetrical dimethylhydrazine to its tumorigenic metabolites (75). Category 3 includes inhibitors termed "suppressing agents" which suppress the expression of neoplasia in cells exposed to a tumorigen, e.g., the retinoids, vitamin A and related compounds (76).

Much has been written about the adverse health effects of the PAHs listed in Table 2 as tumorigenic components of cigarette MSS (4,10,11,12,16,17,18) but little has been written about the role of nontumorigenic MSS PAHs reported to counteract the tumorigenicity in laboratory animals of the potent tumorigens B[*a*]P, DBA, and 7,12-dimethylbenz[*a*]anthracene (DMBA).

PAH tumorigenicities depend on many factors (48,49). For example, at appropriate concentrations, tumorigenic B[*a*]P and DBA induce carcinomas in the rodent skin-painting bioassay but induce sarcomas on subcutaneous injection. In the 1940s, CRABTREE (77) reported the anticarcinogenicity of several nontumorigenic PAHs when administered with a potently tumorigenic PAH: Administration of benzene or naphthalene or anthracene with B[*a*]P or DBA significantly diminished the B[*a*]P and DBA tumorigenicity. Benzene, B[*a*]P, and DBA are listed as MSS tumorigens (4,10,11,12,16,17,18) in Table 2. Discussed in Table 3 is the noncarcinogenicity of benzene in the solvent-control group when it was used as the solvent for known or suspect tumorigens in a great number of the early skin-painting bioassays.

STEINER and FALK (78) reported that B[*a*]A, categorized as either an extremely weak or an inactive mouse-skin tumorigen (79), significantly diminished DBA tumorigenicity when both DBA and B[*a*]A were administered simultaneously by subcutaneous injection. Despite this and similar bioassay results plus the presence of B[*a*]A and DBA in MSS, both PAHs were repeatedly categorized, as shown in Table 2, as significant tumorigens in cigarette MSS (4,10,11,12,16,17,18).

SLAGA *et al*. (80) reported and DIGIOVANNI *et al.* (81) confirmed the anticarcinogenicity of the nontumorigenic PAHs fluoranthene and pyrene vs. the tumorigenic DMBA. Phenanthrene also diminished DMBA tumorigenicity (81). In skin-painting studies, pyrene and fluoranthene, both nontumorigenic, significantly inhibited tumor induction by B[*a*]P and DMBA (80). These nontumorigenic aromatic hydrocarbons (benzene, naphthalene, anthracene phenanthrene, fluoranthene, pyrene) are MSS components, present at per cigarette delivery levels far in excess of those of B[*a*]P, DBA, or any of the other 11 PAHs listed as tumorigens in Table 2.

From the voluminous evidence collected since the early 1930s on PAH tumorigenicity, it is now accepted that their tumorigenicity is not inherent but depends on the formation of specific metabolites, i.e., B[*a*]P and DBA are not tumorigenic *per se* but only exert their tumorigenicity if certain metabolites are formed after administration of the PAH to the host. The metabolites comprise one or more epoxides, dihydroxy compounds, and dihydroxy epoxides (79). This is true for B[*a*]P for which more than a dozen metabolites have been identified (79).

The tumorigenicities of PAHs such as B[*a*]P vary with the mode of administration, e.g., skin painting, intraperitoneal or subcutaneous injection (48,49). Also, the metabolites generated differ among species. Such differences have been used to explain the observed different responses of different species to the administration of PAHs such as B[*a*]P. Some species generate high levels of the more tumorigenic metabolites plus low levels of the nontumorigenic or borderline tumorigenic metabolites with subsequent tumor induction in the host. Other species generate zero or low levels of the tumorigenic metabolites plus high levels of the nontumorigenic metabolites with the result that no or few tumors are induced.

Conversion of B[*a*]P in an inhaled MSS particle to a particular metabolite cannot be a simple process. The more than 500 PAHs in cigarette MSS range from bicyclic to decacyclic. In a variety of chemical reactions, the rate of reaction decreased as the molecular weight (number of rings) of the PAH increased. That is, with stoichiometric levels of the PAH and the reactant, bicyclic PAHs reacted faster than tricyclic PAHs which in turn reacted faster than tetracyclic PAHs, etc.

Diol, epoxide, and/or diol-epoxide metabolites structurally similar to those described for B[*a*]P have been reported for many PAHs, e.g., naphthalene, anthracene, phenanthrene, benzo[*c*]phenanthrene, B[*a*]A, pyrene, chrysene, DBA, benzo[*b*]triphenylene, and DMBA (79). All of these and structurally similar PAHs have been reported as cigarette MSS components (82).

In a situation, such as the formation of metabolites, where an equimolar mixture of bicyclic through hexacyclic aromatic hydrocarbons is present, a pentacyclic aromatic hydrocarbon such as B[*a*]P will form little of its metabolite(s) compared to the levels formed by a more reactive bicyclic or tricyclic aromatic hydrocarbons. Numerous *in vitro* studies have demonstrated that inclusion of equimolar quantities of lower molecular weight PAHs such as phenanthrene or anthracene inhibited the hydroxylation-epoxidation of B[*a*]P in hepatic microsomes (83).

However, the PAH classes (bicyclic, tricyclic, etc.) in cigarette MSS are not present at levels equimolar vs. that of B[*a*]P or DBA but are present at significantly higher molar levels. Table 7 presents a combination of results from cigarette MSS PAH studies by HOFFMANN and WYNDER (23) and by RODGMAN and COOK (84). If the hydroxylation of B[*a*]P is inhibited by an equimolar amount of a lower molecular weight PAH, then inhibition should be even more pronounced when the PAH**:**B[*a*]P ratio is not unity but exceeds 15 or 35 or 250 as shown in Table 7. In an *in vitro* study, the nontumorigenic PAHs pyrene and fluoranthene significantly inhibited the binding of a tumorigenic PAH to calf thymus DNA (enzyme source =

Table 7. Levels of PAH classes in mainstream smoke

PAH category	Assumed approximate mol.wt	ng/cig	Approximate nanomoles[a]	Nanomolar ratio, PAH:B[*a*]P
Bicyclic aromatic hydrocarbons	128[b]	4140 (77.1)[c]	32.3	293
Tricyclic aromatic hydrocarbons	178[d]	720 (13.4)	4.0	36
Tetracyclic aromatic hydrocarbons	228	420 (7.9)	1.8	16
Pentacyclic aromatic hydrocarbons	278	72 (1.3)	0.26	2.4
Benzo[*a*]pyrene	252	27 [0.49][e]	0.11	1.0
Non-benzo[*a*]pyrene pentacyclic aromatic hydrocarbons	278	45 [0.81][e]	0.16	1.5
Hexacyclic aromatic hydrocarbons	328	14 (0.3)	0.04	0.36
Totals		*5366 (100.0)*		

[a] Nanomoles calculated with the approximate molecular weights in Column 2.
[b] The molecular weight of naphthalene is 128, that of indene is 116. It is realized that the average molecular weight of the bicyclic PAH mixture will differ slightly from those of the parent PAH because of the presence of numerous homologs (methylnaphthalenes, dimethylnaphthalenes, etc.).
[c] Values in parentheses represent the fraction % of the PAH category in the total PAH fraction.
[d] The presence of tricyclic PAH homologs results in an average molecular weight slightly different from 178.
[e] The sum of the fraction % of B[*a*]P and the fraction % of non-B[*a*]P pentacyclic PAHs equals 1.3%.

mouse skin homogenate) (80,85,86). The *in vitro* inhibition of the hydroxylation reaction is paralleled by a reduction of *in vivo* tumorigenicity.

Mouse skin-painting experiments involving repeated applications of solutions of equimolar quantities of similarly configured PAHs (one a potent tumorigen, the other inactive or weakly active) produced two effects: a) a slower induction of tumors and b) fewer tumor-bearing animals (TBA) with the mixture than with the tumorigen alone (87). A similar inhibition was reported in skin-painting studies with mixtures of DMBA and several inactive PAHs (88).

Despite the fragmentary knowledge of the reactions involved in PAH metabolite formation and reaction of the metabolite(s) with cellular components, these observations on anticarcinogenesis were explained in the early 1950s as the result of the competition for specific cellular sites between the metabolite(s) formed from the inactive PAH and the metabolite(s) formed from the tumorigenic PAH (89,90). Generally, the metabolite(s) from the lower molecular weight (and usually inactive) PAH win the competition.

From their comparison of the specific carcinogenicities and PAH contents of gasoline engine exhaust "tar" (EET) and CSC in skin-painting bioassays, WYNDER and HOFFMANN (91) acknowledged the possible efficacy of the saturated hydrocarbons (see below) and noncarcinogenic PAHs as anticarcinogens vs. tumorigenic PAHs:

> laboratory findings as presented in this report cannot be directly applied to man . . . just because the condensates used in this study produced skin cancer in experimental animals under the conditions described does not prove that they will produce cancer in man . . .
>
> it was anticipated that the exhaust gas "tar" would be many times more active than tobacco smoke condensate. However, as shown, it is only approximately twice as active. This relatively small increase in biological activity of exhaust gas "tar" raises the question of possible anticarcinogenic factors that may be more prevalent in engine exhaust "tar" . . . one may theorize that some of the noncarcinogenic polynuclear hydrocarbons that are present in engine exhaust gas "tar" in far greater concentrations than in tobacco smoke condensate may interfere with the resorption of the "tar." Some of the oily materials in gasoline engine exhaust "tar" and the paraffins in tobacco smoke condensate may also act as anticarcinogens.

Because of their vapor pressure properties, tumorigenic PAHs are reported to be present primarily in the MSS particulate phase. Similarly, many of the reported anticarcinogens or inhibitors occur in the MSS particulate phase (37,38,39), e.g., paraffinic hydrocarbons (92), β-sitosterol and cholesterol (92), α-tocopherol (93), indole (94), indole-3-acetonitrile (95), the duvatrienediols (96), and the PAHs (anthracene, phenanthrene, pyrene, fluoranthene, B[*e*]P) [see (39)].

Despite the fact that the anticarcinogenicity of certain components of tobacco (97) and tobacco smoke (90,98) and of tobacco smoke itself (90) has been known for over four decades, most discussions are directed at those components alleged to be tumorigenic to the smoker. Seldom is any significant discussion directed at smoke components known to possess anticarcinogenic properties.

In a 1964 review, WYNDER and HOFFMANN (99) did briefly discuss the possibility of anticarcinogenic agents in tobacco smoke:

> Thought must be given to possible antitumorigenic agents both in terms of "antiinitiators" as well as "tumor retarders." The former fits into the general concept of competitive carcinogenesis between strong and weak PAH, as well demonstrated in studies by Steiner and Falk [78] and recently by Kotin and Falk [100], using subcutaneous tissues as test tissue and with our own studies [101]) with epithelial tissue. Of particular interest is the inhibiting effect of benz[*a*]anthracene to B[*a*]P. The concept of anti-tumor promoters represents an area in which very little has been done . . .

In 1961, WYNDER and HOFFMANN (102) reported an example of MSS components inhibiting the action of a "tumorigen" currently included on the three lists. The finding was an outgrowth of their investigation of the effect of organic solvent extraction of tobacco on the PAH content of MSS (103). Hexane extraction of tobacco removes almost totally or to a substantial degree the major precursors of the MSS PAHs. These precursors include alkanes (104,105), phytosterols (106,107,108), and terpenoid com-

pounds other than phytosterols (106). Cigarettes fabricated from the extracted tobacco yield lower quantities in MSS of B[*a*]P and DBA (109). Skin-painting bioassays with MS CSCs from the control and extracted tobaccos give a lower percentage of tumor-bearing animals (% TBA) in the group treated with extracted tobacco CSC. However, the decrease in % TBA is considerably less than the percent decrease in the level in the CSC of tumorigenic PAHs (105,106, 107, 110).

One explanation for this difference is that the solvent extracted the alkanes from the tobacco and thus they are absent from the extracted-tobacco cigarettes MSS. The alkane fraction (approximately 3% of MS CSC) inhibits B[*a*]P tumorigenicity (111,112).

Mouse skin-painting studies with B[*a*]P and *n*-hentriacontane and *n*-pentatriacontane, where the alkane**:**B[*a*]P ratios are 200**:**1 and 100**:**1, show that both alkanes at both levels significantly inhibit the B[*a*]P tumorigenicity (111,112). The MSS of a cigarette delivering 20 mg of CSC contains about 0.6 mg (600 000 ng) of this alkane fraction and 10 ng of B[*a*]P, an alkane**:**B[*a*]P ratio far in excess of the 200**:**1 or 100**:**1 ratio that significantly inhibited the B[*a*]P tumorigenicity (6,111,113). Other early studies on MSS and CSC anticarcinogenicity include those of Homburger and his colleagues (114).

While they did discuss the anticarcinogenicity of B[*a*]A vs. B[*a*]P in the KOTIN-FALK report and in their own study (101), WYNDER and HOFFMANN (99) did not mention the KOTIN-FALK discussion (100) of the anticarcinogenicity vs. B[*a*]P or vs. DBA of nine PAHs (anthracene, benzo[*a*]fluorene, B[*a*]A, chrysene, pyrene, benzo[*e*]pyrene (B[*e*]P), benzo[*k*]fluoranthene, benzo[*ghi*]fluoranthene, perylene), two aza-arenes (benzo[*a*]carbazole, benz[*c*]acridine), and 2-naphthol. Only the two aza-arenes had not been identified in cigarette MSS prior to their review. Subsequently, both were identified in MSS (115,116).

WYNDER and HOFFMANN (117) again briefly discussed anticarcinogenic components of tobacco smoke:

> Any discussion of as complex a carcinogen as tobacco smoke should at least mention the existence of anticarcinogens. These are substances that reduce or "neutralize" the effect of a carcinogen by reacting with the carcinogen or a carcinogenic metabolite, thereby deactivating it, or by competing for reaction with cell constituents, or by interfering with the resorption of a carcinogen. Experiments with subcutaneous injections, as conducted by Steiner and Falk [78], have clearly demonstrated that a weak carcinogen such as benz[*a*]anthracene can reduce the effect of a potent carcinogen such as B[*a*]P. In similar experiments using mouse skin as test organ, Hoffmann and Wynder [[a]] showed that benz[*a*]anthracene may also reduce the activity of B[*a*]P in this setting. Whether this interaction applies to a similar extent when the substances are contained in an admixture such as tobacco "tar" requires separate investigations [[b]]. In one such study, painting mice with a dilute solution of benz[*a*]anthracene in addition to tobacco "tar," or adding this component to tobacco "tar" did not significantly alter the tumorigenic activity of the "tar" [[a]] . . .
>
> The existence of anticarcinogens, however, must be considered in evaluating any complex mixture such as tobacco smoke condensate . . .
>
> An explanation of the tumorigenic activity of tobacco smoke condensate in terms of single constituents is made more difficult by the presence of substances that may act as anticarcinogens and/or absorption retarders, especially for tumorigenic agents. It is known that structurally related noncarcinogenic hydrocarbons can inhibit the effect of carcinogenic hydrocarbons.
>
> [a] Citation is to unpublished research findings.
>
> [b] Claims on the tumorigenicity of various PAHs in cigarette MSS by the EPA, OSHA, IARC, and others seldom consider the importance of this statement. Such agencies generally assert that the biological effects observed with an individual PAH (or some other smoke component) are extrapolable to its effect in a complex mixture such as cigarette MSS or CSC.

WYNDER and HOFFMANN continued:

> The principle of anticarcinogens in the sense of "competitive" effect on tissue constituents may also apply to phenols . . . Paraffins represent an example of components that may interfere with the absorption of carcinogens [as shown] by Hoffmann and Wynder [112] . . . these interactions are readily demonstrable when testing two different components, but they may be less clear-cut when evaluated as part of a "tar" mixture. The existence of anticarcinogens, however, must be considered in evaluating any complex mixture such as tobacco smoke condensate.
>
> Several investigators have noticed some inhibition of tumor growth by tobacco smoke condensate . . . [including] Hoffman and Griffin [98] . . . Falk *et al.* [97] . . . [and] Homburger and Tregier [*sic*][118] . . . it should not come as a surprise that a material which has been proved to be carcinogenic may also interfere with tumor development, if not with tumor initiation . . .

WYNDER and HOFFMANN (119) added:

> An explanation of the tumorigenic activity of tobacco smoke condensate in terms of single constituents is made more difficult by the presence of substances that may act as anticarcinogens and/or absorption retarders, especially for tumorigenic agents. It is known that structurally related noncarcinogenic hydrocarbons can inhibit the effect of carcinogenic hydrocarbons. The same interrelationship may apply to tumor-promoting and nontumor-promoting phenols.

From their comparison of the specific tumorigenicities and PAH contents of gasoline engine exhaust "tar" (EET) and CSC in mouse skin-painting bioassays, WYNDER and HOFFMANN (120) acknowledged the efficacy of the alkanes and nontumorigenic PAHs (pyrene, fluoranthene, B[*e*]P) as anticarcinogens vs. tumorigenic PAHs. Two other interesting aspects of this study included: a) Successive dilutions of the EET and CSC solutions from 33% to 25% to 10% reduced the specific tumorigenicity of the EET from 54% to 48% to 32% and that of the CSC from 20% to 8% to 0%! b) The statement that

> laboratory findings as presented in this report cannot be directly applied to man just because the condensates used in this study produced skin cancer in experimental animals under the conditions described does not prove that they will produce cancer in man

Numerous compounds demonstrated in various laboratory animal bioassays to be highly effective anticarcinogens against many of the MSS components in the lists in Table 2 have been identified in MSS at per cigarette delivery levels far in excess of those of the alleged carcinogens. Seldom have these MSS anticarcinogenic components been discussed or even mentioned in the numerous reviews of the biological properties of cigarette MSS. Even though some of the earliest data on MSS components, e.g., the alkanes, that inhibit B[*a*]P tumorigenicity to mouse skin were provided by WYNDER and HOFFMANN (121), they more often preferred to discuss the alkanes as major precursors of MSS PAHs (6,20,23,107) rather than as inhibitors of B[*a*]P tumorigenicity. MSS components

known to possess significant inhibitory or anticarcinogenic action against various tumorigenic PAHs and NNAs have been cataloged (37,38,39).

Numerically, the anticarcinogens and inhibitors in cigarette MSS may exceed the number of "tumorigens" listed in Tables 2 and 3. However, many anticarcinogens are present in MSS at levels far in excess of the levels of many of the alleged "tumorigens", e.g., α-tocopherol vs. B[*a*]P, phenanthrene vs. B[*a*]P, β-sitosterol vs. B[*a*]P. This is also true for the inhibitor alkane fraction vs. B[*a*]P. A list of anticarcinogens and inhibitors with discussion of their smoke level and reported action is provided in the text accompanying Table 8. A smoke component listed as a "tumorigen", benzene, was one of the earliest compounds reported (77) to be an effective anticarcinogen in mammalian bioassays against several tumorigenic PAHs!

Despite the fact that the anticarcinogenicity of certain tobacco components (97), tobacco smoke components (98,122), and tobacco smoke *per se* (123) has been known for over four decades, most discussions have been limited to smoke components alleged to be tumorigenic to the smoker. Discussion of smoke components reported to possess anticarcinogenic properties has been minimal. However, the same is not true about carcinogens, anticarcinogens, and inhibitors in foodstuffs [see SLAGA and DIGIOVANNI (76), GRASSO (61)]. Those opposed to tobacco smoking view the complex mixture tobacco smoke differently from other complex mixtures such as raw or cooked foods, gasoline and Diesel engine exhausts, etc.

Other MSS components may have also influenced the mouse skin-painting results obtained with control tobacco and extracted tobacco CSCs. Hexane extraction of tobacco not only removes saturated aliphatic hydrocarbon inhibitors thus making impossible their transfer to MSS but also removes substantial amounts of β-sitosterol (108), α-tocopherol (vitamin E) (93,124), indole (125), α- and β-4,8,13-duvane-1,3-diol (96,126,127), and *d*-limonene (*p*-mentha-1,8-diene) (128), thus eliminating or drastically reducing their transfer to MSS during smoking. Subsequently, it was demonstrated that: a) These smoke components are present by transfer from tobacco to MSS during smoking and to SSS during smolder between puffs or they are generated during smoking. b) The compounds listed are anticarcinogenic vs. several of the listed tumorigens, e.g., PAHs, NNAs, ethyl carbamate. However, in the 1950s, neither the identity of several of these tobacco or smoke components nor their anticarcinogenicity was known.

Comparison of identified MSS components (129) with lists of compounds (76,130) reported to possess inhibitory or anticarcinogenic action in tumorigenesis experiments reveals not only that tobacco smoke contains numerous anticarcinogens but also that their levels in smoke usually exceed those of the "tumorigens" listed in Tables 2 and 3. A few inhibitory and anticarcinogenic MSS components were discussed previously, but they represent only a small fraction of the identified MSS components reported to possess one or other of these properties. From a review by SLAGA and DIGIOVANNI (76) and other publications (130), a list was compiled of MSS components reported to be inhibitors and anticarcinogens that counteract the tumorigenicity of MSS components (Table 8).

From the per cigarette MSS deliveries in Table 2, it may be calculated that the tumorigenic PAHs listed constitute from 4 to 10 μg/g of MS CSC. Nontumorigenic PAHs (naphthalene, anthracene, pyrene, phenanthrene, fluoranthene, B[*e*]P, benzo[*b*]triphenylene) total 90 to 180 μg/g of CSC. The anticarcinogenic effect of nontumorigenic PAHs and weakly tumorigenic or nontumorigenic aza-arenes vs. carcinogenic PAHs has been known since the 1940s (76,78,87).

As previously noted, when PAHs metabolize, a mixture of epoxides, dihydroxy compounds, and dihydroxy epoxides may be formed. This is true for B[*a*]P for which more than a dozen metabolites have been identified. In 1996, DENISSENKO *et al.* (131) reported the effect of a specific B[*a*]P metabolite on a cellular system and interpreted the result as an indication of the involvement of B[*a*]P in cigarette MSS in the induction of lung cancer in smokers. However, when B[*a*]P metabolizes, it does not necessarily yield 100% of the specific isomer used in the study by DENISSENKO *et al*. They selected (±)-*anti*-7β,8*a*-dihydroxy-9*a*,10*a*-7,8,9,10-tetrahydroB[*a*]P (BPDE), long recognized as the most important B[*a*]P metabolite with regard not only to tumorigenicity but also to DNA binding (132).

An interesting aspect of Table 8 is that it includes the dioxins as antitumorigens. SLAGA and DIGIOVANNI (76) summarize the studies in which dioxins were shown to interfere with the enzyme pathways responsible for the tumorigenicity of several of the most potent PAHs. The dioxins were not listed as MSS toxicants in previous tabulations similar to Table 8 (38,39). Is the omission of such MSS toxicants related in any way to the fact that dioxins are significant antitumorigens vs. some of the most potent mouse-skin tumorigenic PAHs present in MSS? In Chapter 6 of its 1964 Report, the Advisory Committee mentions that 27 nontumorigenic PAHs had been identified in MSS, but none by name [see Chapt. 6, p. 55 in (22)]. Was the omission of their identities related to the fact that several were known to be antitumorigenic to several potent mouse-skin tumorigens such as B[*a*]P?

Just as there are many MSS components known to inhibit or diminish the activity of MSS components classified as tumorigens, there are MSS components known to offset the activity of other MSS components shown to be mutagenic. In their investigation of the antimutagenicity of nicotine vs. *N*-nitrosodimethylamine (NDMA) and nicotine vs. B[*a*]P in the Ames test (*Salmonella typhimurium* TA 100), LEE and REED (133) reported that nicotine inhibits the mutagenicity of NDMA but not of B[*a*]P. Although the mechanism was not elucidated, a report by MURPHY and HEILBRUN (134) on the inhibition of NNN metabolism by nicotine suggests nicotine inhibition of NNA activation may be involved. In a repetition of their earlier experiment, LEE *et al.* (135) not only confirmed the nicotine antimutagenicity vs. NDMA but also the similar activity of nornicotine and cotinine. Recently, BROWN *et al.* (136) reported the antimutagenicity of nicotine and cotinine vs. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL).

LEE *et al.* (137) reported that CSC inhibits the mutagenicity of several *N*-heterocyclic amines listed as MSS carcinogens (11,12,16,17) when tested in the Ames assay (*Salmonella typhimurium* TA 98, S-9 activation system). The *N*-heterocyclic amines tested included Glu-P-1, Glu-P-2, Trp-P-1, Trp-P-2, IQ, and MeIQ, known to be potent mutagens

Table 8. Inhibitors, anticarcinogens, and antimutagens in tobacco smoke[a]

Component	Approx. delivery µg/g MS CSC	Effective against	AT, AM[b]	Representative references to inhibition, anticarcinogenicity, and/or antimutagenicity[c]
		Aliphatic hydrocarbons		
Saturated aliphatic hydrocarbons[d] e.g., $C_{31}H_{64}$, $C_{35}H_{72}$	30000 [2500][e]	B[*a*]P	AT	Wynder and Hoffmann (111)
d-Limonene	15–50	NNK	AT	Wattenberg and Coccia (203)
		DB[*a,i*]P	AT	Homburger *et al.* (204)
		Aromatic hydrocarbons		
Benzene	480–1900	B[*a*]P, DBA	AT	Crabtree (77)
Naphthalene	80–160	B[*a*]P, DBA	AT	Crabtree (77)
Anthracene	4–7	B[*a*]P, DBA	AT	Crabtree (77)
Phenanthrene	2–4	DMBA	AT	DiGiovanni *et al.* (81)[c]
Fluoranthene	3–4	DMBA	AT	DiGiovanni *et al.* (81)[c], Slaga *et al.* (80)[c]
Pyrene	3–4	DMBA	AT	DiGiovanni *et al.* (81)[c], Slaga *et al.* (80[c]
Benz[*a*]anthracene	0.8–2.8	DBA	AT	Steiner and Falk (78)
Benzo[*e*]pyrene	0.2	DMBA	AT	DiGiovanni *et al.* (81)[c], Slaga *et al.* (80)[c]
Benzo[*b*]triphenylene[f]	0.05	MC, DBA, DMBA	AT	Slaga and Boutwell (85)[c], Slaga et al. (80)[c]
		Alcohols		
Ethanol		NNN	AT	Waddell and Marlowe (205)[c]
		NNN	AM	Farinati *et al.* (206)
1-Butanol		NNN	AT	Waddell and Marlowe (205)[c]
2-Propanol, 2-methyl- {*tert*-butanol}		NNN	AT	Waddell and Marlowe (205)[c]
α-4,8,13-Cyclodecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-; {α-4,8,13-duvane-1,3-diol}	8–20	DMBA	AT	Saito *et al.* (127)[c]
β-4,8,13-Cyclodecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-; {β-4,8,13-duvane-1,3-diol}	12–25	DMBA	AT	Saito *et al.* (127)[c]
β-Sitosterol	400–500	NNA PAH	AT	Wattenberg (207)[c] Yasukawa *et al.*[c]
Cholesterol	120–240	NNA	AT	Cohen *et al.*[c]
		Acids		
Acids, long-chained aliphatic e.g., $C_{16}H_{32}O_2$; $C_{18}H_{36}O_2$		NNA	AM	Takeda *et al.* (208)
Benzoic acid, 3,4,5-trihydroxy- {gallic acid}		NNA	AT	Mirvish *et al.*[c]
1-Propene-1,2,3-tricarboxylic acid {aconitic acid}		B[*a*]P	AT	Kallistratos[c], Kallistratos and Fasske[c]
2-Propenoic acid, 3-(3,4-dihydroxyphenyl)- {cinnamic acid, 3,4-dihydroxy-} {caffeic acid}		B[*a*]P	AT	Wattenberg *et al.*[c]
2-Propenoic acid, 3-(3-hydroxy-4-methoxyphenyl)- {cinnamic acid, 3-hydroxy-4-methoxy-} {ferulic acid}		B[*a*]P	AT	Wattenberg (207)
2-Propenoic acid, 3-(2-hydroxyphenyl)- {cinnamic acid, 2-hydroxy-}		B[*a*]P	AT	Wattenberg *et al.*[c]
2-Propenoic, 3-phenyl- {cinnamic acid}		NPYR, NNN	AT	Chung *et al.* (209,210)
		Phenols		
Phenol	1000–7000	B[*a*]P	AT	Van Duuren *et al.* (211)
		NNN, NPYR		Chung *et al.* (209, 210)
Phenol, 4-methoxy-		B[*a*]P	AT	Wattenberg *et al.*[c]
α-Tocopherol {vitamin E}	400–600	MC, DMBA, DB[*a,i*]P, 1,2-DMH	AT	Shamberger[c], Shklar[c], Slaga and Bracken[c], Viaje *et al.*[c], Weerapradist and Shklar[c]
		NNA	AT	Thompson (212)
		CSC	AM	Rosin[c]
2*H*-1-Benzopyran-2-one, 6,7-dihydroxy- {esculetin}		NNK	AT	Teel and Castonguay (213)

Table 8 (*cont.*)[a]

Component	Approx. delivery µg/g MS CSC	Effective against	AT, AM[b]	Representative references to inhibition, anticarcinogenicity, and/or antimutagenicity[c]
		N-Containing components		
Indole	400–600	NNA	AT	Matsumoto *et al.*[c]
		NNN, NPYR	AT	Chung *et al.* (209, 210)
		NNK	AT	Chung *et al.* (214)
Indole-3-acetonitrile		B[*a*]P	AT	Kovacs and Somogyi[c]
1*H*-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl- {theobromine}		EC	AT	Nomura[c]
1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl- {caffeine}		EC, DMB, NNA	AT	Nomura[c], Perchellet and Boutwell[c], Mirvish *et al.*[c]
Nicotine		NNK	AT	Schüller *et al.* (215)
		NDMA	AM	Lee *et al.* (135)
		NNAL	AM	Brown *et al.* (136)
Nornicotine		NDMA	AM	Lee *et al.* (135)
		NNAL	AM	Brown *et al.* (136)
Cotinine		NDMA	AM	Lee *et al.* (135)
		NNAL	AM	Brown *et al.* (136)
		Miscellaneous components		
2*H*-Benzopyran-2-one {coumarin}		B[*a*]P, DMBA	AT	Wattenberg *et al.*[c]
3*H*-2-Furanone, dihydro-5-methyl- {α-angelica lactone}		B[*a*]P	AT	Wattenberg *et al.*[c]
Benzoic acid, 3,4,5-trihydroxy-, propyl ester[d] {propyl gallate}		NNK	AT	Lo and Stich[c], Teel and Castonguay (213)
Dioxin		DMBA, MC, B[*a*]P, 7-MBA, 12-MBA, 5-MeC, DBA	AT	Berry *et al.* (216), Cohen *et al.* (217), DiGiovanni *et al.* (81, 218)
Carbon disulfide		1,2-DMH	AT	Wattenberg and Fiala[c]
Maleic anhydride		PAH, DMBA	AT	Klein[c], Slaga *et al.*[c]
Selenium		DMBA	AT	Shamberger[c]
		NNA	AT	Thompson (212)
Cysteine		NDMA	AT	Lo and Stich[c]

[a] *Abbreviations*: B[*a*]P = benzo[*a*]pyrene; DBA = dibenz[*a,h*]anthracene; DB[*a,i*]P = dibenzo[*a,i*]pyrene = benzo[*rst*]pentaphene; DMBA = 7,12-dimethylbenz[*a*]anthracene; 1,2-DMH = 1,2-dimethylhydrazine; 7-MBA = 7-methylbenz[*a*]anthracene; 12-MBA = 12-methylbenz[*a*]anthracene; 5-MeC = 5-methylchrysene; EC = ethyl carbamate; MC = 3-methylcholanthrene = 1,2-dihydro-3-methylbenz[*j*]aceanthrylene; NDMA = *N*-nitrosodimethylamine; NNA = *N*-nitrosamine; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNN = *N'*-nitrosonornicotine; NNK = 4-(*N*-methylnitrosamino)-1-(3-pyridinyl)-1-butanone; NPYR = *N*-nitrosopyrrolidine; PAH = polycyclic aromatic hydrocarbon.

[b] AT = test for antitumorigenicity; AM = test for antimutagenicity.

[c] Details of this reference may be found in Fay *et al*. (130) and/or Rodgman (38). Additional references may be found in (38,76,81, 130).

[d] This fraction consists primarily of the *normal*-, *iso*- (2-methyl-), and *anteiso*- (3-methyl-) alkanes from C_{15} to C_{40}.

[e] Average weight (µg/g MS CSC) of each hydrocarbon isomer.

[f] Benzo[*b*]triphenylene was formerly known as dibenz[*a,c*]anthracene.

(53,138,139,140). Several are tumorigenic in mammalian bioassays (141). LEE *et al*. (137) reported that 50 to 100 µg of CSC per plate suppress the mutagenicity of these compounds by as much as 80%. Enzymatic studies indicate that CSC is a potent inhibitor of cytochrome P-450 dependent monooxygenase. Thus, it appears that CSC exerts its antimutagenicity by inhibiting the P-450 system.

The SHEAR-LEITER admonition about prediction not only of complex mixture tumorigenicity from individual component data but also the tumorigenicity of an individual component in MSS is also applicable to the tumorigen-antitumorigen situation. Bioassay results that show one-on-one inhibition in a study involving a tumorigen and an antitumorigen may not be extrapolable to the two compounds in a complex mixture such as MSS.

6 INTERNAL DIFFERENCES AMONG THE LISTS

Examination of the data in Table 2 from the various lists reveals many numerical inconsistencies and unit assignments (ng vs. µg or µg vs. mg). Rather than list the numerous inconsistencies, they are indicated in bold print in Table 2. Many were listed in detail previously (29). Examples of the most obvious inconsistencies include: a) The listing of a single value for DBA – in 1958 VAN DUUREN (142) listed a cigarette MSS delivery of 5 ng/cig for DBA, a value not found in most of the lists (2,3,4,5,10,11,12,16,17,18). b) The delivery data presented in several publications for dibenzo[*a,i*]pyrene (1.7–3.2 ng) and dibenzo[*a,l*]pyrene (present) are interchanged. Also, the particular dibenzo[*a,l*]pyrene is not specified. Do the

citations refer to the dibenzo[*a,l*]pyrene reported in the 1950s but later shown by LAVIT-LAMY and BUU-HOÏ (143) to be dibenz[*a,e*]aceanthrylene (dibenzo[*a,e*]fluoranthene) or to the authentic dibenzo[*a,l*]pyrene (82)? Neither the IARC list or any of the other lists include dibenz[*a,e*]aceanthrylene as a MSS tumorigen. The evidence on its tumorigenicity is classified by IARC as "limited" in laboratory animals (144), but that is the same classification IARC assigns to styrene, a component IARC includes in its MSS tumorigen list (3).

While it does not seem necessary to discuss the numerous listed inconsistencies (2,3,4,5,11,12) readily apparent to the perceptive reader of Table 2, a few pertinent comments about two of the more recent listings (16,17) may be appropriate. Of course, of particular interest is the 2001 article by HOFFMANN and HOFFMANN (16) published in the highly publicized NCI Monograph 13. With ample opportunity to correct the numerous previously listed errors noted by RODGMAN (29) in 1998, the HOFFMANNs did not do so but in a subsequent 2001 publication (17) they not only repeated the same errors listed in (16) but also introduced several new ones, e.g., HOFFMANN and HOFFMANN (16) list the MSS delivery of 2,6-dimethylaniline as *4–50 μg/cig* whereas HOFFMANN *et al*. (17) list it as *4–50 ng/cig*; quinoline delivery is listed as *1–2 ng/cig* in (16) vs. *1–2 μg/cig* in (17).

In their NCI Monograph 13 article, HOFFMANN and HOFFMANN (16) also criticized the Tobacco Industry:

> Major modifications in the makeup of the commercial cigarette were introduced between 1950 and 1975. Since then, there have been no substantive changes toward a further reduction of the toxic and carcinogenic potential of cigarette smoke beyond reducing MS yields of tar, nicotine, and carbon monoxide. Some of these modifications have also resulted in diminished yields of several toxic and carcinogenic smoke constituents.

The modifications noted by HOFFMANN and HOFFMANN were the eight technologies considered significant in the design of "less hazardous" cigarettes by the NCI (145), the US Surgeon General (24,25), and various individuals opposed to cigarette smoking. Several reports in which the various authorities commended these eight design technologies were recently listed chronologically (1960 through 1997) (19,146). It should be noted that all eight design technologies had been incorporated into one or more US commercial cigarette products prior to the first meeting of the Tobacco Working Group formed in 1968 for the NCI program. In other words, from 1968 to 1978, no new significant design technology was generated in the NCI Smoking and Health Program on the "less hazardous" cigarette!

The HOFFMANN and HOFFMANN criticism of the Tobacco Industry for its failure to generate any new significant cigarette design technologies since 1975 (16) is totally without merit. Since 1975, the eight design technologies, when used in concert but to different degrees, have continued to reduce the sales-weighted FTC "tar" substantially below the goal originally recommended by WYNDER (147), i.e., a 50% reduction from the mid-1950 "tar" yield. Despite their knowledge in tobacco and smoke composition and cigarette design, no critic has ever developed a cigarette design technology to match the significance of the eight in US and worldwide commercial cigarette production since the late 1960s. In fact, several cigarette design technologies asserted by such critics to be beneficial were found to be inadequate both chemically and biologically when studied in the NCI "less hazardous" cigarette program (145).

Examination of the graphical representation of the sales-weighed "tar" and nicotine values for US commercial cigarettes [see Figure 5-1 in (16)] reveals that from 1975 to date the FTC "tar" value has decreased from about 18 to 11 mg/cig (~40%). The HOFFMANNs apparently ignored this information readily apparent in the graph they presented as Figure 5-1 in their Monograph 13 publication (16). The fact that the use of the eight technologies from 1975 to date resulted in about a 40% decrease in the sale-weighted average FTC "tar" yield was obviously not considered. This "tar" yield decrease was accompanied by decreases in the yields of MSS particulate-phase components considered toxic.

Another interesting dichotomy exists with respect to dibenzo[*a,l*]pyrene. In 1999, HECHT stated (148):

> The presence in cigarette smoke of dibenzo[*a,l*]pyrene, a highly carcinogenic PAH, has not been confirmed.

Does the statement by HECHT suggest that lack of confirmation of the presence of a compound in MSS means it should not be considered as an adverse biological component? If so, why does HECHT list in the same article as pulmonary carcinogens the three aza-arenes whose presence in MSS numerous competent investigators have not confirmed? If HECHT is discounting the presence in cigarette MSS of dibenzo[*a,l*]pyrene because its identification by SNOOK *et al*. (82) at the USDA has not been confirmed by other investigators, then he should discount reports on the following MSS components: a) Over 200 of the more than 500 PAHs that SNOOK *et al*. reported in their monumental study of PAHs in cigarette MSS (82,149,150). b) About 50% of the aza-arenes reported for the first time by SNOOK *et al*. (116). c) Many of the nitrogen-containing components of MSS reported by HECKMAN and BEST (151). d) Many of the ether-soluble MSS components reported by NEWELL *et al*. (152). e) Several hundred of the water-soluble MSS components reported for the first time by SCHUMACHER *et al.* (153). In the latter three publications, 828 previously unreported MSS components were described. Fewer than a third of the 828 new components reported in these studies in the late 1970s/early 1980s have been confirmed by other investigators! However, the data on the unconfirmed compounds in these three studies are irrefutable. According to HECHT (148), at least 3500 components are present in the MSS particulate phase. The only way that number can be attained is by counting the unconfirmed MSS components in the reports listed above (82,116,149,150,151,152,153). The reason for lack of confirmation of many of the reported MSS components in these studies is that very few large-scale isolation/identification studies have been conducted on MSS since the early 1980s. SSS and ETS compositions have been emphasized with the main objective to show that the significant toxicants in SSS and ETS are the same ones present in MSS and to determine the levels of such components in SSS and ETS.

Several other problems exist with the lists, e.g., the inclusion of smoke components whose presence may be highly

questionable [dibenz[*a,h*]acridine; dibenz[*a,j*]acridine; dibenzo[*c,g*]carbazole; di(2-ethylhexyl) phthalate] or for which sparse or no delivery data are available (dibenzo[*a,e*]pyrene; dibenzo[*a,h*]pyrene; benzo[*b*]furan, 1,1-dimethylhydrazine). Also problematic is the listing of components whose precursors are no longer used in tobacco agronomy, e.g., *N*-nitrosodiethanolamine vs. the diethanolamine salt of maleic hydrazide. Such components are listed in bold print in Tables 2 and 3. The omission of di(2-ethylhexyl) phthalate from recent lists (16,17,18,19) is because of its removal from the "Group 2B Carcinogen" classification by IARC in 2000.

7 CONCLUSIONS

Even if the frequently cited lists of "tumorigenic" compounds reported in cigarette MSS were revised to improve accuracy and consistency, their use for the purpose of assessing carcinogenic risk to humans is highly questionable. This practice ignores two important factors: a) the conditions under which the carcinogenicity of a specific component was determined, and b) a large body of evidence demonstrating that the carcinogenic potency of a complex mixture is not a summation of the carcinogenicity of its individual components. This lack of additivity noted in b) can result not only from complex chemical interactions among the constituents, but also from biological alterations in absorption, distribution, metabolism, and excretion which may be differentially induced by one or more constituents (55). In some cases, complex mixtures of mutagenic and carcinogenic compounds may show reduced biological activity when compared with the activity anticipated by summation of the contributions of the individual compounds [SLAGA and DIGIOVANNI (76); LEE *et al.* (135, 137)]. As noted by SMITH *et al*. in their reviews (13,14,15), an extensive literature exists that demonstrates the inability to attribute the carcinogenic risk associated with cigarette smoking to a particular compound or family of compounds in the MSS.

Acknowledgments: I am greatly indebted to Drs. Thomas A. Perfetti and Carr J. Smith of the Research and Development Department of the R.J. Reynolds Tobacco Company for their encouragement to write this manuscript and submit it for publication. The capable assistance provided by Ms. Helen S. Chung and the staff of RJRT Science Information in the acquisition of numerous references is greatly appreciated.

REFERENCES

Note: Listed RJRT research department memoranda (RDM) and reports (RDR) plus R&D memoranda (R&DM) and reports (R&DR) are available on the Internet at www.rjrdocs.com.
The Bates numbers for the pages of the documents are also indicated. In some instances, several copies of a report are on file in the repository. The Bates numbers for only one copy are listed.

1. Rodgman, A.: The *N*-nitrosamines in tobacco and tobacco smoke; October, 1993: pp. i-xv, 1–259: see www.rjrtdocs.com 509752851 -3134
2. Hoffmann, D. and E.L. Wynder: Chemical constituents and bioactivity of tobacco smoke; *in*: Tobacco: A major health hazard, edited by D.G. Zardidze and R. Peto, IARC, Lyon, France, IARC Sci. Publ. No. 74 (1986) 145–165.
3. IARC: Chemistry and analysis of tobacco smoke; *in*: Evaluation of the carcinogenic risk of chemicals to humans: Tobacco smoking; IARC, Lyon, France, IARC Monograph 38, 1986, pp. 83–126, 387–394.
4. Hoffmann, D. and S.S. Hecht: Advances in tobacco carcinogenesis; *in*: Chemical carcinogenesis and mutagenesis. I, edited by C.S. Cooper and P. Grover, Springer-Verlag, London, U.K., 1990, Chapter 3, pp. 63–102.
5. Hoffmann, D., A. Rivenson, F.L. Chung, and E.L. Wynder: Potential inhibitors of tobacco carcinogenesis; *in*: Tobacco smoking and nutrition: Influence of nutrition on tobacco-associated health risks, edited by J.N. Diana and W.A. Prior, Ann. N.Y. Acad. Sci. 686 (1993) 140–160.
6. Wynder, E.L. and D. Hoffmann: Tobacco and tobacco smoke: Studies in experimental carcinogenesis; Academic Press, New York, N.Y., 1967, pp. 496–501.
7. Wynder, E.L. and D. Hoffmann: Tobacco and health: A societal challenge; New Eng. J. Med. 300 (1979) 894–903.
8. Wynder, E.L. and D. Hoffmann: Tobacco; *in*: Cancer epidemiology and prevention, edited by D. Schottenfeld and J.F. Frauneni Jr, W.B. Saunders, Philadelphia PA, 1982, pp. 277–292.
9. Closing Quotes Department: Dietrich Hoffmann: Author of the list; Tobacco Reporter (July 2002) pp. 70–72.
10. Occupational Safety and Health Administration: Indoor air quality; Fed. Reg. 59 (No. 65) (1994) 15968–16039.
11. Hoffmann, D. and I. Hoffmann: The changing cigarette: 1950–1995; J. Toxicol. Environ. Hlth. 50 (1997) 307–364.
12. Hoffmann, D. and I. Hoffmann: Tobacco smoke components. Letter to the Editor; Beitr. Tabakforsch. Int. 18 (1998) 49–52.
13. Smith C.J., S.D. Livingston, and D.J. Doolittle: An international literature survey of "IARC Group 1 carcinogens" reported in mainstream smoke; Food Chem. Toxicol. 35 (1997) 1107–1130; Smith, C.J., T.A. Perfetti, M.A. Mullens, A. Rodgman, and D.J. Doolittle: An international literature survey of IARC carcinogens in cigarette mainstream smoke; 53rd Tobacco Science Research Conference, Program Booklet and Abstracts, Vol. 53, Paper No. 28, 1999, pp. 34–35.
14. Smith C.J., T.A. Perfetti, M.A. Rumple, A. Rodgman, and D.J. Doolittle: "IARC Group 2A carcinogens" reported in cigarette mainstream smoke; Food Chem. Toxicol. 38 (2000) 371–383.
15. Smith C.J., T.A. Perfetti, M.A. Rumple, A. Rodgman, and D.J. Doolittle: "IARC Group 2B carcinogens" reported in cigarette mainstream smoke; Food Chem.

Toxicol. 39 (2001) 183–205.
16. Hoffmann, D. and I. Hoffmann: The changing cigarette: Chemical studies and bioassays; *in*: Risks associated with cigarettes with low machine-measured yields of tar and nicotine, NCI smoking and tobacco control, Monograph 13, edited by D.M. Burns and N.L. Benowitz, United States Department of Health and Human Services, Bethesda MD, Chapter 5 (2001) 159–191.
17. Hoffmann, D., I. Hoffmann, and K. El-Bayoumy: The less harmful cigarette: A controversial issue. A tribute to Ernst L. Wynder; Chem. Res. Toxicol. 14 (2001) 767–790.
18. Fowles, J. and M. Bates: The chemical constituents in cigarettes and cigarette smoke: Priorities for harm reduction. A Report to the New Zealand Ministry of Health, March 2000, pp. 1–65.
19. Rodgman, A. and C.R. Green: Toxic chemicals in cigarette mainstream smoke – hazard and hoopla; *in*: Cigarette risk and the potential for risk reduction, Invited Speaker Symposium Proceedings, 2002 CORESTA Congress, New Orleans LA, pp. 2–52.
20. Wynder, E.L. and D. Hoffmann: Experimental tobacco carcinogenesis; Science 162 (1968) 862–871.
21. Van Duuren, B.L., J.A. Bilbao, and C.A. Joseph: The origin and nature of the nitrogen heterocyclics in cigarette smoke condensate; Proc. Am. Chem. Soc. Mtg.-in-Miniature, New York, N.Y., 1960; The carcinogenic nitrogen heterocycles in cigarette smoke condensate; J. Natl. Cancer Inst. 25 (1950) 53–61.
22. United States Public Health Service: Smoking and health. Report of the Advisory Committee to the Surgeon General of the Public Health Service; DHEW Publ. No. (PHS) 1103, 1964.
23. Hoffmann, D. and E.L. Wynder: Selective reduction of the tumorigenicity of tobacco smoke. Experimental approaches; *in*: Toward a less harmful cigarette, Proceedings of Workshop on Smoking and Health, September, 1967, edited by E.L. Wynder and D. Hoffmann, Natl. Cancer Inst. Monograph 28, Washington, D.C., 1968, pp. 151–172.
24. United States Public Health Service: Smoking and health. A report of the Surgeon General; DHEW Publ. No. (PHS) 79-50066, 1979.
25. United States Public Health Service: The health consequences of smoking. The changing cigarette. A report of the Surgeon General; DHHS Publ. No. (PHS) 81-50156, 1981.
26. United States Public Health Service: The health consequences of smoking. Cancer. A report of the Surgeon General; DHHS Publ. No. (PHS) 82-50179, 1982.
27. United States Public Health Service: The health consequences of involuntary smoking. A report of the Surgeon General, 1986; DHHS Publ. No. (PHS) 87-8398, 1987.
28. Editors: Seminars in tobacco science: Tobacco smoke components; Beitr. Tabakforsch. Int. 17 (1997) 61–66: see Table 6.
29. Rodgman, A.: Tobacco smoke components. Letter to the Editor; Beitr.Tabakforsch. Int. 18 (1998) 127–129.
30. Kamata, K., N. Motohashi, R. Meyer, and Y. Yamamoto: Analysis of benz[*c*]acridines in cigarette smoke by high-performance liquid chromatography; J. Liq. Chromatog. 15 (1992) 1907–1920.
31. Sasaki, T.A. and S.C. Moldoveanu: Analysis of dibenz[*a,j*]acridine in particulate-phase cigarette smoke; 53rd Tobacco Science Research Conference, Program Booklet and Abstracts, Vol. 53, Paper No. 32, 1999, p. 37; Determination of dibenz[*a,j*]acridine in the particulate phase of cigarette smoke; Beitr. Tabakforsch. Int. 19 (2000) 25–31.
32. Baker, R.R: Smoke chemistry; *in*: Tobacco: Production, chemistry and technology, edited by D.L. Davis and M.T. Nielsen, Blackwell Science, Oxford, U.K., 1999, pp. 398–439: see pp. 423–424 and Table 12-7.
33. Rodgman, A., C.J. Smith, and T.A. Perfetti: The composition of cigarette smoke: A retrospective with emphasis on polycyclic compounds; Human Exptl. Tox. 19 (2000) 573–595.
34. Rustemeier, K., R. Stabbert, H.J. Haussmann, E. Roemer, and E.L. Carrnines: Evaluation of the potential effects of ingredients added to cigarettes. Part 2: Chemical composition of mainstream smoke: Food Chem. Toxicol. 40 (2002) 93–104.
35. Environmental Protection Agency: Health effects of passive smoking: assessment of lung cancer in adults and respiratory disorders in children; Draft Document EPA/600/6-90/006A (May, 1990);. Environmental tobacco smoke: A guide to workplace smoking policies. Draft Document EPA/400/6-90/004 (June 25, 1990).
36. Environmental Protection Agency: Respiratory health effects of passive smoking: lung cancer and other disorders; Draft Document EPA/600/6-90/006B (May 1992).
37. Rodgman, A.: A comparison of the chemical and physical properties of cigarette mainstream smoke (MS), cigarette sidestream smoke (SS), and environmental tobacco smoke (ETS). Document submitted to the Environmental Protection Agency, December, 1991. Revised version submitted, June, 1992, pp. vii + 117, www.rjrtdocs.com 510649075-9111; 508137542 -7573.
38. Rodgman, A.: The chemical composition of environmental tobacco smoke: Some comments on the Occupational Safety and Health Administration's notice on 'Indoor air quality;' Document submitted to Occupational Safety and Health Administration, 5 August, 1994, pp. xiii + 172: see www.rjrtdocs.com 515923456 -3645; 515926645 -6833.
39. Rodgman, A.: Environmental tobacco smoke; Regul. Toxicol. Pharmacol. 16 (1992) 223–244.
40. IARC: Tobacco habits other than smoking: Betel-quid and areca-nut chewing and some related nitrosamines; IARC, Lyon, France, IARC Monograph 37, 1985.
41. United States Public Health Service: Reducing the health consequences of smoking, 25 years of progress. A report of the Surgeon General; DHHS Publ. No. (CDC) 89-8411, 1989: see pp. 82–85.
42. Harley, N.H., B.S. Cohen, and T.C. Tso: Polonium-210. A questionable risk factor in smoking-related carcinogenesis; *in*: A safe cigarette? Banbury Report 3, edited by G.B. Gori and F.G. Bock, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1980, pp. 93–104.

43. Dorland, I. and (W.A. Newman): Dorland's illustrated medical dictionary, 27th Edition, edited by E.J. Taylor, W.B. Saunders Company, Philadelphia, PA, 1988.
44. Dorland, I.: Dorland's illustrated medical dictionary, 13th Edition; W.B. Saunders Company, Philadelphia, PA, 1927.
45. Wynder, E.L. and D. Hoffmann: Selected laboratory methods in tobacco carcinogenesis; *in*: Methods in cancer research. Vol. 4, edited by H. Busch, Academic Press, New York, N.Y., 1968, pp. 3–52.
46. Wynder E.L. and D. Hoffmann: Bioassays in tobacco carcinogenesis; Prog. Exp. Tumor Res. 11 (1969) 163–193.
47. Hoffmann, D. and E.L. Wynder: A study of tobacco carcinogenesis. XV. Chemical composition and tumorigenicity of tobacco smoke; *in*: The chemistry of tobacco and tobacco smoke, edited by I. Schmeltz, Plenum Publishing Co., 1972, pp. 123–147.
48. Shear, M.J. and J. Leiter: Studies in carcinogenesis. XVI. Production of subcutaneous tumors in mice by miscellaneous polycyclic compounds; J. Natl. Cancer Inst. 2 (1941) 241–258.
49. Hartwell, J.L.: Survey of compounds which have been tested for carcinogenic activity; USPHS Publ. No. 149, 2nd Edition, Washington, D.C., 1951, pp. 1–2.
50. Registry of Toxic Effects of Chemical Substances: 1985–1986 Edition user's guide; DHHS Publ. No. (PHS) (1987) 87–114.
51. Gori, G.B.: Less hazardous cigarettes: Theory and practice; *in*: A safe cigarette? Banbury Report 3, edited by G.B. Gori and F.G. Bock, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1980, pp. 261–279.
52. Hoffmann, D., M.V. Djordjevic, and K.D. Brunnemann: Changes in cigarette design and composition over time and how they influence the yields of smoke constituents; J. Smoking-Related Dis. 6 (1995) 9–23; Hoffmann, D., M.V. Djordjevic, and I. Hoffmann: The changing cigarette; Prev. Med. 26 (1997) 427–434.
53. Sugimura, T.: Past, present, and future of mutagens in cooked foods; Environmental Hlth. Perspect**.** 67 (1986) 5–10.
54. Coultson, F.: Overall view of the conference; *in*: Human epidemiology and animal laboratory correlations in chemical carcinogenesis, edited by F. Coultson and P. Shubik, Ablex Publishing Corporation, Norwood, N.J., 1980, pp. 395–402.
55. Rozman, K.K. and C.D. Klaassen: Absorption, distribution, and excretion of toxicants; *in*: Casarett and Doull's toxicology: The basic science of poison, edited by C.D. Klaassen, McGraw-Hill, New York, N.Y., 1996, pp. 91–112.
56. Maga, J.A.: Potential health concerns associated with smoke; *in*: Smoke in food processing, by J.A. Maga, CRC Press Inc., Boca Raton, FL, 1988, pp. 113–144.
57. Waldman, J.M., P.J. Lioy, A. Greenberg, and J.P. Butler: Analysis of human exposure to benzo[a]pyrene [*sic*] via inhalation and food ingestion in the total human exposure study (THEES); J. Exptl. Anal. Environ. Epidemiol. 1 (1991) 93–225.
58. Hattemeyer-Frey, H.A. and C.C. Travis: Benzo-*a*-pyrene [*sic*]: Environmental partitioning and human exposure; Toxicol. Ind. Hlth. 7 (1991) 141–157.
59. Kazerouni, N., R. Sinha, C.-H. Hsu, A. Greenberg, and N. Rothman: Analysis of 200 food items for benzo[*a*]pyrene and estimation of its intake in an epidemiologic study; Food Chem. Toxicol. 39 (2001) 423–436.
60. Fieser, L.F.: Chemical carcinogenesis; Arthur Stolle Festschrift (1957) 489–498.
61. Grasso, P.: Carcinogens in food; *in*: Chemical carcinogens, Second edition, edited by C.E. Searle, American Chemical Society Monograph 182, American Chemical Society, Washington, D.C. 1984, Chapter 19, pp. 1205–1239.
62. Neish, W.J.P.: [Solubility of PAHs in aqueous purine solutions (caffeine, theobromine, xanthine)]; Rec. Trav. Chim. 67 (1948) 361.
63. Rothwell, K. and J.K. Whitehead: Complex formation, isolation and carcinogenicity of polycyclic aromatic hydrocarbons; Nature 213 (1967) 797; A method for the isolation of polycyclic aromatic hydrocarbons from complex hydrocarbon mixtures; Chem. and Ind. (London) (1967) 784–786; A method for the concentration of basic polycyclic heterocyclic compounds and the separation of polycyclic aromatic hydrocarbons from cigarette smoke condensate; Chem. and Ind. (London) (1969) 1628–1630.
64. Phillips, D.H.: Polycyclic aromatic hydrocarbons in the diet; Mutat. Res. 443 (1999) 139–147.
65. Lijinsky, W.: *N*-Nitroso compounds in the diet; Mutat. Res. 443 (1999) 129–138.
66. Keating. G.A., D.W. Layton, and J.S. Felton: Factors determining dietary intake of heterocyclic amines in cooked foods; Mutat. Res. 443 (1999) 149–156
67. Rojas, E., L.A. Herrera, L.A. Poirier, and P. Ostrowsky-Wegman: Are metals dietary carcinogens? Mutat. Res. 443 (1999) 157–181.
68. Ferguson, L.R.: Natural and man-made mutagens and carcinogens in the human diet; Mutat. Res. 443 (1999) 1–10.
69. Huber G.L.: Physical, chemical, and biological properties of tobacco, cigarette smoke, and other tobacco products; *in*: Tobacco and smoking cessation. I, edited by G.L. Huber, Sem. Resp. Med. 10 (1989) 297–332: see p. 312, Table 5.
70. Wattenberg, L.W.: Chemoprevention of cancer; Cancer Res. 45 (1985) 1–8.
71. Mirvish, S.S.: Ascorbic acid inhibition of *N*-nitroso compound formation in chemical, food and biological systems; *in*: Inhibition of tumor induction and development, edited by M.S. Zedeck and M. Lipkin, Plenum Publishing Corp., New York, N.Y., 1981, pp. 101–126; Inhibition of the formation of carcinogenic *N*-nitroso compounds by ascorbic acid and other compounds; *in:* Cancer achievements, challenges and prospects for the 1980's, edited by J.H. Burchenal and H.F. Oettgen, Plenum Publishing Corp., New York, N.Y., pp. 557–588.
72. Newmark, H. and W. Mergens: α-Tocopherol (vitamin E) and its relationship to tumor induction; *in*: Inhibition of tumor induction and development, edited by M.S. Zedeck and M. Lipkin, Plenum Publishing, New

York, N.Y., 1981, pp. 127–168.
73. Kuenzi, W., J. Chau, E. Norkus, H. Holowaschenko, H. Newmark, W. Mergens, and A.N. Conney: Caffeic and ferulic acid as blockers of nitrosamine formation; Carcinogenesis 5 (1984) 309–314.
74. Wattenberg, L.W.: Inhibition of dimethylhydrazine-induced neoplasia of the large intestine by disulfiram; J. Natl. Cancer Inst. 54 (1975) 1005–1006.
75. Fiala, E.S., G. Bobotas, C. Kulakis, L.W. Wattenberg, and J.H. Weisburger: The effect of disulfiram and related compounds on the *in vivo* metabolism of the colon carcinogen 1,2-dimethylhydrazine; Biochem. Pharmacol. 26 (1977) 1763–1768.
76. Slaga, T.J. and J. DiGiovanni: Inhibition of chemical carcinogenesis; *in*: Chemical carcinogens, 2nd Edition, edited by C.E. Searle, American Chemical Society Monograph 182, American Chemical Society, Washington, D.C., 1984, pp. 1279–1321.
77. Crabtree, H.G.: Influence of bromobenzene on the induction of skin tumors by 3,4-benzopyrene; Cancer Res. 4 (1944) 688–693; Influence of unsaturated dibasic acids on the induction of skin tumors by chemical carcinogens; Cancer Res. 5 (1945) 346–351; Some effects of aromatic hydrocarbons on sulfur metabolism and tumor induction in mice; Cancer Res. 6 (1946) 553–559; Anticarcinogenesis; Brit. Med. Bull. 4 (1947) 345–348.
78. Steiner, P.E. and H.L. Falk: Summation and inhibition effects of weak and strong carcinogenic hydrocarbons, 1:2-benzanthracene, chrysene, 1:2:5:6-dibenzanthracene, and 20-methylcholanthrene; Cancer Res. 11 (1951) 56–63.
79. Dipple, A., R.C. Moschel, and C.A.H. Bigger: Polynuclear hydrocarbons; *in*: Chemical carcinogens, Second edition, edited by C.E. Searle, American Chemical Society Monograph 182, American Chemical Society, Washington, D.C., 1984, Chapter 2, pp. 41–163.
80. Slaga, T.J., L. Jecker, W.M. Bracken, and C.E. Weeks: The effects of weak or non-carcinogenic polycyclic hydrocarbons on 7,12-dimethylbenz[*a*]anthracene and benzo[*a*]pyrene; Cancer Lett. 7 (1979) 51–59.
81. DiGiovanni, J., T.J. Slaga, D.L. Berry, and M.R. Juchau: Inhibitory effects of environmental chemicals on polycyclic aromatic hydrocarbon carcinogenesis; *in*: Carcinogenesis. A comprehensive survey. Vol. 5, edited by T.J. Slaga, Raven Press, New York, N.Y., 1980, pp. 145–168.
82. Snook, M.E., R.F. Severson, R.F. Arrendale, H.C. Higman, and O.T. Chortyk: The identification of high molecular weight polynuclear aromatic hydrocarbons in a biologically active fraction of cigarette smoke condensate; Beitr. Tabakforsch. Int. 9 (1977) 79–101.
83. Williams, D., F.I. Wiebel, J.C. Leutz, and H.V. Gelboin: [phenanthrene/anthracene inhibition of hydroxylation-epoxidation of BaP in hepatic microsomes]; Biochem. Pharmacol. 20 (1971) 2130.
84. Rodgman, A. and L.C. Cook: The analysis of cigarette smoke condensate. XIV. Polycyclic aromatic hydrocarbons; RJRT RDR, 1960, No. 20, May 26: see www.rjrtdocs.com 501008592 -8660.
85. Slaga, T.J. and R.K. Boutwell: Inhibition of the tumor-initiating ability of the potent carcinogen 7,12-dimethylbenz[*a*]anthracene by the weak tumor initiator 1,2,3,4-dibenzanthracene; Cancer Res. 37 (1977) 129–133.
86. Slaga, T.J., A. Viaje, S.G. Buty, and W.M. Bracken: Dibenz[*a*,*c*]anthracene: A potent inhibitor of skin-tumor initiation by 7,12-dimethylbenz[*a*]anthracene; Res. Comm. Chem. Pathol. Pharmacol. 19 (1978) 477–483.
87. Lacassagne, A., N.P. Buu-Hoï, and G. Rudall: Inhibition of the carcinogenic action produced by a weakly carcinogenic hydrocarbon on a highly active hydrocarbon; Brit. J. Exptl. Path**.** 26 (1945) 5–12.
88. Hill, W.T., D.W. Stanger, A. Pizzo, B. Riegel, P. Shubik, and W.B. Wartman; Cancer Res. 11 (1951) 892–897.
89. Badger, G.M.: Chemical constitution and carcinogenic activity; Adv. Cancer Res. 2 (1954) 73–127.
90. Homburger, F., A. Treger, and E. Boger: Experimental studies on the inhibition of carcinogenesis by cigarette-smoke condensates and carcinogen-related substances; *in*: Toward a less harmful cigarette, Proceedings of Workshop on Smoking and Health, September, 1967, edited by E.L. Wynder and D. Hoffmann,. Natl. Cancer Inst. Monograph 28, Washington, D.C., 1968, pp. 259–270.
91. Wynder, E.L. and D. Hoffmann: A study of air pollution carcinogenesis. III. Carcinogenic activity of gasoline engine exhaust condensate; Cancer 15 (1962) 103–108.
92. Eatough, D.J., L.D. Hansen, and E.A. Lewis: The chemical characterization of environmental tobacco smoke; *in*: Environmental tobacco smoke, edited by D.J. Ecobichon and J.M. Wu, Proc. International Symposium at McGill University, PQ, Canada, 1989, Lexington Books, D.C. Heath and Company, Lexington MA, 1990, pp. 3–39.
93. Rodgman, A. and L.C. Cook: The composition of cigarette smoke. IV. α-Tocopherol; Tob. Sci. 4 (1960) 7–8.
94. Rodgman, A. and L.C. Cook: The composition of cigarette smoke. XI. Heterocyclic nitrogen compounds from Turkish tobacco smoke; Tob. Sci. 6 (1962) 176–179.
95. Izard, C., J. LaCharpagne, and P. Testa: Sur l'activité biologique de divers condensats de fumée de cigarettes, revelée par les tests auxiniques; Compt. Rend. 262D (1966) 1859–1861.
96. Rowland, R.L., A. Rodgman, J.N. Schumacher, D.L. Roberts, L.C. Cook, and Walker, W.E. Jr.: Macrocyclic diterpenes. Hydroxyethers from tobacco and tobacco smoke; 17th Tobacco Chemists' Research Conference, Program Booklet and Abstracts, Vol. 17, Paper No. 16, 1963, p. 13; Macrocyclic diterpene hydroxyethers from tobacco and cigarette smoke; J. Org. Chem. 29 (1964) 16–21.
97. Falk, H.L., P. Kotin, and S. Thompson: Inhibition of carcinogenesis. The effect of hydrocarbons and related compounds; Arch. Environ. Hlth. 9 (1964) 169–179.
98. Hoffman, H.E. and A.C. Griffin: Action of cigarette tar and smoke on chemically induced carcinogenesis;

Texas Rep. Biol. Med. 16 (1958) 333–345.
99. Wynder, E.L. and D. Hoffmann: Experimental tobacco carcinogenesis; Adv. Cancer Res. 8 (1964) 249–453: see p. 296, 330.
100. Kotin, P. and H.L. Falk: Atmospheric factors in pathogenesis of lung cancer; Adv. Cancer Res. 7 (1953) 475–514: see pp. 489–490.
101. Wynder, E.L., and D. Hoffmann: Studies with gaseous and particulate phase of cigarette smoke; Proc. Am. Assoc. Cancer Res. 3(4) (1962) 373; Bioassays on the carcinogenicity of tobacco smoke condensate and air pollutants; Proc. Am. Assoc. Cancer Res. 4(1) (1963) 73.
102. Wynder, E.L. and D. Hoffmann: Biological and chemical studies of tobacco smoke condensate; Proc. Am. Assoc. Cancer Res. 3(3) (1961) 280.
103. Wynder, E.L. and G.F Wright: A study of tobacco carcinogenesis. I. The primary fractions; Cancer 10 (1957) 255–271.
104. Lam, J.: 3,4-Benzopyrene as a product of the pyrolysis of aliphatic hydrocarbons; Acta Path. Microbiol. Scand. 37 (1955) 421–428.
105. Wynder, E.L.: Human and experimental relation of tobacco and cancer; Tobacco Symposium, Long Island Subsection, American Chemical Society, 1956.
106. Wright, G.F: Personal communication. [See Rodgman, A.: Tobacco tar fractionation and the pretreatment of tobacco: A conversation with Dr. George F Wright of the University of Toronto, Toronto, ON, Canada; RDM, 1957, No. 25, July 22: see www.rjrtdocs.com 500610651 -0656].
107. Wynder, E.L., G.F Wright, and J. Lam: A study of tobacco carcinogenesis. V. The role of pyrolysis; Proc. Am. Assoc. Cancer Res. 2(4) (1958) 357–358; Cancer 11 (1958) 1140–1148.
108. Wynder, E.L., G.F Wright, and J. Lam: A study of tobacco carcinogenesis. VI. The role of precursors; Cancer 12 (1959) 1073–1078.
109. Rodgman, A.: The analysis of cigarette smoke condensate. II. The pretreatment of *Camel* blend tobacco; RDR, 1956, No. 12, November 1: see www.rjrtdocs.com 501008294 -8336; The analysis of cigarette smoke condensate. III. Flue-cured tobacco; RDR, 1957, No. 4, March 14: see www.rjrtdocs.com 501008337 –8377; Some studies on the effects of additives on cigarette mainstream smoke properties. I. Flavorants; Beitr. Tabakforsch. Int. 20 (2001) 83–103.
110. Wynder, E.L. and D. Hoffmann: The role of higher polycyclic hydrocarbons in tobacco carcinogenesis; Proc. Am. Assoc. Cancer Res. 3(1) (1959) 74; A study of tobacco carcinogenesis. VII. The role of higher polycyclic hydrocarbons; Cancer 12 (1959) 1079–1086.
111. Wynder, E.L. and D. Hoffmann: Biological and chemical studies of tobacco smoke condensate; Proc. Am. Assoc. Cancer Res. 3(3) (1961) 280; Studies with the gaseous and particulate phase of tobacco smoke; Proc. Am. Assoc. Cancer Res. 3(4) (1962) 373.
112. Hoffmann, D. and E.L. Wynder: A study of air pollution carcinogens. II. The isolation and identification of polynuclear aromatic hydrocarbons from gasoline engine exhaust condensate; Cancer 15 (1962) 93–102.
113. Wynder, E.L. and D. Hoffmann: Experimental tobacco carcinogenesis; Adv. Cancer Res. 8 (1964) 249–453.
114. Homburger, F.: Les rapports entre tabac et cancer: pathologie expérimentale; Med. Hyg. (Switz.) 23 (1965) 179–181; Homburger, F. and A. Treger: Effects of intravenous carcinogen and tobacco condensate injections upon the incidence of lung tumors in A/He mice; *in:* Lung tumors in animals, edited by L. Severi, Division of Cancer Research, University of Perugia, Italy, 1965, pp. 527–536; Homburger, F., A. Treger, and E. Boger: Experimental studies on the inhibition of carcinogenesis by cigarette-smoke condensates and carcinogen-related substances; *in*: Toward a less harmful cigarette, edited by E.L. Wynder and D. Hoffmann, Natl. Cancer Inst. Monograph 28 (1968) 259–270; Inhibition of murine subcutaneous and intravenous benzopentaphene carcinogenesis by sweet orange oils and *d*-limonene; Oncology 25 (1971) 1–10.
115. Rothwell, K. and J.K. Whitehead: A method for the concentration of basic polycyclic heterocyclic compounds and the separation of polycyclic aromatic hydrocarbons from cigarette smoke condensate; Chem. and Ind. (London) (1969) 1628–1630.
116. Snook, M.E., R.F. Arrendale, H.C. Higman, and O.T. Chortyk: Isolation of indoles and carbazoles from cigarette smoke condensate; Anal. Chem. 50 (1978) 88–90; Snook, M.E., P.J. Fortson, L.B. Smith, and O.T. Chortyk: Isolation and identification of aza-arenes of tobacco smoke; 32nd Tobacco Chemists' Research Conference, Program Booklet and Abstracts, Vol. 32, Paper No. 46, 1978, p. 25; Snook, M.E., P.J. Fortson, and O.T. Chortyk: Isolation and identification of aza-arenes of tobacco smoke; Beitr. Tabakforsch. Int. 11 (1981) 67–78.
117. Wynder, E.L. and D. Hoffmann: Tobacco and tobacco smoke: Studies in experimental carcinogenesis; Academic Press, New York, N.Y., 1967, pp. 245–247, 628.
118. Homburger, F. and A. Treger: Effects of intravenous carcinogen and tobacco condensate injections upon the incidence of lung tumors in A/He mice; *in*: Lung tumors in animals, edited by L. Severi, Division of Cancer Research, University of Perugia, Italy, 1965, pp. 527–536.
119. Wynder, E.L. and D. Hoffmann: Tobacco and tobacco smoke: Studies in experimental carcinogenesis; Academic Press, New York, N.Y., 1967, pp. 628–629.
120. Wynder, E.L. and D. Hoffmann: A study of air pollution carcinogenesis. III. Carcinogenic activity of gasoline engine exhaust condensate; Cancer 15 (1962) 103–108.
121. Wynder, E.L. and D. Hoffmann: Studies with the gaseous and particulate phase of tobacco smoke; Proc. Am. Assoc. Cancer Res. 3(4) (1962) 373; Tobacco and tobacco smoke: Studies in experimental carcinogenesis; Academic Press, New York, N.Y., 1967, pp. 370–371, 628–629.
122. Homburger, F.: Les rapports entre tabac et cancer: Pathologie expérimentale; Med. Hyg. (Switz.) 23 (1965) 179–181.
123. Homburger, F., A. Treger, and E. Boger: Experimental

studies on the inhibition of carcinogenesis by cigarette-smoke condensates and carcinogen-related substances; *in*: Toward a less harmful cigarette; Proceedings of Workshop on Smoking and Health, September, 1967, edited by E.L. Wynder and D. Hoffmann, Natl. Cancer Inst. Monograph 28 (1968) 259–270.
124. Rowland, R.L.: Flue-cured tobacco. III. Solanachromene and α-tocopherol; J. Am. Chem. Soc. 80 (1958) 6130–6133.
125. Rodgman, A. and L.C. Cook: The composition of cigarette smoke. XI. Heterocyclic nitrogen compounds from Turkish tobacco smoke; 16th Tobacco Chemists' Research Conference, Program Booklet and Abstracts, Vol. 16, Paper No. 23, 1962, p. 14; Tob. Sci. 6 (1962) 176–179.
126. Roberts, D.L. and R.L. Rowland: Macrocyclic diterpenes. α- and β-4,8,13-duvatriene-1,3-diols from tobacco; J. Org. Chem. 27 (1962) 3989–3995.
127. Saito, Y., H. Takizawa, S. Konishi, D. Yoshida, and S. Mizusaki: Identification of cembratriene-4,6-diol as a antitumor-promoting agent from cigarette smoke condensate; Carcinogenesis 6 (1985) 1189–1194.
128. Clemo, G.R.: Some aspects of the chemistry of tobacco smoke. I; Tetrahedron 3 (1958) 168–174; Kosak, A.I. and P.D. Rosen: Components of cigarette smoke; 7th International Cancer Congress, London, England, 1958; Kosak, A.I., P.D. Rosen, and J.S. Swinehart: Components of cigarette smoke; Acta Unio Internat. Contra Cancrum 15 (1959) 612.
129. Green, C.R. and A. Rodgman: The Tobacco Chemists' Research Conference: A half century forum for advances in analytical methodology of tobacco and its products; Recent Adv. Tob. Sci. 22 (1996) 131–304.
130. Fay, J.R., L.R. Perry, L.A. Kanerva, C.C. Sigman, and C.T. Helmes: Inhibitors of chemical carcinogenesis; Document prepared in 1984, revised in 1985 for Sci. Coordinator Environ. Cancer, National Cancer Institute, Bethesda, MD, 1985, pp. 1–96.
131. Denissenko, M.F., A. Pao, M. Tang, and G.P. Pfeifer: Preferential formation of benzo[*a*]pyrene adducts at lung cancer mutational hotspots in *P53;* Science 274 (1996) 430–432.
132. Jerina, D.M., R. Lehr, M. Schaefer-Ridden, H. Yagi, J.M. Karle, D.R. Thakker, A.W. Wood, A.Y.H. Lu, D. Ryan, S. West, W. Levi, and A.H. Connery: *in*: Origins of human cancer, edited by H.H. Hiatt, J.D Watson, and J.A. Winston, Cold Spring Harbor Laboratory, N.Y., 1977, p. 639.
133. Lee, C.K. and E.A. Reed: Ames test on smoke condensates: A summary; RJRT R&DM, 1983, No. 20, May 9: see www.rjrtdocs.com 508352301 -2303.
134. Murphy, S.E. and R. Heilbrun: Effect of nicotine and tobacco-specific nitrosamines on the metabolism of *N*'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by rat oral tissue; Carcinogenesis 11 (1990) 1663–1666.
135. Lee, C.K., C.W. Fulp, D.W. Bombick, and D.J. Doolittle: Nicotine and cotinine inhibit the mutagenicity of *N*-nitrosamines present in tobacco smoke; 48th Tobacco Chemists' Research Conference, Paper No. 44; Vol. 48, Paper No. 44, 1994, p. 51; Inhibition of mutagenicity of *N*-nitrosamines by tobacco smoke and its constituents; Mutat. Res. 367 (1996) 83–92.
136. Brown, B., J.T. Avalos, C.K. Lee, and D.J. Doolittle: The effect of tobacco smoke, nicotine, and cotinine on the mutagenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL); 55th Tobacco Science Research Conference, Program Booklet and Abstracts, Vol. 55, Paper No. 10, 2001, p. 26.
137. Lee, C.K., J.A. Munoz, C.W. Fulp, K.M. Chang, J. Rogers, M.F. Borgerding, and D.J. Doolittle: Inhibitory activity of cigarette-smoke condensate on the mutagenicity of heterocyclic amines; Mutat. Res. 322 (1993) 21–32.
138. Sugimura, T., T. Kawachi, M. Nagao, T. Yohagi, Y. Seino, T. Okamoto, K. Shudo, T. Kosuge, K. Tsuji, K. Watabayashi, Y. Iitaka, and A. Ita: Mutagenic principle(s) in tryptophan and phenylalanine pyrolysis products; Proc. Japan Acad. 53B (1977) 58–61; Sugimura T, M. Nagao, T. Kawachi, M. Honda, T. Yahagi, Y. Seino, S. Sato, N. Matsukura, T. Matsushima, A. Shitai, M. Sawamura, and H. Matsumoto: Mutagens-carcinogens in food, with special reference to highly mutagenic pyrolytic products in broiled foods; *in*: Origins of human cancer, edited by H.H. Hiatt, J.D. Watson, and J.A. Winsten, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1977, pp. 1561–1577.
139. Yamamoto, T., K. Tsuji, T. Kosuge, T. Okamoto, K. Shudo, K. Takeda, Y. Iitaka, K. Yamaguchi, Y. Seino, T. Yahagi, M. Nagao, and T. Sugimura: Isolation and structure determination of mutagenic substances in L-glutamic acid pyrolysate; Proc. Japan Acad. 54B (1978) 248–250.
140. Yamashita, M., K. Wakabayashi, M. Nagao, S. Sato, and N. Kinea: Amounts of heterocyclic amines in the basic fraction of cigarette smoke condensates; Environ. Mutagen Soc. Japan Mtg., Akita, Japan: see Abstract in Mutat. Res. 164 (1986) 286; Yamashita, M., K. Wakabayashi, M. Nagao, S. Sato, Z. Yamaizumi, M. Takahashi, N. Kinea, I. Tomita, and T. Sugimura: Detection of 2-amino-3-methylimidazo[4,5-*f*]quinoline in cigarette smoke condensate; Gann 77 (1986) 419–422.
141. Felton, K.S. and M.G. Knize: Heterocyclic amine mutagens/carcinogens in foods; *in*: Chemical mutagenesis and carcinogenesis, edited by C.S. Cooper and P.L. Grover, Springer-Verlag, Berlin/Heidelberg, 1990, pp. 471–502.
142. Van Duuren, B.L.: The polynuclear aromatic hydrocarbons in cigarette-smoke condensate. II; J. Natl. Cancer Inst. 21 (1958) 623–630: see Footnote added in proof, p. 629.
143. Lavit-Lamy, D. and N.P. Buu-Hoï: The true nature of "dibenzo[*a*,*l*]pyrene" and its known derivatives; Chem. Comm. 4 (1966) 92–94.
144. IARC: Polynuclear aromatic compounds, Part 1, Chemical, environmental and experimental data; *in*: IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Monograph 32 (1983) 321–325.
145. National Cancer Institute: Report No. 5. Toward less hazardous cigarettes. Summary: Four skin painting bioassays using condensate from experimental cigarettes; DHEW Publ. (NIH) (September 1980).

146. Rodgman, A.: Studies of polycyclic aromatic hydrocarbons in cigarette mainstream smoke: Identification, tobacco precursors, control of levels: A review; Beitr. Tabakforsch. Int. 19 (2001) 361–379.
147. Wynder, E.L.: Statement on lung cancer-cigarette smoking controversy: Chemical fractionation of cigarette smoke condensate; *in*: False and misleading advertising (Filter-tip cigarettes), Wynder reported on the studies of G.F Wright at the Hearing before Subcommittee on Government Operations (the Blatnik Hearings on Filtered Cigarettes) (July, 1957), pp. 63–114.
148. Hecht, S.S.: Tobacco smoke carcinogens and lung cancer; J. Natl. Cancer Inst. 91 (1999) 1194–1210.
149. Snook, M.E., R.F. Severson, H.C. Higman, R.F. Arrendale, and O.T. Chortyk: Polynuclear aromatic hydrocarbons of tobacco smoke: isolation and identification; Beitr. Tabakforsch. 8 (1976) 250–272.
150. Snook, M.E., R.F. Severson, R.F. Arrendale, H.C. Higman, and O.T. Chortyk: Multi-alkylated polynuclear aromatic hydrocarbons of tobacco smoke: separation and identification; Beitr. Tabakforsch. Int. 9 (1978) 222–247.
151. Heckman, R.A. and F.W. Best: An investigation of the lipophilic bases of cigarette smoke condensate; Tob. Sci. 25 (1981) 33–39.
152. Newell, M.P., R.A. Heckman, R.F. Moates, C.R. Green, F.W. Best, and J.N. Schumacher: Isolation and identification of new components of the ether-soluble portion of cigarette smoke condensate; Tob. Sci. 22 (1978) 6–11.
153. Schumacher, J.N., C.R. Green, F.W. Best, and M.P. Newell: Smoke composition. An extensive investigation of the water-soluble portion of cigarette smoke; J. Agr. Food Chem. 25 (1977) 310–320.
154. Binder, H.: Ethylene oxide and chlorohydrin in tobacco and in smoke; Fachliche Mitt. Österr. Tabakregie 15 (1974) 294–301.
155. Binder, H. and W. Lindner: Bestimmung von Äthylenoxid im Rauch garantiert unbegaster Zigaretten; Fachliche Mitt. Österr. Tabakregie 13 (1972) 215–220.
156. Deutsch-Wenzel, R.P., H. Brune, G. Grimmer, G. Dettbarn, and J. Misfeld: Experimental studies in rat lungs on the carcinogenicity and dose-response relationships of eight frequently occurring polycyclic aromatic hydrocarbons; J. Natl. Cancer Inst. 71 (1983) 539–544.
157. Adams, J.D., K.J. O'Mara-Adams, and D. Hoffmann: On the mainstream-sidestream distribution of smoke components from commercial cigarettes; 39th Tobacco Chemists' Research Conference, Program Booklet and Abstracts, Vol. 39, Paper No. 34, 1985, p. 18; Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes; Carcinogenesis 8 (1987) 729–731.
158. Wynder, E.L., L. Fritz, and N. Furth: Effect of concentration of benzopyrene in skin carcinogenesis; J. Natl. Cancer Inst. 19 (1957) 361–370.
159. Poel, W.E.: Carcinogens and minimal carcinogenic doses; Science 123 (1956) 588.
160. Poel, W.E. and A.G. Kammer: Preliminary studies in a quantitative approach to skin carcinogenesis; J. Natl. Cancer Inst. 16 (1958) 989–994.
161. Hecht, S.S., W.E. Bondinell, and D. Hoffmann: Isolation and identification of alkylchrysenes in cigarette smoke; 27th Tobacco Chemists' Research Conference, Program Booklet and Abstracts, Vol. 27, Paper No. 32, 1973, p. 23; Chrysene and methylchrysenes: Presence in tobacco smoke and carcinogenicity; J. Natl. Cancer Inst. 53 (1974) 1121–1133.
162. Wynder, E.L. and D. Hoffmann: Ein experimenteller Beitrag zur Tabakrauchkanzerogenese; Deut. Med. Wchnschr. 88 (1963) 623–628.
163. Dobrowolskaïa-Zavadskaïa, N.: Doses of 1,2,5,6-dibenzanthracene capable of producing cancer in mice; Comp. Rend. Soc. Biol. 129 (1938) 1055.
164. Lyons, M.J. and H. Johnston: Chemical analysis of the neutral fraction of cigarettes smoke tar; Brit. J. Cancer 11 (1957) 554–562.
165. Candeli, A., D. Hoffmann, and E.L. Wynder: Unpublished data cited in E.L. Wynder and D. Hoffmann: Experimental tobacco carcinogenesis; Adv. Cancer Res. 8 (1964) 249–453: see 323–333; also cited in Wynder, E.L. and D. Hoffmann: Tobacco and tobacco smoke: Studies in experimental carcinogenesis; Academic Press, New York N.Y., 1967: see 373–374, Table VIII-14.
166. Schmeltz, I., W.S. Schlotzhauer, and E.B. Higman: Characteristic products from pyrolysis of nitrogenous organic substances; Beitr. Tabakforsch. 6 (1972) 134–138.
167. Schmeltz, I., A. Wenger, D. Hoffmann, and T.C. Tso: Chemical studies on tobacco smoke. 63. On the fate of nicotine during pyrolysis and in a burning cigarette; J. Agr. Food Chem. 27 (1979) 602–608.
168. Snook, M.E.: Nitrogen analogues of polynuclear aromatic hydrocarbons in tobacco smoke; *in*: Carcinogenesis: polynuclear aromatic hydrocarbons. Vol. 3, edited by P.W. Jones and R.I. Freudenthal, Raven Press, New York, N.Y., 1978, pp. 203–215.
169. Grimmer, G., K.W. Naujack, and G. Dettbarn: Gas chromatographic determination of polycyclic aromatic hydrocarbons, aza-arenes, aromatic amines in the particle and vapor phase of mainstream and sidestream smoke of cigarettes; Internat. Exptl. Toxicol. Symp. on Passive Smoking, Essen FRG; Gas chromatographic determination of polycyclic aromatic hydrocarbons, aza-arenes, aromatic amines in the particle and vapor phase of mainstream and sidestream smoke of cigarettes; Toxicol. Lett. 35 (1987) 117–124.
170. Kaburaki, Y., S. Sugawara, U. Kobashi, and T. Doihara: Studies on the composition of tobacco smoke. XIV. The formation of pyridines in the pyrolysis of nicotine; J. Agr. Chem. Soc. Japan 44 (1970) 224–231.
171. Caldwell W. S. and J.M. Conner: Artifact formation during smoke trapping. An improved method for the determination of *N*-nitrosamines in cigarette smoke; 43rd Tobacco Chemists' Research Conference, Program Booklet and Abstracts, Vol. 43, Paper No. 45, 1989, p. 37; Caldwell W.S. and J.M. Conner: Artifact formation during smoke trapping: An improved method for the determination of *N*-nitros-

amines in cigarette smoke; J. Assoc. Official Anal. Chem.. 73 (1990) 783–789.
172. Environmental Protection Agency: Maleic hydrazide: Notification of issuances of notice of intent to suspend pesticide registrations; Fed. Reg. 46 (No. 179) (1981) 46000.
173. Griffin, H.R., M.B. Hocking, and D.G. Lowery: Arsenic determination in tobacco by atomic absorption spectrometry; Anal. Chem. 47 (1975) 229–233.
174. Hoffmann, D., K.D. Brunnemann, J.D. Adams, and S.S. Hecht: Formation and analysis of *N*-nitrosamines in tobacco products and their endogenous formation in consumers; *in*: *N*-Nitroso compounds: Occurrence, biological effects and relationship to human cancer, edited by I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long, and H. Bartsch, IARC, Lyon, France, IARC Sci. Publ. No. 57, 1984, pp. 743–762.
175. Hecht, S.S. and D. Hoffmann: 4-(*N*-Methylnitrosamino)-1-(3-pyridyl)-1-butanone, a nicotine-derived tobacco-specific nitrosamine, and cancer of the lung and pancreas in humans; *in*: The origins of human cancer: A comprehensive review, edited by J. Brugge, T. Curran, E. Harlow, and F. McCormick, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. 1991, pp. 745–755.
176. IARC: 2-Naphthylamine; IARC, Lyon, France, IARC Monograph 4 (1974) 97–111.
177. Hoffmann, D., Y. Masuda, and E.L. Wynder: α-Naphthylamine and β-naphthylamine in cigarette smoke; Nature 221(1969) 254–256.
178. Schmeltz, I. and D. Hoffmann: Nitrogen-containing compounds in tobacco and tobacco smoke; Chem. Rev. 77 (1977) 295–311.
179. IARC: 4-Aminobiphenyl; IARC, Lyon, France, IARC Monograph 1 (1972) 74–79.
180. IARC: Formaldehyde; IARC, Lyon, France, IARC Monograph [Suppl. 4] (1982) 131–132.
181. Dalhamn, T., M.L. Edfors, and R. Rylander: Mouth absorption of various compounds in cigarette smoke; Arch. Environ. Hlth. 16 (1968) 831–835; Retention of cigarette smoke components in human lungs; Arch. Environ. Hlth. 17 (1968) 746–748.
182. IARC: Benzene; IARC, Lyon, France, IARC Monograph 7 (1974) 203–211; Benzene; IARC, Lyon, France, IARC Monograph 29 (1982) 93–148.
183. Shubik, P. and J.L. Hartwell: Survey of compounds which have been tested for carcinogenic activity; Suppl. 1, USPHS Publ. No. 149, Washington, D.C., 1957; Suppl. 2, USPHS Publ. No. 149, Washington, D.C., 1969.
184. Thomas, J.I. *et al*.: Survey of compounds which have been tested for carcinogenic activity; USPHS Publ. No. 149, Washington D.C., 1968/1969; 1970/1971.
185. IARC: Acrylonitrile; IARC, Lyon, France, IARC Monograph 19 (1979) 73–113.
186. IARC: Vinyl chloride; IARC, Lyon, France, IARC Monograph 19 (1979) 377–438.
187. Schepartz, A.I.: The chemistry of cigar smoke. II. Some components of the neutral fraction; Tob. Sci. 4 (1960) 12–16.
188. Dymicky, M., O.T. Chortyk, and R.L. Stedman: Composition studies on tobacco. XXVII. Polyphenol-amino acid leaf pigment: Further structural investigations; Tob. Sci. 11 (1967) 42–44; Dymicky, M. and R.L. Stedman: Composition studies on tobacco. XXV. Moieties in a high molecular weight smoke pigment: Alkaloids and a silicone; Phytochem. 6 (1967) 1025–1031.
189. Nesemann, E., R. Schröder, and F. Seehofer: Methoden zur quantitativen Bestimmung von Insektiziden in Tabak und Tabakrauch. I. Mitteilung: Zur Bestimmung von Organo-Chlor-Insektiziden; Beitr. Tabakforsch. 4 (1968) 182–188.
190. Hoffmann, D., G. Rathkamp, and E.L. Wynder: Chemical studies on tobacco smoke. IX. Quantitative analysis of chlorinated hydrocarbon insecticides; Beitr. Tabakforsch. 5 (1969) 140–148.
191. IARC: Hydrazine; IARC, Lyon, France, IARC Monograph 4 (1974) 127–136, 173–175.
192. Cogbill, E.C. and M.E. Hobbs: The transfer of metallic constituents to the mainstream smoke; Tob. Sci. 1 (1957) 68–73.
193. Satterlee, H.S.: The problem of arsenic in American cigarettes; New Eng. J. Med. 254 (1956) 1149–1154.
194. IARC: Arsenic and arsenic compounds; IARC, Lyon, France, IARC Monograph 23 (1980) 39–141.
195. IARC: Nickel and inorganic nickel compounds; IARC, Lyon, France, IARC Monograph 3 (1973) 126–149.
196. IARC: Chromium and chromium compounds; IARC, Lyon, France, IARC Monograph 23 (1980) 205–323.
197. IARC: Lead and lead compounds; IARC, Lyon, France, IARC Monograph 23 (1980) 325–415.
198. Grimmer, G., H. Brune, R. Deutsch-Wenzel, K.W. Naujack, J. Misfeld, and J. Timm: On the contribution of polycyclic aromatic hydrocarbons to the carcinogenic impact of automobile exhaust condensate evaluated by local application onto mouse; Cancer Lett. 21 (1983) 105–113.
199. Grimmer, G., H. Brune, R. Deutsch-Wenzel, G. Dettbarn, and J. Misfeld: Contribution of polycyclic aromatic hydrocarbons to the carcinogenic impact of gasoline engine exhaust condensate evaluated by implantation into the lungs of rats; J. Natl. Cancer Inst. 72: (1984) 733–739.
200. Grimmer, G., H. Brune, R. Deutsch-Wenzel, G. Dettbarn, J. Misfeld, U. Abel, and J. Timm: The contribution of polycyclic aromatic hydrocarbon fractions with different boiling ranges to the carcinogenic impact of emission condensate from coal fired residential furnaces as evaluated by topical application to the skin of mice; Cancer Lett. 28 (1985) 203–211.
201. Tricker, A.R.; *N*-Nitroso compounds and man: Sources of exposure, endogenous formation and occurrence in body fluids; Eur. J. Cancer Prev. 6 (1997) 226–268.
202. Preussmann, R. and G. Eisenbrand: *N*-Nitroso carcinogens in the environment; *in*: Chemical carcinogens. Second edition, edited by C.E. Searle, American Chemical Society Monograph 182, American Chemical Society, Washington, D.C., 1984, Chapter 13, pp. 829–868.
203. Wattenberg, L.W. and J.B. Coccia: Inhibition of 4-methylnitrosamino-1-(3-pyridyl)-1-butanone carcino-

genesis in mice by *d*-limonene and citrus fruit oils; Carcinogenesis 12 (1991) 115–117.
204. Homburger, F., A. Treger, and E. Boger: Inhibition of murine subcutaneous and intravenous benzopentaphene carcinogenesis by sweet orange oils and *d*-limonene; Oncology 25 (1971) 1–10.
205. Waddell, W. and C. Marlowe: Inhibition by alcohols of the localization of radioactive nitrosonornicotine in sites of tumor formation; Science 221 (1983) 51–52.
206. Farinati, F., Z. Zhou, J. Bellah, C.S. Liebers, and A.J. Garro: Effect of chronic ethanol consumption on activation of nitrosopyrrolidine to a mutagen by rat upper alimentary tract, lung and hepatic tissue; Drug Metab. Dispos. 13 (1985) 210–214.
207. Wattenberg, L.W.: Inhibitors of chemical carcinogens; *in*: Cancer: Achievements, challenges and prospects for the 1980's, edited by J.H. Burchenal, Grune and Stratton, New York, N.Y., 1981, pp. 517–539.
208. Takeda, K., S. Ukawa, and M. Mochizuki: Inhibition by fatty acids of direct mutagenicity of *N*-nitroso compounds; *in*: Relevance to human cancer of *N*-nitroso compounds, tobacco and mycotoxins, edited by I.K. O'Neill, J. Chen, and H. Bartsch, IARC, Lyon, France, IARC Sci. Publ. No. 105 (1991) 558–563.
209. Chung, F.L., A. Juchatz, J. Vitarius, and S.S. Hecht: Effects of dietary compounds on α-hydroxylation of *N*-nitrosopyrrolidine and *N*'-nitrosonornicotine in rat target tissues; Cancer Res. 44 (1984) 2924.
210. Chung, F.L., A. Juchatz, J. Vitarius, B. Reiss, and S.S. Hecht: Inhibition of target tissue activation of *N*'-nitrosonornicotine and *N*-nitrosopyrrolidine by dietary components; *in*: *N*-Nitroso compounds: Occurrence, biological effects and relevance to human cancer, edited by I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long, and H. Bartsch, IARC, Lyon, France, IARC Sci. Publ. No. 57 (1984) 797–804.
211. Van Duuren, B.L., A. Sivak, C. Katz, and S. Melchionne: Cigarette smoke carcinogenesis: Importance of tumor promoters; J. Natl. Cancer Inst. 47 (1971) 235–240.
212. Thompson, H.J.: Effect of deficiencies of selenium and vitamin E alone or in combination on the induction of mammary carcinogenesis by 1-methyl-1-nitrosourea; Carcinogenesis 12 (1991) 2175–2179.
213. Teel, R. and A. Castonguay: Antimutagenic effects of polyphenolic compounds; Cancer Lett. 66 (1992) 107–113.
214. Chung, F.L., M.A. Morse, K.I. Eklind, and Y. Xu: Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis by compounds derived from cruciferous vegetables and green tea; *in*: Tobacco smoking and nutrition: Influence of nutrition on tobacco-associated health risks, edited by J.N. Diana and W.A. Pryor, Ann. N.Y. Acad. Sci. 686 (1993) 186–202.
215. Schüller, H.M., A. Castonguay, M. Orloff, and G. Rossignol: Modulation of the uptake and metabolism of 4-(*N*-methylnitrosamino)-1-(3-pyridyl)-1-butanone by nicotine; Cancer Res. 51 (1991) 2009–2114.
216. Berry, D.L., T.J. Slaga, J. DiGiovanni, and M.R. Juchau: Chlorinated dibenzo-*p*-dioxins, polybrominated biphenyls, and polychlorinated biphenyls in a two-stage system of mouse skin tumorigenesis: Potent anticarcinogenic effects; Ann. N.Y. Acad. Sci. 320 (1979) 405–414.
217. Cohen, G.M.; W.P. Bracken, R.P. Iyer, D.L. Berry, and T.J. Slaga: Anticarcinogenic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene tumor initiation and its relationship to DNA binding; Cancer Res. 39 (1979) 4027–4033.
218. DiGiovanni, J.; D.L. Berry, G.L. Gleason, G.S. Kishore, and T.J. Slaga: Time-dependent inhibition by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin of skin tumorigenesis with polycyclic hydrocarbons; Cancer Res. 40 (1980) 1580–1587.

Address for correspondence:

Alan Rodgman
2828 Birchwood Drive
Winston-Salem, North Carolina, 27103-3410
USA