Problems with the Tobacco Products Scientific Advisory Committee (TPSAC) List of Harmful or Potentially Harmful Tobacco and/or Tobacco Smoke Components*

by

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SUMMARY

The draft initial list of harmful or potentially harmful tobacco and/or smoke components prepared by the Constituent Subcommittee of the TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC) differs significantly from the similar lists prepared by HOFFMANN and colleagues who had over four decades of experience and knowledge in tobacco and/or tobacco smoke components and their chemical and biological properties. The draft list comprises 106 components, 60 of which were included in the recent HOFFMANN *et al.* lists but does not include nine of the HOFFMANN-listed components. All of the 106 components appear in a list by RODGMAN and GREEN of 162 tobacco and/or tobacco smoke components, each of which was defined as biologically adverse at one time or another over the previous years by one or more investigators. As with the HOFFMANN *et al.* lists, the list by the TPSAC Constituent Subcommittee contains numerous anomalies.

- Three harmful components (dibenz[*a,j*]acridine, dibenz[*a,h*]acridine, 7*H*-dibenzo[*c,g*]carbazole) first reported in tobacco smoke in the 1960s that were not confirmed over the next forty years by many talented investigators in Japan, Germany, and the USA, including several at the U.S. Department of Agriculture (USDA).
- Two harmful components (arsenic, *N*-nitrosodiethanolamine) the levels of which have decreased significantly because their precursors have not been used in tobacco agronomy for over three decades.
- The many water-soluble components that reach the lung at a much reduced level to exert their ciliastasis.
- A component (chrysene) that the INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) has removed from its tumorigenicity listing, a decision accepted by HOFFMANN *et al.* who removed chrysene from their more recent tobacco/tobacco smoke listings of adverse components.

TPSAC gives no indication of the following:

- The relationship between the per cigarette delivery of some of the harmful components and their level of permissibility by Occupational Safety & Health Administration (OSHA).
- The components on its list that significantly offset the adverse biological activity of several others of its listed components.
- Many components in tobacco and/or tobacco smoke not listed by TPSAC have been reported to significantly reduce the adverse biological effect of several components on the TPSAC list plus several others.

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ZUSAMMENFASSUNG

Der vom Unterausschuss des TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC) erarbeitete erste Entwurf einer Liste schädlicher oder potenziell schädlicher Bestandteile des Tabaks bzw. des Tabakrauches unterscheidet sich signifikant von ähnlichen Listen, die von HOFFMANN *et al.* auf der Grundlage von mehr als vier Jahrzehnten Beschäftigung mit den Inhaltsstoffen von Tabak bzw. Tabakrauch und deren chemischen und biologischen Eigenschaften erarbeitet wurden. Der Entwurf der Liste enthält 106 Bestandteile, von denen sich 60 in der jüngsten Liste von HOFFMANN *et al.* finden, jedoch fehlen neun der von HOFFMANN gelisteten Bestandteile. Alle 106 Bestandteile sind in einer Liste von RODGMAN und GREEN mit insgesamt 162 Tabak- bzw. Tabakrauchbestandteilen enthalten, die in der jüngsten Vergangenheit von einem oder mehreren Wissenschaftlern jeweils als biologisch

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nachteilig beurteilt wurden. Wie die Listen von HOFFMANN *et al.*, so enthält auch die Liste des TPSAC-Unterausschusses zahlreiche Abweichungen:

- Drei schädliche Bestandteile (Dibenz[*a,j*]acridin, Dibenz[*a,h*]acridin, 7*H*-Dibenzo[*c,g*]carbazol), die in den 1960er Jahren erstmals in Tabakrauch beschrieben worden waren, sind in den folgenden 40 Jahren von zahlreichen anerkannten Wissenschaftlern in Japan, Deutschland und den USA, einschließlich des US Department of Agriculture, nicht bestätigt worden;
- zwei schädliche Bestandteile (Arsen, *N*-Nitrosodiethanolamin), deren Mengen deutlich gesunken sind, weil ihre Vorläufer seit mehr als 30 Jahren nicht mehr im Tabakanbau eingesetzt werden;
- die zahlreichen wasserlöslichen Bestandteile, die die Lunge in stark verminderter Konzentration erreichen, ohne Ziliostase auszulösen;
- ein Bestandteil (Chrysen), den die INTERNATIONALE AGENTUR FÜR KREBSFORSCHUNG (IARC) von ihrer Tumorigenizitätsliste gestrichen hat, eine Entscheidung, die von HOFFMANN *et al.* akzeptiert wurde, die ihrerseits Chrysen von ihrer aktuellen Liste negativer Bestandteile im Tabak bzw. Tabakrauch genommen haben.

Das TPSAC gibt keinerlei Hinweise auf

- den Zusammenhang zwischen der Freisetzung einiger schädlicher Bestandteile pro Zigarette und deren von der OSHA festgelegten zulässigen Grenzwerten;
- die gelisteten Bestandteile, die die nachteiligen biologischen Wirkungen mehrerer anderer gelisteter Bestandteile signifikant kompensieren;
- die Tatsache, dass bei zahlreichen Tabak- bzw. Rauchinhaltsstoffen, die nicht vom TPSAC gelistet wurden, eine signifikante Reduzierung nachteiliger biologischer Wirkungen mehrerer in der TPSAC-Liste geführter sowie verschiedener anderer Bestandteile beschrieben wurde.

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RESUME

L'ébauche de liste initiale de composants nocifs ou potentiellement nocifs du tabac et/ou de la fumée du tabac préparée par le Sous-comité constitutif du Comité de conseil scientifique pour les produits du tabac (Constituent Subcommittee of the Tobacco Products Scientific Advisory Committee, TPSAC) diffère largement des listes similaires préparées par HOFFMANN et collègues, ces derniers se distinguant par plus de quatre décennies d'experience et de savoirs en matière de composants du tabac et/ou de la fumée du tabac et de leurs propriétés biologiques et chimiques. La liste ébauchée comprend 106 composants, dont 60 ont été inclus dans les listes HOFFMANN *et al*. récentes mais n'inclut pas neuf des composants listés par HOFFMANN. Tous les 106 composants sont présents dans une liste établie par RODGMAN et GREEN de 162 composants du tabac et/ou de la fumée du tabac, chacun ayant été défini comme biologiquement nocif à un moment ou à un autre au cours des années passées par un ou plusieurs investigateurs. Comme pour les listes établies par HOFFMANN *et al*., la liste du Sous-comité constitutif du TPSAC contient de nombreuses anomalies.

- Trois composants nocifs (dibenz[*a,j*]acridine, dibenz[*a,h*]acridine, 7*H*-dibenzo[*c,g*]carbazole) dans la fumée du tabac ont été rapportés pour la première fois dans les années 1960, mais n'ont pas été confirmés au cours des quarante années suivantes par de nombreux investigateurs compétents au Japon, en Allemagne et aux U.S.A., y compris plusieurs du Ministère de l'Agriculture des Etats-Unis.
- Deux composants nocifs (arsenic, *N*-nitrosodiéthanolamine), dont les taux ont nettement diminué car leurs précurseurs n'ont pas été utilisés dans la production agricole du tabac depuis plus de trois décennies.
- Les nombreux composants hydrosolubles qui atteignent le poumon à un taux nettement réduit pour produire la ciliastase.
- Un composant (le chrysène) que le CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER (CIRC) a retiré de sa liste des produits tumorigènes, une décision acceptée par HOFFMANN *et al*. qui a retiré le chrysène de ses listes plus récentes de composants nocifs du tabac/de la fumée de tabac.

TPSAC ne fournit aucune indication concernant :

- La relation entre l'apport par cigarette de certains composants nocifs et leur degré de permissibilité tel que défini par l'OSHA (administration pour la sécurité et la santé au travail aux USA).
- Les composants sur sa liste qui compensent largement l'activité biologique nocive de plusieurs autres de ses composants listés.
- On a rapporté que de nombreux composants dans le tabac et/ou la fumée du tabac non listés par le TPSAC réduisent nettement l'action biologique nocive de plusieurs composants de la liste du TPSAC et de plusieurs autres composants.

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INTRODUCTION

In 1986, the INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) issued its monograph *Tobacco Smoking* (1). It led to a series of publications between 1986 and 2002 in which various tobacco and/or tobacco smoke components were classified as toxicants, tumorigens, carcinogens, mutagens, or ciliastats [HOFFMANN and WYNDER (2), HOFFMANN and HECHT (3), HOFFMANN *et al.* (4), HOFFMANN and HOFFMANN (5–7), HOFFMANN *et al.* (8), FOWLES and BATES (9), OCCUPATIONAL SAFETY AND HEALTH ASSOCIATION (OSHA) (10)]. Because so many of the publications were co-authored by HOFFMANN, many of the adverse biological components listed were eventually defined as the "Hoffmann analytes". Because of his numerous published lists, Hoffmann was consequently defined as "Author of the list" (11). Examination of these various lists revealed several anomalies which were described and discussed in detail by RODGMAN (12). In 2002 and 2003, RODGMAN and GREEN (13) published a list of the 162 tobacco and/or tobacco smoke components that at one time or another were categorized by one or more investigators as harmful in one way or another to tobacco users or smokers. RODGMAN and GREEN summarized the deficiencies and anomalies for many of the listed compo

nents. Many of the same anomalies noted previously (12, 13) are present for the components classified as harmful/potentially harmful in the 2010 draft list recently issued by the Constituent Subcommittee of the TPSAC (see Table 1) (13a), a list prepared for eventual use by the U.S. Food and Drug Administration (FDA).

In the left-hand column of Table 1, a number has been assigned to each of the 106 components tabulated by the TPSAC Constituent Subcommittee and published on August 30, 2010. The reason for the numbering is that some, but not all, of the Table 1 components will be subsequently discussed in Table 3 with regard to the negation effect of various other tobacco and/or tobacco smoke components (some listed in Table 1, some not listed in Table 1) on the proposed harmful or potentially harmful effect of several components listed in Table 1. The right-hand column indicates those toxic and/or tumorigenic components listed by HOFFMANN and his colleagues in their most recent lists published from 1997 to 2001 (5–8). The last nine lines of Table 1 catalog nine components in the numerous HOFFMANN *et al.* articles on hazardous tobacco and/or tobacco smoke components that were not included by the TPSAC Constituent Subcommittee in its list of 106 components. Its list of 106 compounds includes 60 of the compounds cataloged by HOFFMANN *et al.* but does not include nine other compounds in the HOFFMANN *et al.* lists.

Table 1. Tobacco Products Scientific Advisory Committee (TPSAC) list of harmful or potentially harmful components in tobacco and/or tobacco smoke (S = smoke, T = tobacco, S T = smoke and tobacco; 1 = in Hoffmann list, 0 = not in Hoffmann list)**.**

TPSAC No.	CAS No.	S	T	S T	Name (per CA Collective Index)		Hoffmann lists
1	75-07-0	1	0	0	Acetaldehyde		1
2	60-35-5	1	0	0	Acetamide		1
3	67-64-1	1	1	1	Acetone	{2-propanone}	0
4	107-02-8	1	1	1	Acrolein	{2-propenal}	1
5	79-06-1	1	1	1	Acrylamide	{2-propenamide}	1
6	107-13-1	1	0	0	Acrylonitrile	{2-propenenitrile}	1
7	1162-65-8	0	1	0	Aflatoxin B_1	{cyclopenta[*c*]furo[3',2':4,5]furo[2,3-*h*][1]benzopyran-1,11-dione, 2,3,6a,9a-tetrahydro-4-methoxy-, (6aR-*cis*)-}	0
8	92-67-1	1	0	0	4-Aminobiphenyl	{[1,1'-biphenyl]-4-amine}	1
9	134-32-7	1	0	0	1-Aminonaphthalenamine	{naphthalene, 1-amino-; α-naphthylamine}	0
10	91-59-8	1	0	0	2-Aminonaphthalenamine	{naphthalene, 2-amino-; β-naphthylamine}	1
11	7664-41-7	1	1	1	Ammonia		0
12	14798-03-9	1	1	1	Ammonium ion		0
13	494-52-0	1	1	1	Anabasine	{pyridine, 3-(2-piperidinyl)-, (S)-}	0
14	90-04-0	1	1	1	*o*-Anisidine	{benzenamine, 2-methoxy}	0
15	7440-38-2	1	1	1	Arsenic		1
16	26148-68-5	1	0	0	AαC	{9*H*-pyrido[2,3-*b*]indol-2-amine}	1
17	56-55-3	1	1	1	Benz[*a*]anthracene	{B*a*A or B[*a*]A}	1
18	202-33-5	1	0	0	Benz[*j*]aceanthrylene	{cholanthrylene}	0
19	71-43-2	1	1	1	Benzene		1
20	205-99-2	1	1	1	Benzo[*b*]fluoranthene	{benz[*e*]acephenanthrylene}	1
21	207-08-9	1	0	0	Benzo[*k*]fluoranthene		1
22	271-89-6	1	0	0	Benzo[*b*]furan	{benzofuran; coumarone}	1
23	50-32-8	1	1	1	Benzo[*a*]pyrene	{B[*a*]P}	1
24	195-19-7	1	0	0	Benzo[*c*]phenanthrene		0
25	7440-41-7	1	1	1	Beryllium		1
26	106-99-0	1	0	0	1,3-Butadiene		1
27	123-72-8	1	1	1	Butyraldehyde	{butanal}	0
28	7440-43-9	1	1	1	Cadmium		1
29	331-39-5	1	1	1	Caffeic acid	{2-propenoic acid, 3-(3,4-dihydroxyphenyl)-}	1
30	630-08-0	1	0	0	Carbon monoxide		0
31	120-80-9	1	1	1	Catechol	{1,2-benzenediol; pyrocatechol}	1
32		1	0	0	Chlorinated dioxins/furans	{dibenzo[*b,e*][1,4]dioxin, polychloro-}	0
	67562-39-4	1	1	1	• Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-		
	55673-89-7	1	0	0	• Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-		
	70648-26-9	1	0	0	• Dibenzofuran, 1,2,3,4,7,8-hexachloro-		
	91538-84-0	1	0	0	• Dibenzofuran, 1,2,3,4,7,9-hexachloro-		
	67517-48-0	1	0	0	• Dibenzofuran, 1,2,3,4,8-pentachloro-		
	57117-44-9	1	0	0	• Dibenzofuran, 1,2,3,6,7,8-hexachloro-		
	72918-21-9	1	0	0	• Dibenzofuran, 1,2,3,7,8,9-hexachloro-		
	57117-41-6	1	0	0	• Dibenzofuran, 1,2,3,7,8-pentachloro-		
	60851-34-5	1	0	0	• Dibenzofuran, 2,3,4,6,7,8-hexachloro-		
	57117-31-4	1	0	0	• Dibenzofuran, 2,3,4,7,8-pentachloro-		
	83704-32-9	1	0	0	• Dibenzofuran, 2,3,4,8-tetrachloro-		
	51207-31-9	1	0	0	• Dibenzofuran, 2,3,7,8-tetrachloro-		
33	7440-47-3	1	1	1	Chromium		0
34	218-01-9	1	1	1	Chrysene	{1,2-benzophenanthrene}	0
35	7440-48-4	1	1	1	Cobalt		1

Table 1. contd.

TPSAC No.	CAS No.	S	T	S T	Name (per CA Collective Index)	Hoffmann lists
36	91-64-5	1	1	1	Coumarin {2*H*-1-benzopyran-2-one}	0
37	1319-77-3	1	1	1	Cresols {phenol, methyl-}	0
	95-48-7	1	1	1	• *o*-cresol {phenol, 2-methyl-}	
	108-39-4	1	1	1	• *m*-cresol {phenol, 2-methyl-}	
	106-44-5	1	1	1	• *p*-cresol {phenol, 2-methyl-}	
38	123-73-9, 4170-30-3	1	1	1	Crotonaldehyde {2-butenal}	1
39	27208-37-3	1	0	0	Cyclopenta[*cd*]pyrene	0
40	226-36-8	1	0	0	Dibenz[*a,h*]acridine	1
41	224-42-0	1	0	0	Dibenz[*a,j*]acridine	1
42	53-70-3	1	0	0	Dibenz[*a,h*]anthracene {DB[*a,h*]A}	1
43	194-59-2	1	0	0	7*H*-Dibenzo[*c,g*]carbazole	1
44	192-65-4	1	0	0	Dibenzo[*a,e*]pyrene {naphtho[1,2,3,4-*def*]chrysene}	1
45	189-64-0	1	0	0	Dibenzo[*a,h*]pyrene {dibenzo[*b,def*]chrysene}	0
46	189-55-9	1	0	0	Dibenzo[*a,i*]pyrene {benzo[*rst*]pentaphene}	0
47	191-30-0	1	0	0	Dibenzo[*a,l*]pyrene {dibenzo[*def,p*]chrysene}	1
48	87-62-7	1	1	1	2,6-Dimethylaniline {benzenamine, 2,6-dimethyl-; 2,6-xylidine}	1
49	51-79-6	1	1	1	Ethyl carbamate {carbamic acid, ethyl ester; urethan}	1
50	100-41-4	1	1	1	Ethylbenzene {benzene, ethyl-}	0
51	75-21-8	1	0	0	Ethylene oxide {oxirane}	1
52	97-53-0	1	1	1	Eugenol {phenol, 2-methoxy-4-(2-propenyl)-}	0
53	50-00-0	1	1	1	Formaldehyde	1
54	110-00-9	1	0	0	Furan	1
55	67730-11-4	1	0	0	Glu-P-1 {dipyrido[1,2-*a*:3',2'-*d*]imidazol-2-amine, 6-methyl-}	1
56	67730-10-3	1	0	0	Glu-P-2 {dipyrido[1,2-*a*:3',2'-*d*]imidazol-2-amine}	1
57	302-01-2	1	1	1	Hydrazine	1
58	74-90-8	1	1	1	Hydrogen cyanide {hydrocyanic acid}	0
59	193-39-5	1	0	0	Indeno[1,2,3-*cd*]pyrene {*o*-phenylenepyrene}	1
60	76180-96-6	1	0	0	IQ {3*H*-imidazo[4,5-*f*]quinolin-2-amine, 3-methyl-}	1
61	78-79-5	1	0	0	Isoprene {1,3-butadiene, 2-methyl-}	1
62	7439-92-1	1	1	1	Lead	1
63	68006-83-7	1	0	0	MeAαC {9*H*-pyrido[2,3-*b*]indol-2-amine, 3-methyl-}	1
64	7439-97-6	1	1	1	Mercury	0
65	78-93-3	1	1	1	Methyl ethyl ketone {2-butanone}	0
66	3697-24-3	1	0	0	5-Methylchrysene {chrysene, 5-methyl-}	1
67	64091-91-4, 121268-99-3, 26165-82-0	1	1	1	4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone {NNK; 1-butanone, 4-[(nitrosomethyl)amino]-1-(3-pyridinyl)-}	1
68	91-20-3	1	1	1	Naphthalene	0
69	7440-02-0	1	1	1	Nickel	1
70	54-11-5	1	1	1	Nicotine {pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-}	0
71	14797-55-8	1	1	1	Nitrate	0
72	10024-97-2	1	1	1	Nitrous oxide {nitrogen oxide, N_2O}	0
	10102-43-9	1	1	1	• Nitric oxide {nitrogen oxide, NO}	
	10102-44-0	1	0	0	• Nitrogen dioxide {nitrogen oxide, NO_2}	
	11104-93-1	1	0	0	• Nitrogen oxides	
73	14797-65-0	1	1	1	Nitrite	0
74	98-95-3	1	0	0	Nitrobenzene {benzene, nitro-}	1
75	75-52-5	1	0	0	Nitromethane {methane, nitro-}	1
76	79-46-9	1	0	0	2-Nitropropane {propane, 2-nitro-}	1
77	1133-64-8 37620-20-5	1	1	1	*N*-Nitrosoanabasine {NAB; pyridine, 3-(1-nitroso-2-piperidinyl)-, (*S*)-}	0
78	1116-54-7	1	1	1	*N*-Nitrosodiethanolamine {NDELA; ethanol, 2,2'-(nitrosoimino)bis-}	1
79	55-18-5	1	1	1	*N*-Nitrosodiethylamine {NDEA; ethanamine, *N*-ethyl-*N*-nitroso-}	1
80	62-75-9	1	1	1	*N*-Nitrosodimethylamine {NDMA; methanamine, *N*-methyl-*N*-nitroso-}	1
81	10595-95-6	1	1	1	*N*-Nitrosoethylmethylamine {NEMA; ethanamine, *N*-methyl-*N*-nitroso-}	1
82	59-89-2	1	1	1	*N*-Nitrosomorpholine {NMOR; morpholine, 4-nitroso-}	0
83	16543-55-8	1	1	1	*N*-Nitrosonornicotine {NNN; pyridine, 3-(1-nitroso-2-pyrrolidinyl)-, (*S*)-}	1
84	100-75-4	1	1	1	*N*-Nitrosopiperidine {NPIP; piperidine, 1-nitroso-}	1
85	930-55-2	1	1	1	*N*-Nitrosopyrrolidine {NPYR; pyrrolidine, 1-nitroso-}	1
86	13256-22-9	1	1	1	*N*-Nitrososarcosine {NSAR; glycine, *N*-methyl-*N*-nitroso-}	0
87	494-97-3	1	1	1	Pyridine, 3-(2-pyrrolidinyl)-, (S)- {*l*-nornicotine}	0
88	108-95-2	1	1	1	Phenol	0
89	105650-23-5	1	0	0	PhIP {1*H*-imidazo[4,5-*b*]pyridin-2-amine,1-methyl-6-phenyl-}	1

Table 1. contd.

TPSAC No.	CAS No.	S	T	S T	Name (per CA Collective Index)		Hoffmann lists
90	13981-52-7	1	1	1	Polonium, isotope of mass 210	{^{210}polonium}	1
91	123-38-6	1	1	1	Propionaldehyde	{propanal}	0
92	75-56-9	1	0	0	Propylene oxide	{oxirane, methyl-}	1
93	110-86-1	1	1	1	Pyridine		0
94	91-22-5	1	1	1	Quinoline	{1-azanaphthalene}	1
95	108-46-3	1	1	1	Resorcinol	{1,3-benzenediol}	0
96	7782-49-2	1	1	1	Selenium		0
97	100-42-5	1	1	1	Styrene	{benzene, ethenyl-}	1
98		1	0	0	"Tar"		0
99	95-53-4	1	1	1	*o*-Toluidine	{2-toluidine; benzenamine, 2-methyl-}	1
100	108-88-3	1	1	1	Toluene	{benzene, methyl-}	1
101	62450-06-0	1	0	0	Trp-P-1	{3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole; 5*H*-pyrido[4,3-*b*]indol-3-amine, 1,4-dimethyl-}	1
102	62450-07-1	1	0	0	Trp-P-2	{1-methyl-3-amino 5*H*-pyrido[4,3-*b*]indole; 5*H*-pyrido[4,3-*b*]indol-3-amine, 1-methyl-}	1
103	15117-96-1	0	1	0	Uranium-235	{^{235}uranium}	0
104	7440-61-1	1	1	1	Uranium-238	{^{238}uranium}	0
105	108-05-4	1	0	0	Vinyl acetate	{acetic acid, ethenyl ester}	0
106	75-01-4	0	1	0	Vinyl chloride	{ethene, chloro-}	1
	205-82-3	1	0	0	Benzo[*j*]fluoranthene		1
	14392-02-0	1	1	1	Chromium, isotope of mass 51	{^{51}chromium}	1
	117-81-7	1	1	1	Di(2-ethylhexyl) phthalate		1
	789-02-6	1	1	1	DDT		1
	72-55-9	1	1	1	DDE		1
	93-15-2	1	0	0	Eugenol, methyl-		1
	57-14-7	1	1	1	Hydrazine, 1,1-dimethyl-		1
	924-16-3	1	0	0	*N*-Nitrosodi-*n*-butylamine	{NDBA}	1
	621-64-7	1	1	1	*N*-Nitrosodi-*n*-propylamine	{NDPA}	1

In addition to comparing the TPSAC Constituent Subcommittee list of 106 components classified as harmful or potentially harmful with the most recent HOFFMANN *et al.* lists, the TPSAC list may be compared to that listed by RODGMAN and GREEN [see Table 1 in (13)] who listed all those components described by various investigators over the years as tobacco and/or tobacco smoke toxicants. The components in the RODGMAN-GREEN list numbered 162. Every one of the 106 listed components appears in the RODGMAN-GREEN list (Table 2). Obviously overlooked by TPSAC were the various anomalies and errors that RODGMAN and GREEN had noted for many of the components claimed by numerous investigators to be toxicants.

In many instances, the selection of a component for the list of harmful components was based on the observed biological property of the component administered individually in a specific way to a specific host and the result was extrapolated. Early in the field of tumorigenicity, the rules for defining tumorigenicity were elucidated. One definite rule was that the biological result obtained by administration of a

Table 2. Comparison of TPSAC August 30, 2010 List of toxicants and tumorigens with the RODGMAN-GREEN List (13)
(0 = not in TPSAC list, 1 = in TPSAC list).

No.	CAS-No.	Name (per CA Collective Index)	TPSAC list	No.	CAS-No.	Name (per CA Collective Index)	TPSAC list
Polycyclic aromatic hydrocarbons				*Polycyclic aromatic hydrocarbons* (contd.)			
1	83-32-9	Acenaphthene	0	16	27208-37-3	Cyclopenta[*cd*]pyrene	1
2	208-96-8	Acenaphthylene	0	17	53-70-3	Dibenz[*a,h*]anthracene	1
3	120-12-7	Anthracene	0	18	189-64-0	Dibenzo[*b*,*def*]chrysene {dibenzo[*a*,*h*]pyrene}	1
4	202-33-5	Benz[*j*]aceanthrylene {cholanthrylene}	1				
5	56-55-3	Benz[*a*]anthracene	1	19	191-30-0	Dibenzo[*def*,*p*]chrysene {dibenzo[*a*,*l*]pyrene}	1
6	205-99-2	Benz[*e*]acephenanthrylene {benzo[*b*]fluoranthene}	1	20	206-44-0	Fluoranthene	0
7	50-32-8	Benzo[*a*]pyrene	1	21	86-73-7	Fluorene	0
8	195-19-7	Benzo[*c*]phenanthrene	1	22	193-39-5	Indeno[1,2,3-*cd*]pyrene	1
9	192-97-2	Benzo[*e*]pyrene	0	23	91-20-3	Naphthalene	1
10	191-24-2	Benzo[*ghi*]perylene	0	24	90-12-0	Naphthalene, 1-methyl-	0
11	205-82-3	Benzo[*j*]fluoranthene	0	25	91-57-6	Naphthalene, 2-methyl-	0
12	207-08-9	Benzo[*k*]fluoranthene	1	26	192-65-4	Naphtho[1,2,3,4-*def*]chrysene {dibenzo[*a*,*e*]pyrene}	1
13	189-55-9	Benzo[*rst*]pentaphene {dibenzo[*a*,*l*]pyrene}	1	27	85-01-8	Phenanthrene	0
14	218-01-9	Chrysene	1	28	129-00-0	Pyrene	0
15	3697-24-3	Chrysene, 5-methyl-	1				

Table 2. contd.

No.	CAS-No.	Name (per CA Collective Index)	TPSAC list
Aza-arenes			
29	194-59-2	7*H*-Dibenzo[*c,g*]carbazole	1
30	494-52-0	Anabasine	1
31	86-74-8	Carbazole	0
32	1484-12-4	Carbazole, 9-methyl-	0
33	226-36-8	Dibenz[*a,h*]acridine	1
34	224-42-0	Dibenz[*a,j*]acridine	1
35	120-72-9	Indole	0
36	603-76-9	Indole, 1-methyl-	0
37	54-11-5	Nicotine	1
38	494-97-3	Nornicotine	1
39	110-86-1	Pyridine	1
40	1121-55-7	Pyridine, 3-ethenyl-	0
41	109-06-8	Pyridine, 2-methyl-	0
42	108-99-6	Pyridine, 3-methyl-	0
43	108-89-4	Pyridine, 4-methyl-	0
44	91-22-5	Quinoline	1
Aromatic amines			
45	62-53-3	Aniline	0
46	87-62-7	Aniline, 2,6-dimethyl-	1
47	90-04-0	Aniline, 2-methoxy- {*o*-anisidine}	1
48	95-53-4	Aniline, 2-methyl-	1
49	2243-47-2	Biphenyl, 3-amino-	0
50	92-67-1	Biphenyl, 4-amino-	1
51	134-32-7	Naphthalene, 1-amino-	1
52	91-59-8	Naphthalene, 2-amino-	1
N-Heterocyclic amines			
53	26148-68-5	AαC	1
54	67730-11-4	Glu-P-1	1
55	67730-10-3	Glu-P-2	1
56	76180-96-6	IQ	1
57	68006-83-7	MeAαC	1
58	77094-11-2	MeIQ	0
59	105650-23-5	PhIP	1
60	62450-06-0	Trp-P-1	1
61	62450-07-1	Trp-P-2	1
N-Nitrosamines			
62	64091-91-4	4-(*N*-Methylnitrosamino)-1-(3-pyridinyl)-1-butanone	1
63	37620-20-5	*N'*-Nitrosoanabasine	1
64	71267-22-6	*N'*-Nitrosoanatabine	0
65	16543-55-8	*N'*-Nitrosonornicotine	1
66	1116-54-7	*N-N*itrosodiethanolamine	1
67	55-18-5	*N-N*itrosodiethylamine	1
68	62-75-9	*N*-Nitrosodimethylamine	1
69	924-16-3	*N*-Nitrosodi-*n*-butylamine	0
70	621-64-7	*N*-Nitrosodi-*n*-propylamine	0
71	10595-95-6	*N*-Nitrosoethylmethylamine	1
72	7068-83-9	*N-N*itroso-*n*-butylmethylamine	0
73	100-75-4	*N*-Nitrosopiperidine	1
74	930-55-2	*N*-Nitrosopyrrolidine	1
75	59-89-2	*N*-Nitrosomorpholine	1
76	13256-22-9	*N*-Nitrososarcosine	1
Aldehydes and ketones			
77	75-07-0	Acetaldehyde	1
78	67-64-1	Acetone	1
79	107-02-8	Acrolein	1
80	57-71-6	2,3-Butanedione	0
81	78-93-3	2-Butanone	1
Aldehydes and ketones (contd.)			
82	123-72-8	Butyraldehyde	1
83	123-73-9	Crotonaldehyde	1
84	50-0-0	Formaldehyde	1
85	98-01-1	Furfural	0
86	123-38-6	Propionaldehyde	1
Acids			
87	64-19-7	Acetic acid	0
88	64-18-6	Formic acid	0
89	79-09-4	Propionic acid	0
Phenols			
90	331-39-5	Caffeic acid	1
91	120-80-9	Catechol	1
92	97-53-0	Eugenol	1
93	93-15-2	Eugenol, methyl	0
94	123-31-9	Hydroquinone	0
95	108-95-2	Phenol	1
96	95-48-7	Phenol, 2-methyl-	1
	108-39-4	Phenol, 3-methyl-	0
	106-44-5	Phenol, 4-methyl-	0
97	108-46-3	Resorcinol	1
Volatile hydrocarbons			
98	71-43-2	Benzene	1
99	100-41-4	Benzene, ethyl-	1
100	106-99-0	1,3-Butadiene	1
101	5989-27-5	*d*-Limonene	0
102	78-79-5	Isoprene	1
103	100-42-4	Styrene {benzene, ethenyl-}	1
104	108-88-3	Toluene	1
Polychlorinated heterocycles			
105		Polychlorodibenzo-*p*-dioxins	1
		Polychlorodibenzofurans	0
Organic nitro compounds			
106	98-95-3	Nitrobenzene	1
107	75-52-5	Nitromethane	1
108	79-46-9	Propane, 2-nitro	1
Miscellaneous organic compounds			
109	60-35-5	Acetamide	1
110	79-06-1	Acrylamide	1
111	75-05-8	Acetonitrile	0
112	107-13-1	Acrylonitrile	1
113	1162-65-8	Aflatoxin B_1	1
114	271-89-6	Benzo[*b*]furan	1
115	96-48-0	γ-Butyrolactone	0
116	75-15-0	Carbon disulfide	0
117	630-08-0	Carbon monoxide	1
118	463-58-1	Carbonyl sulfide	0
119	91-64-5	Coumarin	1
120	460-19-5	Cyanogen,	0
121	72-55-9	DDE	0
122	50-29-3	DDT	0
123	124-40-3	Dimethylamine	0
124	51-79-6	Ethyl carbamate {urethane}	1
125	75-21-8	Ethylene oxide	1
126	96-45-7	Ethylenethiourea	0
127	110-00-9	Furan	1
128	57-14-7	Hydrazine, 1,1-dimethyl-	0

Table 2. contd.

No.	CAS-No.	Name (per CA Collective Index)	TPSAC list	No.	CAS-No.	Name (per CA Collective Index)	TPSAC list
Miscellaneous organic compounds (contd.)				*Inorganic compounds* (contd.)			1
129	74-90-8	Hydrogen cyanide	1	146	14797-55-8	Nitrate	0
130	13463-39-3	Nickel carbonyl	0	147	10102-43-9	Nitric oxide	0
131	123-33-1	Maleic hydrazide	0	148	14797-65-0	Nitrite	1
132	67-56-1	Methanol	0	149	7446-09-5	Sulfur dioxide	0
133	107-31-3	Methyl formate	0				
134	624-83-9	Methyl isocyanate	0	*Metals*			0
135	74-89-5	Methylamine	1	150	7440-38-2	Arsenic	1
136	117-81-7	Di(2-ethylhexyl)phthalate	1	151	7440-41-7	Beryllium	1
137	75-56-9	Propylene oxide	0	152	7440-43-9	Cadmium	1
138	106-51-4	Quinone	0	153	7440-47-3	Chromium	0
139		"Tar"	1	154	1333-82-0	Chromium (VI)	1
140	108-05-4	Vinyl acetate	1	155	7440-48-4	Cobalt	1
141	75-01-4	Vinyl chloride	0	156	7439-92-1	Lead	1
				157	7439-97-6	Mercury	
Inorganic compounds			1	158	7440-02-0	Nickel	
142	7664-41-7	Ammonia	1	159	7440-08-6	Polonium-210, pCi	1
143	14798-03-9	Ammonium ion	1	160	7782-49-2	Selenium	1
144	302-01-2	Hydrazine	0	161	15117-96-1	Uranium-235	1
145	7783-06-4	Hydrogen sulfide	0	162	7440-61-1	Uranium-238	1

particular individual compound by a specific method to a specific host could not be extrapolated to the administration of a mixture containing the particular component and administered by a different route to a different host. For example, the biological result obtained with B[*a*]P by a prolonged mouse skin-painting study with a solution of B[*a*]P should not be extrapolated as the effect of B[*a*]P contained in a complex mixture such as an aerosol-like cigarette smoke or an air pollutant and inhaled by a human. This rule and related ones, still meaningful in 2010, were outlined in detail in 1941 by SHEAR and LEITER (14). SHEAR eventually became a member of the upper management of the National Cancer Institute.

Table 3 contains a list of those tobacco and tobacco smoke

Table 3. Effect of other tobacco and/or tobacco smoke components on components classified as harmful or potentially harmful. The components in bold print are listed in the TPSAC list (see Table 1).

TPSAC No.	Component [CAS No.] Comments
Polycyclic aromatic hydrocarbons	
17	Benz[*a*]anthracene {B[*a*]A} [56-55-3]
	Since the demonstration of the tumorigenicity of dibenz[*a,h*]anthracene) (DB[*a,h*]A) (16) and benzo[*a*]pyrene (B[*a*]P) (17), many similar studies of benz[*a*]anthracene (B[*a*]A) have been performed. Eighteen studies conducted between 1930 and 1945 were summarized in 1951 by HARTWELL (18). Only four instances of tumorigenicity were reported, two mice with papillomas and two mice with epitheliomas. In the experiments summarized by SHUBIK and HARTWELL in 1957 (19), only two papillomas were initiated in 30 hosts by skin painting, but 88 sarcomas were initiated in 625 hosts by injection. DIPPLE *et al.* in the 1984 2nd Edition of *Chemical Carcinogenesis*, edited by SEARLE (20), classified the carcinogenic activity of B[*a*]A as "Disputed." In 1951, STEINER and FALK (21) reported that B[*a*]A, categorized at that time as either an extremely weak or an inactive mouse-skin tumorigen, significantly diminished DB[*a,h*]A specific tumorigenicity when both DB[*a,h*]A and B[*a*]A were administered simultaneously by subcutaneous injection. They also noted the reported antitumorigenic activity of B[*a*]A against the highly tumorigenic 7,12-dimethylbenz[*a*]anthracene (DMB[*a*]A), another tobacco smoke component not listed in Table 1. Despite this and similar bioassay results plus the presence of B[*a*]A and DB[*a,h*]A in mainstream smoke (MSS), both have been repeatedly categorized as significant tumorigens in cigarette MSS (2–9). Similar inhibition was reported with mixtures of DMB[*a*]A and several inactive PAHs known to be tobacco smoke components (22). HOFFMANN and WYNDER [unpublished data cited on pp. 246, 292 in (23)] reported two effects of B[*a*]A. Addition of additional B[*a*]A to cigarette smoke condensate (CSC) skin painted on laboratory animals did not increase the observed specific tumorigenicity and co-administration of B[*a*]A and B[*a*]P during skin painting gave less specific tumorigenicity than that observed with the same level of B[*a*]P administered alone. The latter was a confirmation of the findings reported by STEINER and FALK (21). While working with the late W.R. Franks at the Banting and Best Department of Medical Research, University of Toronto, Rodgman was involved in 1948–1949 in a comparison of the tumorigenicities of several PAHs (B[*a*]P; DB[*a,h*]A; B[*a*]A) administered by skin painting or by subcutaneous injection. Equimolar doses of each PAH were administered to groups of mice (50 per group) so that the % Tumor Bearing Animals (% TBA) with B[*a*]P and DB[*a,h*]A exceeded 80% in both the skin-painted and subcutaneously-injected groups. The equimolar dose of B[*a*]A, a commercial sample, m.p. 166–167 °C, gave only 2% TBA in the skin-painted group, i.e., one mouse with a carcinoma, and 4% TBA in the injected group, i.e., two mice with sarcoma. Purification of the B[*a*]A by sequential complex formation with picric acid, column chromatography on alumina, and several recrystallizations not only increased the melting point and diminished the m.p. range (167.2–167.5 °C), but significantly improved the UV absorption spectrum. An equimolar dose of the purified B[*a*]A gave 0% TBA; quintupling the dose gave 0% TBA in both the skin painted and injected groups. The following question remained unanswered: Was the 2% (painted) and 4% (injected) TBA with the commercial sample due to the B[*a*]A or to a contaminant? Unfortunately, the results of the study were never published because of the unwillingness of journals in the late 1940s to accept reports describing negative results.

Table 3. contd.

TPSAC No.	Component [CAS No.] Comments

23 Benzo[*a*]pyrene {B[*a*]P} [50-32-8]

Because it was not only one of the first compounds shown to be tumorigenic in the early 1930s but also was subsequently rated as one of the most tumorigenic compounds known, B[*a*]P was subjected to much study over the years. The co-administration of many compounds with B[*a*]P has been studied and many produce significant reduction of the specific tumorigenicity of the B[*a*]P. Many of the antitumorigenic compounds studied are also identified components of tobacco and/or tobacco smoke. The components in bold print throughout the following tabulation are in the TPSAC list of 106 harmful or potentially harmful components of tobacco and/or tobacco smoke (see Table 1). The tobacco and/or tobacco smoke compounds reported to significantly reduce the specific tumorigenicity of B[*a*]P include:

- Anthracene [CAS No. 120-12-7] (24)
- **Benz[*a*]anthracene {B[*a*]A}** [(21), see also pp. 246, 292 in (23)]
- **Benzene** (24)
- **Naphthalene** (24)
- Hentriacontane [CAS No. 630-04-6] [(25), see also p. 369 in (23)]
- Pentatriacontane [CAS No. 630-07-9] [(25) see also p. 369 in (23)]
- Aconitic acid {1-propene-1,2,3-tricarboxylic acid} [CAS No. 499-12-7] (26, 27)
- **Caffeic acid {2-propenoic acid, 3-(3,4-dihydroxyphenyl)-}** (28)
- Ferulic acid {2-propenoic acid, 3-(3-hydroxy-4-methoxyphenyl-} [CAS No. 1135-24-6] (29)
- *o*-Coumaric acid {2-propenoic acid, 3-(2-hydroxyphenyl)-} [CAS No. 583-17-5, 614-60-8] (28)
- **Coumarin {2*H*-benzopyran-2-one}** (30)
- α-Angelica lactone {3H-2-furanone, dihydro-5-methyl-} [CAS No. 108-29-2] (30)
- **Dioxin {various polychloro derivatives of benzo[*b,e*][1,4]dioxin}** (31–33)
- **Phenol** (34)
- Chlorogenic acid {cyclohexanecarboxylic acid, 3-[[3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]oxy]-1,4,5-trihydroxy-} [CAS No. 327-97-9, 93451-46-8] (35)
- Indole-3-acetonitrile [CAS No. 771-51-7] (36)
- Manganese [CAS No. 7439-96-5] (37)
- Phenol, 2-(1,1-dimethylethyl)- [CAS No. 88-18-6] (38)
- Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl- [CAS No. 128-37-0] (39–41)
- Phenol, 4-methoxy-. [CAS No. 150-76-5] (28, 40)

34 Chrysene [218-01-9]

In its 1983 monograph on polycyclic aromatic hydrocarbons (42) and 1986 monograph on tobacco smoking (1), the IARC categorized chrysene as tumorigenic. However, its viewpoint was changed in the late 1990s. As a result, HOFFMANN and colleagues who had listed chrysene as a tumorigenic cigarette smoke component in several of their earlier list articles (2–4) subsequently deleted chrysene from their more recent lists (5–8). The U.S. OCCUPATIONAL SAFETY AND HEALTH ASSOCIATION (OSHA), in its 1994 article (10), did not include chrysene as a possible tumorigen in cigarette smoke.

42 Dibenz[*a,h*]anthracene {DB[*a,h*]A} [53-70-3]

DB[*a,h*]A, the first individual compound demonstrated to be tumorigenic in 1930 (16), not only was one of the four most potent tumorigens known but also the effect of other compounds on its specific tumorigenicity was, like that of B[*a*]P, much studied. The tobacco and/or tobacco smoke compounds demonstrated to significantly reduce the specific tumorigenicity of DB[*a,h*]A include:

- **Benzene** (24)
- **Naphthalene** (24)
- Anthracene [CAS No. 120-12-7] (24)
- Phenanthrene [CAS No. 85-01-8] (43)
- Fluoranthene [CAS No. 206-44-0] (43)
- Pyrene [CAS No. 129-00-0] (43, 44)
- **Benz[*a*]anthracene {B[*a*]A}** (21)
- **Dioxin {various polychloro derivatives of benzo[*b,e*][1,4]dioxin}** (31–33)

In many instances, the studies indicated that the specific tumorigenicity of DB[*a,h*]A was significantly reduced when the antitumorigenic PAH was co-administered at close to the same molar quantity as the DB[*a,h*]A. However, we know that the molar quantity in cigarette smoke of most of the above noted PAHs greatly exceed that of DB[*a,h*]A or B[*a*]P. Therefore, it is possible that the tumorigenicity of the highly tumorigenic PAH will be lowered even more than when the molar ratio is approximately 1 : 1. Also, the effect of multiple antitumorigenic compounds rather than just one should be considered.

46 Dibenzo[*a,i*]pyrene {benzo[*rst*]pentaphene} [189-55-9]

- *d*-Limonene [CAS No. 5989-27-5] was reported to significantly reduce the specific tumorigenicity of dibenzo[*a,i*]pyrene {benzo[*rst*]pentaphene} (45).

68 Naphthalene [91-20-3]

- **Naphthalene**, on co-administration, significantly reduced the specific tumorigenicity of the potent tumorigens B*[a]*P and DB[*a,h*]A (24)

The four PAHs considered to be the most highly tumorigenic and subjected to much study since the 1930s were DB[*a,h*]A, B[*a*]P, 7,12-dimethylbenz[*a*]anthracene (DMB[*a*]A, and 1,2-dihydro-3-methylbenz[*j*]aceanthrylene (3-methylcholanthrene) (3-MC) (18, 19). Two of them, B[*a*]P and DB[*a,h*]A, were included in the TSPAC list of harmful or potentially harmful tobacco and/or tobacco smoke components. The other two, DMB[*a*]A and 3-MC, were not. However, the potent tumorigenicity of DMB[*a*]A was also shown to be significantly reduced by co-administration of the following compounds, all of which are known tobacco and/or tobacco smoke components:

Table 3. contd.

TPSAC No.	Component [CAS No.] Comments
68	Naphthalene [91-20-3] (Contd.) • β,β-Carotene [CAS No. 7235-40-7] (46) • Phenanthrene [CAS No. 85-01-8] (43) • Fluoranthene [CAS No. 206-44-0] (43, 44) • Pyrene [CAS No. 129-00-0] (43, 44) • Benzo[*e*]pyrene {B[*e*]P} [CAS No. 192-97-2] (43, 44) • Benzo[*b*]triphenylene {dibenz[*a,c*]anthracene} [CAS No. 215-58-7] (47, 48) • α-4,8,13-Duvane-1,3-diol {α-4,8,13-cyclotetradecatriene-1,3-diol, 1,5,9- trimethyl-12-(1-methylethyl)-} [CAS No. 57605-80-8] (49) • β-4,8,13-Duvane-1,3-diol {β-4,8,13-cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-} [CAS No. 57605-81-9] (49) • Retinol {2,4,6,8-Nonatetraen-1-ol, 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-} [CAS No. 68-26-8] (50) • Ascorbic acid [CAS No. 50-81-7] (39, 43) • **Coumarin {2*H*-benzopyran-2-one}** (30) • Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl- [CAS No. 128-37-0] (40) • Phenol, 4-methoxy- [CAS No. 150-76-5] (40) • α-Tocopherol {vitamin E} [CAS No. 59-02-9] (39) • 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl- {caffeine} [CAS No. 58-08-2] (51) • Benzene, (isothiocyanatomethyl)- [CAS No. 2257-09-2] (52, 53) • **Dioxin {various polychloro derivatives of benzo[*b,e*][1,4]dioxin**} (31–33) This item was also effective in significantly reducing the tumorigenicity of 3-MC. • Maleic anhydride [CAS No. 108-31-6] (54) • **Selenium** (55) Other results have been reported on studies in which various tobacco/tobacco smoke compounds were examined for their effect on reducing the specific tumorigenicity of various PAHs. The compounds studied that produced the reduction in tumorigenesis included: • β-Sitosterol [CAS No. 83-46-5] (29, 56) • Maleic anhydride [CAS No. 108-31-6] (54) • α-Tocopherol {vitamin E} [CAS No. 59-02-9] (39, 57–59)
	Aza-arenes
40	Dibenz[*a,h*]acridine [226-36-8]
41	Dibenz[*a,j*]acridine [224-42-0]
43	7*H*-Dibenzo[*c,g*]carbazole [194-59-2] VAN DUUREN *et al.* (60) reported the identification of three *N*-heterocyclic compounds, dibenz[*a,h*]acridine {I}, dibenz[*a,j*]acridine {II}, and 7*H*-dibenzo[*c,g*]carbazole {III} in mainstream cigarette smoke condensate (CSC) and two of them [dibenz[*a,h*]acridine {I}, dibenz[*a,j*]acridine {II}] in a nicotine pyrolysate (Nic Pyr); whereas, CANDELI *et al.* (64) identified {II} but not {I} in mainstream CSC. The 1963 CANDELI *et al.* findings on {II} in MS CSC were not confirmed in 1979 by investigators (68) from the same laboratory: HOFFMANN participated in both the 1963 and 1979 studies. Two studies (67, 68) confirmed the 1960 report by VAN DUUREN *et al.* that 7*H*-dibenzo[*c,g*]carbazole {III} was not present in a nicotine pyrolysate. Despite the fact that the failure between the mid-1960s and 2000 of competent investigators at several laboratories in the U.S., Germany, and Japan to confirm the presence of dibenz[*a,h*]acridine {I}, dibenz[*a,j*]acridine {II}, and 7*H*-dibenzo[*c,g*]carbazole {III} in CSC had been reported several times (12, 61, 62) in the late 1990s and an earlier version of the following tabulation was provided in a memorandum to the U.S. ENVIRONMENTAL PROTECTION AGENCY in 1992 (63), many articles on the harmful tobacco smoke components still listed dibenz[*a,h*]acridine {I}, dibenz[*a,j*]acridine {II}, and 7*H*-dibenzo[*c,g*]carbazole {III} as significant tobacco smoke tumorigens (3–10).

Investigators	Dibenz[*a,h*]acridine		Dibenz[*a,j*]acridine		7*H*-Dibenzo[*c,g*]carbazol	
	Nic Pyr	CSC	Nic Pyr	CSC	Nic Pyr	CSC
VAN DUUREN *et al.* (60)	yes [a]	yes	yes	yes	no	yes
CANDELI *et al.* (64); WYNDER and HOFFMANN (23, 65)	NE	no	NE	yes	NE	NE
KABURAKI *et al.* (66)	no	NE	no	NE	NE	NE
SCHMELTZ *et al.* (67)	no	NE	no	NE	no	NE
SCHMELTZ *et al.* (68)	no	no	no	no	no	no
SNOOK (69)	NE	no	NE	no	NE	no
SNOOK *et al.* (70)	NE	no	NE	no	NE	no
GRIMMER *et al.* (70a)	NE	no	NE	no	NE	no
KAMATA *et al.* (71)	NE	no	NE	no	NE	NE
SASAKI and MOLDOVEANU (72)	NE	no	NE	no	NE	NE
RUSTEMEIER *et al.* (73)	NE	no	NE	yes	NE	NE

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

Table 3. contd.

TPSAC No.	Component [CAS No.] Comments

70 Nicotine [54-11-5]

- **Nicotine** diminished the harmful effect of the following *N*-nitrosamines listed by TPSAC as harmful or potentially harmful components in tobacco and/or tobacco smoke:
  (*N*-Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (74)
  N-Nitrosodimethylamine (NDMA) (75)

87 Nornicotine [494-97-3]

- **Nornicotine** diminished the harmful effect of *N*-nitrosodimethylamine (NDMA) (75)

N-Heterocyclic amines

The *N*-heterocyclic amines originally were considered harmful components of grilled or roasted foodstuffs. They were defined as "cooked food" mutagens because of their inordinately high mutagenicity. After the identification of several of them in cigarette smoke at extremely low levels compared to the levels of the noted PAH tumorigens B[*a*]P and DB[*a,h*]A, their presence in cigarette smoke was emphasized over their presence at much higher levels in cooked foodstuffs. In a study on the effect of CSC or "tar" on the mutagenicity of the following *N*-heterocyclic amines, it was determined that co-administration of each of them with "tar" reduced their mutagenicity by more than 80%.

55	Glu-P-1	[67730-11-4]	"tar" (76)
56	Glu-P-2	[67730-10-3]	"tar" (76)
60	IQ	[76180-96-6]	"tar" (76)
101	Trp-P-1	[62450-06-0]	"tar" (76)
102	Trp-P-2	[62450-07-1]	"tar" (76)

N-Nitrosamines

In numerous co-administration studies with *N*-nitrosamines, it was reported that many compounds significantly reduced their tumorigenicity. The following is a list of tobacco and/or tobacco smoke components that exert such inhibitory effects:

- β-Sitosterol [CAS No. 83-46-5] (29, 56)
- Cholesterol [CAS No. 57-88-5] (77)
- Palmitic acid {hexadecanoic acid} [CAS No. 57-10-3] (78)
- Stearic acid {octadecanoic acid} [CAS No. 57-11-4] (78)
- Benzoic acid, 3,4,5-trihydroxy- {gallic acid} [CAS No. 149-91-7] (79)
- **Selenium** (80)
- 1*H*-Indole [CAS No. 120-72-9] (81)
- α-Tocopherol {vitamin E } [CAS No. 59-02-9] (80)
- 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl- {caffeine} [CAS No. 58-08-2] (79)

67 4-(*N*-Methylnitrosamino)-1-(3-pyridinyl)-1-butanone {NNK} [64091-91-4]

- *d*-Limonene [CAS No. 5989-27-5] (82)
- Benzoic acid, 3,4,5-trihydroxy-, propyl ester {propyl gallate} [CAS No. 121-79-9] (83, 84)
- 2*H*-1-Benzopyran-2-one, 6,7-dihydroxy- {esculetin}[CAS No. 305-01-1] (84)
- **Nicotine** (85)
- 1*H*-Indole [CAS No. 120-72-9] (86)

83 *N'*-Nitrosonornicotine {NNN} [16543-55-8]

- Ethanol [CAS No. 64-17-5] (87, 88)
- Butanol [CAS No. 71-36-3] (88)
- 2-Propanol, 2-methyl- {*tert*-butanol} [CAS No. 75-65-0] (88)
- 2-Propenoic acid, 3-phenyl- {cinnamic acid} [CAS No. 621-82-9] (89, 90)
- **Phenol** (89, 90)
- Indole [CAS No. 120-72-9] (89, 90)

78 *N*-Nitrosodiethanolamine {NDELA} [1116-54-7]

The inclusion of NDELA as a harmful or potentially harmful component of tobacco and/or tobacco smoke overlooks the fact that its precursor, the diethanolamine salt of maleic hydrazide, was banned from agronomic use in the USA in 1981. As a result, it has been predicted that the NDELA level would significantly decrease. For example, HOFFMANN *et al.* (91) predicted that the NDELA level in tobacco would decrease:

> At present, NDELA [*N*-nitrosodiethanolamine] levels are relatively high in US brands (290–300 mg/kg) but they are expected to decrease, since the herbicide was banned from use on tobacco as of October 1981 (92).

In its review of tumorigenic components of tobacco and tobacco smoke, the IARC [see p. 112 in (1)] noted for NDELA:

> Its presence in tobacco products has been related to the use of the sucker growth inhibitor, maleic hydrazide when formulated with the diethanolamine salt ('MH-30' or 'MH-40'); in the USA, that formulation has been replaced by the potassium salt… Tobaccos grown in a pesticide-free environment and smoke generated from such tobaccos are devoid of *N*-nitrosodiethanolamine (NDELA).

Should NDELA be listed as a harmful or potentially harmful component of tobacco and/or tobacco smoke since its precursor has been banned from tobacco agriculture for nearly three decades?

81 *N*-Nitrosodiethylamine {NDEA} [55-18-5]

- Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl- [CAS No. 128-37-0] (93, 94)

Table 3. contd.

TPSAC No.	Component [CAS No.] Comments
80	*N*-Nitrosodimethylamine {NDMA} [62-75-9]
	• **Nicotine** (75)
	• **Nornicotine** (75)
	• Cotinine [CAS No. 486-56-6] (75)
	• Cysteine [CAS No. 52-90-4] (83)
85	*N*-Nitrosopyrrolidine {NPYR} [930-55-2]
	• 2-Propenoic acid, 3-phenyl- {cinnamic acid} [CAS No. 621-82-9] (89, 90)
	• **Phenol** (89, 90)
	• Indole [CAS No. 120-72-9] (89, 90)
82	*N*-Nitrosomorpholine {NMOR} [59-89-2]
	• 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl- {caffeine} [CAS No. 58-08-2] (79)
	Aldehydes and ketones
1	Acetaldehyde [75-07-0]
3	Acetone {2-propanone} [67-64-1]
4	Acrolein {2-propenal} [107-02-8]
38	Crotonaldehyde {2-Butenal} [123-73-9, 4170-30-3]
	Despite the earlier comments by WYNDER and HOFFMANN on the aldehydes and ketones in cigarette smoke, they repeatedly included many of them in their lists of toxic substances in cigarette smoke. In 1965, they wrote (95):
	The principle volatile ciliatoxic components appear to be water-soluble… Important considerations are the temperature of the respiratory tract ... and the nature of the overlying mucous coat, the layer that all ciliastatic components penetrate to act upon cilia…
	Later, WYNDER and HOFFMANN commented several times that most of the components of MSS demonstrated to be ciliastatic in various *in vitro* systems were water-soluble and this property would markedly influence their fate and behavior during and after human inhalation. They noted (96):
	As far as human smoking habits are concerned, it remains also to be estimated to which extent volatile smoke components reach the bronchial tree. Preliminary studies indicate that a significant proportion of the gaseous components is being retained within the oral cavity.
	They also wrote [see p. 542 in (23)]:
	Water-soluble volatile components, which are primarily responsible for the results of the acute *in vitro* short-term cilia toxicity tests, are, to a large extent, removed when cigarette smoke contacts the saliva in the mouth and the abundant secretions of the trachea and main bronchi.
	And added [see p. 646 in (23)]:
	In man's manner of smoking, however, volatile components are retained to a significant degree in the oral cavity and may, therefore, be far less important than when tested experimentally.
	These words had been shown to be true by RODGMAN *et al.* (97) in 1964 and were reported to be true by DALHAMN *et al.* in 1968 (98). In 1964, RODGMAN *et al.* reported the mouth absorption of components of the MSS from five different cigarette brands: The total absorption of all vapor-phase aldehydes and ketones averaged 53%; the absorption of isoprene averaged less than 10%. In a much more sophisticated study, DALHAMN *et al.* later reported that as much as 60% of the water-soluble (and ciliastatic) components of cigarette MSS were absorbed in the human smoker's oral cavity, whereas the absorption of water-insoluble (and nonciliastatic) components such as isoprene was low (< 20%). DALHAMN *et al.* also reported that about 16% of the MSS particulate matter was retained in the mouth. Mouth absorption of acetaldehyde and acetone averaged about 57%.
	Phenols
29	Caffeic acid {2-propenoic acid, 3-(3,4-dihydroxyphenyl)-} [331-39-5]
	• B[*a*]P (28)
88	Phenol [108-95-2]
	Co-administration of phenol and B[*a*]P or phenol and NNN or phenol and NPYR resulted in significant decrease in the adverse biological property of the B[*a*]P, NNN, and NPYR:
	• B[*a*]P (34)
	• NNN (89, 90)
	• NPYR (89, 90)
	Phenol [108-95-2]
	Phenol, 2-methyl- [95-48-7]
37	Phenol, 3-methyl- [108-39-4]
	Phenol, 4-methyl- [106-44-5]
	Unable to explain the observed mouse-skin tumorigenicity of mainstream cigarette smoke condensate (CSC) by summation of the tumorigenic properties of more than a dozen PAHs and several aza-arenes, WYNDER and HOFFMANN attempted to account for the CSC tumorigenicity by incorporation of the promoting effect of various low molecular weight phenols present in cigarette mainstream smoke. The promoting effect of phenols on tumorigenic PAHs had been demonstrated in the 1950s by BOUTWELL *et al.* (99). It was determined by numerous investigators, including HOFFMANN and WYNDER (100), that highly volatile, low molecular weight phenols such as phenol and the isomeric cresols were selectively filtered from cigarette MSS by the filter tip and its plasticizer (usually triacetin) (101–103). Between 1962 and 1994, over 30 studies were conducted and reported on the selective filtration of phenols from cigarette smoke [see Table IX.A-17 in (104)]. Several investigators also noticed inhibition of tumor growth by tobacco smoke condensate (105–107). WYNDER and HOFFMANN [see pp. 628–629 in (23)] wrote about the promoting effect of phenols:

Table 3. contd.

TPSAC No.	Component [CAS No.] Comments

Phenols (Contd.)

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 non-tumor-promoting phenols.

Despite their many previous assertions of the promoting activity of the phenols in tobacco smoke, numerous subsequent statements by WYNDER, HOFFMANN, and their colleagues described their conclusions with respect to volatile phenols removal vs. tumorigenicity of the phenols-depleted CSC [see p. 626 in (23)]. A typical statement follows (108):

Volatile phenols represent one type of tumor promoter in tobacco smoke. In mouse-skin carcinogenesis, however, they evidently do not play an essential role as such, since a significant reduction of phenols in the smoke condensate is not accompanied by a similar reduction in carcinogenic activity of the "tar".

In 1974, HECHT *et al.* (109), citing WYNDER and HOFFMANN (23), stated:

Phenol and some substituted phenols are weak promoters, but they alone contribute only a small part of the promoting activity, since selective filtration of phenol does not change significantly the biological activity of the resulting condensate.

In their 1986 article (2), HOFFMANN and WYNDER discussed tumor initiators and cocarcinogens in cigarette smoke but did not mention the phenolic promoters they had discussed repeatedly in the previous two decades. In its 1986 IARC monograph *Tobacco Smoking* in which many Wynder and Hoffmann references on tobacco smoke chemistry were cited, IARC defined phenols as major promoting agents in tobacco smoke [see p. 104 in (1)], but did not cite the WYNDER-HOFFMANN statements that significant removal of phenols from MSS had little effect on its specific tumorigenicity.

Volatile hydrocarbons

19 Benzene [71-43-2]
- B[*a*]P (24)
- DB[*a,h*]A (24)

Polychlorinated heterocycles

32 Polychlorinated heterocycles / polychlorodibenzo-*p*-dioxins / polychlorodibenzofurans
- B[*a*]P (31–33)
- DB[*a,h*]A (31–33)

Miscellaneous organic components

36 Coumarin {2*H*-benzopyran-2-one} [91-64-5]
- B[*a*]P (30)

98 “Tar”
- Glu-P-1 (76)
- Glu-P-2 (76)
- Trp-P-1 (76)
- Trp-P-2 (76)
- IQ (76)
- MeIQ (76)

LEE *et al.* (76) reported that the "tar" (CSC) from cigarette MSS significantly reduced the mutagenicity of several *N*-heterocyclic aromatic amines as measured in the Ames assay with *Salmonella typhimurium*, strain TA 98 in presence of S-9 mix. As indicated above, the mutagenic *N*-heterocyclic amines tested included: IQ, MeIQ, Glu-P-1, Glu-P-2, Trp-P-1, and Trp-P-2. The mutagenic activities of these mutagens were suppressed as much as 80% by addition of 50 to 100 µg of CSC per plate.

Metals

96 Selenium [7782-49-2]
- NNAs (80)

components in Table 1 that have been studied in numerous experiments where a harmful or potentially harmful component was co-administered with another tobacco and tobacco smoke component at a 1:1 molar ratio and the biological effect of the harmful or potentially harmful component was significantly reduced. Such laboratory studies have an extensive history and have been reported since the mid-1940s. The reporting of such studies involving numerous compounds is not a peculiarity of personnel related to compounds identified in tobacco and/or tobacco smoke research. Such reporting was also done by personnel involved in the carcinogenicity of various air pollutants and food components. In 1985, an extensive summary of the various compounds reported since 1929 to inhibit chemical tumorigenesis was prepared and published by members of the National Cancer Institute (15).

In one instance, Table 3 contains another type of experiment. It involves the water-soluble components, the aldehydes and ketones, and their inhaled amounts that actually reach the lung to initiate ciliastasis. In another instance, the presence of three components reported in cigarette smoke and listed by TPSAC was not confirmed in several laboratories, including that of the USDA.

There is an alternate way to examine the information summarized in Table 3. While the tobacco and/or smoke components listed in Table 1 were classified by TPSAC as harmful or potentially harmful, several in its list have been demonstrated to have pronounced biological properties that, when co-administered in a biological test, significantly reduced the undesired biological activity of the other component. Tables 4 and 5 summarize the alternative.

Table 4. Components in the TPSAC list that reduce the harmful effect of other tobacco and/or tobacco smoke components.

TPSAC No.	CAS No.	TPSAC listed components	Tobacco and/or tobacco smoke component with reduced adverse biological property
17	56-55-3	Benz[*a*]anthracene (B[*a*]A)	B[*a*]P, DB[*a,h*]A
19	71-43-2	Benzene	B[*a*]P, DB[*a,h*]A
29	331-39-5	Caffeic acid {2-propenoic acid, 3-(3,4-dihydroxyphenyl)-}	B[*a*]P
32		Dioxin {various polychloro derivatives of benzo[*b,e*][1,4]dioxin}	B[*a*]P, DB[*a,h*]A
36	91-64-5	Coumarin {2*H*-benzopyran-2-one}	B[*a*]P
68	91-20-3	Naphthalene	B[*a*]P, DB[*a,h*]A
70	54-11-5	Nicotine	NNAs, NNK, NDMA
87	494-97-3	Nornicotine	NDMA
88	108-95-2	Phenol	B[*a*]P, NNN, NPYR
96	7782-49-2	Selenium	NNAs
98		"Tar"	Glu-P-1,Glu-P-2, Trp-P-1,Trp-P-2, IQ, MeIQ

Table 4 lists those components in the TPSAC list that exhibit such properties and the components, the hazardous activity of which are significantly reduced on co-administration. The following has been demonstrated over the years by highly competent investigators:

- Co-administration of almost equal molar quantities of naphthalene and B[*a*]P in a biological study resulted in significant lowering of the adverse biological property of the highly tumorigenic B[*a*]P.
- Co-administration of almost equal molar quantities of anthracene and B[*a*]P in a biological study resulted in significant lowering of the adverse biological property of the highly tumorigenic B[*a*]P.
- Co-administration of almost equal molar quantities of phenanthrene and B[*a*]P in a biological study resulted in significant lowering of the adverse biological property of the highly tumorigenic B[*a*]P.

The summaries in Tables 4 and 5 raise several interesting questions.

What would be the effect on the tumorigenicity of the B[*a*]P of co-administration of equal molar quantities of naphthalene, anthracene, phenanthrene, and B[*a*]P?

What would be the effect on the tumorigenicity of the B[*a*]P of co-administration of molar quantities of naphthalene, anthracene, phenanthrene that greatly exceed that of the B[*a*]P as their levels in cigarette mainstream do?

What is the effect on the tumorigenicity of the tobacco smoke components B[*a*]P of all the components listed in Tables 4 and 5 that occur in the complex mixture of tobacco smoke and that have been demonstrated on individual co-administration with B[*a*]P to significantly reduce the tumorigenicity of B[*a*]P?

As indicated in Tables 4 and 5, there is quite a number of known tobacco and/or tobacco smoke components that significantly reduce the tumorigenicity of B[*a*]P. Is their individual or combined antitumorigenic action the reason why the results reported by ROE (110) and LAZAR *et al.* (111) were obtained? Prior to the biological testing, ROE (110) increased the level of B[*a*]P in a cigarete smoke condensate (CSC) sample by a factor of 10. The 10-fold increase in the CSC content of B[*a*]P produced no change in the specific tumorigenicity of the B[*a*]P-augmented CSC vs. the untreated CSC. In a similar experiment, LAZAR *et al.* (111) increased the level of B[*a*]P in a CSC sample by a factor of 30. The 30-fold increase in the CSC content of B[*a*]P produced no change in the specific tumorigenicity of the B[*a*]P-augmented CSC vs. the untreated CSC.

Derived from RODGMAN and GREEN [see Table 3 in (13)], Table 6 indicates that it is perfectly acceptable for an employee to work in an area where the % of OSHA 8-hr time weighted average (TWA_8) is less than 100%. Only those components among the 106 listed by TPSAC for FDA are included in the abbreviated Table 6. Of course, this assumes that none of the listed compounds has a short-term exposure limit (STEL) that would be exceeded by smoking one cigarette. For the agents listed, none of the STELs is exceeded by smoking one cigarette. One factor in the RODGMAN-GREEN table is that the smoke component values were derived by analysis of the mainstream smoke (MSS) from cigarettes machine-smoked under the Federal Trade Commission (FTC) procedure. It should be kept in mind that, unlike the human smoker, the smoking machine does not exhale. It has been demonstrated in many studies over the years that cigarette smokers retain 50% to 90% of the inhaled MSS, i.e., smokers exhale between 10% to 50% of the inhaled smoke. The smoking machine exhales 0%. Thus, the percentages calculated for Table 6 are higher than those actually expected.

Among the TPSAC listings for a pack-a-day cigarette smoker, nicotine is the only smoke component that exceeds the TWA_8 permissible concentration. However, it is obvious that acrolein and carbon monoxide are reasonably high. For a two pack-a-day cigarette smoker, both nicotine and acrolein would exceed the TWA_8 permissible concentrations and carbon monoxide would be close to the limit.

Typically, OSHA does not deal with occupational exposure to known carcinogens such as B[*a*]P, DB[*a,h*]A, 2-aminonaphthalene, etc. other than to note that exposures to these compounds should be eliminated either by engineering controls or respiratory protection. However, in Table 6, a number of compounds are considered to be carcinogens, e.g., ethylene oxide, acrylamide, acrylonitrile, benzene. These are exceptions to the general OSHA rule. The cigarette smoke component data and the OSHA TWA_8 numbers for the components in Table 6 that were used to calculate the % of OSHA TWA_8 may be seen in RODGMAN and GREEN [see Table 3 in (13)].

Table 5. Tobacco and/or tobacco smoke components that minimize the known adverse biological effect of other components.

CAS No.	Tobacco and/or smoke component	Tobacco and/or tobacco smoke component with reduced adverse biological property
499-12-7	Aconitic acid {1-propene-1,2,3-tricarboxylic acid}	B[*a*]P
108-29-2	α-Angelica lactone {3*H*-2-furanone, dihydro-5-methyl-}	B[*a*]P
120-12-7	Anthracene	B[*a*]P
50-81-7	Ascorbic acid	DMB[*a*]A
2257-09-2	Benzene, (isothiocyanatomethyl)-	DMB[*a*]A
192-97-2	Benzo[*e*]pyrene {B[*e*]P}	DMB[*a*]A
215-58-7	Benzo[*b*]triphenylene {dibenz[*a,c*]anthracene}	DMB[*a*]A
71-36-3	Butanol	NNN
58-08-2	Caffeine {1*H*-purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-}	DMB[*a*]A, NNAs, NMOR
7235-40-7	β,β-Carotene	DMB[*a*]A
327-97-9, 93451-46-8	Chlorogenic acid {cyclohexanecarboxylic acid, 3-[[3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]oxy]-1,4,5-trihydroxy-}	B[*a*]P
57-88-5	Cholesterol	NNAs
621-82-9	Cinnamic acid {2-propenoic acid, 3-phenyl-}	NNN, NPYR
486-56-6	Cotinine {2-pyrrolidinone, 1-methyl-5-(3-pyridinyl)-}	NDMA
583-17-5, 614-60-8	*o*-Coumaric acid {2-propenoic acid, 3-(2-hydroxyphenyl)-}	B[*a*]P
52-90-4	Cysteine	NDMA
57605-80-8	α-4,8,13-Duvane-1,3-diol {α-4,8,13-cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-}	DMB[*a*]A
57605-81-9	α-4,8,13-Duvane-1,3-diol {β-4,8,13-cyclotetradecatriene-1,3-diol, 1,5,9-trimethyl-12-(1-methylethyl)-}	DMB[*a*]A
305-01-1	Esculetin {2*H*-1-benzopyran-2-one, 6,7-dihydroxy-}	NNK
64-17-5	Ethanol	NNN
1135-24-6	Ferulic acid {2-propenoic acid, 3-(3-hydroxy-4-methoxyphenyl-}	B[*a*]P
206-44-0	Fluoranthene	DMB[*a*]A
149-91-7	Gallic acid {benzoic acid, 3,4,5-trihydroxy-}	NNAs
630-04-6	Hentriacontane	B[*a*]P
120-72-9	1*H*-Indole	NNAs, NNN, NPYR
771-51-7	Indole-3-acetonitrile	B[*a*]P
5989-27-5	*d*-Limonene	DB[*a,i*]P, NNK
7439-96-5	Manganese	B[*a*]P
108-31-6	Maleic anhydride	DMB[*a*]A, various tumorigenic PAHs
57-10-3	Palmitic acid {hexadecanoic acid}	NNAs
630-07-9	Pentatriacontane	B[*a*]P
85-01-8	Phenanthrene	DMB[*a*]A
128-37-0	Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-	B[*a*]P, DMB[*a*]A, NDEA
88-18-6	Phenol, 2-(1,1-dimethylethyl)-	B[*a*]P
150-76-5	Phenol, 4-methoxy-.	B[*a*]P, DMB[*a*]A
75-65-0	2-Propanol, 2-methyl- {*tert*-butanol}	NNN
121-79-9	Propyl gallate {benzoic acid, 3,4,5-trihydroxy-, propyl ester}	NNK
129-00-0	Pyrene	DMB[*a*]A
68-26-8	Retinol {2,4,6,8-Nonatetraen-1-ol, 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-}	DMB[*a*]A
83-46-5	β-Sitosterol	NNAs, various tumorigenic PAHs
57-11-4	Stearic acid {octadecanoic acid}	NNAs
59-02-9	α-Tocopherol {vitamin E}	DMB[*a*]A, various tumorigenic PAHs, NNAs

CONCLUSIONS AND RECOMMENDATION

The draft list of harmful or potentially harmful tobacco and/or smoke components prepared by the Constituent Subcommittee of the TPSAC suffers from many of the same problems and anomalies previously described (12, 13, 61, 104) for the numerous other published lists of tobacco and/or tobacco smoke toxicants (2, 5–10).

The problems and anomalies include:

1. Three components (dibenz[*a,j*]acridine, dibenz[*a,h*]acridine, 7*H*-dibenzo[*c,g*]carbazole) are classified as harmful/potentially harmful despite the fact that their presence, first reported in 1960 (60), has not been confirmed by many talented investigators in Japan, Germany, and the USA, including several investigators at the USDA (64–72).
2. Two components (arsenic, *N*-nitrosodiethanolamine) are classified as harmful/potentially harmful despite the fact their levels in tobacco and its smoke have decreased significantly since their precursors were banned three decades ago from use in USA tobacco agronomy (92).
3. Many water-soluble components such as acetaldehyde and acrolein in tobacco smoke are classified as harmful/potentially harmful despite the fact they have been

Table 6. Comparison of the uptake of components mentioned in the TPSAC list by a one pack-a-day-smoker with OSHA permissible 8-hr time weighted average concentration.

TPSAC No.	CAS No.	Component	% of OSHA TWA_8
70	54-11-5	Nicotine	316.0
4	107-02-8	Acrolein	52.0
30	630-08-0	Carbon monoxide	45.1
53	50-0-0	Formaldehyde	5.0
26	106-99-0	1,3-Butadiene	3.7
19	71-43-2	Benzene	3.0
58	74-90-8	Hydrogen cyanide	3.0
28	7440-43-9	Cadmium	2.7
72	10102-43-9	Nitric oxide	1.84
5	79-06-1	Acrylamide	1.47
74	98-95-3	Nitrobenzene	1.00
51	75-21-8	Ethylene oxide	0.778
38	123-73-9	Crotonaldehyde	0.727
6	107-13-1	Acrylonitrile	0.631
31	120-80-9	Catechol	0.453
1	75-07-0	Acetaldehyde	0.356
62	7439-92-1	Lead	0.156
15	7440-38-2	Arsenic	0.116
37	106-44-5	Phenol, 4-methyl-	0.113
88	108-95-2	Phenol	0.111
93	110-86-1	Pyridine	0.101
11	7664-41-7	Ammonia	0.0914
35	7440-48-4	Cobalt	0.0752
25	7440-41-7	Beryllium	0.0500
37	108-39-4	Phenol, 3-methyl-	0.0452
65	78-93-3	2-Butanone	0.0305
37	95-48-7	Phenol, 2-methyl-	0.0303
3	67-64-1	Acetone	0.0242
100	108-88-3	Toluene	0.0234
64	7439-97-6	Mercury	0.0119
57	302-01-2	Hydrazine	0.00662
76	79-46-9	Propane, 2-nitro-	0.00489
97	100-42-4	Styrene {benzene, ethenyl-}	0.00357
95	108-46-3	Resorcinol	0.00284
106	75-01-4	Vinyl chloride	0.00234
68	91-20-3	Naphthalene	0.00137
96	7782-49-2	Selenium	0.00120
69	7440-02-0	Nickel	0.00112
33	7440-47-3	Chromium	0.000862
75	75-52-5	Nitromethane	0.000480
48	87-62-7	Aniline, 2,6-dimethyl-	0.000400
92	75-56-9	Propylene oxide	0.000083

shown to reach the lung at a level significantly reduced from that required to exert serious ciliastasis (97, 98).

4. The PAH chrysene is classified as harmful/potentially harmful despite the fact it was removed by the International Agency for Research on Cancer (IARC) from its tumorigenicity listing, a ruling accepted and noted by HOFFMANN and colleagues who, because of the IARC ruling, deleted chrysene from their recent tobacco/tobacco smoke listings of toxicants (5–8).
5. The exposure to some of the tobacco smoke components classified as harmful/potentially harmful is significantly less than their level of permissible 8-hr exposure by OSHA. See Table 6.
6. Several components are classified as harmful/potentially harmful despite the fact they have been shown to significantly offset the adverse biological activity of several other components classified by TPSAC as harmful/potentially harmful, e.g., phenol and B[*a*]P; nicotine and NNK. For other examples see Table 4.
7. Numerous tobacco and/or tobacco smoke components not listed by TPSAC have been reported to significantly reduce the adverse biological effect of several components classified by TPSAC as harmful/potentially harmful plus others in several other toxicant lists. See Table 5.

While the above problems and anomalies were published in 1998, 2002, 2003, and 2008 (12, 13, 61, 104) in response to the numerous lists on tobacco and/or tobacco smoke toxicants (2–10), no toxicant list author - whether WYNDER, HOFFMANN, HECHT, EL-BAYOUMY, FOWLES, BATES, OR OSHA - has ever published a single contradiction to any item in the above list of problems and anomalies.

In view of this fact and the above conclusions, it is recommended that the TPSAC review the Constituent Subcommittee's list of harmful/potentially harmful tobacco and/or tobacco smoke components and amend the list to reduce the number of problems and anomalies in it. It should also convey such amendments to the Food and Drug Administration.

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