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Identification and Reduction of Carcinogens in the Respiratory Environment[1]

Identifizierung und Reduktion von Respirationskarzinogenen

Dietrich Hoffmann and Ernst L. Wynder

With 7 Figures

Abstract

Epidemiological studies have implicated three factors in the overall increase of lung cancer – tobacco, especially cigarette smoking, urban pollution and, to a lesser extent, certain industrial respiratory environments. Some data were discussed on carcinogenic industrial inhalants, and on the possible effect of urban pollution. The reduction of pollution and that of specific environmental agents is stressed. Laboratory studies on the identification of carcinogens in cigarette smoke and their reduction toward the "less harmful cigarette" represent a part of this aspect.

Zusammenfassung

Während der letzten drei Jahrzehnte ist in den meisten entwickelten Ländern ein starker Anstieg des Lungenkrebses beim Manne beobachtet worden. Der gleichzeitig ansteigende Tabakkonsum, besonders in Form von Zigaretten, wie auch anwachsende Luftverunreinigung in den Städten und in begrenztem Maße, die Entwicklung neuer Industriezweige, sind in epidemiologischen Arbeiten als bedeutende Faktoren für die steigende Lungenkrebsrate genannt worden.

Auf dem Gebiet des Berufskrebses erkannte man innerhalb der letzten Dekade, daß Chlormethyläther Bronchialkarzinome induzieren kann, daß Vinylchlorid Angiosarkome in der Leber hervorruft, und daß Chloropren wahrscheinlich für Karzinome der Lunge wie auch der Haut verantwortlich ist. Auch Benzol muß als potenzielles Leukaemogen angesehen werden.

Alle diese Beobachtungen haben zu verschärften arbeitshygienischen Vorschriften geführt.

[1] Herrn Professor Dr. Adolf Butenandt zum 75. Geburtstag gewidmet.

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Retrospektive Untersuchungen haben auch gezeigt, daß Berufsumwelt und Zigarettenrauchen synergistisch wirken. So besteht z.B. ein höheres Risiko für Bronchialkrebs unter Asbest-Arbeitern, die rauchen, als unter solchen, die nicht rauchen oder unter Arbeitern außerhalb der Asbest-Industrie, die rauchen. Ähnliche Beweise für Synkarzinogenese gibt es bei Urangruben-Arbeitern, die rauchen, gegenüber solchen, die nicht rauchen.

Auch die Beobachtung von „Stadtfaktoren" in der vergleichenden Lungenkrebsstatistik bei Rauchern in Städten gegenüber solchen in ländlichen Gebieten, deutet auf Synkarzinogenese von Umweltkarzinogenen des Menschen hin. In diesem Falle bewertet man neben verschiedenen anderen Faktoren die Luftverunreinigung in den Großstädten als Synkarzinogen zum Tabakrauch.

Analytische und biologische Studien mit Extrakten von Luftverunreinigungspartikeln, die in 3 USA-Großstädten gesammelt wurden, haben gezeigt, daß PAK fast ausschließlich für die im Tierversuch beobachteten Karzinome verantwortlich waren. – Eine Reduktion von karzinogenen Kohlenwasserstoffen in der Luft mehrerer Großstädte ist während der letzten 10–15 Jahre durch Umstellung von Kohle auf Ölheizung und durch spezifische Reduktion der toxischen Abgase von Otto- und Dieselmotoren erzielt worden.

Tabakrauch enthält auch karzinogene Kohlenwasserstoffe, jedoch stellen die karzinogenen Verbindungen dieser Stoffklasse im Rauch nur einen Teil der Gesamtaktivität dar. Eine Reduktion der karzinogenen Wirkung des Tabakrauches muß deshalb auch von einer Reduktion der cokarzinogenen oder tumorfördernden Rauchkomponenten begleitet werden. – Da für Tabakrauch nach statistischen Erhebungen für das Lungenkrebsrisiko, wie auch im Tierexperiment eine klare Beziehung zwischen Dosis und Wirkung festgestellt wurde, war eine Reduktion des Teergehaltes des Zigarettenrauches der erste Schritt zu einer Risikoverminderung. Gleichzeitig wurde auch eine Reduktion des Nikotins und anderer physiologischer Noxen angestrebt. Die Filterzigarette war das erste Entwicklungsprodukt in dieser Richtung. Darüberhinaus hat man aber auch durch Selektion von Tabakarten mit Beimischungen von Tabakstengeln und Tabakfolie (rekonstituiert aus Tabakstaub) Veränderungen des Tabakrauches bewirkt, die sowohl geringere Mengen Teer produzieren als auch geringere tumorerzeugende Wirkung des Teeres zur Folge haben. Statistisch ergeben sich erste Anzeichen einer erfolgreichen Verminderung des Lungenkrebsrisikos für Raucher der „modifizierten" und Filterzigaretten. Jedoch bleibt die Enthaltung die sicherste Risikoverminderung.

Introduction

In 1912, ADLER published a monograph on lung cancer (1). The rare occurrence of the disease then prompted the authors to ask: "Is it worthwhile to write a monograph on primary malignant tumors of the lung?" Today, cancer of the respiratory tract is one of the most common causes of death in developed countries (48). In the United States, the United Kingdom and the Federal Republic of Germany, for instance, respiratory tract cancers are now the most common cause of cancer death among males. In 1966–67 lung cancer constituted about one fourth of all male cancer deaths (24.8%) in West Germany (48).

A detailed study of the epidemiological history of lung cancer illustrated that environmental factors play a crucial role in the incidence rate of this disease. Thirty years ago, more women than men died of cancer; the reverse is true today. This remarkable change is due mainly to a sharp increase in the incidence of lung cancer in men (Fig. 1).

Prospective and retrospective studies have implicated three factors in the overall increase of lung cancer – tobacco, especially cigarette smoking, urban pollution and, to a minor extent, newly emerging industrial environments (Table 1). The epidemiological studies which demonstrated the dramatic increase in lung cancer provided the main impetus for the chemical-analytical studies and bioassays in tobacco and air pollution carcinogenesis and for laboratory studies of occupational factors involved in cancer of the respiratory tract. In addition to these research activities, increased emphasis has been placed on the reduction and removal of carcinogens from the human respiratory environment.

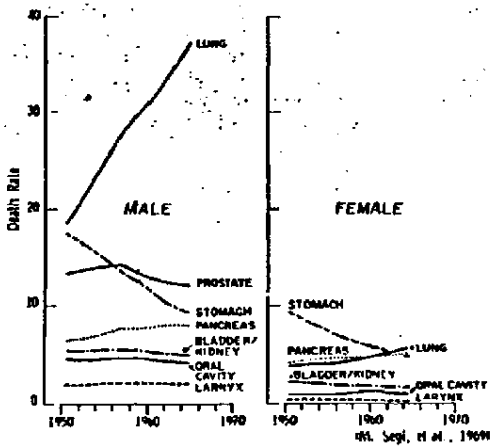


Fig. 1. Time trends for cancers reportedly related to tobacco smoke and other air pollutants; U.S. white.

Abb. 1. Zeitlicher Trend für Krebserkrankungen, die vermutlich auf Tabakrauch und andere luftverunreinigende Stoffe zurückzuführen sind.

Table 1. Relative contribution of suggested carcinogenic inhalants to cancer death rates[1]

Tabelle 1. Relativer Beitrag der vorgeschlagenen karzinogenen Inhalate zu den krebsbedingten Sterberaten

Cancer site	Tobacco smoke	Polluted air	Occupational *environment*
Respiratory tract			
Oral cavity	++++	–	–
Larynx	++++	–	?
Lung	++++	+?	+
Gastrointestinal tract			
Esophagus	+++	–	–
Stomach	–	?	–
Pancreas	++	–	–
Liver	–	–	+
Genitourinary tract			
Kidney	+++	–	+
Bladder	+++	–	+
Prostate	–	?	?

[1] Excess deaths as percentage of total cancer deaths at specific site: ++++ = ≥ 50%, +++ = 10–50%, ++ = 1–10%, + = 0.1–1%, – = 0.0%.

Industrial Carcinogenesis

Carcinogenic stimuli in occupational respiratory environments appear to have relatively little effect on the overall incidence of human cancers (Table 1). HIGGENSON has estimated that cancers related to occupational factors amount to less than 1 % of all cancers (21). Whatever influence does exist, it must be separated from the tumorigenic stimulus of tobacco smoke (24). Nevertheless, for specific industrial groups, certain exposures to inhaled pollutants are of obvious importance, especially since such exposure is usually preventable. The major industrial respiratory carcinogens are listed in Table 2.

During the last decade, several new industrial carcinogenic inhalants have been identified. These are volatile alkylating agents and reactive monomers which are characterized by the vinyl-group. They are widely used for the large scale production of inexpensive polymeric plastics and liquids. Chloromethyl ethers, vinyl chloride and chloroprene (Fig. 2) are major representatives of this group of industrial carcinogens.

Table 2. Epidemiological and experimental evidence for carcinogenicity of industrial inhalants

Tabelle 2. Epidemiologische und experimentelle Nachweise für die krebserzeugende Wirkung industrieller Inhalate

Carcinogens	Site[1]	Evidences[2]	
		Epidemiological	Experimental
Aromatic amines	Bladder (1895)	++	++
Arsenic	Skin (1820)	++	?
	Bronchi (1951)	++	–
Asbestos	Bronchi (1935)	++	++
	Mesothelium (1955)	++	++
Benzene	Haematopoietic system (1936)	+	?
Beryllium	Lung (1954)	?	+
Chloromethyl ethers	Bronchi (1968)	++	++
Chloroprene	Skin (1972)	+	–
	Lung (1972)	+	–
Chromate	Bronchi (1936)	++	++
	Nose (1953)	?	?
Coke oven fumes	Bronchi (1971)	++	++
	Kidney (1972)	+	?
Isopropyl oil	Nasal cavity (1946)	+	?
Mustard gas	Bronchi (1925)	++	+
Nickel	Bronchi (1933)	++	++
	Nasal cavity (1933)	++	–
Radioactive aerosols	Lung (1879)	++	++
Vinyl chloride	Angiosarcoma of the liver (1974)	++	++
Wood dust	Nasal cavity (1951)	++	?

[1] Number in parenthesis is the year the agent was first suspected to be a human carcinogen.

[2] ++ = established, + = suggestive, – = negative, ? = questionable or not tested.

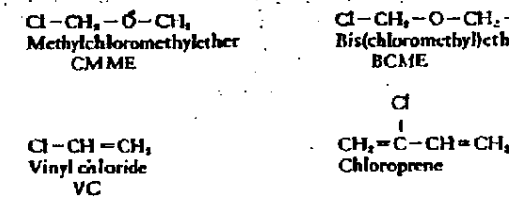


Fig. 2. Volatile industrial carcinogens.

Abb. 2. Flüchtige industrielle karzinogene Stoffe.

Bis(chloromethyl)ether

Scientists at New York University reported in 1968 and 1971 that bis(chloromethyl)ether (BCME) induces tumors in the skin of mice and bronchiogenic carcinomas in the lungs of rats which were exposed to concentrations as low as 0.1 ppm (32, 34, 53). Subsequently epidemiological studies on an industry-wide basis in the United States have disclosed some 30 cases of lung cancer in association with BCME and chloromethyl/methyl ether (CMME) (41). Among 14 cases in the first report 12 had confirmed oat cell carcinoma, four were younger than 40 years and none was older than 53 years, thus demonstrating that these chloromethyl ethers are powerful carcinogens (14). In the U.S.A. BCME and CMME are now recognized as human carcinogens (42) and their industrial use has been practically stopped. Recently the possibility has been discussed that BCME may be spontaneously formed from formaldehyde and hydrochloride. This applies not only to certain industrial environments but also to the general environment.

Vinyl chloride (VC)

VC was also first found to be carcinogenic in laboratory studies and was then shown to be responsible for inducing angiosarcoma of the liver and likely also to elicit bronchiogenic carcinoma in workers (50). Up to 1975 about 50 cases of angiosarcoma were recorded among VC and polyvinyl chloride (PVC) workers in the chemical industry, including a few cases in Germany (28, 50). Studies of the environment of VC and PVC plants have shown pollution of the air up to 33 ppm of VC at a distance of 0.5 km (10). A recent study of cancer mortality among populations residing near VC polymerization plants suggests an increased risk of dying from CNS and lymphatic cancer (28). Today most VC and PVC factories must observe very strict standards of pollution control (USA $\leq$ 1 ppm), and air and water effluents from these plants are monitored. Nevertheless, greater preventive efforts are needed, especially since the combustion of chlorine-containing organic matter leads to the formation of VC (22).

Benzene

The carcinogenic, industrial inhalants in Table 2 include benzene. In 1974 the

Deutsche Forschungsgemeinschaft (8) and the International Agency for Research on Cancer (30) did not consider benzene as a carcinogen. In the meantime several epidemiological studies including one survey of 28,500 shoe-workers (2) and one study on benzene workers (29) have suggested leukemogenic activity of benzene. In this context it is of interest to note that according to a study in the United States of America and in Sweden, chemists face an increased risk of death from malignant lymphomas and leukemia (35). We concur with the U.S. National Research Council which stated in 1976 "Based on available literature, it can be concluded that benzene may be associated with leukemia. Therefore, benzene must be considered as a suspect leukemogen" (51) In the U.S.A. 1 ppm is considered to be the standard limit of exposure for benzene (40).

Coke Oven Effluents

Coal tar was shown to be a skin carcinogen as early as 1875 by VOLKMANN (54). ECKARDT reviewed the world literature on this subject in 1959 and estimated the total number of skin cancer in coal tar workers to exceed 3,000 (9). The very basic studies on coal tar by COOK et al. in 1933 which led to the isolation of benzo(a)pyrene as the first organic carcinogen (7) were followed by many studies which have shown that polynuclear aromatic hydrocarbons (PAH) are the major carcinogens in coal tar (Table 3).

In 1936 sixty one cases of lung cancer were reported among workers of one steel company in Japan (31). Since then, lung cancer has also been observed in coke oven and gas retort workers in England, the U. S., Canada, and Norway (27). However, it was not until 1971–72 that detailed background information became available for coke oven workers who developed lung cancer (37, 43). At that time LLOYD and his group found that these workers had a 2.5 times higher risk to develop lung cancer than the general population. An especially high risk with 6.9 times that expected was found for the loaders on topsides of coke ovens. Although data on smoking were absent, it is unquestionably clear from the study that coke oven workers face higher risks of death from lung cancer.

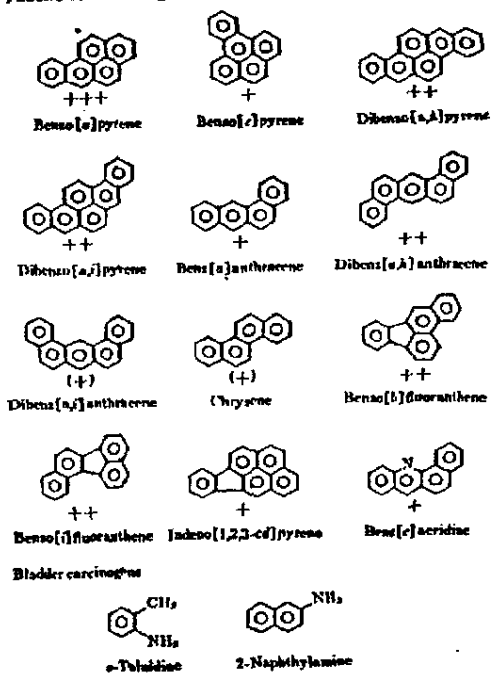
A study of the high concentration of PAH in the coke oven effluents during the loading periods strongly supports the concept that carcinogenic hydrocarbons at least contribute to the high incidence of lung cancer (46). In recent years new exhaust systems and preventive measures have significantly decreased the risk of exposure to carcinogenic PAH.

The next step which is now under way in the U.S.A. is the environmental pollution control of the effluents from these coke ovens. Recently, relatively high concentrations of PAH have been found in the air of the surroundings of these plants (11). Although it is not likely that the PAH-containing effluents alone will lead to an increased risk for bronchiogenic carcinoma in nonsmokers, the contribution of these aerosols to the total burden with environmental carcinogens of persons residing near coke ovens must be considered.

Asbestos

Another example of combined exposure to two environmental carcinogens is found in asbestos workers. Employees in the asbestos industry have long been known to have a high risk for mesothelioma of the pleura and peritoneum and a somewhat higher risk for bronchiogenic carcinoma. HAMMOND and SELIKOFF

Table 3. Carcinogens in coal tar
Tabelle 3. Karzinogene Stoffe in Kohlenteer



*+++ = high, ++ = moderate, + = weak, (+) = possibly weak. Relative carcinogenic activity on mouse skin. Chrysene is present in the coal tar of the Ruhr district (Germany) with an average concentration of 1.6%.

documented in 1973 that asbestos workers who are also cigarette smokers face a significantly higher risk for lung cancer than the nonsmoking asbestos workers, or cigarette smokers outside the industry (18).

In recent years, several investigators have been concerned with the exposure of the general population to asbestos dust from construction sites, brake linings, and from polluted air in the vicinity of asbestos factories. LANGER and SELIKOFF identified chrysotile in the lungs of New York City residents without occupational exposure (33). BOHLIG and HAIN reported 38 cases of mesothelioma between 1950 and 1968 in residents in Hamburg-Bergedorf where an asbestos factory is located (6). These observations make it possible to theorize that the inhalation of air polluted with asbestos particles, may increase the lung cancer risk of cigarette smokers and workers exposed to other carcinogenic inhalants even further.

Increased efforts should be made to protect the workers, as well as the city residents from asbestos dust exposure, since the material is still widely employed as insulating material.

Nitrosamines

Today more than 100 nitrosamines are known to be carcinogenic in experimental animals (38). Yet, we are still missing the direct evidence that the nitrosamines cause cancer in man. In view of the fact that nitrosamines are carcinogenic to the usual laboratory animals, as well as to monkeys, birds, amphibia and fish, and because of similarities in the metabolism of N-nitrosodimethylamine in human and animal tissues *in vitro*, there is a strong possibility that some nitrosamines are *carcinogenic to man*.

These considerations alone dictate that great caution be exercised in the industrial use of nitrosamines and that these agents be excluded from household goods and from food. The example, the carcinogenic N-nitrosodiethanolamine (38, 45) has been found up to 3 % in synthetic and semisynthetic cutting fluids and up to 200 ppb in certain cosmetics (12, 13, 58). Epidemiological studies have not thus far been undertaken to evaluate the role of this nitrosamine and certain volatile nitrosamines as possible risk factors in occupational environments.

The thermal energy analyzer (TEA) represents a new analytical tool which increases our capacity to determine traces of nitrosamines in environmental agents down to 10^{-12}g (15). The application of TEA-techniques to the examination of general and occupational environments as well as to detection of N-nitrosamines in body fluids will further elucidate our knowledge on the importance of nitrosamines in carcinogenesis. *In vivo* formation of nitrosamines from amines and nitrite is possible and is also substantiated by a recent report of induction of squamous cell carcinomas in the lung of rats given high oral doses of heptamethyleneimine hydrochloride and sodium nitrite (36).

Other Industrial Respiratory Carcinogens

It is certainly beyond the scope of this discussion to present data on some or all other known or suspected industrial inhalants with carcinogenic potential (Table 2). For detailed information we refer to the subject literature (9, 27, 44, 47). We will, however, emphasize a few points. During the last few decades we witnessed a significant reduction of the cancers caused by industrial agents alone. Despite the fact that, even in the most industrialized nations, occupational cancers account for merely a few percent of all environmental cancers, we must consider their occurrence as a neglect of society.

A fresh approach of scientists toward the elimination of occupational cancer is needed. For example, factories with large volume production of plastics and other polymers from reactive monomers with vinyl configuration may represent new *carcinogenic environments*. This area needs our attention. The exposure of the workforce, or even that of the general population, to small amounts of certain specific chemicals alone may not represent a carcinogenic hazard, however, these trace compounds increase man's burden with agents which have to be detoxified *in vivo*, or else will induce irreversible cellular changes. Examples are the significantly higher risks for lung cancer of uranium miners and asbestos workers who are also cigarette smokers.

Air Pollution

Urban air pollution may well represent another factor which contributes to the carcinogenic burden of man in industrialized countries. The effect of atmospheric pollution alone on the induction of respiratory cancer is difficult to evaluate because of the overriding effect of cigarette smoke (44, 52). Lung cancer, however, does occur more commonly in cities, and in fact, a committee of the National Academy of Sciences estimated that urban dwellers may have twice as high an incidence rate of lung cancer as those in rural areas (39).

Epidemiological Considerations

A number of retrospective and prospective studies have been concerned with the relative influence and nature of the "urban factor" in the etiology of lung cancer. It appears that the urban factor is not only a consequence of atmospheric pollution, but also of several variables (Table 4).

Table 4. Contributors to the "urban factor" in respiratory carcinogenesis
Tabelle 4. Stoffe, die bei der atmungsbedingten Krebsentstehung zum „Städtischen Faktor" beitragen

More accurate reporting and recording of death certificates
Higher degree of atmospheric pollution
More industrial exposure
More cancer diagnosed and treated
Different immigration/migration patterns
Differences in socioeconomic factors
More cigarettes smoked

Investigations of these various contributions to the "urban factor" in respiratory carcinogenesis do not eliminate the role of polluted air. Within each urban/rural grouping, lung cancer death rates increase strongly with cigarette smoking and show always somewhat higher rates for the city smokers (Fig. 3; 17). Atmospheric pollution appears to offer a reasonable explanation for the persistence in the urban-rural ratio of lung cancer.

It appears to us that air pollution contributes to man's burden with carcinogens and, as such, may increase the risk to develop lung cancer for cigarette smokers and possibly for asbestos workers (17, 49).

Laboratory Studies

The findings from bioassays and physiochemical studies are equally significant to the epidemiological data in relating atmospheric pollution to the pathogenesis of respiratory cancer. The elucidation of the mechanisms leading to lung cancer induction remains primarily the domain of the physical and biological sciences. In environmental carcinogenesis, demonstrable parallelism between epidemiological data and laboratory findings add to both. Carcinogenesis bioassay data from

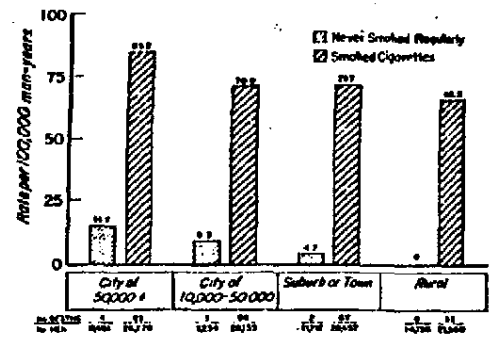


Fig. 3. Age-standardized rates for well established cases of bronchiogenic carcinoma, by rural-urban classification. Rates for cigarette smokers are compared with those for men who never smoked regularly (17).

Abb. 3. Altersgenormte Werte für nachgewiesene Fälle des bronchogenen Karzinoms, nach einer Land/Stadt-bezogenen Einteilung. Die Häufigkeitswerte für Zigarettenraucher werden mit denen verglichen, die bei unregelmäßig rauchenden Männern auftraten (17).

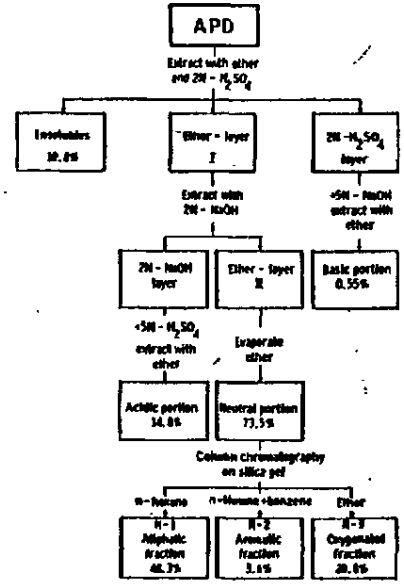


Fig. 4. Separation scheme of organic particulate matter from air pollutants (Detroit) (25).

Abb. 4. Trennungsschema für organische Partikel in Luftverunreinigungen (Detroit) (25).

mammalian species with air pollutants lend support to the concept that air pollution represents one factor in the increased risk of urban dwellers to develop lung cancer. Above all, laboratory studies offer the possibility of reducing the emission of potentially harmful carcinogens into our environment.

Extensive studies in many laboratories have shown that the particulate matter of urban pollutants contains the majority of the respiratory carcinogen (25).

For the identification of the carcinogens, the organic particulate matter of air pollutants sampled in a number of cities was fractionated (Fig. 4).

The total organic matter and the aromatic, neutral subfractions of these air pollutant concentrates induced papillomas and carcinomas in the skin of 50–95 % of the mice. The insoluble and acidic portions and the aliphatic and oxygenated neutral subfractions were inactive as complete carcinogens. The basic portions were not tested since they amounted to only 0.55–3.4 % of the total organic matter.

A detailed chemical analysis of the aromatic neutral subfraction revealed the enrichment of practically all of the PAH from the total particulates in this subfraction and also revealed the presence of at least six known carcinogenic PAH in the organic pollutants. In the bioassayed organic particulates from four different locations in Detroit and New York, the concentrations of the strong carcinogen, benzo(a)pyrene (BaP), varied between 0.011 and 0.035 % and of the weak carcinogen, benz(a)anthracene (BaA), varied between 0.017 and 0.06 %. Using chemically purified BaP as positive control, we estimated that 45–55 % of the carcinogenicity of the total organic particulates and of the aromatic neutral subfractions could be explained by BaP alone.

From the bioassays of the organic particulates, one can conclude that polluted air contains trace amounts of carcinogens. The most important types of these carcinogens are the active species of the PAH group. BaP is the most active compound of this group. Minor carcinogens are aza-heterocyclic hydrocarbons and certain types of epoxides and peroxides. However, the total amount of carcinogens in urban pollutants is very small. The highest amount reported for the U.S. is 74 μg BaP in 1000 m³ polluted air. Taking this value, if one stayed outdoors for 24 h, there would be approximately 0.9–1.5 μg BaP in the air one breathes (11–20 m³). The average value for a U.S. city is more near 0.07–0.12 μg. These very low values certainly appear in line with the human data showing only slightly elevated lung cancer risk for the urban nonsmoker and a somewhat more elevated lung cancer risk for the urban cigarette smoker compared with rural cigarette smokers. Whatever the demonstrated increase in the relative risk factor for lung cancer caused by present day urban pollution, the established presence of potentially harmful carcinogens in the atmosphere should increase our efforts to remove the agents to whatever degree possible.

Sources for Atmospheric Carcinogens

Carcinogenic PAH are formed primarily during the incomplete combustion of organic matter by a few distinct mechanisms. The prevailing pyrolytic route for PAH is the initial formation of C, H-radicals in zones with highly elevated temperatures (> 600 °C) and the subsequent combining of C, H-radicals to the thermodynamically preferred aromatic hydrocarbons including those of carcinogenic hydrocarbons with four to six condensed aromatic rings (Fig. 4). This route

is enhanced during the burning of precursors with an aromatic ring system. These data suggest that all combustions can contribute PAH to urban pollution.

It has been estimated that in the U.S.A. alone 880–1,000 metric tons of BaP are emitted annually into the environment from combustions (Table 5; 39). Although data for other carcinogenic hydrocarbons are presently lacking, we can assume that their total emission exceeds that of BaP by at least 3–5 times.

Table 5. Estimated benzo(a)pyrene emissions in the United States (1972)[1]
Tabelle 5. Geschätzte Abgabe von Benzpyren in den Vereinigten Staaten (1972)

Source type	Emissions MT/yr
Stationary sources	
Coal, hand-stroked residential furnace	300
Coal, intermediate-size units	7
Coal, steam power plants	< 1
Oil, residential through steam power type	2
Gas, residential through steam power type	2
Wood, home fireplace	25
Enclosed incineration – apartment through municipal	3
Vehicle disposal	25
Forest and agriculture	11
Other open burning	10
Petroleum, catalytic cracking	310
Asphalt air blowing	< 1
Coke production	(0.06)–170
Mobile source (20–25 MT/yr)[2]	
Gasoline-powered automobiles and trucks	11
Diesel-powered trucks and buses	< 1
Tire degradation	11

[1] U. S. Environmental Protection Agency, 1974.
[2] Other estimates 40–50 MT/yr (5).

The nation-wide estimates cannot be applied to individual areas. For example, the major emission sources for the coal mining and steel producing states are coal-fired furnaces, coal refuse burning and coke production. In our major cities, motor vehicles contribute significantly to the PAH atmospheric burden. This applies specifically to downtown areas of New York City and Los Angeles. The only motor vehicle data available for Detroit show a surprisingly small contribution of 5 % of the BaP in the downtown area, 15 % of which was located in the freeway area and 42 % in the suburban atmosphere (25).

Reduction of Atmospheric Carcinogens

In recent years, some progress has been made in reducing urban pollution. London represents one example of such progress after her citizens suffered through air pollution episodes in 1952 and 1962. Since then, the British Government and

the city have enforced strict regulations for industry and a change from coal to oil heating for private and public housing. The United Kingdom has, furthermore, made emission control devices mandatory. The maximal emission values for motor vehicles per km are 4.2 g of hydrocarbons and 48 g of carbon monoxide; the U.S. standards are 2.1 g and 24 g, respectively (3). These regulations led to a significant reduction of gaseous air pollutants, especially of the cilia-toxic sulfur dioxide as well as to a reduction of particulate matter, including that of carcinogenic hydrocarbons (4).

In the U.S., many communities and countries have enacted new ordinances which set limits for the sulfur content of coal and heating oil. Industries have shown initiative in controlling the emission of pollutants. Nevertheless, new control measures are still needed. As discussed under "Sources for Atmospheric Carcinogens", coal refuse burning represents still a major source of atmospheric pollution in the coal-mining states. Coal refuse is a major by-product of the coal mining industry resulting in large dumps or heaps of rocks intermixed with small pieces of coal. Unfortunately, on occasion, these dumps can selfignite and emit very dense smoke for weeks. Hopefully, the mining industry will increase the use of coal refuse for filling abandoned mine shafts or find new applications for this by-product and thereby reduce a major source of atmospheric pollution.

In the last decade, some cars have been equipped with emission control devices. These devices have been estimated to reduce the emission of PAH by 85 % (Table 6; 39). The central reason for the lower PAH yields from current emission controlled vehicles is the shifting from rich carburation (2.85 % carbon monoxide) to clean carburation (0.9–1.4 % carbon monoxide). However, aging of an internal combustion engine can increase PAH emissions. HANGEBRAUCK et al. reported five times the BaP emission for a car after 50,000 mi of operation (19).

A significantly higher emission of PAH also correlated with an increased oil consumption (Table 7; 26). Hopefully, future developments will make annual emission rate inspections mandatory in all states for cars, trucks, buses, and motorcycles. The measure should significantly reduce atmospheric pollution in urban communities.

In recent years, the public has been increasingly concerned with the emission of lead from gasoline engines, which brought about the introduction of low-lead fuels. In order to keep the anti-knock number high, the aromatic portion (benzene,

Table 6. Automotive benzo(a)pyrene emission factors (19)
Tabelle 6. Benzpyren-Abgabefaktoren für Kraftwagen (19)

Source	Benzo(a)pyrene Emission factors (μg/gal of fuel consumed)
Uncontrolled car (1956–1964)	170
1966 Uncontrolled car	45–70
1968 Emission-controlled vehicle	20–30
Advanced systems	< 10

Table 7. Emission rates of polynuclear aromatic hydrocarbons from a gasoline engine
Tabelle 7. Abgabewerte für polyzyklische aromatische Kohlenwasserstoffe bei Benzinmotoren (25)

	"Tar" emission		"Tar" analysis (ppm)			
	(g/hr)	(g/gal fuel)	BaP[2]	BaA[3]	Pyrene	Fluoranthene
Standard run[1]	4.4	2.2	100	180	2400	1330
Run with high oil consumption[1]	10.2	4.8	566	925	4100	2200

[1] 1 qt/1600 mi.
[2] 1 qt/200 mi.
[3] Quantitative values (± 5%) determined by isotype dilution technique using BaP-6-C^{14} and BaA-9-C^{14}, respectively. BaP = benzo(a)pyrene; BaA = benz(a)anthracene

Table 8. BaP and BaA Emission Rates from a Gasoline Engine Operated with Different Fuels cd. (25)
Tabelle 8. Abgabewerte für BaP und BaA bei Benzinmotoren mit experimentellen Treibstoffen

Fuel	(μg) BaP	(μg) BaA
Gasoline	9.6	17.3
2,3,4-Trimethylpentane	2.6	0.8
2,4,4-Trimethyl-1-pentene	0.7	0.4
50% o-Xylene plus 50% benzene	25.8	56.3
25% 2,4,4-Trimethylpentane plus 25% isopentane plus 50% xylene	9.0	32.3

One-minute run.
BaP = benzo(a)pyrene; BaA = benz(a)anthracene

toluene, and xylenes) in some of these fuels has been significantly increased. Experimental engines operated only on aromatic fuels have demonstrated that this will increase PAH emission (Table 8). The recent practice of synthesizing isooctance (anti-knock number 100) from cracking gases and adding it to gasoline will eventually reduce the aromatic portion in fuels.

Tobacco Smoke

For more than a quarter century, epidemiological data have causatively linked tobacco smoking with lung cancer (26). Human studies have also shown a reduction in risk for lung cancer when cigarettes with reduced "tar" yield have been smoked for 10 years or more (56). It is the purpose of this discussion to define the less harmful cigarette in terms of its chemistry and biological activity on the basis

of progress already achieved, as well as in regard to future developments in methods of prevention of cancerous diseases related to smoking. We have to recognize that educational efforts and smoking cessation techniques are only partially successful. In addition, data have clearly indicated that the lower the educational status of an adult the more likely he or she is to smoke. We have to face the reality, therefore, that in decades to come, we will have tens of millions of cigarette smokers in the U.S.A., as well as in the BRD. On the basis of these considerations, we concur with the statement by Dr. G. GORI of the U.S. National Cancer Institute "to leave millions of smokers to their fate is neither humane nor economical" (16). The answer, therefore, for these people who continue to smoke is the "Less Harmful Cigarette".

Tumorigenic Agents in Tobacco Smoke

The development of the less harmful cigarette will be based primarily upon our knowledge of the toxic constituents of tobacco smoke. The predominant role of lung cancer among smoking-related diseases has focused attention on the carcinogenicity of tobacco smoke. Animal studies conducted in numerous countries have demonstrated carcinogenicity for cigarette smoke and mainly for its particulate matter, commonly known as "tar". Fractionations and bioassays have revealed that tobacco smoke contains trace amounts of carcinogens, which act as tumor initiators, cocarcinogens and organ specific carcinogens (Tables 9 and 10; 23, 57). Whereas, most tumor initiators in "tar" have been identified, current studies are directed toward determining the chemical nature of the neutral and weakly acidic cocarcinogens. Several of these compounds are tobacco specific, and their precursors in the tobacco leaf can be selectively removed through the breeding of new tobacco varieties and/or by extraction and treatment of the tobacco.

Since little is known about the organ-specific carcinogens in tobacco smoke, their role in tobacco carcinogenesis needs to be examined. It was shown that tobacco proteins give rise to traces of several aromatic amines in the smoke. Compounds of this type are known animal and human bladder carcinogens, β-naphthylamine being the best known representative of the group.

The presence in the smoke of volatile nitrosamines and nonvolatile nitrosamines, such as the tobacco specific N'-nitrosonornicotine, which are derived from tobacco alkaloids, appears to be an equally important factor. These compounds do not exist in fresh, green tobacco, but their formation occurs during tobacco curing as well as during smoking (20). Nitrosonornicotine is an organ specific carcinogen which induces esophageal tumors in rats as well as lung tumors in mice and in Syrian golden hamster (20). Other tobacco specific nitrosamines and their carcinogenicity are currently being studied.

Reduction of Tumorigenicity and Toxicity of Cigarette Smoke

The formation of organ specific carcinogens during tobacco curing, their partial transfer into the smoke and their formation during smoking provide a framework for intervention towards their reduction in the smoke. These efforts are still in their early stages. Significant progress has been achieved in the nonselective reduction of "tar" and nicotine, in the selective reduction of several carcinogenic and cocarcinogenic agents and of toxic smoke constituents such as carbon monoxide and hydrogen cyanide.

Table 9. Major toxic agents in the gas phase of cigarette smoke[1] (unaged)
Tabelle 9. Größere toxische Stoffe in der Gasphase des Zigarettenrauchs (ohne Alterung)

Agent	Biological Activity[2]	Concentration in 1 Cigarette Range Reported	U.S. Cig.[3]
Dimethylnitrosamine	C	1 – 300 ng	13 ng
Ethylmethylnitrosamine	C	0.1– 10 ng	1.8 ng
Diethylnitrosamine	C	0 – 10 ng	1.5 ng
Nitrosopyrrolidine	C	2 – 42 ng	11 ng
Other Nitrosamines (4 compounds)	C	0 – 20 ng	?
Hydrazine	C	24 – 43 ng	32 ng
Vinyl Chloride	C	1 – 16 ng	12 ng
Urethane	TI	10 – 35 ng	30 ng
Formaldehyde	CT, CoC	20 – 90 µg	30 µg
Hydrogen Cyanide	CT, T	30 – 200 µg	110 µg
Acrolein	CT	25 – 140 µg	70 µg
Acetaldehyde	CT	18 –1400 µg	800 µg
Nitrogen Oxides (NO_x)[4]	T	10 – 600 µg	350 µg
Ammonia	T?[5]	10 – 150 µg	60 µg
Pyridine	T?[5]	9 – 93 µg	10 µg
Carbon Monoxide	T	2 – 20 mg	17 mg

[1] May also contain such carcinogens as arsine, nickel carbonyl and possibly volatile chlorinated olefins and nitro-olefins.
[2] Biological activities: C carcinogen; BC bladder carcinogen; TI tumor initiator; CoC cocarcinogen; CT cilia toxic agent; T toxic agent.
[3] 85 mm cigarette without filter tip bought on the open market 1973–76.
[4] NO_x > 95% NO, rest NO_2.
[5] Not toxic in smoke of blended U.S. cigarettes because pH < 6.5 and therefore ammonia and pyridines are present only in protonated form.

Undesirable tobacco smoke constituents can be reduced through the elimination of precursors by selection of specific tobacco varieties and plant components, also by selective filtration. Dose reduction can be effected by smoke dilution through air filtration, or by reducing inhalability. Table 11 presents the major methods which have been employed in an effort to reduce the biological activity of cigarette smoke. New concepts continue to emerge and together with the presently available techniques, they will further reduce the harmful effects of tobacco products.

Whether progress has been made in reducing the smoker's risk by modification of the commercial cigarette can be measured to some extent by chemical analyses and in bioassays. However, ultimate confirmation must come from epidemiological surveys. We would predict increasing consumer acceptance of low "tar" brands, particularly if they could provide sufficient "satisfaction" for the smoker. Flavoring agents derived from tobacco, from synthetic compounds and/or mixtures of plant extracts, enhance consumer acceptance. Such nontobacco flavor additives and

Table 10. Major toxic agents in the particulate matter of cigarette smoke[1] (unaged)
Tabelle 10. Größere toxische Stoffe in den Partikeln von Zigarettenrauch (ohne Alterung)

Agent	Biological Activity[2]	Concentration in 1 Cigarette Range Reported	U.S. Cig.[3]
Benzo(a)pyrene	TI	8 – 50 ng	20 ng
5-Methylchrysene	TI	0.5 – 2 ng	0.6 ng
Benzo(j)fluoranthene	TI	5 – 40 ng	10 ng
Benz(a)anthracene	TI	5 – 80 ng	40 ng
Other PAH (> 20 compounds)	TI	?	?
Dibenz(a,j)acridine	TI	3 – 10 ng	8 ng
Dibenz(a,h)acridine	TI	?	?
Dibenzo(c,g)carbazole	TI	0.7 ng	0.7 ng
Pyrene	CoC	50 –200 ng	150 ng
Fluoranthene	CoC	50 –250 ng	170 ng
Benzo(g,h,i)perylene	CoC	10 – 60 ng	30 ng
Other PAH (> 10 compounds)	CoC	?	?
Naphthalenes	CoC	1 – 10 µg	6 µg
1-Methylindoles	CoC	0.3 – 0.9 µg	0.8 µg
9-Methylcarbazoles	CoC	0.005– 0.2 µg	0.1 µg
Other Neutral Compounds	CoC	?	?
Catechol	CoC	40 –460 µg	270 µg
3- and 4-Methylcatechols	CoC	30 – 40 µg	32 µg
Other Catechols (> 4 compounds)	CoC	?	?
Unknown Phenols and Acids	CoC	?	?
N'-Nitrosonornicotine	C	100 –250 ng	250 ng
Other Nonvolatile Nitrosamines	C	?	?
β-Naphthylamine	BC	0 – 25 ng	20 ng
Other Aromatic Amines	BC	?	?
Unknown Nitro Compounds	BC	?	?
Polonium-210	C	0.03 – 1.3 pCi	?
Nickel Compounds	C	10 –600 ng	?
Cadmium Compounds	C	9 – 70 ng	?
Arsenic	C	1 – 25 µg	?
Nicotine	T	0.1 – 2.0 mg	1.5 mg
Minor Tobacco Alkaloids	T	0.01 – 0.2 mg	0.1 mg
Phenol	CT	10 –200 µg	85 µg
Cresols (3 compounds)	CT	10 –150 µg	70 µg

[1] Incomplete list.
[2] Abbreviations for Biological Activity, see footnote 2 of Table 9.
[3] See footnote 3 of Table 9.

Table 11. Reduction of biological activity of cigarette smoke[1]
Tabelle 11. Verminderung der biologischen Aktivität von Zigarettenrauch

Method	"Tar"	Nicotine	BaP	Select. Biolog. Carcinogen	Reduction Promoters
Agricultural Aspects					
Tobacco Varieties (Bright-Burley)	+	+	+	+	+
New Tobacco Cultivars	+	+	+	?	?
Leaf Position[a]	+	+	+	?	?
Selection by NO_3^-	+	+	+	+	?
Tobacco Processing					
Extraction:					
Organic Solvents[b]	+	+	+	+	?
Cut	±	±	±	± ?	?
Stems	+	+	−	+ +	+ +
Reconstituted Tobacco Sheets (RTS)[c]	+	+	+	+	±
Reconstituted Tobacco Sheets (Paper Process)	+ +	+	+	+ +	?
Expanded Tobacco	+ +	+ +	+ +	± ?	±
Cigarette Production					
Porosity of Paper	+	+	+	±	?
Perforated Filters	+	+	+	±	?
Cellulose Acetate Filter	+	+	+	±	±
Charcoal Filter[a]	+	+	+	+	±
Additives: NO_3^-[b]	+	+	+	+	±
Tobacco Substitutes	+ +	+ +	+	+ +	+

[1] Reductions: + + > 50%; + significant; ± insignificant; ± ? questionable; − increase; ? unknown.
[2] Data given for reconstituted tobacco sheets relate to those not made by the paper process.
[a] Reductions of "tar", nicotine, and BaP are in general greater with cellulose acetate filters than with charcoal filters.
[a] Lowest stalk position highest reduction
[b] Only of academic interest
[c] Some RTS give high CO

their combustion products require testing with respect to their biologic activities. We have emphasized the importance of such testing for a number of years since there is a dearth of information in this area. Concerted efforts of governmental agencies and institutional and industrial research groups are needed to study these aspects so that the least harmful product can be offered to those who continue to smoke.

The data from K. H. Weber in Fig. 5 and 6, are for sales weighted average "tar" and nicotine delivery of U.S. and German cigarettes (55). A gradual reduction of "tar" and nicotine has occurred, not only in the U.S.A., but also

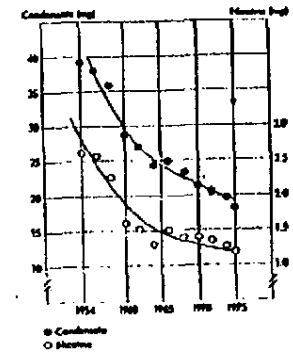


Fig. 5

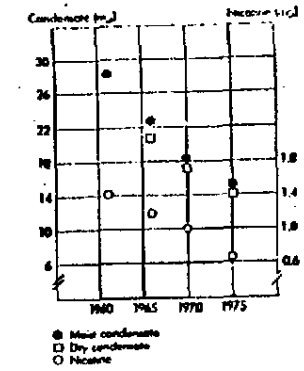


Fig. 6

Fig. 5. USA. Sales weighted average deliveries of total condensate (dry) and nicotine per cigarette 1954–1975 (55).
Abb. 5. USA. Umsatzbewertete Durchschnittsabgaben von Gesamtkondensat (trocken) und Nikotin pro Zigarette 1954–1975 (55).

Fig. 6. Germany. Sales weighted average deliveries of total condensate and nicotine per cigarette 1961–1975 (55).
Abb. 6. Deutschland. Umsatzbewertete Durchschnittsabgaben von Gesamtkondensat und Nikotin pro Zigarette 1961–1975 (55).

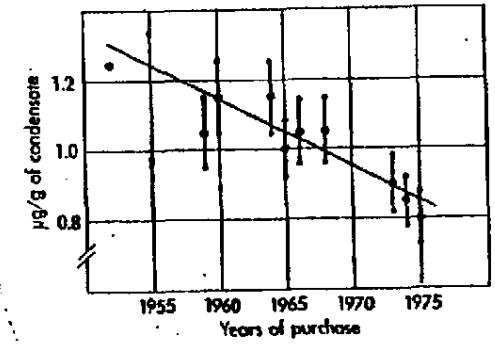


Fig. 7. USA. Decreasing concentration of benzo(a)pyrene in the condensate of a leading non-filter-cigarette (Hoffmann, 1952–1975).
Abb. 7. USA. Abnehmende Konzentration von Benzpyren im Kondensat einer führenden filterlosen Zigarette (Hoffmann, 1952–1975).

in Austria, Canada, the Federal Republic of Germany, France, Japan, Sweden, Switzerland, the United Kingdom and other countries. Fig. 7 demonstrates the decrease in benzo(a)pyrene values in the smoke of a popular representative U.S. cigarette since 1953. Benzo(a)pyrene has been chosen to indicate the levels of tumorigenic polycyclic hydrocarbons in the smoke, and its reduction can be correlated with a steady decrease in tumorigenicity of "tar", in U.S. cigarettes since 1950 (Fig. 5).

Incorporating all available techniques in cigarette manufacturing and assuming that none of the flavor additives induce additional toxic effects, we propose certain limits for smoke components for a less harmful cigarette (Table 12). Some of the cigarettes sold in 1977 have, at least in some specifications, reached the suggested levels. We must realize, however, that these cigarettes constitute only a small percentage of current total sales. The data in Table 12 are to be considered as a starting point for discussions. It is imperative that additional smoke components be evaluated in the continuing search for a less harmful cigarette.

Table 12. Maximum concentrations of some selected toxic agents in the smoke
Tabelle 12. Max. Konzentrationen einiger ausgewählter Giftstoffe im Rauch

Toxic Component	Maximal Proposed Concentration
Total Particulate Matter[1]	8 mg
Nicotine	0.6 mg
Carbon Monoxide	6 mg
Hydrogen Cyanide	100 µg
Benzo(a)pyrene[2]	8 ng
Dimethylnitrosamine[3]	5 ng
N'-Nitrosonornicotine	60 ng
Catechol	90 µg
Phenol	20 µg
Acrolein[4]	30 µg
Oxides of Nitrogen	100 µg

[1] Total Particulate Matter = Tar + Water + Nicotine.
[2] Serves as indicator for tumorigenic PAH.
[3] Serves as indicator for volatile nitrosamines.
[4] Serves as indicator for organic cilia toxic agents.

Conclusion

In summary, we wish to stress that cessation of smoking is the best option, but a less harmful cigarette must be realized for millions of current and future smokers, and for those who do not want to give up smoking. It would be irresponsible to leave those millions of current and future smokers to their fate, since this is neither humane nor just.

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