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The Changing Cigarette[1]

Dietrich Hoffmann, Ph.D.,[2] Mirjana V. Djordjevic, Ph.D., and Ilse Hoffmann

American Health Foundation, Valhalla, New York 10595

Background. **Epidemiologic surveys have revealed accelerated increases in adenocarcinoma but less rapid increases in squamous cell carcinoma of the lung among cigarette smokers in recent decades. Changes in the makeup of cigarettes and corresponding changes in smoke composition along with nicotine-compensating smoking patterns, such as the frequency of puff drawing and depth of inhalation, are suggested to have contributed to the observed epidemiologic profiles of these major histologic types of lung cancers.**

Methods. **The various changes in cigarette makeup leading to declining smoke yields from sales-weighted averages of 38 mg "tar" and 2.7 mg nicotine to 12 mg "tar" and 0.9 mg nicotine per cigarette are described.**

Results. **Higher nitrate content of tobacco blends is shown to be one of the major influences on lower smoke yields of carcinogenic polynuclear aromatic hydrocarbons (PAH) while causing increased yields of carcinogenic, tobacco-specific *N*-nitrosamines (TSNA). *In vivo* and *in vitro* bioassays incriminate PAH as inducers of squamous cell carcinoma, while TSNA are known to elicit primarily adenocarcinoma of the lung.**

Conclusions. **The product changes, the smokers' dependence on nicotine which governs their smoking patterns, and the modified smoke chemistry support the hypothesis that differences in PAH and TSNA exposure may be linked to the observed different incidences of squamous cell cancer and adenocarcinoma of the lung.**

Key Words: **cigarette smoke; aldehydes; polynuclear aromatic hydrocarbons; nitrosamines; adenocarcinoma; squamous cell carcinoma; lung cancer.**

INTRODUCTION

The initial impetus for the development of new types of cigarettes can be traced back to the landmark articles by Doll and Hill in the United Kingdom and by Wynder and Graham in the United States in 1950 [*1,2*]. Both studies indicated a dose–response relationship between the number of cigarettes smoked and the risk for lung cancer. These observations were supported by bioassays that demonstrated dose responses between the amount of "tar" applied to mouse skin and the incidence rates of skin tumors and between the exposure to whole cigarette smoke and the occurrence of tumors in the upper respiratory tract of hamsters [*3–5*]. Consequently, emphasis was placed on reducing the smoke yields of cigarettes. Yields of "tar" and nicotine in the smoke are determined by a standardized laboratory procedure that requires that each cigarette is machine-smoked with a 35-ml puff volume, drawn over 2 sec, once a minute. This method had been developed in 1936 and was adapted, with a few minor changes, by the U.S. Federal Trade Commission in 1969 for the analysis of "tar," nicotine, and carbon monoxide in the smoke of all U.S. commercial cigarette brands [*6,7*]. The employed smoking parameters may have approximated the habits of the consumers who smoked cigarettes yielding ⩾2.0 mg nicotine, but they are certainly not reflective of the smoking practices of men and women at the present time, when sales-weighted averages of 0.85–0.9 mg nicotine per cigarette are measured by the standardized machine-smoking procedure [*8*].

MAJOR TOXIC AGENTS IN CIGARETTE SMOKE

Tobacco smoke contains more than 4,000 components of which at least 50 are carcinogenic [*9,10*]. Table 1 lists the likely causative agents for cigarette smoke-related diseases [*11–14*]. The major inducer of tobacco dependence for smokers and for tobacco chewers is nicotine [*11*]. Acetaldehyde, one of the volatile smoke constituents, appears to enhance the pharmacological activity of nicotine [*15*]. The increased risk for cardiovascular diseases among cigarette smokers is likely related to the exposure to "tar," carbon monoxide, hydrogen cyanide, nitrogen oxides, carbon disulfide, cadmium, and other smoke constituents [*13*], while chronic obstructive lung diseases are linked with exposure to "tar," nitrogen oxides, hydrogen cyanide, and volatile aldehydes [*14*].

In respect to lung cancer, the most important agents

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[2] To whom correspondence and reprint requests should be addressed at the American Health Foundation, 1 Dana Road, Valhalla, New York, 10595. Fax: (914) 592-6317.

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TABLE 1

Likely Causative Agents for Cigarette Smoke-Related Chronic Diseases

Chronic disease	Contributor	Enhancing agent
Tobacco dependence	Major: Nicotine	Minor tobacco alkaloids, flavor components, acetaldehyde (?)
Lung cancer	Major: PAH, TSNA	Catechol (cocarcinogen)
	Minor: ^{210}Po, formaldehyde, acetaldehyde	Weakly acidic promoters, volatile aldehydes, NO_x (precursor of *N*-nitrosamines)
Cardiovascular diseases	Major: "Tar", CO	Nicotine, 1,3-butadiene
	Minor: HCN, NO_x, CS_2, Cd, Zn	
Chronic obstructive lung diseases	Major: "Tar", NO_x, HCN, volatile aldehydes	Inducers of superoxide and H_2O_2

are the carcinogenic polynuclear aromatic hydrocarbons (PAHs) and the carcinogenic, tobacco-specific *N*-nitrosamines. Of lesser weight, but certainly also important, are polonium-210 and volatile aldehydes. Tobacco smoke-induced tumorigenesis is enhanced by the cocarcinogenic catechol, by weakly acidic agents that act as tumor promoters, and by nitrogen oxides that may serve as precursors in the exogenous and endogenous formation of carcinogenic *N*-nitrosamines (Table 1).

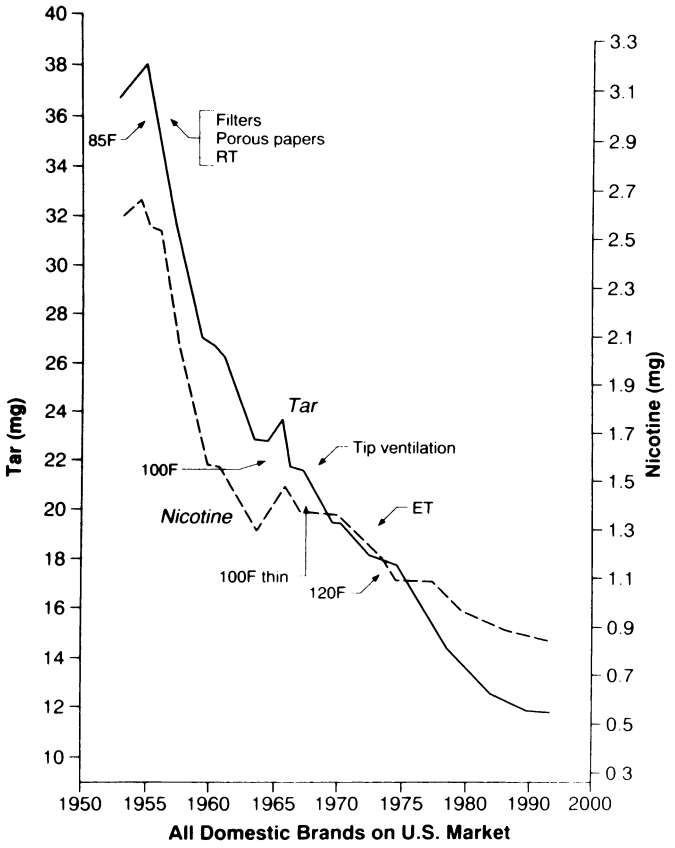

FIG. 1. Sales-weighted average "tar" and nicotine yields of U.S. cigarettes, 1954–1993. RT, reconstituted tobacco; F, filter; ET, expanded tobacco. Reproduced, by permission of the publisher, from Hoffmann *et al.,* 1994 [*53*].

CHANGES IN THE MAKEUP OF U.S. CIGARETTES

Figure 1 depicts the gradual decline of the sales-weighted average "tar" and nicotine yields of U.S. cigarettes [*16*]. Since 1954, the sales-weighted "tar" and nicotine emissions in cigarette smoke have decreased from 38 and 2.7 to 12 and 0.9 mg, respectively. The pronounced changes in the smoke yields of the blended U.S. cigarette were primarily achieved by using filter tips, highly porous cigarette paper, reconstituted tobacco (RT), perforated filter tips (filter tip ventilation), and expanded tobacco (ET), and by incorporating RT, ET, as well as ribs and stems, into the tobacco [*17,18*]. Since the fifties, the tobacco blend has greater filling power because of the increased use of expanded tobacco and reconstituted tobacco. The filling weight of the tobacco in the U.S. cigarette decreased from about 1.2–1.3 g in the fifties to 0.7–0.8 mg in present-day products [*17*]. In 1950, only 0.56% of all U.S. cigarettes had filter tips. Presently, filter cigarettes make up more than 97% of the domestic U.S. market [*19,20*]. About 1% of the cigarettes here have charcoal-containing filter tips. All of the filter tips of cigarettes are made of cellulose acetate tow with plasticizers. More than 50% of all U.S. cigarettes have filter tips with one or more rows of small perforations (Fig. 2). When this type of filter cigarette is smoked, air entering the perforations in the filter tip serves to dilute the smoke and reduces the velocity of the air entering the burning cone. It also slows the velocity of the smoke stream that passes through the filter tip during puff drawing. This increases the efficiency of the filter tip for reducing the "tar" delivery in the smoke. Because of the reduced velocity of air passing through the burning cone, the combustion (oxygen feed) of the tobacco is more complete, which leads to a selective reduction of certain volatile toxic agents such as CO, NO, and several volatile aldehydes (Fig. 3) [*18*]. The composition of the tobacco blend is a major determinant of smoke yields.

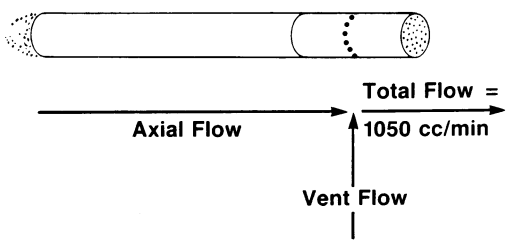

FIG. 2. Dilution of air flow of cigarette with perforated filter tip.

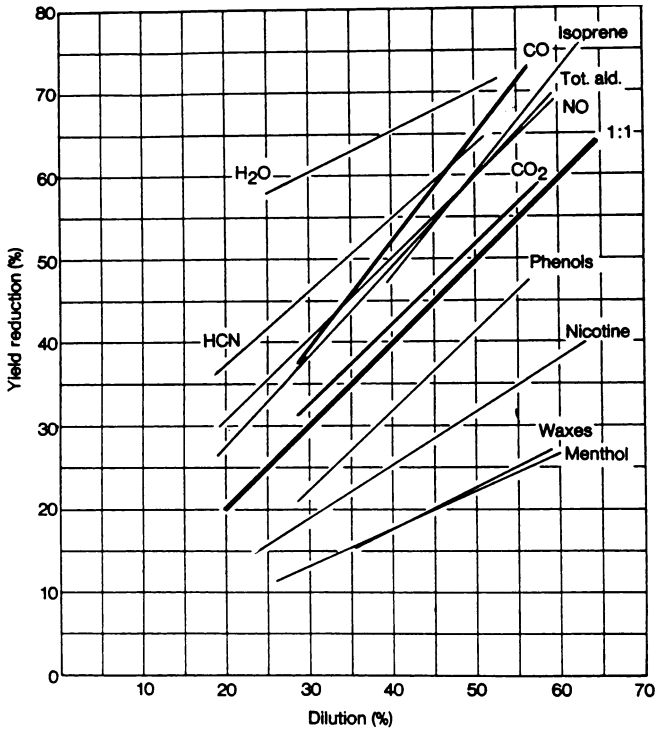

FIG. 3. Regression lines for several smoke components of cigarettes with perforated filter tips with smoke dilution from 20 to 65%. Reproduced, by permission of the publisher, from Norman, 1974 [*18*].

Currently, 25–30% of the U.S. cigarette blends comprise reconstituted tobacco, expanded tobacco, and opened ribs and stems [*16–18*]. The remainder consists of laminae and a few percentages of humectants. In the past, the laminae portion of the U.S. cigarette blend was composed of about 58% bright (flue-cured) tobacco and about 34% burley (air-cured) tobacco with a few percentages of Turkish (sun-cured) and Maryland (air-cured) tobacco. In 1991, the blend consisted of 35% bright and 30% burley tobaccos [*19,20*]. To these were added about 30% stems and ribs from both bright and burley tobaccos in about equal portions. This manner of blending results in an increase of nitrate (from 0.3–0.5 to 0.6–1.35%) [*21,22*], a change that has a major effect on the combustion of the blend and on the composition of the smoke, especially with respect to toxic and tumorigenic agents.

How important the relative proportions of bright tobacco and burley tobacco in the blend are becomes evident when one compares the smoke data for cigarettes made exclusively from only one of these two tobacco types (Table 2) [*5,22–41*]. In general, the smoke of cigarettes made exclusively from bright tobacco or from tobacco blends with low-to-medium nitrate content [*22,42,43*] contains lower concentrations of all types of *N*-nitroso compounds and aromatic amines, while levels of carcinogenic PAHs are higher than in the smoke of cigarettes made exclusively from burley tobacco. Burley tobacco contains up to 5% nitrate and its smoke is, therefore, rich in nitrogen oxides, whereas bright tobacco has low nitrate levels ($\leq$0.5%) and low smoke concentrations of nitrogen oxides. Nitrogen oxides serve as scavengers of pyrolytically formed CH radicals, which are the precursors of carcinogenic PAHs. Nitrogen oxides also serve as precursors in the formation of *N*-nitrosamines from secondary and tertiary amines and in the C-nitrosation of aliphatic and aromatic hydrocarbons. During smoking, the pyrosynthesized nitrohydrocarbons are reduced to amines. The ribs and stems of burley tobacco are especially rich in nitrate [*42,44*].

CHANGES IN SMOKE COMPOSITION

The changes that have occurred in the makeup of U.S. cigarettes over a period of 45 years have significantly altered smoke composition. Table 3 compares data for individual components in the smoke of the U.S. blended cigarettes of the fifties with corresponding data for the cigarette smoke composition profiles that have been established for the past 15 years. Whereas all those toxic agents that are being formed with nitrogen oxides as precursors have increased in the smoke of the U.S. blended cigarette (NO_x, nitrosodimethylamine, 2-naphthylamine, nitrosonornicotine [NNN], and 4-(methylnitrosamino)-1-(3-pyridyl-1-butanone [NNK]), it is evident from Table 3 that the levels of all other toxic smoke constituents have decreased by 60–70%. We have monitored the smoke profiles of the leading American nonfilter cigarette with regard to benzo[*a*]pyrene (B*a*P) content since 1959 and with regard to NNK since 1978. B*a*P in the smoke decreased by 62% and NNK rose by 73% (Fig. 4) [*45*] in smoke analyses based on standardized machine-smoking of cigarettes [7]. In terms of human exposures, the standardized smoking conditions used for analytical comparisons do not reflect the smoking patterns of most contemporary cigarette smokers in North America who consume low-nicotine cigarettes. These smokers adjust their smoke intake to satisfy a conditioned need for the pharmacologically active agent nicotine, so that the volume of smoke inhaled delivers far more carcinogens and toxins than those measured in the smoke of cigarettes smoked by machine with standardized analytical parameters [*8,46*].

POSTSCRIPT

Since 1950, we have seen in the United States a remarkable decrease in the age-adjusted death rate from heart disease but a significant increase of deaths from chronic obstructive pulmonary disease (COPD) and from lung cancer (Fig. 5) [*47*]. Whereas smoking is only one of several factors contributing to death from coronary artery disease, the cigarette habit is clearly a major contributor to COPD, respiratory cancers, and premature deaths from various respiratory diseases. In

TABLE 2

Known Carcinogens in the Smoke of Bright or Blond and Burley or Black Tobacco[a]

Carcinogens	Cigarette type	Bright or blended tobacco (ng/cigarette)	Burley or black tobacco (ng/cigarette)
I. Volatile nitrosamines			
NDMA	NF	6.8–13.8	29
	F	1.8–5.7	4.3
NEMA	NF	<0.1–1.8	2.7
	F	0.4–1.0	0.5
NPYR	NF	11.0–30.3	25
	F	3.1–8.7	10.5
NDMA	NF	9.4–48.4	38.8–76.4
NEMA	NF	<0.1–7.1	21–63
NPYR	NF	6.9–41.2	22.7–36.1
II. NDELA	NF (Exp. cigarettes)[b]	30–51	290
III. TSNA			
NNN	NF (Exp. cigarettes)[b]	620	3,700
NNK	NF (Exp. cigarettes)[b]	420	320
NAT[c]	NF (Exp. cigarettes)[b]	410	4,600
NNN	NF	85–255	512–625
NNK	NF	70–156	108–432
NAT[c]	NF	81–225	266–353
NNN	NF	29	203
NNK	NF	40–136	
NAT[c]	NF	45	108
NNN	NF	79–885	550–800
NNK	NF	62–185	84–470
NAT[c]	NF	75–380	225–520
NNN	F	213	117–389
NNK	F	32	13–55
NAT[c]	F	92	74–196
IV. Aromatic amines			
2-Toluidine	NF	32.2	162
	F	41.0	66.8
2-Naphthylamine	NF	1.0	1.7
	F	2.1	1.8
4-Aminobiphenyl	NF	2.4	4.6
	F	0.3–0.2	23
V. 2-Nitropropane	NF	220–1,190	1,430–2,180
VI. PAH			
B*a*A	NF (Exp. cigarettes)[b]	21.0–25.9	10.7–16.7
B*a*P	NF (Exp. cigarettes)[b]	38–53	24
	NF (Exp. cigarettes)[b]	7.5–9.6	25
	NF (Exp. cigarettes)[b]	35.4	19.7
VII. Volatile aldehydes			
Formaldehyde	NF (Exp. cigarettes)[b]	26,800–36,300	16,100–25,100
Acetaldehyde	NF (Exp. cigarettes)[b]	797,000–906,000	726,000–966,000
VIII. Benzene		27,000	30,000
IX. Quinoline	F	620	1,200

Note. Abbreviations: NDMA, nitrosodimethylamine; NEMA, nitrosoethylmethylamine; NPYR, nitrosopyrrolidine; NDELA, nitrosodiethanolamine; TSNA, tobacco-specific *N*-nitrosamines; NNN, N′-nitrosonornicotine; NNK, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone; NAT, N′-nitrosoanatabine; B*a*A, benz[*a*]anthracene; B*a*P, benzo[*a*]pyrene; NF, nonfilter; F, filter. The pH of the smoke of blond-type cigarettes varies between 6.15 (first puff) and 5.7 (last puff). The pH of the French black cigarette with filter tip increases from 6.8 to 7.4 and without filter tip from 6.6 to 6.95. With pH increasing above 6 the toxicity of the smoke increases.

[a] Black cigarettes, French-type black cigarettes made exclusively from Burley tobacco; blond cigarettes, Virginia-type cigarettes and U.S. blended cigarettes.

[b] Cigarettes were not commercial cigarettes, but were made for specific research projects.

[c] NAT contains some N′-nitrosoanabasine (NAB).

the case of lung cancer, more than 90% of all deaths among males and more than 78% of all lung cancer deaths among women are attributed to cigarette smoking [*48*]. Furthermore, there has been a distinct change in the ratio of the two major histological types of lung cancer: squamous cell carcinoma (SCC) and adenocarcinoma (AC). In 1950, the ratio of SCC to AC was 17:1. Today it is between 1.2 and 1.4:1 [*2,49*]. As reported in a study by Devesa *et al.,* covering 7% of the U.S. population, 16,288 lung cancer cases were registered be-

TABLE 3

Changes in the Yields of Selected Toxic Agents in the Smoke of U.S. Cigarettes

Smoke component	Earlier cigarettes[a]		Current cigarettes[a]	
	Year	Concentration/cig.	Year	Concentration/cig.
Carbon monoxide (CO)	1953	33–38 mg (NF)	1994	11 mg (F)
Nitrogen oxides (NO_x)	1965	330 μg (NF)	1994	500 μg (NF)
Benzene	1962	30 μg (NF)	1988	48 μg (NF)
	1962	25–30 μg (F)	1990	42 μg (F)
Acetaldehyde	1960	1,000 μg (NF)	1992	400 μg (F)
NDMA	1976	43 ng (NF)	1989	65 ng (NF)
"Tar"	1953	38 mg (NF)	1994	12 mg (F)
Nicotine	1953	2.7 mg (NF)	1994	0.85 mg (F)
	1959	1.7 mg (F)	1994	1.1 mg (F)
Phenol	1960	100 μg (NF)	1994	70 μg (NF)
	1960	46 μg (F)	1994	35 μg (F)
Catechol	1965	390 μg (NF)	1994	
	1976	790 μg (F)	1994	140 μg (F)
2-Naphthylamine	1968	22 ng (NF)	1985	35 ng (F)
B*a*P	1959	50 ng (NF)	1995	19 ng (NF)
	1959	27 ng (F)	1995	8 ng (F)
NNN	1978	220 ng (NF)	1995	300 ng (NF)
	1978	240 ng (F)	1995	280 ng (F)
NNK	1978	110 ng (NF)	1995	190 ng (NF)
	1978	100 ng (F)	1995	144 ng (F)

[a] Abbreviations: NF, nonfilter; F, filter; NDMA, *N*-nitrosodimethylamine; B*a*P, benzo[*a*]pyrene; NNN, *N*′-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

tween 1969 and 1971 and a total of 28,703 cases between 1984 and 1986 [*50*]. During this time, the incidences of SCC and AC among white men rose by 25 and 110%, respectively. Among black men, these cancers increased by 50 and 151%. Among white women the increases were 156 and 220% and among black women 209 and 220%. Despite the fact that cigarette consumption by adults (⩾18 years) has declined since 1975 [*51–53*], the lung cancer rate is undiminished (Fig. 5) [*47*]. It appears that the more pronounced increase in AC is correlated with the observation that among younger cohorts, at least among men, AC peaks 10–20 years later than SCC. Devesa *et al.* suggest that smoking intensity, duration, cessation, or other characteristics of exposure to carcinogens in tobacco smoke may influence the development of the various types of lung tumors in various ways [*50*].

On the basis of our laboratory studies, we hypothesize that the smoker of cigarettes with low-nicotine delivery inhales smoke more intensely [*8*] and more deeply [*55*] to satisfy an acquired need for a certain

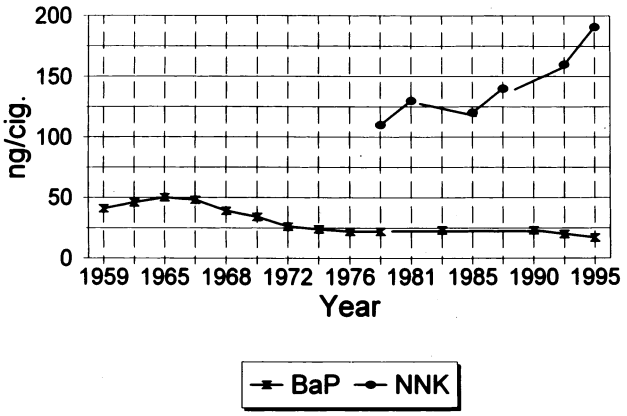

FIG. 4. B*a*P and NNK in mainstream smoke of the U.S. leading nonfilter cigarette, 1959–1995. Reproduced, by permission of the publisher, from Hoffmann and Hoffmann, 1994 [*16*].

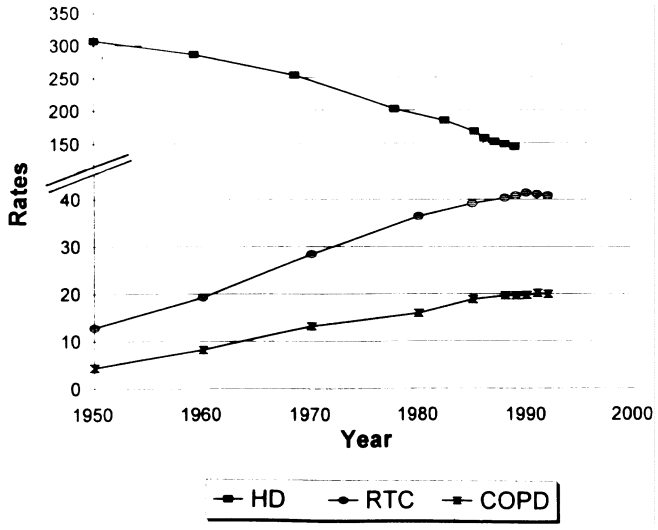

FIG. 5. Age-adjusted death rates from heart disease (HD), respiratory cancer (RT), and chronic obstructive pulmonary disease (COPD). U.S. males and females (1950–1992). Reproduced, by permission of the publisher, from U.S. Department of Health and Human Services, 1995 [*47*].

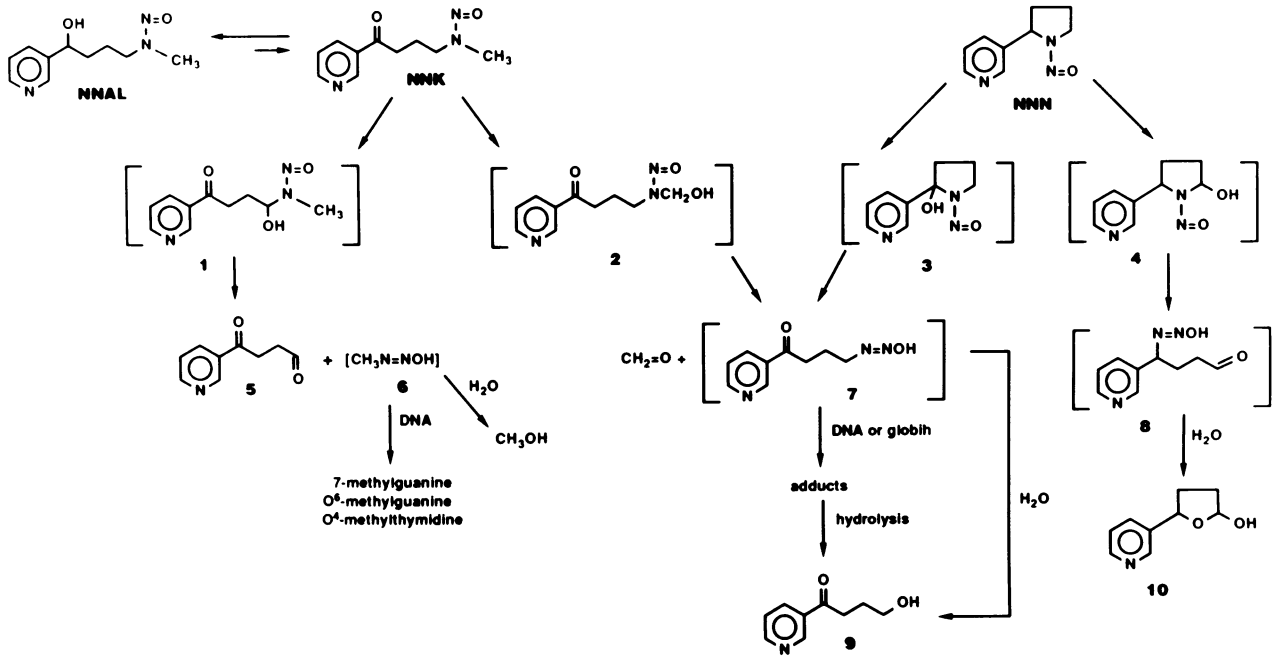

FIG. 6. Metabolism of NNN and NNK. Reproduced, by permission of the publisher, from Hoffmann *et al.,* 1994 [*52*].

dose of nicotine. Consequently, the peripheral lung is exposed to relatively high amounts of lung carcinogens such as TSNA, specifically NNK. Independent of mode or form of application, these *N*-nitrosamines induce primarily lung adenoma and adenocarcinoma in mice, rats, and hamsters. In human lung explants, NNK is metabolically activated by α-hydroxylation to reactive species in the same way it is activated *in vivo* in laboratory animals [*54*]. The resulting reactive species are methane diazohydroxide (Fig. 6) [*53*] and 4-oxo-4-(3-pyridyl)butane diazohydroxide [*55*]. These species alkylate DNA bases, including O^6-methylguanine, and also form pyridyloxobutylated DNA [*55*]. The latter adducts have been found to be elevated in the cells of the lung and in the trachea of smokers, compared with levels in corresponding cells of nonsmokers [*55*]. These aspects of lung carcinogenesis among cigarette smokers continue to be studied.

In 1989, a New York Times editorial on the changing cigarette stated "obviously no smoking is better than smoking, but the best should not be the enemy of the good. There is a strong social case for encouraging manufacturers to develop safer cigarettes that will sell" [*56*]. While one may agree with this premise, the only "safe" cigarette is no cigarette. Because the major reason why both men and women smoke cigarettes lies in their growing dependence on nicotine, Benowitz and Henningfield have suggested a gradual reduction of the nicotine content of present-day cigarette tobaccos from 0.8–0.9 mg to 0.4–0.5 mg per cigarette as an effective measure toward preventing nicotine dependence. Eventually, this weaning effect should eliminate the need for cigarettes [*57*].

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