

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Smoking of tobacco is practised worldwide by over one thousand million people. However, while smoking prevalence has declined in many developed countries, it remains high in others and is increasing among women and in developing countries. Between one-fifth and two-thirds of men in most populations smoke. Women's smoking rates vary more widely but rarely equal male rates.

Tobacco is most commonly smoked as cigarettes, both manufactured — which are a highly sophisticated nicotine-delivery system — and hand-rolled. Pipes, cigars, bidis and other products are used to a lesser extent or predominantly in particular regions. Cigarettes are made from fine-cut tobaccos which are wrapped in paper or a maize leaf. Cigars consist of cut tobacco filler formed in a binder leaf and with a wrapper leaf rolled spirally around the bunch. Bidis contain shredded tobacco wrapped in non-tobacco leaves, usually dried *temburni* leaves.

The chemical composition of tobacco smoke, although influenced by the specific manner in which individuals smoke, is primarily determined by the type of tobacco. It is also influenced by the design of the smoking device or product and, for cigarettes, by the presence or absence of filters, and by other factors including ventilation, paper porosity and types of additives. As a result, concentrations of individual chemicals in smoke vary. Analysis of the ways in which people smoke modern cigarettes shows that actual doses of nicotine, carcinogens and toxins depend on the intensity and method of smoking and have little relation to stated tar yields. The total volume of smoke drawn from cigarettes as a result of specific smoking patterns is the principal determinant of dose to the smoker. All presently available tobacco products that are smoked deliver substantial amounts of established carcinogens to their users.

The yields of tar, nicotine and carbon monoxide from cigarettes, as measured by standard machine-smoking tests, have fallen over recent decades in cigarettes sold in most parts of the world, but have remained higher in some countries. The tar and nicotine yields as currently measured are misleading and have only little value in the assessment of human exposure to carcinogens.

The regulation of smoking and smoke yields varies widely around the world in scope and degree of enforcement. Certain regulatory actions, such as taxes and workplace smoking bans, are effective in reducing smoking rates and protecting nonsmokers.

## 5.2 Human carcinogenicity data

In the previous 1986 *IARC Monograph* on tobacco smoking, cancers of the lung, oral cavity, pharynx, larynx, oesophagus (squamous-cell carcinoma), pancreas, urinary bladder and renal pelvis were identified as caused by cigarette smoking. Many more studies published since this earlier monograph support these causal links. In addition, there is now sufficient evidence for a causal association between cigarette smoking and cancers of the nasal cavities and nasal sinuses, oesophagus (adenocarcinoma), stomach, liver, kidney (renal-cell carcinoma), uterine cervix and myeloid leukaemia.

In cancer sites that were causally linked to cigarette smoking in the previous *IARC Monograph* on tobacco smoking, the observed relative risks ranged generally from approximately 3 for pancreatic cancer to more than 20 for lung cancer. For those cancer sites that were now also linked to cigarette smoking in this monograph, generally two- to threefold increased risks were observed.

### Cigarettes

#### *Lung*

Lung cancer is the most common cause of death from cancer in the world. The total number of cases is now estimated to be 1.2 million annually and is still increasing. The major cause of lung cancer is tobacco smoking, primarily of cigarettes. In populations with prolonged cigarette use, the proportion of lung cancer cases attributable to cigarette smoking has reached 90%.

The duration of smoking is the strongest determinant of lung cancer in smokers. Hence, the earlier the age of starting and the longer the continuation of smoking in adulthood, the greater the risk. Risk of lung cancer also increases in proportion to the numbers of cigarettes smoked.

Tobacco smoking increases the risk of all histological types of lung cancer including squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma (including bronchiolar/alveolar carcinoma) and large-cell carcinoma. The association between adenocarcinoma of the lung and smoking has become stronger over time. The carcinogenic effects of cigarette smoking appear similar in both women and men.

Stopping smoking at any age avoids the further increase in risk of lung cancer incurred by continued smoking. The younger the age at cessation, the greater the benefit.

#### *Urinary tract*

Tobacco smoking is a major cause of transitional-cell carcinomas of the bladder, ureter and renal pelvis. Risk increases with the duration of smoking and number of cigarettes smoked. As for lung cancer, stopping smoking at any age avoids the further increase in risk incurred by continued smoking.

Evidence from several cohort and case-control studies published since the previous *IARC Monograph* on tobacco smoking has indicated that renal-cell carcinoma is associated with tobacco smoking in both men and women. The association is not explained by

confounding. A dose–response relationship with the number of cigarettes smoked has been noted in most studies, and a few also noted a reduction in risk after cessation.

#### *Oral cavity*

Tobacco smoking, including cigarette smoking, is causally associated with cancer of the oral cavity (including lip and tongue) in both men and women. Since the previous *IARC Monograph* on tobacco smoking, evidence from many more studies has accumulated that further confirms this association. Use of smokeless tobacco and/or alcohol in combination with tobacco smoking greatly increases the risk of oral cancer. Risk increases substantially with duration of smoking and number of cigarettes smoked. Risk among former smokers is consistently lower than among current smokers and there is a trend of decreasing risk with increasing number of years since quitting.

#### *Nasal cavity and paranasal sinuses*

An increased risk of sinonasal cancer among cigarette smokers has been reported in all nine case–control studies for which results are available. Of seven studies that have analysed dose–response relationships, a positive trend was found in five and was suggested in the other two. In all the five studies that have analysed squamous-cell carcinoma and adenocarcinoma separately, the relative risk was clearly increased for squamous-cell carcinoma.

#### *Nasopharynx*

An increased risk for nasopharyngeal cancer among cigarette smokers was reported in one cohort study and nine case–control studies. Increased relative risks were reported in both high- and low-risk geographical regions for nasopharyngeal cancer. A dose–response relationship was detected with either duration or amount of smoking. A reduction in risk after quitting was also detected. The potential confounding effect of infection with Epstein–Barr virus was not controlled for in these studies; however, such an effect was not considered to be plausible. No important role was shown for other potential confounders.

#### *Oropharynx and hypopharynx*

Oropharyngeal and hypopharyngeal cancer are causally associated with cigarette smoking. The risk increased with increased duration of smoking and daily cigarette consumption and decreased with increasing time since quitting.

#### *Oesophagus*

Tobacco smoking is causally associated with cancer of the oesophagus, particularly squamous-cell carcinoma. Tobacco smoking is also causally associated with adenocarcinoma of the oesophagus. In most of the epidemiological studies, the risk for all types of oesophageal cancer increased with numbers of cigarettes smoked daily and duration of smoking. However, risk for oesophageal cancer remains elevated many years after cessation of smoking.

Tobacco and alcohol in combination with tobacco smoking greatly increase the risk for squamous-cell carcinoma of the oesophagus. In India, use of smokeless tobacco in combination with smoking also greatly increases the risk.

### *Larynx*

Laryngeal cancer is causally associated with cigarette smoking. The risk increases substantially with duration and number of cigarettes smoked. Use of alcohol in combination with tobacco smoking greatly increases the risk for laryngeal cancer. A few studies also reported that relative risks for cancer of the larynx increased with decreasing age at start of smoking. The relative risk decreased with increasing time since quitting smoking.

### *Pancreas*

Cancer of the pancreas is causally associated with cigarette smoking. The risk increases with duration of smoking and number of cigarettes smoked daily. The risk remains elevated after allowing for potential confounding factors such as alcohol consumption. The relative risk decreased with increasing time since quitting smoking.

### *Stomach*

The data available in 1986 did not permit the earlier IARC Working Group to conclude that the association between tobacco smoking and stomach cancer was causal. Since that time, further studies have shown a consistent association of cancer of the stomach with cigarette smoking in both men and women in many cohort and case-control studies conducted in various parts of the world. Confounding by other factors (e.g. alcohol consumption, *Helicobacter pylori* infection and dietary factors) can be reasonably ruled out. Risk increases with duration of smoking and number of cigarettes smoked, and decreases with increasing duration of successful quitting. In studies that had adequate numbers, the relative risks for men and women were similar.

### *Liver*

In the previous *IARC Monograph* on tobacco smoking, a causal relationship between liver cancer and smoking could not be established, chiefly due to possible confounding from alcohol intake and hepatitis B and hepatitis C virus infections. Many cohort studies and case-control studies have provided additional information on smoking and liver cancer since then. Most of the cohort studies and the largest case-control studies (most notably those that included community controls) showed a moderate association between tobacco smoking and risk of liver cancer. In many studies, the risk for liver cancer increased with the duration of smoking or the number of cigarettes smoked daily. Former smokers who had stopped smoking for more than 10 years showed a decline in liver cancer risk. Confounding from alcohol can be ruled out, at least in the best case-control studies, by means of careful adjustment for drinking habits. An association with smoking has also been demonstrated among non-drinkers. Many studies, most notably from Asia, have shown no attenuation of the association between smoking and liver cancer after adjustment/strati-

fication for markers of hepatitis B/hepatitis C virus infection. There is now sufficient evidence to judge the association between tobacco smoking and liver cancer as causal.

### *Cervix*

An association of invasive cervical squamous-cell carcinoma with smoking has been observed in the large number of studies reviewed. The most recent studies have controlled for infection with human papillomavirus, a known cause of cervical cancer. The effect of smoking was not diminished by the adjustment for human papillomavirus infection, or analysis restricted to cases and controls both positive for human papillomavirus (as ascertained by human papillomavirus DNA or human papillomavirus serological methods). There is now sufficient evidence to establish a causal association of squamous-cell cervical carcinoma with smoking. In the small number of studies available for adeno- and adeno-squamous-cell carcinoma, no consistent association was observed.

### *Leukaemia*

Myeloid leukaemia in adults was observed to be causally related to smoking. Risk increased with amount of tobacco smoked in a substantial number of adequate studies. No clear evidence of any risk was seen for lymphoid leukaemia/lymphoma.

Support for a causal relationship of smoking with myeloid leukaemia is provided by the finding of known leukaemogens in tobacco smoke, one of which (benzene) is present in sufficient amounts to account for up to half of the estimated excess of acute myeloid leukaemia.

### *Colorectal cancer*

There is some evidence from prospective cohort studies and case-control studies that the risk of colorectal cancer is increased among tobacco smokers. However, it is not possible to conclude that the association between tobacco smoking and colorectal cancer is causal. Inadequate adjustment for various potential confounders could account for some of the small increase in risk that appears to be associated with smoking.

### *Female breast*

Most epidemiological studies have found no association with active smoking, after controlling for established risk factors (e.g. age at time of first birth, parity, family history of breast cancer and alcohol). The large multicentre pooled analysis of the association of smoking with breast cancer in non-drinkers confirms the lack of an increased risk of breast cancer associated with smoking.

### *Endometrium*

Cigarette smoking is not associated with an increased risk for endometrial cancer.

An inverse relationship of cigarette smoking with endometrial cancer is observed consistently in most case-control and cohort studies, after adjustment for major confounders. This pattern is stronger in post-menopausal women.

### *Prostate*

No clear evidence of any risk for prostate cancer is seen in case-control studies or in studies of incident cases in cohort studies. The small excess observed in some analytical mortality studies can reasonably be explained by bias in the attribution of the underlying cause of death.

### *Other*

There is inconsistent and/or sparse evidence for association between cigarette smoking and other cancer sites that were considered by the Working Group.

## **Cigars and pipes**

Cigar and/or pipe smoking is strongly related to cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus, the magnitude of risk being similar to that from cigarette smoking. These risks increase with the amount of cigar and/or pipe smoking and with the combination of alcohol and tobacco consumption. Cigar and/or pipe smoking is causally associated with cancer of the lung and there is evidence that cigar and/or pipe smoking are also causally associated with cancers of the pancreas, stomach and urinary bladder.

## **Bidi**

Bidi smoking is the most common form of tobacco smoking in India and is also prevalent in other south-Asian countries and an emerging problem in the USA. Bidi smoke was considered as carcinogenic in the earlier *IARC Monograph* on tobacco smoking, and later studies have provided further evidence of causality. Case-control studies demonstrated a strong association at various sites: oral cavity (including subsites), pharynx, larynx, oesophagus, lung and stomach. Almost all studies show significant trends with duration of bidi smoking and number of bidis smoked.

## **Synergy**

For public health purposes, synergy should be characterized as a positive departure from additivity. The epidemiological literature often inadequately describes combined effects of smoking with co-exposures to other carcinogenic agents and in many studies power is limited for characterizing combined effects. The issue of synergistic effects can be appropriately addressed by epidemiological studies that show stratified analysis and have sufficient power. The studies reviewed found evidence of synergy between smoking and several occupational causes of lung cancer (arsenic, asbestos and radon), and between smoking and alcohol consumption for cancers of the oral cavity, pharynx, larynx and oesophagus and between smoking and human papillomavirus infection for cancer of the cervix. Data were inadequate to evaluate the evidence for synergy between smoking and other known causes of cancer (e.g. hepatitis B and alcohol for liver cancer).

### 5.3 Animal carcinogenicity data

Cigarette smoke has been tested for carcinogenicity by inhalation studies in rodents, rabbits and dogs. The model systems for animal exposure to tobacco smoke do not fully simulate human exposure to tobacco smoke, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of tobacco smoke.

The most compelling evidence for a positive carcinogenic effect of tobacco smoke in animals is the reproducible increase observed in several studies in the occurrence of laryngeal carcinomas in hamsters exposed to whole tobacco smoke or to its particulate phase. In four of five studies in rats, exposure to whole smoke led to modest increases in the occurrence of malignant and/or benign lung tumours. Similarly, in four of eight studies in mice of varying susceptibility to lung tumour development, exposure to whole smoke led to a modest increase in the frequency of lung adenomas. An increased incidence of lung 'tumours' has also been reported in dogs exposed to tobacco smoke, but it is uncertain whether the histopathological features of the lesions are consistent with malignancy. In hamsters exposed to both cigarette smoke and chemical carcinogens (*N*-nitrosodiethylamine and 7,12-dimethylbenz[*a*]anthracene), the tumour response in the respiratory tract was higher than in hamsters exposed to either agent alone. The same is true in rats exposed simultaneously to cigarette smoke and radionuclides (radon progeny and plutonium oxide).

Cigarette smoke condensate both initiates and promotes tumour development in animals. It reproducibly induces both benign and malignant skin tumours in mice following topical application. Similarly, it produces skin tumours in rabbits following topical application. Topical application to the oral mucosa also produced an increased incidence of lung tumours and lymphomas in mice. In rats, cigarette smoke condensate produced lung tumours after intrapulmonary injection. In initiation/promotion assays in mouse skin, a single topical application of cigarette smoke condensate followed by application of croton oil was sufficient to initiate both benign and malignant skin tumours. Smoke condensates of Indian bidi administered to mice by gavage were found to induce tumours in a number of organs. Collectively, these data provide evidence of the carcinogenic effect of mainstream tobacco smoke in experimental animals.

### 5.4 Other relevant data

Causal associations have been clearly established between active smoking and adverse reproductive outcomes and numerous non-neoplastic diseases, including chronic obstructive pulmonary disease and cardiovascular diseases.

Tobacco smoking is addictive, and nicotine has been established as the major addictive constituent of tobacco products. Measurement of the nicotine metabolite, cotinine, in human blood, urine or saliva provides a specific and sensitive test for exposure to tobacco smoke and can be used to distinguish active and passive smokers from nonsmokers.

Active smoking raises the concentrations of carbon monoxide, benzene and volatile organic compounds in exhaled air. The concentrations of urinary metabolites of some important tobacco smoke carcinogens and related compounds are consistently higher in smokers than in nonsmokers. These include metabolites of benzene, a known carcinogen in humans, as well as metabolites of several carcinogens that cause lung tumours in rodents. Covalent binding to blood proteins by carcinogens present in tobacco smoke has been demonstrated to occur at significantly higher levels in smokers than in nonsmokers. The adducts are derived from various compounds including aromatic amines (e.g. 4-aminobiphenyl), polycyclic aromatic hydrocarbons (e.g. benzo[*a*]pyrene), tobacco-specific nitrosamines (e.g. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), benzene, acrylamide and acrylonitrile.

Smoking-related DNA adducts have been detected by a variety of analytical methods in the respiratory tract, urinary bladder, cervix and other tissues. In many studies the levels of carcinogen–DNA adducts have been shown to be higher in tissues of smokers than in tissues of nonsmokers. Some but not all studies have demonstrated elevated levels of these adducts in the peripheral blood and in full-term placenta. Smoking-related adducts have also been detected in cardiovascular tissues. Collectively, the available biomarker data provide convincing evidence that carcinogen uptake, activation and binding to cellular macromolecules, including DNA, are higher in smokers than in nonsmokers.

The exposure of experimental animals, primarily rodents, to mainstream tobacco smoke results in a number of biological effects that include (i) increases or decreases in the activities of phase I and phase II enzymes involved in carcinogen metabolism, (ii) increases in the activation of antioxidant enzymes, (iii) increased expression of nitric oxide synthase and of various protein kinases and collagenase, (iv) the formation of tobacco smoke-related DNA adducts in several tissues and (v) reduced clearance of particulate material from the lung.

Smoking is known to have inhibitory or inducing effects on the activities of many enzymes in human tissues. These include xenobiotic metabolizing enzymes, which affect drug and carcinogen metabolism. Numerous studies have reported effects on enzymes in cells treated in culture with tobacco smoke or tobacco smoke condensates.

In humans, smoking produces gene mutations and chromosomal abnormalities. Urine from smokers is mutagenic. Relative to nonsmokers, lung tumours of smokers contain higher frequencies of *TP53* and *KRAS* mutations, and the spectrum of mutations has unique features. Most of the genetic effects seen in smokers are also observed in cultured cells or in experimental animals exposed to tobacco smoke or smoke condensate. Tobacco smoke is genotoxic in humans and in experimental animals.



## 5.5 Evaluation

There is *sufficient evidence* in humans that tobacco smoking causes cancer of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, oesophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia).

There is *evidence suggesting lack of carcinogenicity* of tobacco smoking in humans for cancers of the female breast and endometrium.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tobacco smoke and tobacco smoke condensates.

### Overall evaluation

Tobacco smoking and tobacco smoke *are carcinogenic to humans (Group 1)*.