

# **Cigarette Smoke Components and Disease: Cigarette Smoke Is More Than a Triad of Tar, Nicotine, and Carbon Monoxide**

Jeffrey E. Harris

**INTRODUCTION** Cigarette smoke is a complex mixture of chemicals. Some smoke components, such as carbon monoxide (CO), hydrogen cyanide (HCN), and nitrogen oxides, are gases. Others, such as formaldehyde, acrolein, benzene, and certain N-nitrosamines, are volatile chemicals contained in the liquid-vapor portion of the smoke aerosol. Still others, such as nicotine, phenol, polyaromatic hydrocarbons (PAHs), and certain tobacco-specific nitrosamines (TSNAs), are contained in the submicron-sized solid particles that are suspended in cigarette smoke.

In view of this chemical complexity, cigarette smoke has multiple, highly diverse effects on human health. It is not unexpected that multiple chemicals in cigarette smoke can contribute to any single adverse health effect.

Thus, HCN may affect the human respiratory system by its toxic effects on the cilia that line the respiratory tract. At the same time, HCN may cross the placenta and have toxic effects on the growing fetus. In addition, HCN also may cause nerve damage in cigarette smokers with optic neuropathy (Costagliola et al., 1989). Although the PAHs and TSNAs in the particulate phase of cigarette smoke are known carcinogens, catechols and phenols in the particulate phase also are considered carcinogens or tumor promoters. Benzene and formaldehyde in the liquid-vapor portion of the smoke also may be carcinogenic.

Aside from specific chemical constituents, certain physical-chemical properties of smoke may participate in disease processes. Thus, the pH of the smoke may affect the site and degree of nicotine absorption as well as the smoker's depth of inhalation. The oxidation-reduction state of the smoke can be important because oxidants influence the maturing of cholesterol-laden plaques in the coronary arteries and other blood vessels. In short, cigarette smoke is far more than a triad of tar, nicotine, and carbon monoxide. This fact needs to be considered carefully in any discussion of the adequacy of current cigarette testing methods or current cigarette labeling practices.

**MAINSTREAM VS. SIDESTREAM CIGARETTE SMOKE** Both smokers and nonsmokers can incur adverse health effects from the smoke of burning cigarettes. Smokers inhale mostly mainstream (MS) smoke, which is drawn through the burning tobacco column and filter tip and exits through the mouthpiece of the cigarette. Nonsmokers inhale mostly sidestream (SS) smoke, which is

emitted into the surrounding air between puffs from the end of the smoldering cigarette. Sidestream smoke is the major source of environmental tobacco smoke (ETS).

Although SS and MS smoke have qualitatively similar chemical compositions, the respective quantities of individual smoke constituents can be quite different (U.S. Department of Health and Human Services, 1987 and 1989). For example, in studies of nonfilter cigarettes smoked by machines, the yield of CO in undiluted SS smoke was 2.5- to 4.7-fold that of MS smoke, whereas the corresponding SS/MS ratio for N-nitrosodimethylamine (NDMA), an animal carcinogen, was 0.2 (U.S. Department of Health and Human Services, 1989). In one compilation of toxic and tumorigenic agents in cigarette smoke, the SS/MS ratio ranged from 0.03 to 130 (Hoffmann and Hecht, 1990). In another study, the concentration of the carcinogen 4-aminobiphenyl in undiluted SS smoke was 32-fold that of MS smoke. The SS smoke from so-called reduced-yield cigarettes does not necessarily have reduced emissions of toxic and carcinogenic chemicals (Adams et al., 1987; Rando et al., 1992).

Whereas exposure to SS smoke depends on the distance from the burning cigarette and conditions of ventilation, the higher concentrations of certain toxic and carcinogenic chemicals in SS smoke result in measurable levels of these chemicals in nonsmokers exposed to ETS. For example, nonsmokers exposed to relatively high concentrations of SS smoke have detectable urinary levels of the metabolites of the tobacco-specific nitrosamine 4-(methylnitrosamine)-1-(3-pyridil)-1-butanone (NNK) (Hecht et al., 1993). Young children exposed to ETS via their smoking mothers have detectable levels of PAH-albumin adducts in their blood (Crawford et al., 1994).

Exposures to specific chemical agents in ETS can in turn produce pathological effects in humans and in animal models. The CO in SS smoke reduces the blood's ability to deliver oxygen to the heart, an effect that is especially important in patients with coronary heart disease (CHD) (Sheps et al., 1990). Secondhand cigarette smoke activates blood platelets, which in turn play a role in the development of atherosclerotic plaques in CHD (Glantz and Parmley, 1995).

The remainder of this chapter focuses on the chemical components of MS smoke and their health effects on cigarette smokers; however, the components of SS smoke and their health effects on nonsmokers cannot be ignored.

### **MAJOR HEALTH EFFECTS OF CIGARETTE SMOKE**

The major health effects of cigarette smoke include:

- cancer;
- noncancerous lung diseases;
- atherosclerotic diseases of the heart and blood vessels; and
- toxicity to the human reproductive system.

Other health effects of cigarette smoke, such as retardation of healing of peptic ulcers and interaction with certain therapeutic drugs, are not considered in detail here.

The epidemiologic evidence on the degree (if any) to which filter-tipped and low-tar cigarettes have reduced the risks of smoking-related diseases are reviewed by Samet (this volume).

The psychoactive drug in cigarette smoke is nicotine. Cigarette smoking is a highly controlled form of self-administration of this drug. Nicotine use is self-reinforcing. Attempts to stop smoking lead to craving, withdrawal symptoms, and high rates of relapse (U.S. Department of Health and Human Services, 1988; Harris, 1993). The psychoactive effects of nicotine are discussed in detail in chapters by Benowitz (this volume) and Henningfield and Schuh (this volume).

## **CANCER**

Cigarette smoking causes cancers of the lung, esophagus, larynx, oral cavity, bladder, and pancreas in male and female smokers. In fact, cigarette smoking is the major cause of lung cancer in the United States, accounting for 90 percent of cases in men and 79 percent in women (U.S. Department of Health and Human Services, 1989). Smoking is also reported to increase the risks of cancers of the kidney, liver, anus, penis, and uterine cervix as well as several forms of acute leukemia (Garfinkel and Bofetta, 1990; U.S. Department of Health and Human Services, 1982, 1989, and 1990).

Numerous epidemiological studies covering the experience of millions of men and women over many years show that smokers' risks of developing cancer increase with the number of cigarettes smoked daily, the lifetime duration of smoking, and early age of starting smoking. Smoking cessation gradually reduces cancer risk, although a persistent excess risk has been observed even two decades after cessation (U.S. Department of Health and Human Services, 1989 and 1990). Cigarette smoke interacts with other causative agents, including alcohol, asbestos, radon daughters, certain viruses, and certain workplace exposures, in the development of human cancers (U.S. Department of Health and Human Services, 1982, 1989, and 1990).

Condensates collected from cigarette smoke cause mutations and damage to DNA (deoxyribonucleic acid) in laboratory assays of mutagenesis (Gairola, 1982) as well as malignant transformation (in laboratory tests) of a chemical's ability to induce malignant changes in mammalian cells. The most widely used experimental system is the mouse skin bioassay, in which cancers are induced by the repeated application of condensates of cigarette smoke to the shaved skins of mice.

Humans naturally puff on cigarettes. The puffed smoke, in a volume of about 30 to 70 mL, is temporarily retained in the smoker's mouth, after which it may be inhaled deeply into the lungs. By contrast, some laboratory animals breath by panting, and others are obligate nose breathers. Even with installation of smoke through artificial airways, it can be quite difficult to get the animals to inhale deeply, as human smokers do. Accordingly, the

distribution and retention of smoke components in the respiratory systems of laboratory animals may not mimic natural human smoking. Nevertheless, long-term smoke inhalation regularly induces tumors of the larynx in Syrian golden hamsters. Direct installation of cigarette tar into the airways of laboratory animals causes lung cancers (Hoffmann and Hecht, 1990; U.S. Department of Health and Human Services, 1982).

MS cigarette smoke contains more than three dozen distinct chemical species considered to be tumorigenic in humans or animals (Hoffmann and Hecht, 1990; U.S. Department of Health and Human Services, 1982 and 1989). Among the most prominent are PAHs such as benzo(a)pyrene (BaP); aza-arenes such as dibenzo-acridine; N-nitrosamines such as NDMA; aromatic amines such as 4-aminobiphenyl; aldehydes such as formaldehyde; other organics such as benzene; and certain inorganic compounds such as arsenic, nickel, and chromium. Some of these chemicals alone are capable of initiating tumors in laboratory animals; others can promote the development of previously initiated cancers. Still others indicate direct human epidemiological evidence of carcinogenicity.

Certain chemical components of smoke may contribute to specific cancers. For example, TSNA's may contribute to cancers of the lung, larynx, esophagus, and pancreas, whereas 4-aminobiphenyl and certain aryl amines may contribute to cancer of the bladder (Vineis, 1991). Benzene in cigarette smoke may play a role in smoking-induced leukemia (Melikian et al., 1993).

**NONCANCEROUS LUNG DISEASES** Cigarette smoking is the main cause of chronic obstructive lung disease (COLD), also called chronic obstructive pulmonary disease (U.S. Department of Health and Human Services, 1984a). Smoking accounts for 84 percent of COLD deaths in men and 79 percent in women (U.S. Department of Health and Human Services, 1989).

COLD is a slowly progressive illness that develops after repeated insults to the lung over many years. In the early years after starting to smoke, an individual may report no symptoms. However, even at this early stage breathing tests can often detect abnormalities in the small terminal airways of the lung (Beck et al., 1981; Seely et al., 1971; U.S. Department of Health and Human Services, 1984a), and these abnormalities have been directly observed in autopsy studies of young smokers who died suddenly (Niewoehner et al., 1974). For smokers in their twenties, there is already a dose-response relationship between the extent of abnormal lung tests and the number of cigarettes smoked daily. In random population surveys, from 17 to 60 percent of adult smokers younger than age 55 have detectable small airway dysfunction (U.S. Department of Health and Human Services, 1984a).

Over the course of an individual's two decades or more of smoking, a constellation of chronic respiratory changes develops. These chronic lung injuries include (1) mucus hypersecretion with chronic cough and phlegm; (2) airway thickening and narrowing, resulting in obstruction to airflow during expiration; and (3) emphysema, that is, abnormal dilation of the air spaces at the end of the respiratory tree, with destruction of the walls lining

the air sacs, resulting in further airflow obstruction. These changes can cause significant respiratory impairment, disability, and death. Although individual patients vary in the relative contribution of these three changes, those with clinically severe COLD typically have all three.

Although a minority of cigarette smokers will develop clinically severe COLD, some chronic deterioration in lung structure or function is demonstrable in most long-term smokers (U.S. Department of Health and Human Services, 1984a). Some smokers show more chronic cough and phlegm, others more airway obstruction. In general, breathing function declines with the increase in a person's cumulative exposure to smoke, measured in pack-years (Dockery et al., 1988).

Cigarette smoke produces pathological changes in the lungs of smokers by a number of different mechanisms (U.S. Department of Health and Human Services, 1990). Cigarette smoke is toxic to the cilia that line the central breathing passages. These cilia, in combination with mucus secretions, defend against deep inhalation of foreign material (U.S. Department of Health and Human Services, 1984a). Smoking also induces many abnormalities in the inflammatory and immune systems within the lung (U.S. Department of Health and Human Services, 1985). In particular, cigarette smoke causes inflammatory cells to produce an enzyme called elastase, which in turn breaks down elastin, an important protein that lines the elastic walls of the air sacs (Fera et al. 1986; U.S. Department of Health and Human Services, 1984a). Moreover, oxidants present in cigarette smoke can inactivate a separate protective enzyme called alpha<sub>1</sub>-antitrypsin, which inhibits the destructive action of elastase (Janoff, 1985; U.S. Department of Health and Human Services, 1984a).

Many organic and inorganic chemicals in the gaseous, volatile, and particulate phases of cigarette smoke appear to contribute to smoke's toxicity to the respiratory system, including hydrocarbons, aldehydes, ketones, organic acids, phenols, cyanides, acrolein, and nitrogen oxides. Some components contribute to the development of chronic mucus hypersecretion in the central airways, whereas others play a greater role in the production of small airway abnormalities and emphysematous injury to the peripheral air sacs. Oxidizing agents in smoke inhibit the enzymes that defend against the destruction of lung elastin (U.S. Department of Health and Human Services, 1984a).

**ATHEROSCLEROTIC  
CARDIOVASCULAR  
DISEASES** Cigarette smoking is a major contributing cause to CHD, stroke, and other atherosclerotic diseases of the circulatory system (U.S. Department of Health and Human Services, 1984b and 1989).

Atherosclerosis is a chronic disease that can affect the arterial blood vessels in virtually every part of the human body. The most important form of atherosclerosis in the United States is coronary atherosclerosis. Its manifestations, which include angina, heart attack, heart failure, and sudden death, are described by the inclusive term coronary heart disease. Atherosclerosis involving the arteries supplying the brain is a form of

cerebrovascular disease. Atherosclerosis involving the arteries to the limbs is called peripheral vascular disease (PVD).

In numerous epidemiologic studies of millions of people, cigarette smokers have been found to have higher rates of heart attack, sudden death, and other manifestations of CHD. They also have higher rates of stroke, PVD, and other atherosclerotic lesions (U.S. Department of Health and Human Services, 1984b and 1989; U.S. Department of Health, Education, and Welfare, 1979). In the Cancer Prevention Study II (CPS-II) of more than 1 million people followed from 1982 through 1986, men currently smoking had a 94-percent greater risk of CHD than lifelong nonsmokers, whereas women currently smoking had a 78-percent greater risk. In smokers younger than age 65, men had a 181-percent greater risk and women a 200-percent greater risk (U.S. Department of Health and Human Services, 1989).

Cigarette smoking is sometimes called an independent risk factor for CHD because smokers' CHD rates are found to be higher even when other risk factors such as gender, blood pressure, and cholesterol level are taken into account. It is sometimes called a modifiable risk factor because one can reduce or stop smoking. Although smoking obviously cannot be a cause of CHD in someone who never smoked, it can be an important contributor to CHD in a smoker. Among 548,000 deaths from CHD in the United States in 1985, an estimated 115,000 would not have occurred but for the presence of cigarette smoking (U.S. Department of Health and Human Services, 1989).

Cigarette smoke appears to enhance the atherosclerotic process by several different mechanisms (U.S. Department of Health and Human Services, 1990; Glantz and Parmley, 1995). Cigarette smoking affects cholesterol metabolism. Smokers repeatedly have been observed to have lower levels of the protective high-density lipoprotein (HDL) cholesterol (Willett et al., 1983), and smoking cessation raises HDL cholesterol (Rabkin, 1984). In animal models, cigarette smoke can damage the inner lining of blood vessels, thus enhancing the transfer of low-density lipoprotein (LDL) cholesterol particles across the arterial wall and into the developing cholesterol-laden plaque (Krupski et al., 1987; Zimmerman and McGeachie, 1987; Penn et al., 1994). Cigarette smoking also can affect the blood clotting system, including the adherence of blood platelets to the lining of arterial blood vessels (Pittilo et al., 1984; U.S. Department of Health and Human Services, 1984b; Burghuber et al., 1986) and the formation of blood clots that block a narrowed artery. Acrolein in cigarette smoke may be partly responsible for its platelet-adhering effects (Selley et al., 1990). Cigarette smoke also can cause spasm of the coronary arteries.

Many chemical components of cigarette smoke have been implicated in the development of atherosclerotic disease. Nicotine, the major psychoactive component of smoke, causes powerful changes in heart rate and blood circulation. Nicotine appears to cause injury to the arterial lining (Krupski et al., 1987). Carbon monoxide in cigarette smoke binds to the hemoglobin in red blood cells, thereby reducing the oxygen-carrying capacity of the blood (Sheps et al., 1990). PAHs, such as 7,12-dimethylbenz(*a,h*)anthracene and

BaP, have been found to accelerate the development of atherosclerosis in animal models; this suggests that cell injury and cell proliferation (or hyperplasia) may contribute to the development of the growing plaque (Glantz and Parmley, 1991). Hydrogen cyanide, nitrogen oxides, and chemical components of cigarette tar also have been implicated. Free radicals in cigarette smoke, which are highly reactive oxygen products, are damaging to the heart muscle cells (Church and Pryor, 1985).

**CIGARETTE SMOKING AND HUMAN REPRODUCTION** Cigarette smoking adversely affects sexual and reproductive function in women in a number of different ways. Cigarette smoking appears to impair female fertility (Baird and Wilcox, 1985; Daling et al., 1987; Mattison, 1982; U.S. Department of Health and Human Services, 1980). Among the possible mechanisms are direct toxicity to eggs, interference with motility in the female reproductive tract, and alterations in immunity that predispose female smokers to infections that block the Fallopian tubes (Chow et al., 1988).

Maternal cigarette smoking has serious adverse effects on the outcome of pregnancy. These include retarded fetal growth; low birth weight; spontaneous abortion; certain complications of pregnancy, labor, and delivery, such as bleeding during pregnancy and prolonged premature rupture of membranes; and infant death (U.S. Department of Health and Human Services, 1980, 1989, and 1990; U.S. Department of Health, Education, and Welfare, 1979). Direct nicotine toxicity has been suggested as a mechanism for spontaneous abortion (U.S. Department of Health and Human Services, 1990). Although a smoking-induced reduction in maternal weight gain contributes to fetal growth retardation (U.S. Department of Health and Human Services, 1980; Werler et al., 1985), the evidence points to oxygen starvation of the fetus and placenta as important factors. Carbon monoxide in cigarette smoke can cross the placenta and bind to the hemoglobin in fetal blood. Smoking causes constriction of the umbilical arteries, impairing placental blood flow. Nicotine, which also crosses the placenta, can have a number of toxic effects on the fetus (U.S. Department of Health and Human Services, 1980). The carcinogen 4-aminobiphenyl crosses the placenta in a mother who smokes and adducts with the hemoglobin in the fetus' blood (Coghlin et al., 1991). Cyanide, another component of cigarette smoke, also has been implicated.

Women currently smoking enter nonsurgical menopause about 1 to 2 years earlier than nonsmokers (U.S. Department of Health and Human Services, 1990). Heavy smokers experience an even earlier menopause than light smokers. This effect has important consequences for women's health, because the rates of osteoporosis and atherosclerotic cardiovascular diseases increase after menopause. One proposed mechanism for early menopause is that PAHs in smoke are directly toxic to ovarian follicles (Mattison, 1980).

Cigarette smoking also may affect male reproductive performance. In several studies, men who report impotence (i.e., the inability to maintain an erection sufficient for intercourse) were more likely to be cigarette smokers. This association between smoking and impotence is particularly common

among men who have high blood pressure or diabetes and appears to be a consequence of increased atherosclerotic disease in the blood vessels supplying the genitalia rather than an effect on sexual drive.

**ABSOLUTE RISK VS. RELATIVE RISK** Human epidemiology can be used to estimate quantitatively the risk of specific diseases to human smokers. For example, in the CPS-II study of smoking practices and mortality rates among 1.2 million U.S. adults followed from 1982 through 1986, about 0.8 percent of current male smokers ages 65 or older died of lung cancer each year (U.S. Department of Health and Human Services, 1989), whereas the comparable annual lung cancer death rate was about 0.04 percent among men ages 65 or older who never smoked. These quantitative risk estimates are often termed "absolute risks." That the continuing smokers' risk of lung cancer was twentyfold that of nonsmokers is an expression of "relative risk."

Estimating relative risks from analyses of chemical composition of different cigarettes is far more complicated. For example, the smoke from cigarette A might contain 0.05 mg of BaP, a known carcinogen, whereas the smoke from cigarette B might contain 0.02 mg of BaP. To estimate human lung cancer risks from these data alone would require a number of assumptions relating the dose of BaP to the incidence lung cancer in humans. Whereas cigarette A had 2.5-fold as much BaP as cigarette B, it cannot be concluded automatically that the relative risk of getting lung cancer for those smoking cigarette A is 2.5-fold greater than those smoking cigarette B. The relative concentrations of benz(a)anthracene, another carcinogen in the PAH group, might be higher or lower.

Toxicity studies in nonhuman species also can give estimates of relative risk, but applying these estimates directly to humans requires caution. The fact that the smoke from cigarette C might produce twice as many revertants as cigarette D in a particular strain of the Ames salmonella assay is an indicator that C contains higher concentrations of certain mutagens. Likewise, if cigarette E produced three times as many tumors as cigarette F in a mouse skin carcinogenesis assay, we can conclude that cigarette E contains higher concentrations of certain carcinogens, including tumor initiators and tumor promoters (DuMouchel and Harris, 1983).

**TAR, NICOTINE, CARBON MONOXIDE, AND OTHER SMOKE CONSTITUENTS** Some studies (e.g., Adams et al., 1987) suggest that the yields of most toxic agents in cigarette smoke are correlated with their tar, nicotine, and CO deliveries. Still other studies show the correlation to be weak at best. Kaiserman and Rickert (1992) found a 0.89 correlation between the declared tar level and the BaP delivery of 35 brands of Canadian cigarettes. However, for 16-mg tar brands, the measured BaP ranged from 15 to 28 ng per cigarette. Fischer and colleagues (1991) found no correlation between tar delivery and the concentration of certain TSNAs in 170 European cigarettes.

The lack of a perfect correlation between tar values and specific chemical yields is not simply an artifact of measurement error. As Hoffmann and colleagues (this volume) report, there are many alternative methods to reduce



cigarette smoke constituents, including various filter designs, changes in paper porosity, mixing of tobacco species, and the use of reconstituted tobacco sheets and expanded tobacco. However, all these methods do not reduce every smoke constituent uniformly. For example, perforated filter tips selectively reduce the volatile and gaseous components of cigarette smoke, whereas reconstituted tobacco sheets reduce BaP and tar but not acrolein or acetaldehyde. Likewise, as reported by Hoffmann and coworkers (this volume), the increased burley tobacco content (and with it, the nitrate content) of at least one marketed cigarette resulted in an increase in the delivery of NNK, a tobacco-specific nitrosamine, over the course of three decades.

In a study of cigarette brands sold in the United Kingdom from 1983 through 1990, Phillips and Waller (1991, p. 469) concluded that, "with the exception of nitrogen monoxide, which is strongly dependent upon the type of tobacco, and the delivery of some phenols and PAHs, which may be affected to a minor extent by the design of cigarette," the three routinely monitored smoke components (tar, nicotine, and CO) provided "an adequate guide" to the yields of the other chemical entities examined. However, as the foregoing review of cigarette smoke constituents and disease suggests, the exceptions may prove the rule. It would be unscientific to claim that the absolute human risk or even the relative risk of a particular brand of cigarettes is lower merely because, on average, everything but TSNA, phenols, and PAHs seems to be lower. With phenols and related flavorant compounds implicated in smoke-induced chromosomal damage (Jansson et al., 1988), it would seem that, at minimum, biological testing would be warranted.

As discussed elsewhere in this volume, the yields of nicotine and carbon monoxide are significantly influenced by the smoker's style or "topography" of smoking, including number of puffs, interval between puffs, velocity and volume of each puff, depth of draw, length of cigarette smoked, depth of inhalation into the lungs, and other factors. It is possible that these differences in smoking topography might selectively influence the yields of some smoke chemicals more than others. Fischer and colleagues (1989) found that TSNA yields depended on the total volume of smoke inhaled by the smoker and that total smoke volume was increased for smokers of low- and medium-tar cigarettes. Studies of smokers' exposure to specific carcinogenic compounds (e.g., by measurement of PAH adducts to DNA) do not always show a relationship between exposure and self-reported smoking intensity (Santella et al., 1992).

**SMOKE CONSTITUENTS,  
CIGARETTE-RELATED  
DISEASE, AND MODIFIED  
LABELING OF CIGARETTES**

Henningfield and colleagues (1994) recently proposed modified labeling of cigarettes. Their proposed new cigarette label included a warning statement; categorization of nicotine yield; nicotine content; tar, nicotine, and CO deliveries (average and maximal); harmful additives; and information about factors affecting nicotine delivery. The use of a nicotine-yield category was intended to replace such marketing terms as "light" and "ultralight." These authors noted, "An additional strategy that could be used

to assist consumers in making informed decisions would be to fully disclose the tobacco smoke constituents of potential health significance, analogous to harmful constituent disclosure of foods" (Henningfield et al., 1994, pp. 312-313).

The new nutritional labels mandated by the Food and Drug Administration (FDA) on all packaged foods contain information on a wide array of vitamins, minerals, cholesterol, total fat, and saturated fat. These labels reflect the product's characteristics. They make no pretense that any two individuals will eat breakfast cereal in the same way. Nor do they imply that each and every consumer will understand or want to understand each and every entry on the label.

In the same way, the author has designed a "mock" cigarette label (Figure 1) to indicate what such an FDA-style label for cigarettes might look like. This is a sample and is not intended to reflect any current brand on the market. The opening box gives an explanation as well as a warning about the ways in which a smoker can obtain higher yields by changing his or her style of smoking. Then some "basic cigarette facts" would be included, such as length, type of filter, and weight of tobacco. In addition to data on the range of yields of tar (total particulates less nicotine) and nicotine, the label would show the range of yields of important smoke chemicals.

The concept of full disclosure of cigarette characteristics is entirely consistent with the current Federal Trade Commission (FTC) method. In fact, the current FTC measurements of tar, nicotine, and CO are included in the proposed mock label. In addition, as we move to an era where both short- and long-term biological testing have become commonplace in industry, one might imagine a rating system based on the Ames test, skin painting, and other studies. Illustrative results for such biological testing are included in the mock label.

One might object that such detailed disclosure of cigarette characteristics will confuse the smoker. Such an assertion is unscientific and unfair. To publish a label that discloses, for example, the tobacco-specific nitrosamine contents of a particular brand of cigarettes is no more confusing or complicated than printing a label that discloses the riboflavin and potassium yields of a particular brand of breakfast cereal. It would be remarkable to discover cereal manufacturers or consumer advocates arguing that the vitamin contents or trace metal levels of cereals should be withheld from consumers because vitamin E and zinc levels might correlate—at least roughly—with dietary fiber contents.

To a limited degree, researchers have studied consumers' responses to advertised tar and nicotine ratings of cigarettes. But there are no data—at least in the public domain—on the possible effects of providing consumers with additional cigarette-specific information of the type considered in the mock label.

Figure 1  
 “Mock” cigarette label

Our tar/nicotine label has changed! The Food and Drug Administration now requires each pack of HARRIS *Ultras* to display the deliveries of the most important chemicals in your cigarette smoke. Your own smoke intake of these chemicals may vary from low to high depending on the size of your puffs, the number of puffs per minute, the depth of your draw, and how far you smoke your cigarette down to the filter overwrap. For a factsheet about the new cigarette label, write to: New Cigarette Label Factsheet, P.O. Box 7551, Brookline, MA 02146.

### Basic Cigarette Facts

Cigarette Length	100 mm
Cigarette Diameter	8 mm
Length of Filter Plus Plugwrap	20 mm
Total Cigarette Weight	1.20 gm
Tobacco Weight	0.90 gm
Type of Filter	Cellulose Acetate
Design of Filter	Perforated
U.S.-Grown Tobacco	55%
Cigarettes Per Pack	20

Delivery Per Cigarette	Low	High
Nicotine	1.0 mg	1.5 mg
Carbon Monoxide	14 mg	20 mg
Carcinogenic PAHs	0.1 µg	0.2 µg
Tobacco-Specific Nitrosamines	0.3 µg	2.0 µg
Hydrogen Cyanide	0.4 mg	0.6 mg
Acrolein	60 µg	140 µg
Formaldehyde	20 µg	100 µg
Nitrogen Oxides	0.1 mg	0.4 mg
Catechols	200 µg	400 µg
Phenols	45 µg	60 µg
Nickel	0.1 µg	0.2 µg
Total Particulates Less Nicotine	6 mg	16 mg
Redox Potential of Smoke	160 mV	240 mV
pH of Whole Smoke	5.8	6.0

### Biological Test Results

Ames Salmonella	+
Tracheal Installation	++
Mammalian Cell Transformation	+
Syrian Golden Hamster Inhalation	+
Mouse Skin Carcinogenesis	++
Antielastase Test	++++

**INGREDIENTS:** Domestic flue-cured, Burley, and oriental leaf tobaccos; flavorants (including menthol in HARRIS ULTRAGREENS), and humectants, including diethylene glycol. Citric acid added to cigarette paper. Residues of maleic hydrazide (a suckercide used in tobacco growing) less than 1 part per million.

**WARNING:** Keep out of reach of children!

Key: PAHs = polyaromatic hydrocarbons.

In any case, smokers constitute only the demand side of the cigarette market. On the supply side are a handful of cigarette manufacturers who, so far as is known, go to considerable lengths to determine the detailed characteristics of competitors' products. From time to time, a cigarette manufacturer will disclose the level of a particular chemical in a particular brand. One classic example is the claim by one manufacturer, in the early 1960's, that a particular brand delivered smoke with reduced phenol, an announcement that coincided with scientific reports that the phenol in cigarette smoke inhibited the cilia lining in the respiratory tract. However, without systematic and complete disclosure requirements, such "competition" will remain haphazard at best. In 1989 the tar content was listed on only 14 percent and the nicotine content on only 11 percent of U.S. cigarette packages (Davis et al., 1990).

Enhanced and complete disclosure of cigarette characteristics by a standardized label would create a basis for more effective competition among manufacturers. If Hoffmann and colleagues' (this volume) data are generalizable, then the growing trend toward use of burley tobaccos in American cigarettes might have resulted in increased deliveries of TSNAs, even as other smoke constituents have declined. Without specific disclosure of tobacco-specific nitrosamines, it is unclear how this deleterious trend would be reversed or even detected. As economists know, competition among manufacturers over a specific brand characteristic, such as a cigarette's TSNA delivery, does not require that the average smoker—or even most smokers—know what a "nitrosamine" is.

#### QUESTION-AND-ANSWER SESSION

DR. HOFFMANN: We go through stages in all research; so we go through stages in tobacco research. The first stage was to identify those agents that, in the laboratory animal, cause disease. The second stage we are in now is a biomarker stage. This gives us 4-aminobiphenol, bihemoglobin, and tobacco-specific nitrosamines.

I do think we are now in a better position to judge the relationship between smoke components and disease. One should not forget that we have now moved past the stage of biomarkers where it is solely the identification of agents, and I do think one should not have such a negative outlook.

DR. HARRIS: Yes. I did not include as possible endpoints by which to compare individual cigarettes the possibility that these components may be found bound to the hemoglobin and red cells, or circulating proteins, or albumen in the blood. It is a fact that certain biomarkers, certain hydrocarbons, 4-aminobiphenols, and other compounds, have been now found bound to blood proteins or other compounds, not only among those who smoke cigarettes, but recently, in the *Journal of the National Cancer Institute*, among those who are exposed passively to cigarette smoke.

Whether those can be used for a comparative analysis of different cigarettes, I do not know. But I would, in order at least to be provocative or speculative,

state that we will soon be entering an era when we can make comparisons among cigarettes by more than merely standards of chemical constituents.

DR. KOZLOWSKI: I imagine that the HARRIS ULTRA is an ultralow-tar cigarette, and it is perforated. And so, like other current 1-mg tar cigarettes, it might be 80 or 90 percent perforated, so you get air dilution of between 80 and 90 percent. I am disappointed that the label, in talking about compensatory smoking factors, does not mention the issues of vent blocking and staying away from the vents, because in fact, increased puff numbers would have a relatively small effect, if this 90-percent dilution factor was not eliminated.

DR. HARRIS: In designing that mock label, I did not attempt to be scientifically precise as to absolutely everything one would put in about proper directions for use or factors that might affect yield. Actually, your yields could vary, and then afterward put in a perforated tip. If you will look carefully, it was a 6-mg tar cigarette but with very high nicotine—1 mg of nicotine.

One could argue, however, that if one is to continue to publish what basically are the FTC data, expanded possibly to include a high or low range, or to include other constituents, that there ought to be something about directions for appropriate use.

DR. HEADEN: Dr. Harris, in proposing a possible design for a cigarette label, I would like to know your opinion of who you think the audience is for that label. Is it the tobacco industry and other regulators who might possibly be able to interpret the information that you have? Is it the consumer, who might smoke that cigarette, many of whom have lower educational levels, or would it be both?

DR. HARRIS: I think it would have to be considerate of everyone and, although it may sound as if I would add the results of additional constituents just to satisfy some intellectually rarified audience, I raise the question, why do we put such a large array of constituents on our ordinary food supply? Some people might argue that we should not insult consumers by assuming that they cannot pick and choose, to understand or use meaningfully some forms of information rather than others. At this point, unless there is a solid confirmation that all those constituents of smoke, or characteristics of cigarettes, are simply summarized by the amount of tar, one wonders whether the lack of that information is at least deceiving some people. That is the best I can do to answer that.

DR. SONDIK: Dr. Harris, the label is intriguing, and I would not want to spend too much time on it, but a couple of points might differentiate it from the FDA label, which I happen to believe is one of the major advances in nutrition. The FDA label is designed to aid people in developing their diets. Their diet consists of all types of food, and the idea is to integrate all of these things together, which is the idea behind putting all of these different measurements on it, not just a single measurement, such as calories, for example, or total fat.

The second thing is, that label must have education along with it. And that is part of the program in NCI, the Department of Agriculture, the FDA, and others who are involved in a very intense education program—to try to be sure that the public knows how to interpret a label like this. So, in a sense, that label is more complex and aimed at a variety of types of decisions.

I would think that a label such as you proposed would be aimed at perhaps a single decision, which is whether or not this is a useful thing for me to do, trading off whatever my immediate gain might be, and pleasure, vs. long-term health effects. Is there a way of getting that onto the label?

DR. HARRIS: I do not know. It also has occurred to me that once more dimensions to cigarettes are specifically disclosed, that would be the basis of further competition among cigarette manufacturers. So, the manufacturers would then be seeing not only whether a cigarette is low or high in tar, nicotine, and carbon monoxide, but in other specific components, too. That means that while the consumer does not specifically choose among high- or low-benzo(a)pyrene cigarettes, the disclosure of such contents provides an incentive for manufacturers to try to reduce that component. This is the same way that the disclosure of saturated fat contents in certain breakfast cereals or other foods, even without consumer knowledge, provides an incentive for some manufacturers to try to reduce that content. Nevertheless, it provides some incentive on the supply side, not just the demand side.

DR. BENOWITZ: I know that you are not intending to be totally comprehensive about your mock insert, or label, and I think it is worthwhile keeping in mind the parallel with foods. If you are talking about limiting intake, there really are only two contents that we know about that might limit intake. One is the amount of the tobacco in the cigarette, which you did put down, and the other is the amount of nicotine contained in there, which is something that people do not often think about. But the amount of nicotine in tobacco limits what a person can get. And the intake of nicotine is not necessarily correlated at all with the yield.

So, I think that when we think about any sort of labeling for content, the nicotine content, which is the maximum available dose one could get, should really be a part of it.

DR. HARRIS: I noticed that that was in your original proposal, and I am not an expert on the degree to which nicotine content is very limiting for how many smokers. I would rather defer that to a later discussion, as to how important that is.

## REFERENCES

- Adams, J.D., O'Mara-Adams, K.J., Hoffmann, D. Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes. *Carcinogenesis* 8(5): 729-731, 1987.
- Baird, D.D., Wilcox, A.J. Cigarette smoking associated with delayed conception. *Journal of the American Medical Association* 253: 2979-2983, 1985.
- Beck, G.J., Doyle, C.A., Schachter, E.N. Smoking and lung function. *American Review of Respiratory Disease* 123: 149-155, 1981.
- Burghuber, O.C., Punzengruber, C., Sinzinger, H., Haber, P., Silberbauer, K. Platelet sensitivity to prostacyclin in smokers and non-smokers. *Chest* 90(1): 34-38, 1986.

- Chow, W.-H., Daling, J.R., Weiss, N.S., Voigt, L.F. Maternal cigarette smoking and tubal pregnancy. *Obstetrics and Gynecology* 7: 167-170, 1988.
- Church, D.F., Pryor, W.A. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environmental Health Perspectives* 64: 111-126, 1985.
- Coghlin, J., Gann, P.H., Hammond, S.K., Skipper, P.L., Taghizadeh, K., Paul, M., Tannenbaum, S.R. 4-Aminobiphenyl hemoglobin adducts in fetuses exposed to the tobacco smoke carcinogen in utero. *Journal of the National Cancer Institute* 83(4): 274-280, 1991.
- Costagliola, C., Rinaldi, M., Giacoia, A., Rosolia, S., Cotticelli, C., Rinaldi, E. Red cell glutathione as a marker of tobacco smoke-induced optic neuropathy. *Experimental Eye Research* 48(4): 583-586, 1989.
- Crawford, F.G., Mayer, J., Santella, R.M., Cooper, T.B., Ottman, R., Tsai, W.Y., Simon-Cerejido, G., Wang, M., Tang, D., Perera, F.P. Biomarkers of environmental tobacco smoke in preschool children and their mothers. *Journal of the National Cancer Institute* 86(18): 1398-1402, 1994.
- Daling, J., Weiss, N., Spadoni, L., Moore, D.E., Voigt, L. Cigarette smoking and primary tubal infertility. In: *Smoking and Reproductive Health*, M.J. Rosenberg (Editor). Littleton, MA: PSG Publishing, 1987, pp. 40-46.
- Davis, R.M., Healy, P., Hawk, S.A. Information on tar and nicotine yields on cigarette packages. *American Journal of Public Health* 80(5): 551-553, 1990.
- Dockery, D.W., Speizer, F.E., Ferris, B.G., Jr., Ware, J.H., Louis, T.A., Spiro, A. III. Cumulative and reversible effects of lifetime smoking on simple tests of lung function in adults. *American Review of Respiratory Disease* 137(2): 286-292, 1988.
- DuMouchel, W.H., Harris, J.E. Bayes methods of combining the results of cancer studies in humans and other species. *Journal of the American Statistical Association* 78: 293-308, 1983.
- Fera, T., Abboud, R.T., Richter, A., Johal, S.S. Acute effect of smoking on elastaselike activity and immunologic neutrophil elastase levels in broncheolar lavage fluid. *American Review of Respiratory Disease* 133: 568-573, 1986.
- Fischer, S., Spiegelhalter, B., Preussmann, R. Influence of smoking parameters on the delivery of tobacco-specific nitrosamines in cigarette smoke—a contribution to relative risk evaluation. *Carcinogenesis* 10: 1059-1066, 1989.
- Fischer, S., Spiegelhalter, B., Preussmann, R. Tobacco-specific nitrosamines in commercial cigarettes: Possibilities for reducing exposure. *IARC Scientific Publications* 105: 489-492, 1991.
- Gairola, C.G. Genetic effects of fresh cigarette smoke in *Saccharomyces cerevisiae*. *Mutation Research* 102: 123-136, 1982.
- Garfinkel, L., Bofetta, P. Association between smoking and leukemia in two American Cancer Society prospective studies. *Cancer* 65: 2356-2360, 1990.
- Glantz, S.A., Parmley, W.W. Passive smoking and heart disease: Epidemiology, physiology, and biochemistry. *Circulation* 83: 1-12, 1991.
- Glantz, S.A., Parmley, W.W. Passive smoking and heart disease: Mechanisms and risk. *Journal of the American Medical Association* 273: 1047-1053, 1995.
- Harris, J.E. Smoking and nothingness. In: *Deadly Choices: Coping with Health Risks in Everyday Life*. New York: Basic Books, 1993, pp. 151-177.
- Hecht, S.S., Carmella, S.G., Murphy, S.E., Akerkar, S., Brunnemann, K.D., Hoffmann, D. A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *New England Journal of Medicine* 329(21): 1543-1546, 1993.
- Henningfield, J.E., Kozlowski, L.T., Benowitz, N.L. A proposal to develop meaningful labeling for cigarettes. *Journal of the American Medical Association* 272(4): 312-314, 1994.
- Hoffmann, D., Hecht, S.S. Advances in tobacco carcinogenesis. *Handbook of Experimental Pharmacology*, Vol. 94, No. 1, C.S. Cooper and P.L. Grover (Editors). Berlin: Springer-Verlag, 1990.
- Janoff, A. Elastases and emphysema: Current assessment of the protease-antiprotease hypothesis. *American Review of Respiratory Disease* 132: 417-433, 1985.
- Jansson, T., Curvall, M., Hedin, A., Enzell, C.R. In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke. A study of structure-activity relationships. *Mutation Research* 206(1): 17-24, 1988.
- Kaiserman, M.J., Rickert, W.S. Carcinogens in tobacco smoke: Benzo(a)pyrene from Canadian cigarettes and cigarette tobaccos. *American Journal of Public Health* 82: 1023-1026, 1992.
- Krupski, W.C., Olive, G.C., Weber, C.A., Rapp, J.H. Comparative effects of hypertension and nicotine on injury-induced myointimal thickening. *Surgery* 102: 409-415, 1987.
- Mattison, D.R. Morphology of oocyte and follicle destruction by polycyclic aromatic hydrocarbons in mice. *Toxicology and Applied Pharmacology* 53: 249-259, 1980.
- Mattison, D.R. The effects of smoking on fertility from gametogenesis to implantation. *Environmental Research* 28: 410-433, 1982.
- Melikian, A.A., Prahalad, A.K., Hoffmann, D. Urinary *trans*, *trans*-muconic acid as an indicator of exposure to benzene in cigarette smokers. *Cancer Epidemiology, Biomarkers and Prevention* 2(1): 47-51, 1993.

- Niewoehner, D.E., Kleinerman, J., Rice, D.B. Pathologic changes in the peripheral airways of young cigarette smokers. *New England Journal of Medicine* 291: 755-758, 1974.
- Penn, A., Chen, L.C., Snyder, C.A. Inhalation of steady-state sidestream smoke from one cigarette promotes atherosclerotic plaque development. *Circulation* 90: 1363-1367, 1994.
- Phillips, G.F., Waller, R.E. Yields of tar and other smoke components from UK cigarettes. *Food and Chemical Toxicology* 29(7): 469-474, 1991.
- Pittilo, R.M., Clarke, J.M., Harris, D., Mackie, I.J., Rowles, P.M., Machin, S.J., Woolf, N. Cigarette smoking and platelet adhesion. *British Journal of Haematology* 58(4): 627-632, 1984.
- Rabkin, S.W. Effect of cigarette smoking cessation on risk factors for coronary atherosclerosis: a control clinical trial. *Atherosclerosis* 53(2): 173-184, 1984.
- Rando, R.J., Menon, P.K., Poovey, H.G., Lehrer, S.B. Assessment of multiple markers of environmental tobacco smoke (ETS) in controlled, steady-state atmospheres in a dynamic test chamber. *American Industrial Hygiene Association Journal* 53(11): 699-704, 1992.
- Santella, R.M., Grinberg-Funes, R.A., Young, T.L., Dickey, C., Singh, V.N., Wang, L.W., Perera, F.P. Cigarette smoking related polycyclic aromatic hydrocarbon-DNA adducts in peripheral mononuclear cells. *Carcinogenesis* 13(11): 2041-2045, 1992.
- Seely, J.E., Zuskin, E., Bouhys, A. Cigarette smoking: Objective evidence for lung damage in teenagers. *Science* 172: 741-743, 1971.
- Selley, M.L., Bartlett, M.R., McGuinness, J.A., Ardlie, N.G. Effects of acrolein on human platelet aggregation. *Chemico-Biological Interactions* 76(1): 101-109, 1990.
- Sheps, D.S., Herbst, M.C., Hinderliter, A.L., Adams, K.F., Ekelund, L.G., O'Neil, J.J., Goldstein, G.M., Bromberg, P.A., Dalton, J.L., Pallenger, M.N., Davis, S.M., Koch, G.G. Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. *Annals of Internal Medicine* 113(5): 343-351, 1990.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking for Women. A Report of the Surgeon General*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General*. DHHS Publication No. (PHS) 82-50179. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1982.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General*. DHHS Publication No. (PHS) 84-50205. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984a.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General*. DHHS Publication No. (PHS) 84-50204. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984b.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Cancer and Chronic Lung Disease in the Workplace. A Report of the Surgeon General*. DHHS Publication No. (PHS) 85-50207. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1985.
- U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General*. DHHS Publication No. (CDC) 87-8398. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health, 1987.
- U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General, 1988*. DHHS Publication No. (CDC) 88-8406. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health, 1988.
- U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General, 1989*. DHHS Publication No. (CDC) 89-8411. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989.
- U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation. A Report of the Surgeon General, 1990*. DHHS Publication No. (CDC) 90-8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990.



U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General.* DHEW Publication No. (PHS) 79-50066. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979.

Vineis, P. Black (air-cured) and blond (flue-cured) tobacco and cancer risk. I: Bladder cancer. *European Journal of Cancer* 27(11): 1491-1493, 1991.

Werler, M.M., Pober, B.R., Holmes, L.B. Smoking and pregnancy. *Teratology* 32: 473-481, 1985.

Willett, W., Hennekens, C.H., Castelli, W., Rosner, B., Evans, D., Taylor, J., Kass, E.H. Effects of cigarette smoking on fasting triglyceride, total cholesterol, and HDL-cholesterol in women. *American Heart Journal* 105(3): 417-421, 1983.

Zimmerman, M., McGeachie, J. The effect of nicotine on aortic endothelium: A comparative study. *Atherosclerosis* 63: 33-41, 1987.

**ACKNOWLEDGMENT** Financial support from the National Cancer Institute is acknowledged, but the contents of this manuscript are the author's sole responsibility.