crimination, visual acuity, and the ability to distinguish relative brightness. McFarland (*40*) observed that COHb levels of 4 to 5 percent caused visual threshold impairment. Ray and Rockwell (*48*), reporting on a study of the driving ability of three subjects under varying CO exposure, observed that the presence of 10 percent COHb was associated with increased response time for taillight discrimination and increased variance in distance estimation. Schulte (*52*) observed that increased errors in cognitive and choice discrimination tests were manifest at levels of COHb as low as 3 percent. Chevalier, et al. (*7*) have also observed that levels of 4 percent COHb in nonsmokers are associated with an increase in oxygen debt formation with exercise similar to that seen in smokers.

On the other hand, other investigators utilizing complex psychomotor tasks in men and monkeys have observed no decrement in function upon exposures to CO at 50 to 250 p.p.m. (*2, 3, 23, 41, 56*).

Animals exposed to low levels of CO (50 to 100 p.p.m.) continuously for weeks have shown varying degrees of cardiac and cerebral damage similar to that produced by hypoxia (*21, 47, 57*).

Finally, the possible effects of exposure to 50–100 p.p.m. CO on patients with coronary heart disease (CHD) were investigated by Ayres, et al. (*1*) who observed a decrease in arterial and mixed venous oxygen tensions with COHb saturations of 5 percent. Certain patients with CHD developed altered lactate and pyruvate metabolism with COHb levels of 5 to 10 percent suggesting myocardial hypoxia.

The evidence concerning the effect of low levels of carbon monoxide has recently been reviewed and evaluated by the National Air Quality Criteria Committee of the National Air Pollution Control Administration (*58*). The following is taken from the published conclusions of the Advisory Committee (also see table 2) :

> "Experimental exposure of nonsmokers to 58 mg/m^3 (50 ppm) for 90 minutes has been associated with impairment in time-interval discrimination.... This exposure will produce an increase of about 2 percent COHb in the blood. This same increase in blood COHb will occur with continuous exposure to 12 to 17 mg/m^3 (10 to 15 ppm) for 8 or more hours....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels of about 5 percent (a level producible by exposure to about 35 mg/m^3 for 8 or more hours) has provided in some instances evidence of impaired performance on certain other psychomotor tests, and an impairment in visual discrimination....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels above 5 percent (a level producible

TABLE 2.—*Effects of carbon monoxide.*

Environmental conditions	Effect	Comment
58 mg./m.^{3} (50 p.p.m.) for 90 minutes	Impairment of time-interval discrimination in non-smokers.	Blood COHb levels not available, but anticipated to be about 2.5 percent. Similar blood COHb levels expected from exposure to 10 to 17 mg./m.^{3} (10 to 15 p.p.m.) for 8 or more hours.
115 mg./m.^{3} (100 p.p.m.) intermittently through a facial mask	Impairment in performance of some psychomotor tests at a COHb level of 5 percent.	Similar results may have been observed at lower COHb levels, but blood measurements were not accurate.
High concentrations of CO were administered for 30 to 120 seconds, and then 10 minutes was allowed for washout of alveolar CO before blood COHb was measured.	Exposure sufficient to produce blood COHb levels above 5 percent has been shown to place a physiologic stress on patients with heart disease.	Data rely on COHb levels produced rapidly after short exposure to high levels of CO; this is not necessarily comparable to exposure over a longer time period or under equilibrium conditions.

SOURCE: Adapted from U.S. Public Health Service, Air Quality Criteria for Carbon Monoxide. Washington, D.C., U.S. Department of Health, Education, and Welfare (58).

by exposure to 35 mg/m^3 or more for 8 or more hours) has provided evidence of physiologic stress in patients with heart disease. . . ."

The levels of carbon monoxide found to be present in "smoked" rooms (20 to 80 p.p.m.) are similar to the levels (30 to 50 p.p.m.) which the Advisory Committee has concluded are associated with adverse health effects:

"An exposure of 8 or more hours to a carbon monoxide concentration of 12 to 17 mg/m^3 (10 to 15 ppm) will produce a blood carboxyhemoglobin level of 2.0 to 2.5 percent in nonsmokers. This level of blood carboxyhemoglobin has been associated with adverse health effects as manifested by impaired time interval discrimination. Evidence also indicates that an exposure of 8 or more hours to a CO concentration of 35 mg/m^3 (30 ppm) will produce blood carboxyhemoglobin levels of about 5 percent in nonsmokers. Adverse health effects as manifested by impaired performance on certain other psychomotor

tests have been associated with this blood carboxyhemoglobin level, and above this level there is evidence of physiologic stress in patients with heart disease."

These levels of CO are also similar to that set as the time-weighted occupational Threshold Limit Value of 50 p.p.m. for a 40-hour week (five 8-hour days) which has been in effect in the United States for the past several years (*13*). A further reduction in this limit to 25 p.p.m. is now under consideration. These levels of CO exceed those recently set by the Environmental Protection Agency as the national primary and secondary ambient air quality standards for CO (*14*). These standards are:

(a) 10 milligrams per cubic meter (9 p.p.m.)—maximum 8-hours concentration not to be exceeded more than once per year.

(b) 40 milligrams per cubic meter (35 p.p.m.)—maximum 1-hour concentration not to be exceeded more than once per year.

ALLERGIC AND IRRITATIVE REACTIONS TO CIGARETTE SMOKE AMONG NONSMOKERS

(A more detailed discussion of this subject is presented in the Allergy chapter of this report.)

Several investigators have reported on the discomfort and symptoms experienced by both allergic and nonallergic individuals upon exposure to tobacco smoke. Johansson and Ronge (*31, 32*) in 1965 and 1966 have observed that the acute irritation experienced by nonsmokers in the presence of tobacco smoke is maximal in warm, dry air and that nonsmokers experience more nasal irritation than ocular irritation as compared with smokers exposed to similar amounts of smoke in the atmosphere. Speer (*54*) studied the reactions of 441 nonsmokers divided into two groups, one composed of individuals with a history of allergic reactions and the other of individuals without such a history. The allergic group underwent skin testing for the presence of sensitivity to tobacco extract while the "nonallergic" group was determined solely by questionnaire concerning subjective allergic responses. Approximately 70 percent of both groups experienced eye irritation while other symptoms differed in their frequency from group to group (nasal symptoms: allergic 67 percent, "nonallergic" 29 percent; headache: allergic 46 percent, "nonallergic" 31 percent; cough: allergic 46 percent, "nonallergic" 25 percent; and wheezing: allergic 22 percent, "nonallergic" 4 percent). Thus, a significant proportion of nonsmoking individuals report discomfort and respiratory symptoms on exposure to tobacco smoke.

Other authors have attempted to separate out those patients who may have specific allergies to smoke. Zussman (*61*) found that in a random series of 200 atopic patients 16 percent were clinically sensitive to tobacco smoke, and that a majority of these were aided by desensitization therapy. In an earlier study, Pipes (*46*) observed that 13 percent of 229 patients with respiratory allergy showed positive skin tests to tobacco smoke. Savel (*49*) has recently reported on eight nonsmokers observed to be clinically hypersensitive to tobacco smoke. After *in vitro* incubation of their lymphocytes with cigarette smoke, increased incorporation of tritiated thymidine was recorded; similar exposure of the lymphocytes of those not sensitive resulted in depression of tritiated thymidine uptake.

Luquette, et al. (*39*) have recently reported on the immediate effects of exposure to cigarette smoke in school-age children. They observed that heart rate and blood pressure rose with such exposure, although questions remain about the adequacy of their controls and the manner in which the experimental situation may have excited the subjects. Finally, Cameron, et al. (*6*) observed that acute respiratory illnesses were more frequent among children from homes in which the parents smoked than among children of nonsmoking parents. The meaning of these results is uncertain since smoking by the children was not considered and the level of exposure to cigarette smoke in their homes was not measured. Shy, et al. (*53*) in a study of second grade Chattanooga school children failed to demonstrate a relationship between parental smoking habits and the respiratory illness rates of their children.

THE KNOWN HARMFUL EFFECTS OF THE PASSIVE INHALATION OF CIGARETTE SMOKE IN ANIMALS

A number of investigators have studied the effects of the passive inhalation of high concentrations of cigarette smoke on the pulmonary parenchyma and tracheobronchial tree of animals. The results of these investigations are listed in detail in the recent report to Congress, "The Health Consequences of Smoking," (*59*) in table 9 of the Bronchopulmonary chapter, and table 16 of the Cancer chapter.

The pathologic changes observed in the respiratory tract of the animals included parenchymal disruption, bronchitis, tracheobronchial epithelial dysplasia and metaplasia, and pulmonary adenomatous tumor formation. Leuchtenberger, et al. (*36*) exposed 151 mice to the smoke of from 25 to 1,526 cigarettes over a period of 1 to 23 months and observed that 20 percent of the animals developed severe bronchitis with atypism. Working with 30 control rabbits exposed to up to 20 cigarettes per day for two to five years, Holland, et al. (*30*) observed increased focal and generalized hyperplasia of

the bronchial epithelium and generalized emphysema in the exposed rabbits. Hernandez, et al. (*29*) observed significantly more pulmonary parenchymal disruption in adult greyhound dogs exposed to cigarette smoke 10 times per week for approximately one year than in nonexposed control animals.

Lorenz, et al. (*38*) observed no increase in respiratory tract tumor formation above that seen in controls in 97 Strain A mice exposed to cigarette smoke for up to 693 hours. Essenberg (*15*), however, exposed Strain A mice to cigarette smoke for 12 hours a day for up to one year and observed significantly more papillary adenocarcinomas in the exposed than in the control group. An increased percentage of hybrid mice were found by Mühlbock (*42*) to have alveolar carcinomas among the experimental group exposed to smoke for two hours a day for up to 684 days when compared with a nonexposed group. Similarly, Guerin (*22*) observed that 5.1 percent of rats exposed to cigarette smoke for 45 minutes a day for two to six months showed pulmonary tumors compared to 2.4 percent of the control mice.

Leuchtenberger, et al. (*37*), working with 400 female CF_1 mice, observed only a slight increase in the presence of pulmonary adenomatous tumors among those exposed to cigarette smoke compared with those in the control group. The authors commented that the presence of tumors showed an age relationship independent of smoking exposure. Otto (*43*) found that 11 percent of a group of albino mice exposed to 12 cigarettes a day for up to 24 months showed pulmonary adenomas as compared with five percent of the control non-exposed group. Dontenwill and Wiebecke (*12*) found that increasing the exposure of golden hamsters to up to four cigarettes a day for up to two years was associated with an increasing percentage of animals showing desquamative metaplasia and bronchial papillary metaplasia. Harris and Negroni (*26*) exposed 200 C57BL mice to cigarette smoke for 20 minutes a day every other day for life and found eight adenocarcinomas as compared to none in the control group.

Because the damage observed in these experiments was seen after prolonged exposure to high concentrations of cigarette smoke, and because the comparability of animal exposure to smoke with that of human exposure in smoke-filled rooms is unknown, it is presently impossible to be certain from animal experimentation about the extent of the damage that may occur during long-term intermittent exposure to lower concentrations.

SUMMARY

1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.

2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.

3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to adversely affect animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known.

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CHAPTER 9

Harmful Constituents of Cigarette Smoke

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HARMFUL CONSTITUENTS OF CIGARETTE SMOKE*

Cigarette smoke contains a large number and a wide variety of compounds which may result in complex and multiple pathophysiological effects on various tissues and organ systems. Although the constituents of cigarette smoke are usually divided for convenience into the two categories of particulate and gas phases,** many of them exist in a distribution equilibrium, that is, they are present partially in the gas phase and partially in the particulate phase. This review concerns itself with judgments concerning the harmful constituents of cigarette smoke whether these are found primarily in the gas phase or in the particulate phase.

Constituents of cigarette smoke may enter the body by a variety of routes. Theoretically, the route of entry and subsequent absorption could affect the degree to which various organs are subjected to specific cigarette smoke constituents. Some constituents, particularly the water soluble components of the gas phase, may be absorbed by the nasal and oropharyngeal mucous membranes, or may be dissolved in the saliva and swallowed, thus allowing for possible gastric or intestinal absorption. Other constituents are absorbed along the tracheobronchial tree, and the distance which they reach before being absorbed or deposited depends on such factors as the depth of inhalation and the particle size. The absorption of gases in the tracheobronchial tree appears to be in part dependent on the adsorption of gases to particulate matter. Another factor affecting the route and degree of absorption is the adequacy of pulmonary clearance by which constituents deposited or dissolved in the mucous sheath are delivered to the pharynx and then usually swallowed.

Of the hundreds of compounds identified in cigarette smoke, some occur in the smoke in concentrations which may be considered sufficient to present hazards to health. Other compounds appear in

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* This report attempts to summarize the areas of general consensus reached in a special one-day conference of experts in this field which met in June 1970. This is not to imply that there was unanimous agreement on all statements contained herein. A list of participants in the meeting appears in the Acknowledgments.

** It should be noted that there is, at present, no available instrumentation permitting the separation and individual collection of the particulate and gas phases which duplicates the precise physicochemical conditions prevailing in cigarette smoke as it is inhaled. A widely accepted arbitrary distinction between the two phases is as follows: If 50 percent or more of a given constituent is retained on a Cambridge filter (CM-113) during standardized machine smoking of a cigarette, then the compound is considered to belong to the particulate phase; if on the other hand more than 50 percent of the compound passes through the Cambridge filter under these conditions, then the constituent is considered to belong to the gas phase.

borderline concentrations. Still others, although potentially harmful, are probably not present in sufficient concentrations to contribute to the hazard, and some may be hazardous only when they interact with other substances in the smoke.

Substances and classes of substances in cigarette smoke which have been judged to contribute to the hazard of cigarette smoking have been classified into three priority groups. Those compounds which are judged most likely to contribute to the health hazards of smoking are listed in table 1. Additional substances which probably contribute to the health hazards of smoking are listed in table 2. Those compounds which are suspected contributors to the health hazards of smoking in the concentrations in which they are present in tobacco smoke are listed in table 3. Many other constituents of tobacco smoke are considered to be toxic under some conditions but probably do not present a health hazard in the concentrations in which they are generally found in cigarette smoke; these are not listed. This listing is not presented as final, and may be subject to modification as more information becomes available.*

In 1966, the Public Health Service prepared a technical report on "tar" and nicotine (*60*). Tobacco "tar" is the name given to the aggregate of particulate matter in cigarette smoke after subtracting nicotine and moisture. In that report it was stated:

> "It is clear that the overall risk associated with cigarette smoking increases as the average number of cigarettes consumed per day increases. In the studies which have reported other measures of exposure such as pack-years, degree of inhalation, and maximum level of cigarette consumption, the same type of relationship holds."

Individuals may differ in their inherent susceptibility to diseases in which cigarette smoking plays a role and differ in their exposure to other factors which may increase the likelihood of these diseases. Within these groups of varying risk, the degree of exposure to cigarette smoke appears to be the most critical factor for the development of smoking related disease. Therefore, the general statement that the lower the dosage the lower the risk is the most useful guide available. It was also stated that:

> "It is possible for a cigarette to be altered in such a way that its 'tar' and nicotine content is reduced but certain other harmful effects, for example the effect of the gaseous phase, may be increased. Although this is a theoretical possibility,

* Subsequent to the conference on which this report was based, several studies were published reporting the presence of N-nitrosamines in cigarette smoke. Since these substances are accepted as carcinogens in experimental animals, they represent another portion of the "tar" which probably contributes to the total health hazard (18, 24).

there is no evidence that this has occurred to any serious degree."

The consensus is that there is inadequate evidence to support a change in that view at the present time.

In addition, it was concluded that "the preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the less harmful would be the effect." Several studies reported since that time have added strong support to this position. The present review is an attempt to identify those constituents of the "tar" as well as those constituents considered part of the gas phase which are most likely to contribute to the health hazards from cigarette smoking.

TABLE 1.—*Compounds in cigarette smoke judged most likely to contribute to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Carbon Monoxide	5,240–21,400	G	(1, 10, 23, 26, 29, 34, 35, 37, 42, 46, 49, 61, 63)
Nicotine	200–2,400	P	(9)
[1] "Tar"	3,000–33,000	P	(9)

[1] "Tar" is defined as the total particulate matter collected by a Cambridge filter (CM-113) after subtracting moisture and nicotine and includes the class of compounds known as polycyclic aromatic hydrocarbons (PAH). PAH are generally accepted as being responsible for a substantial portion of the carcinogenic activity of the total "tar." Although "tar" from different cigarettes varies in its carcinogenic potential as measured by the bioassay methods in current use, it remains the most practical single "indicator" of total carcinogenic potential. Special mention should be made of Beta Naphthylamine which is a known human urinary bladder carcinogen for which there is no known safe level of exposure and which has been reported present in tobacco smoke in very low concentrations (16, 28, 30) (0.022 μgm./cigarette).

It is recognized that the substances in cigarette smoke may interact so that the combined pathological effects of several substances may be quite different from the sum of their effects produced in isolation. An example of this type of interaction might be the carcinogenic effects of tobacco "tar" as a result of the combined action of cancer initiating, cancer promoting, and cancer accelerating agents in producing the total effect. Such interactions theoretically could take place among substances within the gas phase, or substances within the particulate phase, or between constituents of the gas phase and constituents of the particulate phase. In the absence of data which identify the interactions of cigarette smoke components, judgments concerning the action or identification of harmful substances in cigarette smoke have, of necessity, been made pri-

TABLE 2.—*Compounds in cigarette smoke judged as probable contributors to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Acrolein	45–140	G	(12, 20, 21, 27, 36, 43, 45)
Cresol (all isomers)	68–97	P	(20, 40)
Hydrocyanic Acid	100–400	G	(26, 38, 43, 45, 46, 49, 53)
Nitric Oxide	0–600	G	(1, 3, 15, 40, 42, 44, 57)
Nitrogen Dioxide	0–10	G	(1, 40, 44, 57)
Phenol	9–202	P	(7, 19, 20, 32, 50, 52)

marily on the basis of the action of the individual substances. Nevertheless, experimental evaluation of modified cigarette smoke should be designed to take into account the possibility of such interaction.

Until there is a better understanding of the relative importance of the interaction of the constituents of cigarette smoke in the development of the diseases associated with cigarette smoking, it will be difficult to assess the significance of the reduction or elimination of one or several of the constituents named in this report. However, it is reasonable to take the position that unless there is positive information to the contrary, cigarettes in which overall "tar" and nicotine levels have been reduced present to the smoker lower concentrations of the harmful substances in the particulate phase. If, at the same time, significant reductions are made in those gas phase constituents which also contribute to the hazards of smoking, the resulting product should be less hazardous to health.*

The consensus is that a progressive and simultaneous reduction of all substances considered likely to be involved in the health hazards of smoking should be encouraged as the most promising step available at the present time towards the development of a less hazardous cigarette. Primary emphasis should be given to the reduction of the three substances or classes of substances named in the first table, and as a second priority to the reduction of those substances or classes of substances in the second table before reducing

* An alternative point of view held by some is that smoking behavior is a response to the need to reach a certain nicotine level and that lowering the amount of nicotine available from a cigarette may result in an increase in the number of cigarettes smoked, the depth of inhalation, or the number of puffs in order to maintain an accustomed level. Such an increase in smoking might result in an increased inhalation of other hazardous substances in the smoke, thereby potentially negating the effect of reducing the amount available in each cigarette.

TABLE 3.—*Compounds in cigarette smoke judged as suspected contributors to the health hazards of smoking.*

Compound	Concentration in cigarette smoke micrograms/cigarette	Primary phase classification G—gas P—particulate	References
Acetaldehyde	180–1,440	G	(4, 21, 27, 36, 43, 45, 48, 49, 53, 59)
Acetone	88–650	G	(12, 21, 27, 36, 43, 45, 48, 49, 53)
Acetonitrile	140–200	G	(12, 43)
Acrylonitrile	10–15	G	(12, 43)
Ammonia	60–330	G	(2, 22, 40, 41, 43, 64)
Benzene	12–100	G	(11, 12, 25, 43, 45, 49, 53)
2,3–Butadione	43–200	G	(43, 46, 49, 53)
Butylamine	3	P	(31, 40, 41)
[1] Carbon Dioxide	23,100–78,300	G	(1, 10, 15, 23, 26, 29, 34, 35, 42, 46, 49, 63)
Crotononitrile	4	G	(43)
Dimethylamine	10–11	P	(31, 40, 41)
DDT	0–0.77	P	(17, 39, 54)
Endrin	0.06	P	(14)
Ethylamine	10–11	G	(22, 31, 40, 41)
Formaldehyde	20–41	G	(4, 36, 43, 48, 53)
Furfural	45–110	P	(4, 13, 36)
Hydrogen Sulphide	12–35	G	(10, 43, 51, 58)
Hydroquinone	83	P	(6, 7)
Methacrolein	9–11	G	(12, 43)
Methyl Alcohol	90–300	G	(12, 21, 43, 46, 49)
Methylamine	20–22	G	(22, 31, 40, 41)
Nickel compounds	0–0.58	P	(5, 8, 47, 55, 56)
Pyridine	25–218	P	(40, 62)

[1] CO_2 is included because of the hazard it may represent to those with CO_2 retention, such as those with advanced COPD.

those named in the third table. In addition to the epidemiological and pathological data gained from human studies, it is important to develop better bioassay systems to evaluate cigarettes modified by these general guidelines.

It should again be emphasized that, in addition to the variation in chemical properties of the cigarette being smoked, procedures within the control of the individual smoker such as how many cigarettes he smokes, how far down he smokes the cigarette, and how frequently and deeply he inhales are critical factors in determining how much of the harmful substances which can be produced by the burning cigarette is given the opportunity to injure him.

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