

## Meeting Report

# Tobacco and Cancer

### Purpose of Meetings

The carcinogenicity to humans from the use of tobacco in all forms has been evaluated within the scope of the IARC<sup>1</sup> Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Two working groups were convened at IARC in Lyon, France, to review all the available data relevant to this issue.<sup>2</sup> The evaluations of the risks of different forms of tobacco were based, as is usual within the IARC Monographs program, on a thorough and critical review of all published epidemiological

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<sup>1</sup> The abbreviation used is: IARC, International Agency for Research on Cancer.

<sup>2</sup> A meeting of the IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Habits Other Than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines took place at IARC headquarters in Lyon, France, on October 23-30, 1984.

Members of the working group are: S. V. Bhide, Cancer Research Institute, Bombay, India; E. Boyland, London School of Hygiene and Tropical Medicine, London, United Kingdom; D. L. Davis, University of Kentucky, Lexington, KY; P. C. Gupta, Tata Institute of Fundamental Research, Bombay, India; S. S. Hecht, Naylor Dana Institute for Disease Prevention, Valhalla, NY; J. M. Hirsch, Public Dental Service, Göteborg, Sweden; D. Hoffmann, Naylor Dana Institute for Disease Prevention, Valhalla, NY; E. Huberman, Argonne National Laboratory, Argonne, IL; D. G. Kaufman, University of North Carolina, Chapel Hill, NC; A. Kneap, National Institute of Public Health and Environmental Hygiene, Bilthoven, The Netherlands; P. N. Magee (Chairman), Fels Research Institute, Philadelphia, PA; A. J. McMichael, CSIRO, Adelaide, SA, Australia; J. J. Pindborg, Royal Dental College, Copenhagen, Denmark; J. M. Ratcliffe, National Institute for Occupational Safety and Health, Cincinnati, OH; J. K. Reddy, Northwestern University Medical School, Chicago, IL; H. F. Stich, British Columbia Cancer Research Centre, Vancouver, BC, Canada; P. F. Swann, Courtauld Institute of Biochemistry, London, United Kingdom; S. R. Tannenbaum, Massachusetts Institute of Technology, Cambridge, MA; and V. Turusov (Vice-Chairman), USSR Academy of Medical Sciences, Moscow, USSR.

The representative of the National Cancer Institute at the meeting was D. M. Winn, National Cancer Institute, Bethesda, MD, and the representative of SRI International was K. E. McCaleb, SRI International, Menlo Park, CA. Observers at the meeting were: A. Englund, Bygghälsan, Stockholm, Sweden; B. H. MacGibbon, Department of Health and Social Security, London, United Kingdom; S. Olin, Tracor Jitco, Inc., Rockville, MD; K. Stanley, WHO, Geneva, Switzerland; and M-T. van der Venne, Commission of the European Communities, Luxembourg, Grand Duchy of Luxembourg.

A meeting of the IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking occurred at IARC headquarters in Lyon, France, on February 12-20, 1985.

Members of this working group are: O. Axelson, University Hospital, Linköping, Sweden; F. G. Bock, The Pap Institute, Miami, FL; M. Caraballero, Institute of Oncology and Radiobiology, Havana, Cuba; I. Chouroulinkov, Institute for Scientific Research on Cancer, Villejuif, France; D. L. Davis, Tobacco and Health Research Institute, University of Kentucky, Lexington, KY; R. Doll (Chairman), Imperial Cancer Research Fund, Oxford, United Kingdom; H. J. Evans, Western General Hospital, Edinburgh, United Kingdom; Y-T. Gao, Shanghai Cancer Institute, Shanghai, People's Republic of China; N. Gray, Anti-Cancer Council of Victoria, Carlton South, Australia; R. A. Griesemer, Oak Ridge National Laboratory, Oak Ridge, TN; T. Hirayama, National Cancer Center Research Institute, Tokyo, Japan; D. Hoffmann, Naylor Dana Institute for Disease Prevention, Valhalla, NY; J. Jacob, Biochemisches Institut für Umweltcarcinogene, Ahrensburg, Federal Republic of Germany; R. E. Kouri, International Biotechnologies, Inc., New Haven, CT; D. M. DeMarini, US Environmental Protection Agency, Research Triangle Park, NC; A. B. Miller, University of Toronto, Toronto, Ontario, Canada; S. Moolgavkar, The Fred Hutchinson Cancer Research Center, Seattle, WA; N. P. Napalkov (Vice-Chairman), N. N. Petrov Research Institute of Oncology, Leningrad, USSR; R. Peto, Radcliffe Infirmary, Oxford, United Kingdom; J. Pritchard, Atomic Energy Research Establishment, Harwell, Oxon, United Kingdom; M. A. H. Russell, The Maudsley Hospital, London, United Kingdom; J. Samet, University of New Mexico, Albuquerque, NM; M. Sorsa, Institute of Occupational Health, Helsinki, Finland; L. Teppo, Finnish Cancer Registry, Helsinki, Finland; T. C. Tso, United States Department of Agriculture, Beltsville, MD; P. Vineis, Istituto di Anatomia Patologica, Turin, Italy; N. J. Wald, The Medical College of St. Bartholomew's Hospital, London, United Kingdom; M. I. Willems, Institute CIVO-Toxicology and Nutrition, TNO, Zeist, The Netherlands; and E. L. Wynder, American Health Foundation, New York, NY. The representatives

studies relevant to this issue as well as on evidence for the presence of carcinogenic chemicals within tobacco products, evidence from studies in experimental animals, and evidence from mutagenicity and related tests.<sup>3</sup>

Tobacco consumption is a worldwide problem. Although, until recently, attention has been directed primarily towards the carcinogenic effects of tobacco smoking, the recent increase in use in North America and northern Europe of so-called "smokeless" tobacco products (chewing tobacco and snuff used orally) has stimulated investigations into the carcinogenic effects of these forms of tobacco use also. In large areas of the world, tobacco is consumed orally, either alone, in betel quids, with lime, or with other ingredients. In many of these areas, cigarette smoking is also prevalent.

IARC believed that it would be useful if the carcinogenic risks of these various habits were evaluated within the IARC Monographs program. Tobacco smoking had not been evaluated previously because its carcinogenicity to humans was considered established. Adequate information on the carcinogenicity of smokeless tobacco products has become available only recently. Thus, although it was felt that it would be desirable to have more information on certain aspects of the problems related to tobacco consumption, especially for instance from Asia, and to have longer follow up of people who chew tobacco and of people who have smoked so-called "low-tar" filter cigarettes all their smoking lives, IARC felt that it was timely to evaluate carefully and objectively the available evidence on the carcinogenic risks of the use of tobacco products of all kinds. It was also considered important to address specific questions related to tobacco smoking and lung cancer such as the effect of smoking different tobacco products, effect of age at start of smoking, effect of the duration and intensity of smoking including an examination of the use of filter versus nonfilter cigarettes, and the risks for cancers at organs other than the lung. It was hoped that reliable evaluations by international experts on the problem of tobacco consumption would be of global interest not only to scientists but to regulators.

### Tobacco Chewing, Snuff Taking, and Betel-Quid Chewing

Chewing of tobacco or the placing of a quid of tobacco next to the gingiva has been practiced throughout the world ever since tobacco was introduced from the Americas. In the Americas, the practice became particularly widespread during the time

of the National Cancer Institute were: J. Cullen, National Cancer Institute, Bethesda, MD, and C. Harris, National Cancer Institute, Bethesda, MD. Observers at this meeting were: D. Davis, National Academy of Sciences, Washington, DC; N. Haley, Naylor Dana Institute for Disease Prevention, Valhalla, NY; D. Kanazir, Serbian Academy of Sciences and Arts, Belgrade, Yugoslavia; R. Masironi, WHO, Geneva, Switzerland; K. Stanley, WHO, Geneva, Switzerland; and R. Turck, WHO, Copenhagen, Denmark.

<sup>3</sup> The monographs resulting from these meetings will be published before the end of 1985 as Vol. 37 and 38 of the series entitled "Tobacco Habits Other Than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines" and "Tobacco Smoking," respectively. The IARC Monographs program is supported by the National Cancer Institute under Department of Health and Human Services Contract U01 CA33193-04.

of the opening up of the West when the pioneers wished to distinguish themselves from the dandified English and east-coast aristocracy by refusing both the habit of smoking and that of nasal use of snuff.

In Southeast Asia, and particularly in India, the habit of betel-quid chewing had existed long before the introduction of tobacco. The betel quid is traditionally made up of a leaf of the *Piper betle* bush, which is used to wrap a piece of areca nut (the fruit of the *Areca* palm) with a source of lime (calcium carbonate derived from chalk or seashells) and various flavoring agents. The addition of a piece of local, sun-dried tobacco augments the feeling of well-being derived from this combination. The habit of chewing tobacco alone is also widespread, especially in the tobacco-growing states of India.

In North America, however, the use of smokeless tobacco was discouraged from the mid-1850s, as the unhygienic nature of the behavior associated with the habit became recognized; spitting became frowned upon with the sophistication of American society. By the 1920s, when mass production of cigarettes began, tobacco chewing declined even further. However, during the late 1960s and early 1970s, a resurgence in tobacco chewing and oral snuff taking occurred in the United States and it is now popular among young adult males. Smokeless tobacco is being promoted as an alternative to smoking since it does not as yet bear the stigma with regard to health issues that is associated with cigarette smoking. Smokeless tobacco can be used in places where smoking is prohibited and it is purported to be more economical; advertisements claim that a wad of tobacco can be kept "alive" in the mouth for several hours. Smokeless tobacco use is being promoted as a recreational activity, with spitting contests, shirts, and membership clubs; free samples are handed out in universities. Sports personalities, who have used smokeless tobacco products longer than other segments of the population because smoking is considered to be deleterious to the respiratory compensation required, because their hands must be kept free and because spitting adds to their rough-hewn image, are being used to extoll the virtues of these products on television and advertisement hoardings.

In northern Europe and particularly in Sweden and Denmark, smokeless tobacco products have been used especially in rural areas for hundreds of years. These countries also have recently seen a large resurgence of use of these products among young men and a wide variety of forms of both chewing tobacco and snuff are available.

The terms "chewing tobacco" and "snuff" in North America and northern Europe cover a wide variety of products, some of which overlap, so that it is sometimes difficult to distinguish between the two. The difference lies basically in the fineness into which the tobacco is cut. Recently in the United States, there has been a reclassification of products within the two major categories, and some types of fine-cut smokeless tobacco that were classified as chewing tobacco prior to 1981 are now categorized as snuff. Snuff has recently become available in small tea bag-like packets, which are easier to use than the loose product. Chewing tobacco is usually pressed into flat bars or rolls ("plug" or "twist") but may be sold as loose-leaf tobacco consisting of strips of fermented cigar leaf tobacco flavored with sweetening agents. The tobacco chewed in most parts of south-east Asia consists of strips of local sun-cured tobacco.

Smokeless tobacco products are usually held in place between the gum or lower lip and the buccal mucosa, although some forms of chewing tobacco may also be chewed from time to time. The saliva generated is either swallowed or expectorated. In the southern United States, the oral use of snuff is known as "snuff dipping" from the practice of dipping a small stick into snuff and either rubbing it on the gums or chewing it. This term has come to be used generally for oral snuff use in whatever form.

Estimates of the number of users of smokeless tobacco products are available only for the United States, but vary from 7 million to 22 million per yr.

**Evaluation of Carcinogenicity of Smokeless Tobacco.** The overall evaluation of the working group on this subject was that "There is *sufficient evidence* that oral use of smokeless tobacco is carcinogenic to humans." This conclusion is based on a large number of case-control and cohort studies, on evidence for the presence of carcinogenic compounds in tobacco and on some experimental studies.

As mentioned above, it is sometimes difficult to distinguish between chewing tobacco and snuff, and in many of the epidemiological studies considered, the type of smokeless tobacco habit was not specified. A careful evaluation of the epidemiological evidence available to the working group showed that the use of smokeless tobacco products significantly increases the risk of oral cancer, on the basis of the following inferences.

**Consistency and Specificity of the Association.** In reports of series of oral cancer patients, high proportions were users of smokeless tobacco and it was noted that the cancer usually developed at the site at which the product was placed.

**Strength of the Association.** In four case-control studies the oral use of snuff specifically was implicated in the etiology of cancer of the oral cavity and pharynx. In one of the studies, in which relative risks could be computed, a strong dose-response relationship was observed between oral use of snuff and the incidence of oral cancer. Four further case-control studies in which the smokeless tobacco habit was not specified showed moderate to strong associations between the use of such products and incidence of oral cancer.

Three cohort mortality studies also provide evidence of a positive association between use of smokeless tobacco and cancer. In one of the studies, there were 2- to 3-fold increases in the risk of death from oral, pharyngeal, and esophageal cancer; in the second, a 2- to 3-fold increase in esophageal cancer was observed.

**Temporal Relationship of the Association.** The cohort studies showed significant occurrence of cancer among users of smokeless tobacco products over a long follow-up period.

**Coherence of the Association.** As mentioned above, a dose-response relationship has been established between use of smokeless tobacco and oral cancer and this supports the coherence of the association. International surveys have also indicated that the oral cancer incidence seen in India is the highest in the world. Although Indians smoke and chew a variety of substances, cancerous and precancerous lesions are found predominantly among those who use smokeless tobacco. Studies of Indian populations indicate that the oral cancer risk is greater for smokeless tobacco users than for smokers and increases with duration of smokeless tobacco use.

**Histopathological Evidence.** An interesting analysis is given in the monograph of the predictive value for oral cancer of the so-called "precancerous lesion," leukoplakia, and of the "precancerous conditions," submucous fibrosis and lichen planus. In particular, leukoplakia has been found to be highly prevalent in the mouths of users of smokeless tobacco products in the United States, northern Europe, and Asia and usually occurs at the site at which the product is held habitually. This lesion has also been found in conjunction with oral cancer in smokeless tobacco users. Estimates are also given of the rate of malignant transformation of leukoplakia, although the number of studies of this subject is limited.

**Experimental Studies.** These persuasive epidemiological data are supported by a certain number of experimental findings. Thus, smokeless tobacco and the saliva of users of such products have been found to contain relatively high levels of tobacco-related *N*-nitrosamines. These compounds were also evaluated for carcinogenicity by the same working group on the basis of available experimental data. There was found to be sufficient evidence of carcinogenicity in animals for the two that occur most commonly, *N*'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and it was determined that these chemicals should therefore for practical purposes be regarded as if they presented a carcinogenic risk to humans. Polynuclear aromatic hydrocarbons and certain carcinogenic metals have also been detected in smokeless tobacco products.

Results of tests on experimental animals were unfortunately not informative, as all of the studies suffered from deficiencies and could not be evaluated.

Extracts of chewing tobacco are genotoxic, inducing mutations in bacteria and in mammalian cells *in vitro*, micronuclei in mammalian cells *in vivo*, sister chromatid exchanges in cultured human lymphocytes and in a human lymphoblastoid cell line, and transformation of Syrian hamster embryo cells.

## Tobacco Smoking

The IARC monograph on the carcinogenic risk of tobacco smoking prepared by the second working group covers in detail national trends with time in the consumption of cigarettes, cigars, and pipes. Although in a few western countries general recognition of the association between smoking and adverse health effects has resulted in a decrease or leveling off of cigarette smoking, in most countries of the world it is still increasing.

**Lung Cancer.** The working group reviewed all of the major cohort studies on the causal relationship between tobacco smoking and lung cancer. With regard to the type of tobacco product smoked, it was concluded that although cigarettes appear to carry the greatest risk, smoking of *bidis* (the small cigarette smoked widely in India) and of cigars and pipes also results in an increased risk for lung cancer. The attempts made by cigarette manufacturers over the last 20–30 years to reduce the harmful effects of cigarettes by using different blends of tobaccos and by use of various kinds of filter-tips were also evaluated. Even though under standard laboratory conditions the smoke of such cigarettes has reduced yields of tar and nicotine, such conditions cannot reproduce human smoking patterns and it is difficult to estimate the actual intake into the body. In addition, it is thought that some people may try to compensate for the lower levels by inhaling more deeply or by smoking more of these than non-filter cigarettes. It is difficult too to detect their effect on a national

scale, as the harmful effects of smoking accumulate over many years and the risk of developing cancer as a result of smoking depends on both recent and past exposure. Populations who have smoked only the newer cigarettes for a long enough time for the risk of cancer to become evident do not yet exist. However, the working group concluded that the risk of lung cancer associated with the types of cigarettes commonly smoked before the middle 1950s is greater than that for the modified cigarettes with low tar levels now generally available in some countries.

Although the group stressed strongly that the health benefits of the cessation of smoking greatly exceed those to be expected from changes in cigarette composition, it was considered that reductions in tar levels, especially in countries where these are still high, would at least slightly reduce the risk for lung cancer. The risk of lung cancer is also related to the duration of smoking and to the age at which smoking begins. Thus a person who began to smoke during adolescence and continues throughout life has a greater risk of lung cancer than someone who started later in life or someone who stops smoking. Lung cancer risk is also proportional to the number of cigarettes smoked, as confirmed by many studies in different countries.

With a long duration and heavy intensity of cigarette usage, the proportion of lung cancer attributable to smoking is of the order of 90%. This attributable proportion applies to men in most western populations; in populations in which more and more women are smoking cigarettes, the proportion is approaching the same level.

The working group also evaluated the evidence with regard to the histological types of lung cancer that are induced by tobacco smoking. Although the risks of squamous and small cell carcinomas of the lung appear to be increased to a greater extent than that of adenocarcinomas, all three types are caused by tobacco smoking.

The nature of the interaction between smoking and certain occupational risk factors was also examined. The group confirmed that the risk of lung cancer associated with cigarette smoking is increased multiplicatively in conjunction with high-dose exposures to asbestos or to radon daughters.

**Cancers of the Urinary Tract.** A large number of case-control and cohort studies have shown that tobacco smoking, particularly of cigarettes, is an important cause of bladder cancer and cancer of the renal pelvis. The proportion of these diseases attributable to smoking in most countries where there has been a long history of cigarette usage is of the order of 50% for men and 25% for women. The relationships of the risk with duration and intensity of smoking are similar to those for lung cancer, although the risks are somewhat lower.

**Other Cancers.** The working group also concluded that tobacco smoking is an important cause of oral, oropharyngeal, hypopharyngeal, laryngeal, and esophageal cancers. Pipe and/or cigar smoking appears to increase the risk of these cancers to approximately the same extent as cigarette smoking. The risks of these cancers in relation to cigarette smoking are substantially increased in people exposed to high doses of alcohol. Tobacco smokers also appear to have an increased risk for cancer of the lip. Cigarette smoking is a cause of pancreatic cancer. The working group also considered evidence on the relationship of tobacco smoking to cancers of the stomach, liver, cervix, endometrium, and breast, but the studies were inadequate.

quate or showed no effect (in the case of endometrial and breast cancers).

**Passive Smoking.** The available information on the carcinogenic effects of exposure to tobacco smoke from other people is still extremely limited. Passive smokers are exposed to relatively smaller amounts of the carcinogenic compounds present in smoke and the effects are unlikely to be detectable unless exposure is substantial and very large numbers of people are observed. The observations on nonsmokers that have been made so far are compatible either with an increased risk from passive smoking or with an absence of risk. Knowledge of the nature of the smoke components to which passive smokers are exposed, of those that are actually absorbed by passive smokers, and of the quantitative relationships between dose and effect that are commonly observed with exposure to carcinogens was considered to justify the conclusion that passive smoking gives rise to some risk of cancer.

**Experimental Data.** The IARC monograph of the findings of this working group contains a detailed description of the chemical composition of tobacco smoke. Mainstream smoke (that taken in by the smoker) differs in composition from sidestream smoke (that given off by the burning cigarette). Both contain chemicals that are carcinogenic, but sidestream smoke appears to contain greater amounts. Although no single carcinogenic factor in tobacco smoke can be pinpointed, those present include *N*-nitroso compounds, polynuclear aromatic compounds, aromatic amines, and some metals. The possibility of endogenous formation of *N*-nitroso compounds is raised by the presence in tobacco smoke of large quantities of the necessary precursors, amines and nitrogen oxides.

In an attempt to provide information useful for quantification of dose and for determining what components of tobacco smoke actually are absorbed in the human body, the working group examined studies on inhalation patterns and on physiological reactions to smoke. Tabulations of the doses of tar, nicotine, and carbon monoxide for different smoking patterns are given in the resulting monograph.

The greatest difficulty in trying to reproduce the carcinogenic effect of tobacco smoking in experimental animals has been that the structure of the rodent respiratory tract differs considerably from that of humans. Rodents are obligatory nose breathers and the pattern of distribution of smoke components is quite different. This difficulty is compounded by the fact that machine smoking of cigarettes also cannot faithfully reproduce human smoking patterns. Tobacco smoking is thus a prime example of a carcinogenic exposure that can be tested to only a limited degree in experimental animals. Nevertheless a large number of studies have been able to show that exposure of hamsters and of rats

to tobacco smoke by inhalation results in the induction of malignant tumors of the respiratory tract.

In an effort to by-pass the problems outlined above, tests have been carried out using cigarette-smoke condensate. Application to the skin of mice and rabbits resulted in skin tumors, and intrapulmonary injection of such condensate to rats induced lung cancers.

Both tobacco smoke and smoke condensate are highly mutagenic in various test systems; they also cause chromosomal damage and the condensate induces neoplastic transformation in mammalian cells *in vitro*. In comparisons of smokers and nonsmokers, the urine of smokers was found to be mutagenic and somatic cells of smokers were found to have more chromosomal damage than those of nonsmokers.

## Conclusions

One of the main aims of IARC and of the Monographs program is to provide data relevant to the prevention of cancer. The two working groups which examined in detail the available data on smokeless tobacco use, betel-quid chewing, and tobacco smoking were able to evaluate all aspects of the problem of tobacco consumption with regard to cancer on an international scale.

All forms of tobacco use have been shown to be associated with increased frequency of cancer. The use of smokeless tobacco is causally associated with cancer of the oral cavity and with cancers of the upper respiratory tract and upper digestive tracts. Tobacco smoking is causally associated with cancers of the lung, bladder, renal pelvis, oral cavity, upper respiratory and digestive tracts, and pancreas.

The accompanying analyses of trends and modalities of induction of cancers associated with the consumption of tobacco in all forms point firmly to the conclusion that the only way in which the cancer risk linked to tobacco can be eliminated completely is not for people to change from one type of consumption to another but for them to stop using tobacco in any form or, better still, never to start.

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