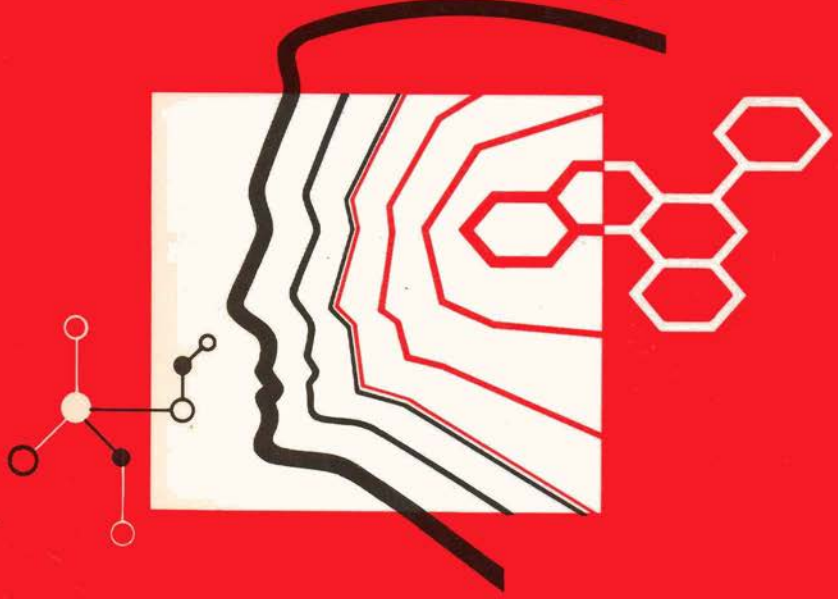
IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

Environmental Health Criteria 211

Health Effects of Interactions between Tobacco Use and Exposure to other Agents



IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

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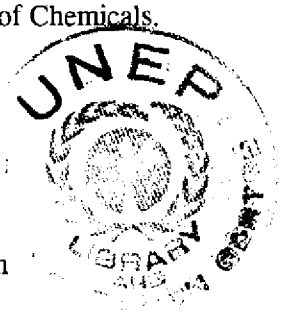
Environmental Health Criteria 211

HEALTH EFFECTS OF INTERACTIONS BETWEEN TOBACCO USE AND EXPOSURE TO OTHER AGENTS

First draft prepared by Dr K. Rothwell, Knaresborough, Yorkshire, United Kingdom

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization
Geneva, 1999

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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CONTENTS

HEALTH EFFECTS OF INTERACTIONS BETWEEN TOBACCO USE AND EXPOSURE TO OTHER AGENTS

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 – 9799111, fax no. + 41 22 – 7973460, E-mail irptc@unep.ch).

* * *

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Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully

recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or

standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary — a review of the salient facts and the risk evaluation of the chemical
- Identity — physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

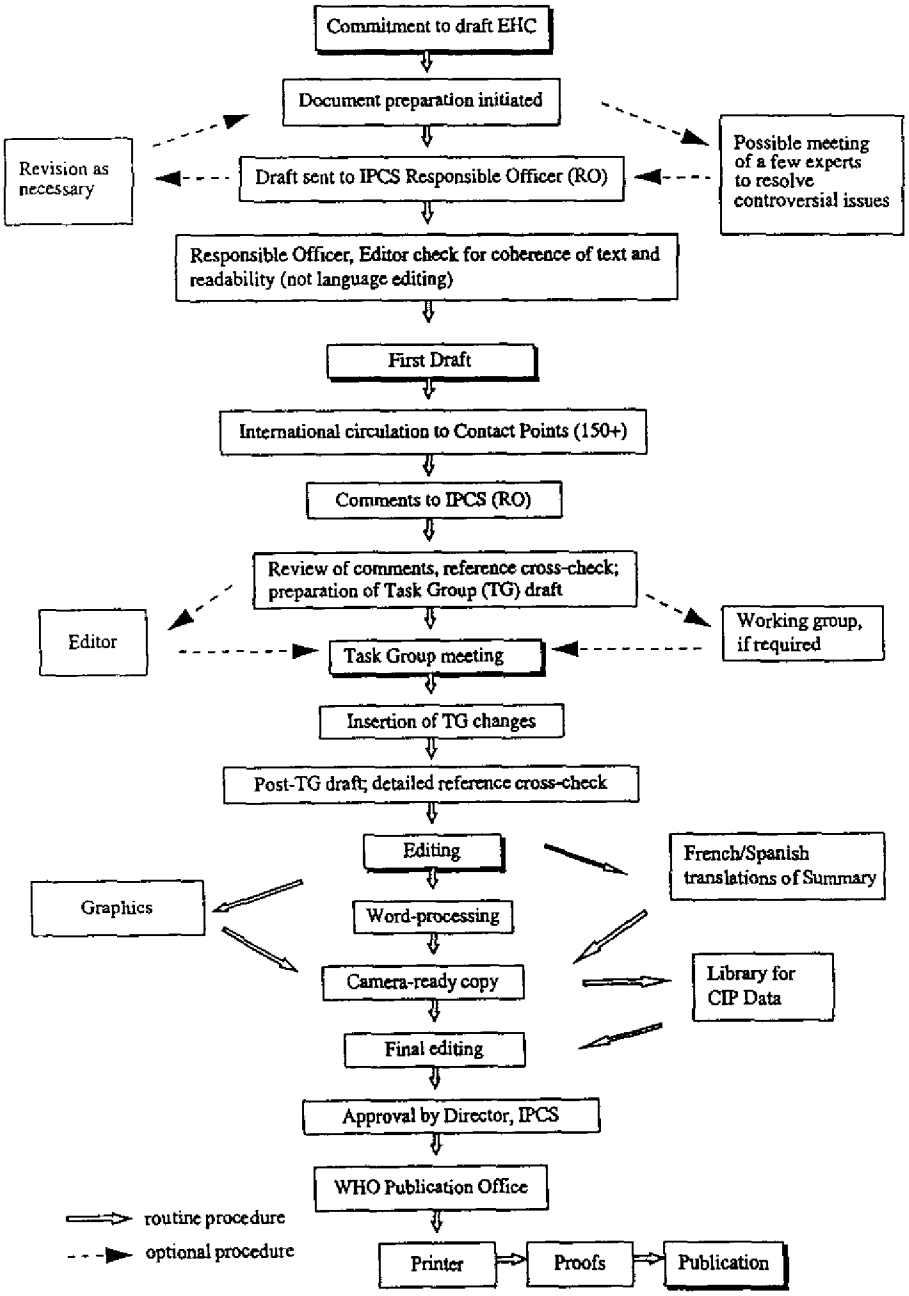
Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

EHC PREPARATION FLOW CHART



The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO WORKING GROUP ON HEALTH RISKS FROM THE COMBINED EFFECTS OF TOBACCO SMOKING AND EXPOSURE TO OTHER CHEMICALS

(Geneva, 25–26 April 1966)

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WHO TASK GROUP ON HEALTH EFFECTS OF INTERACTIONS BETWEEN TOBACCO USE AND EXPOSURE TO OTHER AGENTS

(Geneva, 18–21 February 1997)

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HEALTH EFFECTS OF INTERACTIONS BETWEEN TOBACCO USE AND EXPOSURE TO OTHER AGENTS

A WHO Task Group on Health Effects of Interactions Between Tobacco Use and Exposure to Other Agents met at the World Health Organization, Geneva, from 18 to 21 February 1997. Dr E. Smith, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director IPCS, and the cooperating organizations. The Task Group reviewed and revised the draft monograph and developed a new text.

The first draft of the monograph was prepared by Dr K. Rothwell, Knaresborough, Yorkshire, United Kingdom. This draft was further developed by a Working Group held in WHO, Geneva, 25–26 April 1996, and then circulated for international comment to IPCS contact points for *Environmental Health Criteria* monographs. Comments were incorporated in a second draft prepared by Dr K. Rothwell. This draft was reviewed at the Task Group meeting and a text given further limited circulation to Task Group members and a number of other experts, including the US EPA National Center for Environmental Assessment under the coordination of Dr D. Mukerjee, for final comment. In the development of the monograph, contributions were made by a number of authors listed below.

Dr E. Smith (IPCS Unit for the Assessment of Risk and Methods) was responsible for the scientific content of the monograph and Dr P.G. Jenkins (IPCS Central Unit) for the technical editing.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

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The IPCS expresses its gratitude to the external reviewers who provided comments and other relevant material, in particular the United Kingdom Department of Health, London, and the US Environmental Protection Agency's Office of Research and Development, National Center for Environmental Assessment, Cincinnati, Ohio, USA.

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ABBREVIATIONS

BCME	bis(chloromethyl) ether
CMME	chloromethyl methyl ether
COLD	chronic obstructive lung disease
CHD	coronary heart disease
CVD	cardiovascular disease
ERR	excess relative risk
FIV_1	forced expiratory volume (1 second)
IARC	International Agency for Research on Cancer
LET	linear energy transfer
MMAD	mass median aerodynamic diameter
NO_x	nitrogen oxides
SAD	small airways disease
TSNA	tobacco-specific nitroasamines
URT	upper respiratory tract

1. OVERVIEW

1.1 Introduction

Tobacco use, particularly smoking, causes a range of adverse health effects, is directly implicated in a number of serious diseases, and can increase adverse effects of other chemical, physical and biological agents. Chemicals and other agents in workplaces can cause, if not controlled, disease, incapacity and early death. In the workplace it is clear that adverse effects can be produced by the synergistic interaction of tobacco smoking and other hazards. The majority of interactions of harmful tobacco smoke constituents with toxic chemicals occur when the latter are airborne, although interactions of smoking with ingested and/or absorbed harmful agents have also been reported.

Tobacco use is widespread throughout the world, from countries with low income economies to the most affluent industrialized nations. Tobacco is used by men and women, by children and adults, and millions of people are involuntarily subjected to environmental tobacco smoke. There are numerous explanations for the tobacco habit but the main reason for its ubiquity is the addictive drug nicotine present in all forms of tobacco leaf and delivered in varying amounts to the user by the various methods of tobacco use (chapter 2). The advent of the cigarette, mass produced, easily obtainable, relatively cheap and light in weight, so it can be held in the mouth leaving the hands free, has had a major impact on smoking habits, in general and in workplaces.

In many countries tobacco smoking is recognized as a serious health hazard and a major contributing factor to deaths from a number of common diseases. In these countries health warning legislation and measures to control consumption by taxation have been implemented, as well as public education programmes on the dangers of smoking and the benefits to be gained from not starting or from stopping. However, there are still countries where decisive action has yet to be taken to deal with the problem of tobacco use.

Many work situations involve an element of risk. The nature of the work may generate harmful effects on health, and working

activities may cause environmental contamination. Tobacco growing itself involves the use of pesticides, harvesting of tobacco leaf can cause sickness due to skin absorption of nicotine, and processing exposes workers to health hazards from airborne dust and fungal spores. A high male cancer incidence has been reported in areas with tobacco industries. In mining there are airborne mineral dusts and, in farming and industries using biologically produced raw materials, biological dusts are found. Fumes are produced during welding, and gases, smokes, mists and vapours containing inorganic and/or organic toxic substances present hazards in many industries. Excessive heat or exposure to ultraviolet light can be detrimental to the well-being of workers. Ionizing radiation in mining and modern technology is recognized as a workplace hazard. In many occupations workers are subjected to excessive noise or harmful mechanical vibration. Working conditions can impact adversely on health to a greater extent in smokers than non-smokers. In many countries, smoking at the workplace is prohibited, primarily for reasons of fire/explosion safety. However, in some countries, regulations are not always enforced. In some newly industrializing countries health problems associated with work have not yet been fully addressed and many employers and workers are ignorant of the dangers to health of their occupations. In addition, there is the large "informal sector" of industry, particularly in developing countries, where the home is the workplace, chemicals are used (including solvents, resins, and synthetic dyestuffs), the whole family is exposed, and there are no restrictions on exposure to work hazards or smoking.

The situation for adverse health effects resulting from combined exposure to tobacco smoke, mainstream or environmental, and agents in the domestic environment is much less defined. However, the incidence of lung cancer and the concentration of radon in homes has a similar dose–response to lung cancer and radon in mines, and the risk is higher in smokers.

1.2 Examples of combined effects of tobacco smoking and other exposures

There is evidence for synergism in the production of adverse effects (cancer) between tobacco smoking and exposure to arsenic, asbestos, ethanol, silica and radiation (radon, atomic bomb, X-ray). On

the other hand there is evidence for antagonism in the case of tobacco smoking and the carcinogenic chloromethyl ethers, i.e. chloromethyl methyl ether (CMME) and bis(chloromethyl) ether (BCME) (Hoffmann & Wynder, 1976; IARC, 1986), tobacco smoking and allergic alveolitis, and tobacco smoking and chronic beryllium disease. Tobacco smoking affects the health risks of exposures in coal mining, pesticide handling, and in the rubber and petroleum industries. Coal miners who smoke are at greater risk of developing chronic bronchitis and obstructive airway disease but not emphysema. Lung cancer in coal miners has been attributed entirely to tobacco smoking. Tobacco smoking can increase the health risks of exposure to vegetable dusts that produce chronic respiratory conditions, such as byssinosis produced by cotton dust, and nasal cancer caused by wood dusts.

1.3 Composition of tobacco leaf and tobacco smoke

More than 3040 chemical compounds have been isolated from processed tobacco leaf (Roberts, 1988). Most are leaf constituents, but some arise from growing conditions such as the soil and atmosphere in an area, while others originate from the use of agricultural chemicals, from casings, humectants and flavourings added to the leaves, and from curing methods. Different tobacco varieties grown in different countries, and cured and processed in various ways show differences. The proportions of individual constituents may differ but not the overall composition. Among important toxic compounds identified, other than nicotine, are carcinogenic nitrosamines, derived from nitrites, amines, proteins and alkaloids present in the leaf, polycyclic aromatic hydrocarbons resulting from the curing process, radioactive elements absorbed from the soil and the air, and cadmium in tobacco grown on cadmium-rich soils. When tobacco is burned in the course of smoking, many pyrolysis and other reaction products are formed.

1.4 Mainstream tobacco smoke

Tobacco smoke is an aerosol consisting of a particulate phase of liquid droplets dispersed in a gas/vapour phase. When a cigarette is smoked, many compounds are formed by pyrolysis of the tobacco. These either pass through the cigarette as mainstream smoke, some being condensed a short distance behind the burning cone, or they are

emitted into the air from the burning end as sidestream smoke. With each puff the smoke becomes progressively stronger because previously condensed material is added to the smoke and the length of cigarette available for further condensation is decreasing. The physicochemical nature of the smoke depends on the processing and burning of the tobacco, the porosity and treatment of the paper wrapper, and on the type of filter tip (Hoffmann & Hoffmann, 1997). In the case of a cigarette or Asian "bidi" (tobacco wrapped in vegetable leaf), the smoke chemistry is affected by such factors as dimensions, wrapper porosity and the smoking parameters of puff volume, frequency and duration (NIH, 1998). Variations in smoke chemistry are mainly in the balance of smoke constituents rather than the presence or absence of particular compounds.

Mainstream smoke is generated in a comparatively low-oxygen atmosphere at a burning temperature of 850–950 °C in the fire cone. Initially, mainstream smoke particles have a mass median aerodynamic diameter (MMAD) of 0.2 to 0.3 μm; however, as soon as they encounter the 100% humidity of the respiratory tract, they coalesce into larger particles and behave as if their MMAD was in the micrometre range. Between 50 and 90% of all inhaled particulate matter may be retained in the respiratory tract (Wynder & Hoffmann, 1967; Hinds et al., 1983). From size considerations, the aerosol particulate matter, the vapour phase constituents and the permanent gases are capable of reaching the alveoli when smoke is inhaled. Deposition in the tracheobronchial tree is complicated by the behaviour of hydrophilic constituents in the high humidity conditions, but smoke reaches every part of the airways.

Mainstream smoke contains nearly 4000 identified chemicals and an unknown number of unidentified chemicals (Roberts, 1988). Mainstream smoke can be divided into particulate and gas phases. Mainstream smoke particulate phase contains nicotine, nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN), metals such as cadmium, nickel, zinc and polonium-210, polycyclic hydrocarbons, and carcinogenic amines, such as 4-aminobiphenyl. The vapour phase contains carbon monoxide, carbon dioxide, benzene, ammonia, formaldehyde, hydrogen cyanide, *N*-nitrosodimethylamine, *N*-nitrosodiethylamine and other compounds. Compounds in tobacco smoke can be classified

by their biological activity as asphyxiants, irritants, ciliatoxins, mutagens, carcinogens, enzyme inhibitors, neurotoxins or pharmacologically active compounds. The main point of entry of cigarette smoke into the body is via the airways, but many constituents, particularly from pipe and cigar smoke, dissolve in saliva and are absorbed in the buccal cavity or are swallowed. Cigar and pipe smokers generally do not inhale the smoke and it remains in the oral cavity, is dissolved in the saliva and absorbed through the mucous membranes or swallowed (NIH, 1998). Alcoholic drinks have a solvent effect for the smoke constituents facilitating their absorption.

1.5 Sidestream tobacco smoke

Sidestream smoke is generated at lower burning temperature (500–600 °C) in a reducing atmosphere. Fresh sidestream smoke particles are about the same size as mainstream smoke particles with a mass median aerodynamic diameter (MMAD) of approximately 0.2 μm. Qualitatively, sidestream smoke composition is similar to the composition of mainstream smoke. Some chemicals in sidestream smoke are emitted at higher concentrations per gram of tobacco burned than in mainstream smoke. This is particularly so for carcinogens such as *N*-nitrosodimethylamine and *N*-nitrosodiethylamine, and for metals such as nickel or cadmium. Many carcinogenic compounds are more concentrated in sidestream than in mainstream smoke. Mouse skin-painting bioassays have shown that condensate of sidestream smoke is more carcinogenic than that of mainstream smoke (Wynder & Hoffmann, 1967; US Surgeon General, 1986; NIH, 1998).

1.6 Effects of ways of cigarette smoking on smoke toxicity

The nicotine content of different cigarettes varies, and the smoker adjusts the smoking intensity and depth of inhalation to satisfy the acquired nicotine need. Consequently, the smoker of a filter cigarette with a low nicotine yield (<1.2 mg) smokes more intensively and this influences toxicity (NIH, 1998).

1.7 Summary of conclusions and recommendations

Tobacco use, particularly smoking, is a most important public health hazard and a major preventable cause of morbidity and mortality. In addition to the adverse health effects of active tobacco use, adverse health effects have been demonstrated to result from exposure to environmental tobacco smoke. The risks from tobacco smoking are also increased through interactions with certain chemical, physical and biological hazards found in the workplace and general environment. There are a few instances of antagonistic interactions, but the health risks of tobacco smoke far outweigh any apparent protective effects.

All possible measures should be taken to eliminate tobacco use, particularly smoking, and smoking in public places should be strongly discouraged. To avoid interaction with occupational exposures and to eliminate the risk of exposure to environmental tobacco smoke, smoking in the workplace should be prohibited.

To protect health, in particular that of children, smoking in domestic environments should be strongly discouraged. This will prevent possible harmful interactions between tobacco smoke and residential exposures to other hazards. There is a pressing need for educational programmes on the health hazards of smoking. Health professionals should provide assistance to help smokers quit. Since smoking may result in altered response or adverse reactions to drugs and other treatments, appropriate dose adjustments and patient surveillance should be taken into consideration by clinicians.

2. EXPOSURE TO TOBACCO PRODUCTS AND HEALTH RISKS FROM TOBACCO USE

2.1 Tobacco and its uses

2.1.1 Introduction

The genus *Nicotiana*, a member of the plant family *Solanaceae*, is represented by about 100 species and sub-species (Cromwell, 1955; Tso, 1990) widely distributed throughout the world. The species *N. tabacum* and *N. rustica* are the principal sources of tobacco. The primary intention in using tobacco is to obtain the alkaloid nicotine and, once the habit has been established, nicotine appears to fulfil both a pharmacological and psychological need (US Surgeon General, 1988; NIH, 1998).

Tobacco and its uses were unknown outside America before its discovery by Columbus. In a description of tobacco use in South America at that period, Wilbert (1987) used information from European explorers.

There were six types of tobacco use: chewing, drinking, licking, rectal insertion, nasal and oral snuffing, and smoking. Smoking was by far the most common, while rectal application was only used occasionally. Tobacco smoke was inhaled via the mouth through tubes or rolls of tobacco leaf, or through the nostrils using a Y-shaped tube. Alternatively, it was swallowed and belched back, blown from one person to another, or blown into the eyes. Leaves were chewed, alone or mixed with ash, powdered shells or honey, or they were held in the mouth and sucked. Infusions were drunk or a concentrated infusion was licked or even used as an enema. Many ways of preparing and taking snuff among different tribes were reported. Tobacco use was linked to religious rituals.

The rest of the world adopted tobacco use in the forms of smoking, chewing and snuffing. Smoking has remained the most popular. Tobacco smoking consists of burning the cured leaf, perhaps mixed with fragrant additives, in a pipe or tube. Cigarette smoking has largely replaced other methods in many countries. Reasons for the popularity of cigarettes include their ready availability resulting from

large-scale manufacture and their greater convenience over other forms of tobacco use (IARC, 1986). In developed countries, cigarettes account for at least 80% of overall tobacco consumption, but in most developing countries other ways of using tobacco predominate, although cigarette smoking is increasing. Fig. 1 shows estimated daily cigarette consumption on a regional basis, Tables 1 and 2 show daily smoking prevalences on a regional and national basis and Table 3 shows trends in cigarette consumption.

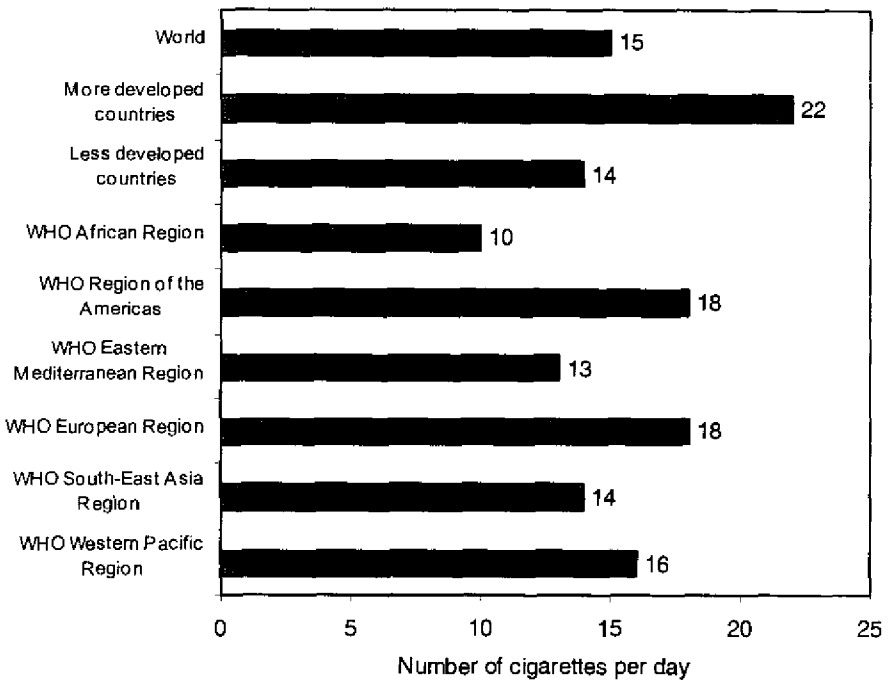

Fig. 1. Number of cigarettes smoked per day per smoker (from WHO, 1997)

2.1.2 Tobacco smoking

Smoking prevalence data and most studies into the effects of smoking have concentrated on cigarette smoking, yet worldwide only about 55% of tobacco is used for cigarettes. The rest, along with

Table 1. Estimated smoking prevalence by WHO Region, early 1990s (from WHO, 1997)

	Men (%)	Women (%)
WHO Regions:		
African Region[a]	29	4
Region of the Americas	35	22
Eastern Mediterranean Region	35	4
European Region	46	26
South-East Asia Region	44	4
Western Pacific Region	60	8
More developed countries	42	24
Less developed countries	48	7
World	47	12

[a] Smoking prevalence estimates for African Region are based on very limited information

significant amounts traded in "farm gate" and "local market" sales or "home grown", is smoked in "bidis" or other hand-rolled devices, or in some form of pipe (IARC, 1986). Tobacco consumption data give an insight into tobacco-related disease distribution, as can information on ways of smoking.

Differences in smoke chemistry occur with different tobacco cultivars and curing methods. Curing removes moisture so that the leaf can be stored without fermenting or rotting, and the time and temperature of curing influences enzyme reactions such as deamination and oxidation, and the content of oils and resins. Air-, flue-, sun-, and fire-curing methods are employed and each produces distinctive tobaccos which are intended for smoking in a specific way or to suit a particular preference.

Between 1933 and the late 1940s, the yields from an average cigarette varied from 33 to 49 mg tar and from < 1 to 3 mg nicotine (Creek et al., 1994). However, in the 1960s and 1970s, the average yield from cigarettes in Western Europe and the USA was around 16 mg tar and 1.5 mg nicotine per cigarette. Current average levels are lower. Changes in the levels of tar and nicotine have resulted in the characteristic more intense puffing and smoke inhalation pattern of smokers of low-yield cigarettes (Djordjevic et al., 1995; NIH, 1996).

Table 2. Estimated smoking prevalence, ranked in order of male smoking prevalence[a]

Rank	Country[b]	Men (%)	Women (%)	Rank	Country	Men (%)	Women (%)
1	Republic of Korea (1989)	68.2	6.7	21	Seychelles (1989)	50.9	10.3
2	Latvia (1993)	67	12	22	Bolivia (1992)	50	21.4
2	Russian Federation (1993)	67	30	23	Albania (1990)	49.8	7.9
4	Dominican Republic (1990)	66.3	13.6	24	Cuba (1990)	49.3	24.5
5	Tonga (1991)	65	14	25	Bulgaria (1989)	49	17
6	Turkey (1988)	63	24	25	Thailand (1995)	49	4
7	China (1984)[c]	61	7	27	Spain (1993)	48	25
8	Bangladesh (1990)	60	15	28	Mauritius (1992)	47.2	3.7
9	Fiji (1988)	59.3	30.6	29	Greece (1994)	46	28
10	Japan (1994)	59	14.8	29	Papua New Guinea (1990)	46	28
11	Sri Lanka (1988)	54.8	0.8	31	Israel (1989)	45	30
12	Algeria (1980)	53	10	32	Cook Islands (1988)	44	26
12	Indonesia (1986)	53	4	33	Czech Republic (1994)	43	31
12	Samoa (1994)	53	18.6	33	Jamaica (1990)	43	13
15	Saudi Arabia (1990)	52.7	N/A[d]	33	Philippines (1987)	43	8
16	Estonia (1994)	52	24	33	Slovakia (1992)	43	26
16	Kuwait (1991)	52	12	37	Cyprus (1990)	42.5	7.2
16	Lithuania (1992)	52	10	38	Austria (1992)	42	27
16	South Africa (1995)	52	17	39	Malaysia (1986)	41	4
20	Poland (1993)	51	29	39	Peru (1989)	41	13

Table 2 (contd).

41	Uruguay (1990)	40.9	26.6	66	Colombia (1992)	35.1	19.1
42	Argentina (1992)	40	23	67	Costa Rica (1988)	35	20
42	France (1993)	40	27	67	Slovenia (1994)	35	23
42	Hungary	40	27	69	Swaziland (1989)	33	8
42	India (1980s)	40	3	70	Luxembourg (1993)	32	26
42	Iraq (1990)	40	5	71	Singapore (1995)	31.9	2.7
42	Malta (1992)	40	18	72	Belgium (1993)	31	19
50	Brazil (1989)	39.9	25.4	72	Canada (1991)	31	29
51	Egypt (1986)	39.8	1	72	Iceland (1994)	31	28
52	Morocco (1990)	39.6	9.1	75	Australia (1993)	29	21
53	Lesotho (1989)	38.3	1	75	Ireland (1993)	29	28
53	Mexico (1990)	38.3	14.4	77	UK (1994)	28	26
55	El Salvador (1988)	38	12	78	USA (1993)	27.7	22.5
55	Italy (1994)	38	26	79	Pakistan (1980)	27.4	4.4
55	Portugal (1994)	38	15	80	Finland (1994)	27	19
58	Chile (1990)	37.9	25.1	81	Turkmenistan (1992)	26.6	0.5
59	Guatemala (1989)	37.8	17.7	82	Nigeria (1990)	24.4	6.7
60	Denmark (1993)	37	37	83	Paraguay (1990)	24.1	5.5
61	Germany (1992)	36.8	21.5	84	Bahrain (1991)	24	6
62	Norway (1994)	36.4	35.5	84	New Zealand (1992)	24	22
63	Honduras (1988)	36	11	86	Sweden (1994)	22	24
63	Netherlands (1994)	36	29	87	Bahamas (1989)	19.3	3.8
63	Switzerland (1992)	36	26				

[a] Adapted from: WHO (1997).
[b] The year given in parentheses is the latest available year for data.
[c] Some 1991 data suggest that there has been little change in smoking prevalence since 1984.
[d] Data not available.

Table 3. Trends in adult consumption of cigarettes from 1970–1972 to 1990–1992 (Adapted from WHO, 1997)

	Annual % change 1970–1972 to 1990–1992
WHO Regions:	
African Region	+1.2
Region of the Americas	-1.5
Eastern Mediterranean Region	+1.4
European Region	0
South-East Asia Region	+1.8
Western Pacific Region	+3
More developed countries	-0.5
Less developed countries	+2.5
World	+0.8

The high tar yields measured in the smoke of cigarettes in developed countries before 1950 are comparable with current tar yields of "bidis", which range from 23 to 48 mg per cigarette (Hoffmann et al., 1974; Jayant & Pakhale, 1985; Ball & Simpson, 1987.) The "kretek" (a cigarette of strong tobacco and cloves) of Indonesia yields up to 71 mg tar (WHO, 1985). Smoking materials in northern Thailand (cigarette or cigar of strong tobacco plus various vegetable materials) produce high levels of tar and nicotine (Simarak et al., 1977).

For smoking, tobacco leaf can be flue-cured, light air-cured, fire-cured or sun-cured, and can be of dark, oriental or *N. rustica* type. Flue-cured tobacco is used for cigarettes and pipe tobacco. Air-cured tobacco is used in blended cigarettes. Dark tobaccos are widely grown, usually air-cured, and mostly used in their countries of origin for dark cigarettes, "bidis", cigars, in pipes and "sheeshas", and for chewing tobaccos and snuff (Voges, 1984). Some tobaccos have low nitrate levels ranging up to 0.9% (Neurath & Ehmke, 1964; Wynder & Hoffmann, 1967) and their smoke contains low nitrogen oxide levels in the range of 50–200 mg NO_x/cigarette (Norman et al., 1983). In the reducing atmosphere of the burning cone, NO_x gives rise to amino radicals, which react with benzene, biphenyl, naphthalene and other ring hydrocarbons to form aromatic amines. Aniline, alkylated anilines, aminobiphenyls, and naphthylamines are therefore found in

higher quantities in the smoke of tobaccos with a high nitrate content (Patrianakos & Hoffmann, 1979; Pieraccini et al., 1992; Grimmer et al., 1995). Smokers of these tobaccos can inhale greater quantities of aromatic amines, such as the human bladder carcinogens 2-naphthylamine and 4-aminobiphenyl, and have higher concentrations of haemoglobin adducts in their blood (Bartsch et al., 1993). This is the basis for the higher risk of bladder cancer among the smokers of cigarettes made from dark tobaccos (Vineis et al., 1984; D'Avanzo et al., 1990; Vineis, 1992).

In the Indian subcontinent, the "bidi" is the common smoking device. It consists of tobacco flakes, loosely packed and hand-rolled in a tendu or temburni leaf (*Diospyros melanoxylon*). It contains less tobacco (0.223 g) than a cigarette (0.782 g) (Ramakrishnan et al., 1995) but up to 8.2% nicotine compared with up to 3.7% in cigarette tobacco. "Bidi" smoke contains 23 to 48 mg tar and 1.7 to 2.9 mg nicotine per cigarette (Hoffmann et al., 1974; Jayant & Pakhale, 1985). In India, where around 7% of world tobacco is consumed (US DA, 1990), around 30% of tobacco is smoked as cigarettes, 50% as "bidis", 10% in other ways, and 10% is used for chewing. "Bidis" need to be puffed frequently to ensure even burning and can generate up to 70 mg of carbon monoxide, while a US non-filter cigarette smoked under identical conditions generated 25 mg carbon monoxide (Hoffmann et al., 1974; Jayant & Pakhale, 1985).

Tar yields for Russian cigarettes were found to be high (21.6–29.2 mg) and cigarettes containing *N. rustica* produced high smoke concentrations of tobacco-specific nitrosamines (TSNA) (up to 620 ng total TSNA/cigarette) (Djordjevic et al., 1991). Indigenous cigarettes and cigars in Thailand, containing tobacco and other vegetable materials, have up to 41 mg and 200 mg tar, up to 5.5 mg and 11.4 mg nicotine, and 41 mg and 820 mg carbon monoxide in cigarette and cigar smoke, respectively. Indonesian cigarette smoke contains up to 100 ng of carcinogenic volatile *N*-nitrosamines and up to 1580 ng of carcinogenic tobacco-specific *N*-nitrosamines (Mitacek et al., 1990, 1991), and high tar cigarettes contain up to 28.1 mg tobacco-specific *N*-nitrosamines per cigarette (Brunnemann et al., 1996).

Many cigar-like devices are smoked throughout Asia. The tobacco can be rolled in a tobacco leaf or in the leaves of the jackfruit

tree (*Artocarpus integrifolia*), banana (*Musa paradisiaca*) or hansali (*Grewia microcos*) (Bhonsle et al., 1976). They may be smoked conventionally or in the reverse manner with the burning end inside the mouth (Reddy, 1974). In Thailand they can contain strong tobacco and a mixture of koi bark (*Streblus asper*), dry tamarind pod (*Tamarindus indica*), khai bark (*Homonoia riparia, Euphorbiaceae*), Areca palm bark (*Areca catechu*) or other tree bark; they can be rolled in a banana leaf or have fragrant additives such as sandalwood Mougne et al. (1982). They contain high levels of tar and nicotine (Simarak et al., 1977; Mitacek et al., 1999).

Additives are used to enhance the fragrance or taste of smoke (Hoffmann & Hoffmann, 1997). "Casing sauces", consisting of sugars, aromatic substances and compounds such as glycerol, propylene glycol, ethylene glycol and diethylene glycol, which resist changes in moisture content, are sprayed on the leaf before it is cut to condition it for processing. Flavouring and dressing compounds are added to cut tobacco after drying and include licorice, menthol, cocoa, chocolate, ginger, cinnamon, vanilla, molasses, angelica, honey, essential oils from anise, clove and juniper, resins and plant extracts and organic compounds such as coumarins. Additives have been widely used in pipe and chewing tobaccos. They have also become important in cigarette tobacco with the development of low-tar and low-nicotine tobaccos and the use of stem, midrib or reconstituted leaf (which lacks the aromas and flavours of natural tobacco leaf lamina) and of tobacco dust requiring additives to ensure its adherence to cut tobacco.

Added glycerol is transferred to mainstream smoke: 3–6% in cigarette smoke and 35–43% in pipe smoke (IARC, 1986) and one of its pyrolysis products is acrolein. Levels of acrolein ranging from 69 mg to 230 mg per cigarette have been reported and air concentrations as high as 0.46 mg/m^3 have been found in smoke-filled rooms (Izard & Liberman, 1978). Acrolein is extremely irritating to the eyes and nasal mucosa, it affects mitotic and ciliary activity, at the cellular level it has cytotoxic and cilia-depressant effects, and it can act as a mutagen (Izard & Liberman, 1978).

In the USA, additives used in cigarette manufacture are food additive compounds that are "generally recognized as safe (GRAS)" and, therefore, also considered "safe" as additives to tobacco.

However, the non-volatile additives are to some extent pyrolized during smoking and can give rise to toxic and/or carcinogenic agents in the smoke. A major group of compounds formed during pyrolysis is that of the polynuclear aromatic hydrocarbons. Ethylene glycol is pyrolytically converted to the human carcinogen ethylene oxide (IARC, 1994a).

Another example of carcinogen formation during tobacco curing and smoking is the case of MH-30, a sucker growth control agent formulated from maleic hydrazide in diethanolamine. Residual MH-30 on tobacco leads to the formation of *N*-nitrosodiethanolamine (NDELA) in the smoke (Brunnemann & Hoffmann, 1981). The use of MH-30 on tobacco has been forbidden in the USA since 1981, and NDELA levels in tobacco and its smoke have declined (Brunnemann & Hoffmann, 1991).

The use of cloves as a tobacco additive can have health effects. In Indonesia, the smoke of "kreteks", a blend of ground cloves with 60–65% of tobacco, contains between 41 and 113 mg of tar, and between 1.2 and 4.5 mg nicotine (WHO, 1985; Wise & Guerin, 1986). Mainstream smoke of kreteks without filter tips contains 19–23 mg of eugenol released from the cloves, while filter-tipped kretek smoke contains up to 15 mg (LGC, 1982; Wise & Guerin, 1986). Inhalation of eugenol in the smoke of kreteks can lead to interstitial haemorrhaging and congestion of the lung, acute emphysema and acute pulmonary oedema. These effects were also seen in Syrian golden hamsters exposed to the smoke of kreteks (LaVoie et al., 1986).

Menthol and other additives that produce a sensation of coolness but without a mint flavour have also been used in cigarettes. There is no evidence that these additives result in a higher risk (Cummings et al., 1987; Sidney et al., 1989).

Many shapes and sizes of smoking pipes are found worldwide (Voges, 1984). Various types of tobacco are used and the smoke can range from mild to very strong. In the sheesha water pipe the tobacco is kept alight by pieces of glowing charcoal and the smoke is drawn through water before being inhaled. Sheesha smoke is mild and low in particulate matter, benzo(a) pyrene and volatile phenols (Hoffmann et

al., 1961), but it has a high level of carbon monoxide, in part from the charcoal that keeps the tobacco burning, and smokers have high carboxyhaemoglobin levels and a reduced FEV_1 (8.5% in women, 45% in men) (Zahran et al., 1985; Al-Fayez et al., 1988).

2.1.3 Tobacco chewing and snuff

The popularity of tobacco chewing and snuff (finely powdered tobacco leaf) has varied. Nasal inhalation of snuff has given way to the oral application of snuff and other tobacco-containing mixtures between the gum and lip, or gum and cheeks, or under the tongue. Chewing tobacco comes in several forms and may have flavour added from syrups, liquorice and brandy. Tobacco chewing has retained its popularity in heavy industries, such as steel and coal mining, woodworking and the petroleum industry, where the flammability hazard precludes smoking. In Sweden, 17% of the population uses oral snuff. In the USA, sales of chewing tobacco have declined but sales of oral snuff have increased by 61% (US DA, 1997) owing to the popularity of the latter with teenagers and young adult men. Oral tobacco use in India is very common but, generally, in developing countries it is declining because urban populations and younger age groups are smoking cigarettes.

"Betel-quid" chewing is common in Asia and Africa. The basic contents of a betel-quid are slices of areca nut (*Areca catechu*), lime and tobacco, wrapped in a betel pepper leaf (*Piper betle*), but it may also contain dried dates, menthol and spices such as cardamom, cloves, coriander, mace and cinnamon.

Other tobacco preparations for oral use often contain lime, calcium carbonate, sodium carbonate, some form of ash or flavouring materials. The lime and other agents assist the release of nicotine (Voges, 1984; Idris et al., 1991).

2.2 Responses to mainstream smoke

Tobacco use has direct effects on health and is responsible for a variety of diseases. These form a basis for studying interactions between tobacco use and chemical, physical and biological agents, and associated effects on health.

2.2.1 Acute responses

Inhaled irritant chemicals cause inflammation of the upper respiratory tract (URT) and paranasal sinuses, sore throat and bronchial oedema. Pulmonary oedema may follow if irritants penetrate the lower respiratory tract. Acute irritation of the URT usually follows inhalation of highly soluble gases. Slightly less soluble gases cause URT and bronchial irritation, while relatively insoluble gases penetrate deeply into the lung and can have delayed effects including pulmonary oedema (Miller & Kimbell, 1995). Cigarette smoke is a complex mixture of organic and inorganic constituents with particulate and vapour phases and highly reactive free radicals (Hocking & Golde, 1979). It contains many compounds with irritant properties, which can affect all parts of the lung. Kremer et al. (1994) examined the association between occupational exposures to a variety of airway irritants and respiratory system effects, and whether the association was modified by smoking, airway hyperresponsiveness and allergy. The irritants were SO_2, HCl, SO_4^{2-}, polyester vapour, polyamide vapour, and oil mist and vapour. Current smoking, airway hyper-responsiveness and allergy were significantly associated with a higher prevalence of chronic respiratory symptoms, independent of each other and of irritant exposure. The association between exposure and the prevalence of chronic respiratory symptoms was greater in smokers than in non- or ex-smokers.

2.2.1.1 Acute bronchitis

Acute bronchitis is an inflammation of the bronchial mucous membrane, initially accompanied by a dry painful cough and followed by mucopurulent sputum. The cause may be infectious agents or chemical agents such as tobacco smoke, dusts, fumes, vapours or gases.

2.2.1.2 Asthma

Asthma is a chronic pulmonary inflammatory disease associated with bronchial hyperreactivity causing paroxysmal dyspnoea due to spasm of the bronchial musculature, swelling of the mucous membranes and the production of viscid mucus. In the majority of asthma cases a clear association exists with atopic IgE-mediated hypersensitivity. Allergic asthma is a response to a specific agent.

Many chemical agents, including mixtures such as tobacco smoke, can induce asthma. Smoking enhances the effect of other agents and can reduce the latent period from first exposure to onset of sensitization.

There has been an increase in the prevalence of asthma in many countries, and roles for environmental factors, increased susceptibility and tobacco smoking have been suggested (ISAAC, 1998). Cigarette smoking together, with atopic status, age, URT infection and genetic factors, has been considered to increase susceptibility (Venables et al., 1985; Seaton et al., 1993). Studies have shown a relationship between cigarette smoking and serum IgE levels. Smokers have higher levels of IgE with increasing age, compared to non-smoking controls. A relationship has also been observed between IgE level and the number of cigarettes smoked (Sherrill et al., 1994).

2.2.2 Chronic responses

2.2.2.1 Chronic obstructive lung diseases

The chronic obstructive lung diseases (COLD) are chronic bronchitis, small airways disease, toxic bronchiolitis obliterans, emphysema and fibrosis (Niewoehner et al., 1974; Niewoehner, 1991).

These diseases form an important group of pulmonary diseases caused by smoking (and by chemical atmospheric pollution) (US Surgeon General, 1984). In a study by Šimeček et al. (1986) of 215 229 adults in a region of former-Czechoslovakia, smoking was the most important risk factor in COLD. Risks for male non-smokers and light smokers under 30 years of age were 1.18% and 2.28%, respectively; for men aged 50 years, smoking more than 20 cigarettes a day, the risk was 20.36% compared with 3.31% for non-smokers of the same age. In the USA, 80–90% of the mortality from COLD has been attributed to cigarette smoking. Cigar and pipe smokers who inhale the smoke also have an increased death rate from COLD (US Surgeon General, 1984, 1989; NIH, 1998). Between 1979 and 1993, the age-adjusted annual death rate from COLD in women increased by 122% to 17.1 per 100 000, while in men it increased by 14% to 27.8 per 100 000. The greater increase of COLD among women during this period reflected the increase in smoking by women.

2.2.2.2 *Chronic bronchitis*

Chronic bronchitis has been variously defined. The United Kingdom Medical Research Council (MRC, 1965) considered it to be a condition with persistent production of sputum, which might be associated with cough, occurring on most days for at least three months in the year for at least two successive years. The Council recommended a classification of simple chronic bronchitis, chronic or recurrent mucopurulent bronchitis or chronic obstructive bronchitis. In a workplace context, Morgan (1982) defined it as "a condition characterized by cough and sputum for at least three months of the year, which may or may not be accompanied by airways obstruction, and which is a consequence of prolonged inhalation of dust or irritant gases at the workplace". Fletcher & Pride (1984) suggested an improved terminology with the term chronic bronchitis meaning chronic or recurrent bronchial hypersecretion only, abandoning the term chronic obstructive bronchitis because this implies a causal connection between mucus hypersecretion and airflow obstruction. In smokers' lungs the irritant constituents of tobacco smoke cause hypersecretion of mucus, alter its physical properties and chemical structure, and impair the mucociliary clearance mechanism. Removal of major ciliatoxins (hydrogen cyanide and volatile aldehydes) from the smoke stream by charcoal filter tips reduces the effects on the lung epithelium (Friedman et al., 1972). Mineral dusts, particularly those encountered in mining, many biological dusts, irritant vapours and gases, inorganic and organic chemical dusts and sprays can all cause chronic bronchitis.

2.2.2.3 *Small airways disease*

Small airways disease (SAD) is a widespread narrowing of membranous bronchioli. It is inflammatory in origin and is often associated with excess mucus and an accumulation of macrophages in the respiratory bronchioli. SAD is mainly caused by smoking, but can be associated with environmental and industrial pollutants (Cosio et al., 1980).

2.2.2.4 *Emphysema*

Emphysema has been defined as a condition of the lung characterized by an abnormal enlargement of the airspaces distal to the

terminal non-respiratory bronchioli, accompanied by destructive changes in the alveolar walls, and without obvious fibrosis. It tends to be prevalent in older age groups and follows SAD. For purposes of postmortem examination of lung slices of miners, Ruckley et al. (1984) defined emphysema as the presence of air spaces of 1 mm or more in size. Macrophages that have engulfed foreign particles, including smoke particulate matter in the lungs of smokers, and which have been found accumulated in the bronchioli (Niewoehner et al., 1974) and in the lung parenchyma (McLaughlin & Tueller, 1971) have been implicated in the pathogenesis of emphysema. There are different forms of emphysema, which vary with the nature of the insult to the tissues. One hypothesis is that tobacco smoke causes increased production and release of proteolytic enzymes, such as elastase, and interferes with normal antiproteolytic mechanisms. Emphysema has been induced experimentally in animals by endotracheal installation of elastase or homogenates of alveolar macrophages or polymorphonuclear leukocytes. Chronic exposure to tobacco smoke has a number of effects on alveolar macrophages, including changes in metabolism, alteration of the enzyme content and impairment of RNA and protein synthesis (Hocking & Golde, 1979). The function of alveolar macrophages is to remove inhaled foreign material from the alveoli and respiratory bronchioles, and their numbers increase when the lungs are exposed to particles and gases. It has been demonstrated that the macrophage count is higher in people exposed to cigarette smoke than in non-exposed people (Harris et al., 1974; Rylander et al., 1979). Alveolar macrophages from smokers are more active than those from non-smokers, numbers are increased, there are morphological changes with an increased cell diameter, crystalline inclusions and surface membrane alteration (Sopori et al., 1994).

2.2.2.5 *Pulmonary fibrosis*

Pulmonary fibrosis is the abnormal formation of fibrous or scar tissue and is the response of bronchiolar tissue to the deposition of an inhaled inciting agent. Mineral and other dusts are causes of pulmonary fibrosis. The radiological changes seen in early stages of dust fibroses are associated with relatively minor lung function impairment, but continuous exposure leads to a greater degree of fibrosis and to progressive massive fibrosis in some subjects. On

histological, animal experimental and radiographic evidence, Weiss (1984) concluded that cigarette smoking could cause diffuse fibrosis.

2.2.2.6 *Effects on the immune system*

Tobacco smoking and exposure to environmental tobacco smoke increase susceptibility to pulmonary infections, and changes in immune processes may be involved. Tobacco smoking affects humoral and cellular immunity in humans and experimental animals, but the magnitude of the changes vary widely among studies. In humans, cigarette smoke has marked effects on alveolar macrophage morphology and physiology, it decreases serum immunoglobulin (IgA, IgG, IgM) but increases IgE, and has a range of effects on B- and T-lymphocytes. Similar effects are found in experimental animals (Sopori et al., 1994). Studies in rats and mice show that cigarette smoke or nicotine induces impaired responses of systemically distributed B- and T-lymphocytes to antigen-induced signalling (Geng et al., 1995, 1996). T-lymphocyte unresponsiveness, with decreased antibody response to T-dependent antigens, is important in response to infection (Sopori et al., 1998).

2.2.3 *Cancer*

Many forms of cancer have been associated with inhaled particulate matter, vapours, fumes and gases. Examples are lung cancer associated with tobacco smoking and inhalation of asbestos, fumes from metal moulding and coking plants, particles and gases inhaled by motor vehicle drivers, dusts in several types of mines where there is an accumulation of α-emitting radioisotopes, and contact with materials such as arsenic, chromates, nickel, chloromethyl ethers, mustard gas and polycyclic aromatic hydrocarbons. Pleural mesothelioma has been associated with asbestos, nasal and sinus cancer with nickel refining and wood dust exposure, leukaemia with ionizing radiations and benzene, bladder cancer with the manufacture and use of dyes and in the rubber industry, and liver cancer with the use of vinyl chloride (IARC, 1987).

Cigarette smoke contains many toxic chemicals, including chemicals that are DNA reactive and cytotoxic or become DNA reactive upon metabolic activation. Consequently, cigarette smoke has

the potential to initiate genetic lesions. Moolgavkar et al. (1989) postulated mechanisms by which cigarette smoke induces lung cancer by fitting the two-stage clonal expansion model of carcinogenesis to lung cancer mortality data derived from a large cohort of British doctors who smoked. This analysis suggested that tobacco smoke affected both the rates of mutation and cell proliferation involved in the model, supporting the hypothesis that tobacco smoke acts as a complete carcinogen.

Cigarette smoking is causally associated with cancer of the lung, larynx, pharynx, oesophagus, pancreas, kidney and urinary bladder. It is also associated with cancer of the nasal cavity, liver, uterine cervix and myeloid leukaemia (RCP, 1962; US Surgeon General, 1982, 1989; IARC, 1986; Winkelstein, 1990; Brownson et al., 1993; Roush, 1996).

In 1991, in the USA, it was estimated that 90.3% of the lung cancer deaths in men and 78.5% of lung cancer deaths in women were attributable to cigarette smoking. Deaths from oesophageal cancer were linked to smoking in 78.2% of the cases in men and 74.3% of the cases in women. Smoking was held responsible for 81.2% of deaths from laryngeal cancer in men and 86.7% in women, for 91.5% and 61.2%, respectively, of deaths from oral cancer, and 46.5% and 36.7%, respectively, of deaths from bladder cancer. Smoking-attributable deaths from cancer of the kidney in men and women were 47.6 and 12.3%, respectively, and for pancreatic cancer the figures were 28.6% and 33.3% respectively. In women, 32.4% of uterine cervical cancer deaths were attributed to cigarette smoking (Shopland et al., 1991).

There has been a change in the rates of different types of lung cancer among smokers. In 1950, squamous cell carcinoma (SCC) occurred 17 times more often than adenocarcinoma (AC) (Wynder & Graham, 1950) in cigarette smokers. In 1991, Devesa et al. (1991) reported that in male cigarette smokers the ratio of SCC to AC was 2.4:1 between 1969 and 1971, and changed to 1.4:1 between 1984 and 1986; in cigarette-smoking women, the SCC to AC ratio changed from 3.6:1 in 1950 to 0.57:1 in 1984–1986. Between 1970 and 1980 some studies showed a 20–50% reduction in risk of lung cancer for long-term smokers of filter cigarettes as compared to smokers of non-filter cigarettes (IARC, 1986) but later studies indicated a similar risk for lung cancer in smokers of filter and non-filter cigarettes (Stellman et

al., 1997; Thun et al., 1997). The changes in the ratio of SCC to AC, and the disappearance of an advantage of filter cigarette smoking in terms of lung cancer risk, have been related to changes in smoke yields, which have caused smokers to modify patterns of puff drawing and smoke inhalation. Smokers regulate the speed and the quantity of their nicotine uptake to achieve the desired pharmacological effects (Benowitz et al., 1988; Djordjevic et al., 1995). Smokers of lower nicotine cigarettes draw puffs of greater volume, at a higher frequency, and inhale more deeply; this is governed by the amount of nicotine in the smoke (Wynder & Hoffmann, 1994).

Smoking is a major risk factor for the early stage development of oesophageal and gastric adenocarcinomas, accounting for 40% of cases, and may have contributed to the increase in the incidence of these cancers, especially in older people (Gammon et al., 1997).

Cigar smoking is causally associated with cancer of the oral cavity, the pharynx and the lung, even though for cigar smokers, who do not or only minimally inhale the smoke, the lung cancer risk is considerably lower than that for cigarette smokers. Cigar smoking is also associated with cancer of the pancreas and of the urinary bladder (NIH, 1998). Oral snuff users have an increased risk of cancer of the oral cavity and, possibly, cancer of the oesophagus, pancreas and urinary bladder (US Surgeon General, 1986).

It has been suggested that around 4–5% of all lung cancer is related to occupational exposure (Wynder & Gori, 1977; Doll & Peto, 1981; Morgan, 1982). Occupational and any other forms of exposure to chemical compounds are of limited importance in the etiology of lung cancer whereas tobacco smoking is the cause of approximately 85–90% of cases (Shopland et al., 1991).

"Reverse smoking", in which rolled tobacco leaves are smoked with the burning end inside the mouth, has been linked to carcinoma of the hard palate (Reddy & Rao, 1957; Mehta et al., 1971; Pindborg et al., 1971; Reddy, 1974; Bhonsle et al., 1976). Reddy et al. (1960) simulated the effect of reverse smoking experimentally by painting the skin of male and female mice on alternate days with the tar from Indian cigars and exposing the painted skin to a temperature of 58 °C for 3 min; the heat treatment enhanced the dermal tumour response.

2.2.4 Cardiovascular effects

Cigarette smoking is a major independent risk factor for cardiovascular disease (CVD). Cigarette smoking acts synergistically with other risk factors, such as elevated cholesterol levels and hypertension (Wilhelmsen, 1977; Gibinski, 1977; US Surgeon General, 1983). Prospective studies indicated that elevated cholesterol and hypertension appear to be prerequisites for CVD in cigarette smokers (Kimura, 1977). It has been estimated that in countries with a long history of cigarette smoking the tobacco habit is responsible for 26–30% of early deaths from CVD (US Surgeon General, 1983; Wald et al., 1985). Those who smoke several cigars a day and inhale the smoke also face an increased risk of CVD (NIH, 1998).

The major contributors to the cardiovascular effects of tobacco smoke are carbon monoxide and nicotine (Lakier, 1992), as well as nitrogen oxides (NO_x), hydrogen cyanide and tar; minor contributors are cadmium, zinc and carbon disulfide (US Surgeon General, 1983). The smoke of cigarettes can be slightly acidic (pH 5.6–5.9) or weakly alkaline (pH 6.7–7.9) depending on the type of tobacco and the blend (Brunnemann & Hoffmann, 1974). In the slightly acidic smoke, nicotine is protonated, i.e., bound to a salt or acid moiety and is part of the particulate phase. Weakly alkaline smoke contains a small percentage of protonated nicotine (often up to 50% of the nicotine is unprotonated) in the vapour phase. In contrast to the protonated variety, unprotonated nicotine is rapidly absorbed through the oral mucosa and this is why smokers of cigarettes with weakly acidic smoke and smokers of cigars do not need to inhale into the lung to experience the pharmacological effects of nicotine. Protonated nicotine in the particulate matter of slightly acidic cigarette smoke is not or is only minimally absorbed through the oral mucosa, so that smokers inhale the smoke and absorption into the bloodstream takes place in the lung (Armitage & Turner, 1970; Russell, 1976; Benowitz et al., 1988).

Smoking has been associated with a two-to-fourfold increased risk of coronary heart disease (CHD), a greater than 70% excess rate of death from CHD, and an elevated risk of sudden death (Lakier, 1992). Nicotine causes increases in heart rate and blood pressure, stimulates nerve endings that are activated by acetylcholine, causes

increased mobilization of free fatty acids in the serum and enhances platelet adhesiveness. These effects increase cardiac load (which for individuals with some forms of heart disease will not be met by increased coronary blood flow) and interfere with metabolic exchange across capillary walls, leading to ischaemic episodes and thrombosis. Carbon monoxide increases carboxyhaemoglobin concentrations in the blood and lowers its oxygen-carrying capacity: increased oxygen debt after exercise and impairment of endurance performance are evident in smokers, compared to non-smokers. Carbon monoxide also has an affinity for myoglobin and interferes with oxygen uptake by the myocardium.

"Bidi" smoke contains a higher concentration of carbon monoxide than cigarette smoke (Hoffmann et al., 1974; Jayant & Pakhale, 1985; Ball & Simpson, 1987). Most of the Asian smoking devices with their non-porous wrappers and dark tobacco contain higher levels of nicotine (Simarak et al., 1977; WHO, 1985). High nicotine and carbon monoxide are also obtained from many dark tobacco cigarettes and from cigars. "Sheesha" water pipe smoke contains small amounts of nicotine but is rich in carbon monoxide; the blood carboxyhaemoglobin concentration in sheesha smokers is higher than in cigarette smokers (Zahran et al., 1985).

Cigarette smoking has been considered to be the primary cause of Buerger's disease (thromboangiitis obliterans), an inflammatory obliterative, non-atherosclerotic, vascular disease. The disease usually becomes quiescent if the patient stops smoking cigarettes (Olin, 1994). It was rare in women but an increasing number of cases has been observed and ascribed to the increased use of tobacco by young women (Yorukoglu et al., 1993).

Cardiovascular disease has been associated with exposure to other factors, which can be classified as physical, chemical and biological, and with occupation or life-style. The combination of smoking with any of these factors will predispose to an increased detrimental cardiovascular effect.

In women who smoke, peripheral vasoconstriction (PV) leading to acute intervillous placental blood flow was measured during smoking and attributed to nicotine, which simultaneously caused

increases in heart rate and blood pressure. It was suggested that PV explained fetal growth retardation and other complications of pregnancy (Lehtovirta & Forss, 1978).

2.2.5 Smoking and occupational accidents, injuries and absenteeism

A survey of public employees found that cigarette smokers took 23% more sick leave than non-smokers (Van Tuinen & Land, 1986). In another study among 2537 postal workers in the USA, cigarette smokers had a 1.29 times higher accident rate (CI 1.07–1.55), and a 1.55 times higher injury rate (CI 1.11–1.77) than non-smokers (Ryan et al., 1992). Other studies confirm the higher rates of injury, occupational accidents and absenteeism in smokers (Naus et al., 1966; Parka, 1983; US Surgeon General, 1985; Hawker & Holtby, 1988). There are higher costs of illness for cigarette smoking employees compared to non-smokers (Van Peenen et al., 1986; Penner & Penner, 1990.

2.3 Health risks from smokeless tobacco use

2.3.1 Introduction

Oral cancers have been linked with oral tobacco use. The consequences of chewing tobacco can be reactional keratosis, irreversible gingival recession, periodontitis, oral dysplasia and leukoplakia, cancer and cardiovascular effects (Chakrabarti et al., 1991; Guggenheimer, 1991). In India, chewing material containing tobacco has been shown to be a primary cause of oral cancer (Jussawalla & Deshpande, 1971).

2.3.2 Cancer

Leukoplakia and oral cancer are common results of oral tobacco use, particularly in the countries of Asia (IARC, 1985a). Simarak et al. (1977) reported a strong association between betel chewing and oral cancer in northern Thailand. Sankaranarayanan et al. (1989a,b, 1990) associated oral cancers in southern India with tobacco chewing. Chakrabarti et al. (1991) reported much higher levels of pre-malignant and malignant lesions of the oral cavity in tobacco chewers; Nandakumar et al. (1990) found the relative risk to be elevated in both

sexes, but appreciably higher in females. From chemical analysis of Indian tobacco products, it was concluded that their use may lead to high exposures to carcinogenic tobacco nitrosamines (Nair et al., 1989).

Case-control studies reported a higher incidence of oral cancer in oral snuff users than in those not using any form of tobacco. There was up to a 50-fold excess risk of cancer of the cheek and gum in long-term oral snuff users (Axéll et al., 1978; US Surgeon General, 1986a; Winn, 1997). Idris et al. (1991, 1994), reported a high incidence rate of oral cancer in men in northern Sudan who used an oral snuff with relatively high concentrations of nicotine (0.8–3.2%) and nornicotine. In a study of baseball players who chewed or (the majority) used snuff orally, there was higher prevalence of leukoplakia, plaque formation, gingivitis and dental disorders compared to non-users (Robertson et al., 1997).

A case-control study on nasal cavity and paranasal sinus cancer and snuff use showed that snuff users have a significantly increased risk for adenocarcinoma and squamous cell carcinoma in the nasal cavity (Brinton et al., 1984). *N*'-nitrosonornicotine is present and is an organ-specific carcinogen that induces benign and malignant tumours of the nasal cavity in rats, hamsters and mink (Rivenson et al., 1991; Koppang et al., 1992, 1997; Hoffmann et al., 1994). Studies conducted in South Africa showed that people using local snuff made from tobacco and aloe plant ash as nasal applications have an increased risk for tumours of the maxillary antrum (Keen et al., 1955). It was thought that this snuff mixture contained high levels of nickel and chromium, which may be associated with the induction of these tumours (Baumslag et al., 1971).

Instillation of snuff into the lips of rats induced benign and malignant tumours in the oral cavity (Hirsch & Thilander, 1981; Hecht et al., 1986; Johansson et al., 1989; Larsson et al., 1989). Instillation of snuff into the buccal pouch of hamsters, which were repeatedly infected with *Herpes simplex* virus type I or II, led to oral tumours, although no tumours occurred when either the virus or tobacco was applied alone (Park et al., 1991b).

More than 3050 chemical compounds have been identified as tobacco constituents (Roberts, 1988) and 50 are known carcinogens (Brunnemann & Hoffmann, 1992). Nitrosamines, especially the tobacco-specific nitrosamines (TSNA), must be regarded as major oral carcinogens. Oral tumours were elicited when an aqueous solution of *N*-nitrosonornicotine (NNN) and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was applied to the oral surfaces of rats (Hecht et al., 1993).

2.3.3 Cardiovascular disease

The effect of tobacco chewing on cardiovascular disease has received less attention than the effect of cancer. Benowitz et al. (1988) compared the cardiovascular effects of smokeless tobacco, cigarettes and nicotine gum and reported that all tobacco use increased heart rate and blood pressure. Nanda & Sharma (1988) recorded incremental increases in heart rate and blood pressure following tobacco chewing. However, Eliasson et al. (1991) found no significant elevation of diastolic blood pressure in young snuff users. Bolinder et al. (1994) found an excess risk of death from cardiovascular and cerebrovascular disease among smokeless tobacco users. Tobacco chewing has detrimental effects on pregnancy (Krishna, 1978) which, in the absence of any anoxia due to carbon monoxide found in smokers, could result from nicotine-induced vasoconstriction.

O'Dell et al. (1987) reported a case of Buerger's disease in a 38-year-old man that was associated with the use of smokeless tobacco. A regimen which included complete abstinence from tobacco resulted in a resolution of the symptoms. Buerger's disease is the commonest vascular disease in the Indian subcontinent where tobacco consumption is high (Jindal & Patel, 1992). In a study of the disease in Bangladesh, 39 patients (38 males, 1 female) were investigated. All but two were current long-term smokers, one male had given up smoking 6 months previously and the one woman with the disease (it is uncommon in women) was a tobacco chewer (Grove & Stansby, 1992).

3. EFFECTS ON HEALTH OF TOBACCO USE AND EXPOSURE TO OTHER CHEMICALS

3.1 Introduction

3.1.1 Interaction

To discuss the interaction between tobacco and other agents as risk factors for cancer and other adverse health effects, it is necessary to define what is meant by the term "interaction". In general terms, interaction represents a departure from additivity, in which the combined effect of exposure to two agents is in some sense the sum of the effects of the individual agents (US EPA, 1988). Synergism occurs when the combined effect is greater than the sum of the component effects; antagonism occurs when the effect of the combination is less than would be suggested by summing the effects of the components.

3.1.2 Measuring interaction

To make these concepts precise, the scale in which risk is measured and the manner in which risks are summed must be specified (Kaldor & L'Abbe, 1990). In epidemiological investigations, the age-adjusted relative risk is often used to characterize risk. In risk assessment applications involving chronic health effects such as cancer, the cumulative risk over a period of time may be of more direct interest. In laboratory studies of carcinogenicity, for example, the lifetime probability of tumour induction is often used to describe risk. In order to take into account the age at which an adverse effect is induced, the expected loss in life expectancy has also been used to evaluate risk (UNSCEAR, 1988).

Kodell & Pounds (1991) discuss interaction in terms of departures from *response additivity* and *dose additivity*. Dose additivity occurs when the combined effect of two agents can be expressed in terms of a total dose of the two agents, taking into account their relative potencies. Dose additivity presumes that the two agents act by the same biological mechanism, and that the effective dose of one agent is simply a dilution of the dose of the other agent. Response additivity occurs when the two agents act independently of each other. In this case, the probabilities of an adverse effect due to each of the agents

can be treated as statistically independent and can be combined accordingly.

The quantification of interaction may be illustrated using the age-specific relative risk (A,B) associated with exposure to two agents A and B. The relative risk is formally defined as:

$$\text{relative risk } (A,B) = I(A,B)/I(0,0)$$

where I(A,B) denotes the incidence rate of the disease of interest at a specified age in the presence of exposure and I(0,0) is the incidence rate in the absence of exposure. Lack of interaction then corresponds to additivity of the excess relative risk (ERR = relative risk – 1).

Specifically,

$$ERR(A,B) = ERR(A,0) + ERR(0,B)$$

where ERR(A,0) and ERR(0,B) denote the excess relative risks for A and B alone, respectively. In terms of relative risk, additivity is equivalent to:

$$\text{relative risk } (A,B) = \text{relative risk } (A,0) + \text{relative risk } (0,B) - 1$$

For a supra-additive relative risk relationship, such as the multiplicative relative risk model:

$$\text{relative risk } (A,B) = \text{relative risk } (A,0)RR(0,B)$$

and reflects a synergistic effect.

It is of interest to note that as the relative risk (A,0) and relative risk (0,B) become small, the multiplicative relative risk model approximates the additive relative risk model. Under this multiplicative model, a strong synergistic relationship may be apparent at high exposures, yet become negligible at low exposures. This, along with the realization that relative risks of less than about two are difficult to detect epidemiologically, suggests that relatively high exposures are likely to be required to evaluate interactive effects reliably.

Brown & Chu (1989) and Kodell et al. (1991) investigated the type of interactions that might be expected under both the Armitage-Doll multi-stage model and the Moolgavkar-Venzon-Knudson two-stage model of carcinogenesis following exposure to two carcinogens that may affect different stages in the model. These theoretical results indicate that a variety of synergistic interactions are possible, including supra-additive, multiplicative, and supra-multiplicative.

Although the additive excess relative risk model described above provides a useful baseline for evaluating interaction, it is not the only model that has been proposed for this purpose. Kaldor & L'Abbe (1990) pointed out that the multiplicative relative risk model will become the baseline model for evaluating interactions following a logarithmic transformation of the relative risk. Thomas & Whittemore (1988) review arguments in favour of the additive and multiplicative models as the basis for evaluating interaction. Steenland & Thun (1986) illustrate how these two models can be applied in evaluating tobacco/occupation interactions in the causation of lung cancer.

This brief overview illustrates that interaction can be measured in different ways, with the most appropriate depending on the nature of the problem at hand. In general, however, all of the commonly encountered measures of synergism indicate that the risk associated with combined exposure to two agents is in some sense greater than would be expected based on the risks of individual exposures. Although no attempt is made throughout this monograph to systematically specify the precise nature of the interactive effects reported in the literature, most interactive effects documented in this monograph have been identified through epidemiological investigations, in which the additive age-specific relative risk model is the predominant approach to describing interaction (Saracci, 1987; Greenland, 1993).

There are four principal ways in which tobacco smoke can interact with other chemicals to impair the health of the smoker. They are not mutually exclusive and in fact there are many situations in which they may occur together, particularly in the workplace or the environs of industry.

a) Modification of effects

Cigarette smoke can modify the harmful effects associated with other toxic agents, in some cases causing a highly elevated risk, e.g., the effects of smoking on diseases related to asbestos, α-radiation, arsenic and some organic compounds.

b) Increased concentration effects

Chemical compounds hazardous to health are often found in both tobacco smoke and the working environment and each source can augment the dose obtained from the other, e.g., carbon monoxide, acrolein, benzene and heavy metal elements.

c) Vector effects

Materials used in the workplace that produce harmful chemical agents when they are burnt or vaporized can contaminate smoking materials and cause the smoke to be far more injurious when the tobacco is smoked, e.g., polytetrafluoroethylene and methylparathion.

d) Other interactions

Tobacco smoke can affect a physiological process and increase the impairment of physical or physiological functions caused by another activity. For instance, impaired lung clearance will affect the residence time of inhaled toxic materials, the effect of smoking on the peripheral vascular system can enhance the detrimental effects of vibration and noise, and smoking may alter the effect of drugs taken for other purposes.

3.1.3 Effects of tobacco smoking on lung deposition and clearance of particles

Pulmonary deposition of inspired particles depends on their physicochemical properties and on airway structure and geometry. Mathematical models describing the deposition of particles in the various airway sections show that in compromised airways, as is the case in patients suffering from asthma and chronic obstructive lung

diseases, particle deposition is enhanced several-fold (ICRP, 1994). Tobacco smoking can be an indirect cause of enhanced deposition of inspirable particles. In addition, during tobacco smoking the breathing pattern is changed to more frequent and deeper inhalation, especially in the case of low-nicotine cigarettes, which can result in an increased inhaled dose and dose rate of inspirable compounds (IARC, 1990).

Clearance of particles deposited in the lung is a complex physiological process involving relatively rapid tracheobronchial clearance, in which mucus is moved upward by ciliary action to the pharynx and swallowed, and slower deep-lung clearance, in which phagocytic cells remove inhaled particles. These processes are balanced by the solubility of the inhaled particles, with relatively insoluble particles having a longer residence time in the alveolar portions of the lungs. A longer residence time in the lung would be accompanied by a greater possibility that harmful effects could occur. Both rapid and slow clearance phases are reduced by smoking, although probably by different mechanisms. Cigarette smoke contains significant concentrations of ciliatoxic agents, such as hydrogen cyanide, formaldehyde, acetaldehyde, acrolein and nitrogen oxides, which greatly contribute to retarded clearance of inhaled particles by inhibiting lung clearance mechanisms (Battista, 1976). Retardation of clearance has been seen for airway-deposited particles, in which decreased mucus transport velocities slow this normally relatively rapid phase of clearance (Lourenco et al., 1971; Chopra et al., 1979).

The deep-lung clearance of relatively insoluble particles is retarded in smokers. Cohen et al. (1979) found that 1 year after a tracer particle exposure, some 50% and 10% of the original lung burden remained in the lungs of smokers and non-smokers, respectively. Bohning et al. (1982) and Philipson et al. (1996) found that smoking retarded long-term particle clearance from the lungs. The mechanism(s) for interference with this longer-term phase of clearance has not been shown definitively, but may be related to impairment of phagocyte function and/or smoke-induced lung damage.

3.2 Interactions between tobacco smoke and other agents

3.2.1 Asbestos

Asbestos is a generic name for a group of fibrous silicates, differing in colour, fibre arrangement and length. Recognition of the health risks of asbestos has led to major reductions in production and uses. Asbestos types are classified according to their physical characteristics as serpentine or amphibole and differ in their relative carcinogenic potential. Amosite and crocidolite are amphiboles and have short and straight needle-like fibres. Chrysotile is a serpentine and consists of long, pliable white fibres. The longer fibre varieties of asbestos can be spun into yarn which can be woven into fabric; short fibre varieties can be incorporated into cement, asbestos board and tiles. Asbestos products have been used in a variety of applications including electrical and thermal insulation in buildings, fire and safety equipment, brake linings of motor vehicles, and shipbuilding. Workers in asbestos mining and processing and a wide range of manufacturing industries are exposed to various forms of asbestos, while others are exposed in maintenance work, demolition and recycling operations.

Occupational exposure to asbestos is associated with asbestosis and cancers at various sites, notably pleural mesothelioma and lung cancer. Differences between the effect of asbestos on the health of smokers and non-smokers have been reported, and studies have been conducted aimed specifically at elucidating the combined effects of smoking and asbestos exposure. Perioccupational exposure to asbestos is a hazard to household contacts of asbestos workers, who bring home dust on their clothes, and to people living in areas where there is environmental contamination by asbestos dust from industry (Anderson et al., 1979).

The amphibole varieties of asbestos (crocidolite and amosite) have the highest carcinogenic risk. Crocidolite presents a greater risk than amosite, which in turn is more dangerous than chrysotile, a serpentine variety. Erionite and tremolite are non-asbestos fibrous minerals used in building in some parts of the world and there is a high prevalence of mesothelioma in these regions (Baris et al., 1979; Yazicioglu et al., 1980).

Because there are many different occupations and environmental situations in which asbestos exposure might occur, along with a wide range of possible levels of exposure and variety of types of asbestos in use, it is difficult to define clearly asbestos exposure or the smoking habits of those exposed. The smoking history of the population sampled is important, because there have been changes in smoking materials and prevalences of smoking in many countries (Cheng & Kong, 1992). In many studies, only the number of smokers within sub-groups of workers with asbestos-related disease have been reported, rather than the detailed smoking habits of the exposed population. A widely used assumption is that the smoking habits of asbestos-exposed workers reflect those of blue collar workers and are thus higher than national average figures. Table 5 gives examples of smoking prevalence in different groups of asbestos-exposed workers.

Table 5. Smoking prevalence in asbestos-exposed workers

Exposure	Smoking habits	References
Asbestos textile workers	75% smokers 46% cigarette smokers 36% ex-cigarette smokers 5.5% pipe/cigar smokers	Weiss (1971)
Electrochemical plant (two areas)	84% to 87% were smokers or ex-smokers	Kobusch et al. (1984)
Population in Telemark, Norway	Asbestos exposed: 44.6% smokers 36.0% ex-smokers Not exposed: 40.95% smokers 28.6% ex-smokers	Hilt (1986)
Survey of 800 000 American men and women in 1982	Asbestos exposed: 33.6% smokers 47.3% ex-smokers	Stellman et al. (1988)
Lung cancer case-referent study; Swedish industrial city	Men: 95% smokers Women: 78% smokers	Järvholm (1993)
Shipyard workers in Gothenburg, Sweden December 1987	46% smokers 31% ex-smokers 21% non-smokers 2% not known	Sanden et al. (1992)
Asbestos factory workers	Men: 74% smokers (male population average 66%) Women: 49% smokers (female population average 40%)	Newhouse & Berry (1979)

3.2.1.1 Asbestos and lung cancer

Exposure to asbestos dust carries a risk of parenchymal and pleural fibrosis, mesothelioma and lung cancer. Selikoff et al. (1968) and Berry et al. (1972) showed that cigarette smoking was an added hazard among asbestos workers. In combination, the two hazards are associated with very high lung cancer rates. Studies were carried out (e.g., Hammond & Selikoff, 1973; Martischnig et al., 1977; Hammond et al., 1979; Selikoff et al., 1980; Acheson et al., 1984; Berry et al., 1985) to determine whether cigarette smoke and asbestos act independently, their combined effect being the sum of the individual effects, or there is an interaction with the ultimate effect being a product of the two risk factors. In some studies, the effects of smoke and asbestos appeared to be additive, in others multiplicative and in others somewhere between the two. Reasons for the lack of consistency among the studies may relate to the size of the population sampled, its average age, social class and residential area, the type of asbestos involved, the time scale covered and the intensity of exposure to asbestos. The weight of evidence favours a synergistic or multiplicative model for the interaction of asbestos and smoking. While the differences may be partly linked to the carcinogenic potential of different types of asbestos and to different smoking materials and ways of smoking, including passive smoking (Cheng & Kong, 1992), they also reflect the complex nature of tobacco smoke, which contains complete carcinogens, tumour promoters and co-carcinogens and other compounds that can influence the multistage carcinogenic process. However, whatever the type of smoking/asbestos interaction influencing the incidence of lung cancer, there is a greatly increased risk for the asbestos-exposed worker who smokes (Table 6).

Hammond et al. (1979) found a very strong synergistic effect and this was supported by studies of shipyard workers in Italy (Bovenzi et al., 1993), asbestos factory workers in London (Newhouse & Berry, 1979), Finnish anthophyllite miners and millers (Meurman et al., 1979), chrysotile workers in China (Cheng & Kong, 1992; Zhu & Wang, 1993) and workers exposed to crocidolite in Western Australia (de Klerk et al., 1991). Cheng & Kong (1992) reported a lower ratio of non-smoking to smoking lung cancer death rates and suggested that this reflected passive smoking among non-smokers and the use by most smokers of hand-rolled cigarettes. Liddell et al. (1984) found that

Table 6. Age-standardized lung cancer death rates[a] for cigarette smoking and/or occupational exposure to asbestos dust compared with no smoking and no occupational exposure to asbestos dust (from: Hammond et al., 1979)

Group	Exposure to asbestos?	History cigarette smoking?	Death rate	Mortality difference	Mortality ratio
Control	No	No	1.3	0.0	1.00
Asbestos workers	Yes	No	58.4	+47.1	5.17
Control	No	Yes	122.6	+111.3	10.85
Asbestos workers	Yes	Yes	601.6	+590.3	53.24

[a] Rate per 100 000 man-years standardized for age on the distribution of the man-years of all the asbestos workers; number of lung cancer deaths based on death certificate information

their data fitted both an additive model and a multiplicative model and concluded that the combined relative risk lay somewhere between the two. Selikoff et al. (1980), from a study of amosite factory workers, and Berry et al. (1985), from a study of asbestos factory workers, favoured an additive model. However, caution is required because of the definitions of additive and multiplicative used by different authors and the overlap between these terms and such words as synergism and promoter.

Molecular biology studies of autopsy specimens of lung tumour tissue from of cigarette smokers have revealed that cigarette smoking induces K-ras mutation (Rodenhuis & Slebos, 1992). It has been suggested that such cigarette-smoke-induced K-ras oncogene mutations are promoted by the presence of asbestos, which creates selective growth conditions for the mutated cells (Vainio et al., 1993). Vainio & Boffetta (1994) concluded that both tobacco smoke and asbestos fibres can be genotoxic and cytotoxic, and cause proliferative lesions in the lungs. Tobacco smoke contains carcinogens that bind to critical genes and cause mutations. Asbestos fibres cause chronic inflammation of the lungs, which releases various cytokines and growth factors, and may provide a selective growth advantage for mutated cells.

3.2.1.2 *Asbestos and pleural mesothelioma*

There is an established relationship between exposure to asbestos – crocidolite, amosite, chrysotile – and pleural mesothelioma (Stellman, 1988). In shipyard workers mainly exposed to chrysotile, Sanden et al. (1992) found an increase in pleural mesotheliomas up to 15 years after cessation of exposure. Asbestos is also linked with peritoneal mesothelioma (Newhouse & Berry, 1976). The risk of lung cancer was found to fall after exposure ceased, suggesting that asbestos acted as a lung cancer promoter, but the risk of mesothelioma long after cessation of exposure indicated that asbestos acted as a complete carcinogen. Mesothelioma can have an extremely long latent period, with cases presenting even 30 years or more after first exposure (Newhouse & Berry, 1976). Up to 90% of cases of pleural mesothelioma have been attributed to asbestos but there is no evidence directly associating smoking with the disease, or showing that smoking has any influence on the incidence of asbestos-related pleural

mesothelioma (Berry et al., 1985; Hughes & Weill, 1991; Sanden & Jarvholm, 1991; Muscat & Wynder, 1991).

3.2.1.3 *Asbestos and other forms of cancer*

Asbestos fibres have been found in many tissues, other than the lungs, of asbestos workers. There is evidence that an asbestos/smoking interaction increases the incidence of cancer of the oesophagus, pharynx, buccal cavity and larynx but not of pleural or peritoneal mesothelioma, or of cancer of the stomach, colon-rectum or kidney, for which smoking and non-smoking asbestos workers are at equal risk (Hammond et al., 1979; Selikoff & Frank, 1983; US ATSDR, 1995).

3.2.1.4 *Asbestosis*

Asbestosis is a fibrotic reaction to asbestos in the lungs. In a review of histological, animal experimental and radiological evidence, Weiss (1984) concluded that cigarette smoking could result in diffuse fibrosis similar to that caused by asbestos, and the fibrosis showed a dose–response to the duration and degree of smoking. Prevalence studies are consistent in showing a higher frequency of diffuse small irregular opacities in asbestos workers who are smokers than in those who are non-smokers. It has been suggested that the effects may be additive. Tobacco smoke affects lung clearance and hence the retention of asbestos fibres in the lungs. In asbestosis the intensity of fibrosis correlates with the number of asbestos bodies in the lungs, and Murai et al. (1994) concluded that reduction of lung clearance by tobacco smoke could increase the intensity of fibrosis. Crocidolite fibres are the most fibrogenic of the various types of asbestos but De Klerk et al. (1991) concluded that smoking had no measurable effect on crocidolite asbestosis.

An interaction between asbestos and smoking causing a greater frequency of obstructive airways disease in asbestos workers who smoke was found in a study of pulmonary function changes caused by asbestosis (Selikoff & Frank, 1983). Miller (1993) presented similar results suggesting an interaction between asbestos and smoking. In a prospective mortality study, Hughes & Weill (1991) concluded that asbestosis is a precursor of asbestos-related lung cancer, but they were unable to assess an interaction between tobacco smoking and

asbestosis because all the cases were in smokers and there were no non-smokers.

In rats, asbestos fibres stimulate alveolar macrophages to generate the inflammatory and fibrogenic mediators, tumour necrosis factor-alpha (TNFα), and this may be the cause of inflammation and lung fibrosis due to asbestos (Ljungman et al., 1994). In *in vitro* studies Morimoto et al. (1993) found synergism between chrysotile fibres and cigarette smoke in the stimulation of the formation of TNF-α by rat alveolar macrophages.

3.3 Non-asbestos fibres

3.3.1 Glass fibre

IARC (1988) classified glasswool as possibly carcinogenic to humans (Group 2B) and glass filaments as not classifiable as to their carcinogenicity to humans (Group 3), based on sufficient evidence for the carcinogenicity of glasswool and inadequate evidence for the carcinogenicity of glass filaments in experimental animals and inadequate evidence for the carcinogenicity of glasswool and glass filaments in humans. There are data on exposure to glass fibre and tobacco smoke. Enterline et al. (1987a) carried out a case control study of 7586 glasswool workers in four plants producing small diameter fibres, less than 3 μm in diameter. Smoking histories were obtained for 75% of the workers. Analysis of data by logistic regression showed that smoking was a powerful variable and multiplied the effect of fibre exposure. In a case-control study of the influence of non-workplace factors on respiratory disease in employees of a glass fibre manufacturing facility, Chiazze et al. (1992, 1995) concluded that smoking, and not exposure to glass fibre, was the most important risk factor for the increased lung cancer risk but was not as important for non-malignant respiratory disease. In a further analysis, using data not previously available, Chiazze et al. (1995) estimated the extent of confounding by cigarette smoking, and suggested that adjusting for the confounding effect could reduce the lung cancer standardized mortality ratio to a non-statistically significant level.

3.3.2 Rockwool, slagwool and ceramic fibres

IARC (1988) concluded that there was limited evidence for the carcinogenicity of rockwool and inadequate evidence for the carcinogenicity of slagwool in experimental animals, with limited evidence for the carcinogenicity of rock-/slagwool in humans: the overall evaluation for both was Group 2B, possibly carcinogenic to humans. For ceramic fibres there was sufficient evidence for their carcinogenicity in experimental animals, with no data on their carcinogenicity in humans: the overall evaluation for ceramic fibres was also Group 2B, possibly carcinogenic to humans.

In a study of insulation workers using rock and glass wool, (Clausen et al., 1993) concluded that exposure was associated with an increased risk of developing obstructive lung disease. In a study of respiratory health in 628 workers in seven European plants manufacturing ceramic fibres, skin, eye and nasal irritation, breathlessness and wheezing were common findings (Trethowan et al., 1995). Respiratory symptoms were more frequent in smokers and increased with the amount smoked. The authors concluded that exposure caused irritation, similar to that caused by other man-made fibres, and that cumulative exposure could cause airways obstruction by promoting the effects of cigarette smoke.

Ljungman et al. (1994) demonstrated in rats that rock wool, slag wool, kaolin ceramic fibre and silicon carbide fibre stimulated alveolar macrophages to generate tumour necrosis factor-alpha (TNF-α), a potent inflammatory and fibrogenic mediator. In *in vitro* studies Morimoto et al. (1993) found synergism between mineral fibres (chrysotile and alumina silicate ceramic fibres) and cigarette smoke in the stimulation of the formation of TNF-α by rat alveolar macrophages. Leanderson & Tagesson (1989) found that cigarette smoke potentiated the DNA-damaging effect of man-made mineral fibres (rockwool, glasswool and ceramic fibres).

3.4 Inorganic chemicals

3.4.1 Arsenic

Compounds of arsenic have been used as pesticides and as preservatives of wood and leather. Arsenic is present in many metal

ores and is released during smelting Radon progeny are frequently encountered as a contaminant of arsenic. In some parts of the world arsenic is found in drinking-water in relatively high concentrations.

Arsenic and its compounds are carcinogenic (WHO, 1980; IARC, 1987; Tsuda et al., 1990, 1995). Skin cancer can occur after ingestion of arsenic (Tseng et al., 1968; Smith et al., 1992), and lung cancer after inhalation of arsenic by smelter workers or by people living nearby (Welch et al., 1982; Pershagen, 1985; Pershagen et al., 1987) or by agricultural workers exposed to the pesticide lead arsenate (Wicklund et al., 1988). IARC (1987) classed arsenic and arsenic compounds as Group 1, carcinogenic to humans. It has been suggested that arsenic in drinking-water may also cause liver, lung, kidney and bladder cancer (Smith et al., 1992).

A study of the lung cancer risk among cadmium-exposed workers suggested that exposure to arsenic and tobacco smoke may have been the cause of an increased rate of lung cancer, rather than exposure to cadmium particulates (Lamm et al., 1992). Tsuda et al. (1990) suggested an interaction between arsenic and smoking in exposed workers in a small Japanese village where arsenic was mined and refined. However, the village water and air were highly polluted by emissions from the smelter and from slag disposal, making interaction between arsenic and smoking difficult to assess. A study of copper smelter workers in the USA indicated that the effect of arsenic was probably more important in lung cancer than that of tobacco smoke (Welch et al., 1982). Studies in Sweden showed increased lung cancer risks from arsenic exposure at a copper smelter; a multiplicative effect for smoking and arsenic was found and age-standardized rate ratios for lung cancer mortality were 3.0 for arsenic-exposed workers, 4.9 for smokers with no arsenic exposure and 14.6 for arsenic-exposed smokers (Pershagen et al., 1981). In a later study, Pershagen (1985) reported an additive effect for smoking and arsenic exposure on lung cancer incidence in situations where the arsenic exposure was lower. In a cohort of 3916 Swedish copper smelter workers, the risk of developing lung cancer from the interaction between arsenic and smoking was intermediate between additive and multiplicative and appeared to be less pronounced among heavy smokers (Jarup & Pershagen, 1991).

There was no evidence of synergism between arsenic and tobacco smoke in tin miners in Yunan Province, China. The lung cancer risk was greater for arsenic than for smoking, and simultaneous assessment of arsenic and radon exposure revealed radon to be the greater risk (Taylor et al., 1989). In Ontario it was concluded that the excess lung cancer mortality of gold miners and uranium miners was probably due to exposure to arsenic and short-lived radon decay products (Kusiak et al., 1991). This was consistent with the hypothesis that the risk of lung cancer from exposure to arsenic is enhanced by exposure to other carcinogens (Kusiak et al., 1993).

Hertz-Picciotto et al. (1992) assembled data from several studies to examine possible synergism between smoking and exposure to arsenic and an increased risk of lung cancer. The joint effect from both exposures consistently exceeded the sum of the separate effects: a minimum of 30% to 54% of lung cancer cases among those with both exposures could not be attributed to either one or the other exposure alone. The conclusion was that arsenic and smoking acted synergistically to cause lung cancer. Arsenic-induced lung cancer was not limited to exposure to inhaled arsenic because there was evidence of synergism between ingested arsenic and smoking (Tsuda et al., 1995). An association of arsenic exposures with bladder cancer was confined to subjects who had been smokers Bates et al. (1995).

In a Swedish study of lung cancer in arsenic workers, it was found that cases among smelter workers who had never smoked showed a histological distribution resembling that of smokers, probably reflecting an exposure to carcinogenic agents at the smelter which influence the risk of different histological types in the same way as smoking (Pershagen et al., 1987). Tobacco smoking primarily induces epidermoid and small cell carcinomas but there are also increased risks for other cell types. The proportion of small cell carcinomas was greater in uranium miners than in the general population (Kusiak et al., 1993). In smokers, there were no pronounced differences in the histological type of lung carcinomas between arsenic exposed smelter workers and controls (Pershagen et al., 1987).

It has been suggested that the potentiation of the carcinogenic properties of arsenic by smoking could be due to inorganic arsenic requiring a strong co-carcinogen to manifest a carcinogenic effect, or

that arsenic itself might be acting as co-carcinogen rather than as a direct carcinogen (Stohrer, 1991; Tsuda et al., 1995).

3.4.2 Beryllium

Beryllium is a metal with a number of uses including alloys, nuclear energy applications, and in the rocket and aerospace industry (IPCS, 1990; IARC, 1993). Fine dusts and fumes of the metal and some of its salts are hazardous and when inhaled are deposited in the lungs from where beryllium may be widely distributed throughout the body.

Beryllium metal, oxide and some salts give rise to acute inflammation on skin contact, particularly when accompanied by friction or perspiration. Short exposure to dusts and fumes can cause acute inflammation of mucous membranes: conjunctivitis, bronchitis, pneumonitis. Granulomatous reaction can follow chronic inflammation of the skin, and lesions may appear in the liver and elsewhere after long periods of absorption from the lungs. Beryllium and its compounds are a cause of delayed pneumonitis and pulmonary granulomas. IARC (1993) classified beryllium and beryllium compounds as Group 1, carcinogenic to humans, on the basis of sufficient evidence in humans and in experimental animals. However, in epidemiological studies the information on smoking was incomplete and the data did not rule out the possibility that the few excess deaths observed could have been due to smoking rather than to any other cause (Steenland & Ward, 1991, 1993; Eisenbud, 1993; MacMahon, 1994; Kotin, 1994).

The prevalence of chronic beryllium disease (CBD) is reduced in smokers compared with non-smokers. The disease is preceded by the development of beryllium-specific sensitization. In two studies examining different worker populations, the prevalence of smoking in those with clinically diagnosed CBD was lower than in those that were sensitized but did not have the disease (Kreiss et al., 1993; Kreiss et al., 1996).

3.4.3 Chromium

Chromium and its compounds are used in metallurgical, chemical, electroplating and leather tanning industries (IARC, 1990).

The principal route of entry to the body is through the lungs. Chromium ulcers of the skin and dermatitis can result from handling chromium products and deposition of chromates on mucous membranes can also cause ulceration which, in the nasal septum, can lead to perforation (Lindberg & Hedenstierna, 1983; IARC, 1990). Chromium and some chromium compounds are respiratory tract sensitizers and a cause asthma. Hexavalent chromium salts have been associated with lung cancer both in experimental animals and in epidemiological studies. IARC (1990) concluded that there is sufficient evidence in humans for the carcinogenicity of hexavalent chromium compounds as encountered in chromate production, chromate pigment production and chromium plating industries.

Langård & Norseth (1975) suggested that cigarette smoking increases the risk for lung cancer in workers exposed to chromate dust. Other studies (Abe et al., 1982; Langård & Vigander, 1983; Yoshizawa, 1984; Nishiyama et al., 1985) have suggested that workers with exposure to chromium compounds who are also smokers may be at greater risk than non-smokers. However, the numbers were too small for conclusions on interactions to be drawn.

3.4.4 Nickel

Exposure to nickel or its compounds occurs in mining, refining, smelting and alloying the metal, in nickel plating and in welding. It is used in battery manufacture, electroplating, enamelling, ceramics, the chemical and petroleum industries and in dyestuffs and ink making. Exposure may be by skin contact or inhalation of dusts, fumes, mists or gaseous nickel carbonyl (IPCS, 1991a). In occupational exposure the daily intake and absorption/retention vary widely between industries (IARC, 1990).

Nickel is absorbed from the soil by the tobacco plant. During smoking, up to 20% of the nickel in the tobacco is transferred to mainstream smoke. This high transfer rate, compared to the much lower transfer rates of other metals, has been explained by the formation of the volatile nickel carbonyl (Sunderman & Sunderman, 1961). Nickel carbonyl is a strong lung carcinogen in rats (IARC, 1990).

IARC (1990) evaluated the carcinogenicity of nickel and nickel compounds and classified nickel compounds as carcinogenic to humans (Group 1) and nickel as possibly carcinogenic to humans (Group 2B). In an epidemiological study on a cohort of 916 workers in a Norwegian nickel refinery, four work categories were defined: i) roasting and smelting; ii) electrolysis; iii) other processes; and iv) other work groups. All groups showed an excess risk of respiratory cancer. In the roasting and smelting department there were excess risks for lung cancer (O/E = 12/2.5) and nasal cavity cancer (O/E = 5/0.1). In the electrolysis department there were also excess risks of lung cancer (O/E = 26/3.6) and nasal cavity cancer (0/E = 6/0.2) (Pedersen et al., 1973). Magnus et al. (1982) updated this study and found evidence of an additive effect of smoking and nickel exposure in the induction of respiratory cancer. Histological examination of nasal biopsy specimens from 59 retired nickel workers, 21 of whom were smokers and snuff users, showed a higher score of nasal epithelial dysplasia in smokers than in non-smokers, and 4 workers with nasal carcinoma were smokers (Boysen et al., 1984). In monitoring nickel exposure by imaging cytometry of nasal smears (Reith et al., 1994), it was possible to distinguish between workers who were exposed to different nickel compounds and to distinguish between smoking and non-smoking nickel workers.

3.4.5 Manganese

There is occupational exposure to manganese in its mining, the ferromanganese and iron and steel industries, the production of dry cell batteries, and the manufacture and use of welding rods. Manganese is released by the combustion of the gasoline additive, methylcyclopentadienyl manganese tricarbonyl (MMT), used in some countries. However, the amount in gasoline (approximately 10 mg/litre) and emitted in vehicle exhausts is small and does not to lead to human exposure (Health Canada, 1994). The principal route of entry of manganese is through the lungs but, because most of the compounds are insoluble, only the smallest particles, as contained in furnace and welding fume, are capable of reaching the alveoli and being phagocytosed and absorbed (IARC, 1986).

Manganese is present in tobacco leaves and it has been reported (IARC, 1986) that 0.003 µg of manganese appears in the mainstream

smoke from one cigarette and thus contributes to a smoker's manganese intake in the form of small and dangerous particles.

Manganese is neurotoxic and long-term occupational exposure can cause a condition resembling Parkinson's disease. It causes lung damage leading to an increased incidence of pneumonia and a higher rate of acute and chronic bronchitis. In studies of manganese alloy production workers and chronic lung disease, smokers were more affected than non-smokers and the relationship between the number of cigarettes smoked and the prevalence of respiratory tract symptoms suggested that smoking acted synergistically with manganese (Saris & Lucic-Palaic, 1977). In a study of workers producing manganese salts and oxide (Roels et al., 1985) smoking and manganese exposure were additive in producing preclinical toxic effects. In studies on workers producing iron-manganese alloys, one concerned with chronic bronchitis (Misiewicz et al., 1994) and the other with pulmonary ventilatory disturbance (Misiewicz et al., 1992), there was no relationship between the occupational exposure or its duration and health effects. The chronic bronchitis and ventilatory disturbance were attributed to cigarette smoking.

3.4.6 *Platinum*

Platinum is used as a catalyst in many chemical processes and in motor vehicle exhausts. Chloroplatinic acid is an intermediate in the preparation of a large number of complex salts, which are used in platinum refining, the chemical industry and, therapeutically, in cancer chemotherapy.

Platinum salt sensitivity is an IgE-mediated immune response (IPCS, 1991b). Ammonium hexachloroplatinate is used as an intermediate in platinum refining, and its inhalation provokes asthmatic responses and elicits immediate skin test responses in sensitized individuals (Pepys et al., 1972). In a cohort study of 91 workers in a platinum refinery (Venables et al., 1989), 22 developed respiratory symptoms and an immediate skin test response to ammonium hexachloroplatinate. The risk was greatest in the first year of employment and smokers had an increased risk of becoming sensitized. In another study, out of 78 workers at a platinum refinery, 32 (41%) had developed platinum salts sensitivity after 24 months of

exposure and the risk of sensitization was about 8 times greater for smokers (Calverley et al., 1995).

Baker et al. (1990) conducted a cross-sectional study of respiratory and dermatological effects of platinum salt sensitization in 136 workers (107 current employees and 29 former employees) at a precious metal refinery. Twenty three workers (22%) had become sensitized. Platinum salts sensitivity was not associated with atopicity but was strongly associated with cigarette smoking status.

3.4.7 Silica

Silicosis (lung fibrosis caused by silica) is not only a hazard of mining. It is also found in bricklayers, cement makers, workers in pottery, porcelain and ceramics, rock drillers, workers chipping, grinding or polishing stone, in sandblasting, using grinding stones to smooth or polish precious stones, metals or optical glass, and in the manufacture of polishing materials such as metal polishes and toothpaste. The number of industries generating silica dust is large. The amount of respirable dust varies from one to another and, because silica is an active adsorbent, it can become contaminated and have its toxic potential changed. Furthermore, freshly fractured silica dust may exhibit a different surface reactivity and cytotoxicity from that of aged silica (Vallyathan et al., 1988).

Hnizdo & Sluis-Cremer (1991), in a study of gold miners, linked high exposure to silica dust with lung cancer and found a combined effect of dust and smoking that fitted a multiplicative model for lung cancer. Amandus et al. (1992) studied lung cancer in men with diagnosed silicosis and suggested that there was an association between the two diseases. In a study of iron foundry workers (Andjelkovich et al., 1994), cigarette smoking was a strong predictor of lung cancer whereas silica exposure showed no association with the disease

Chronic silicosis develops after 20 to 40 years of exposure to silica dust. There are also other types of pneumoconiosis related to the nature of the dust, and chronic bronchitis and airways obstruction have been associated with silica dust exposure. A hypothesis for the pathogenesis of chronic silicosis is that silica particles are phagocytosed by the alveolar macrophages for which they have a

marked selective toxicity. Permanent macrophage activation initiates inflammatory reactions leading to the formation of collagenous fibres. Acute silicosis arises from the inhalation of more highly reactive silica (Vallyathan et al., 1988). The link between silicosis and smoking was examined in a study of smoking and silica exposure on pulmonary epithelial permeability. Faster clearance of a radioaerosol from the upper lung regions was found for smokers (Nery et al., 1988, 1993). The question of silica clearance was considered in an analysis of an association between silicosis and smoking: differences in collagenization for smokers and non-smokers were attributed to differences in the interception of silica particulate matter by mucus (Hessel et al., 1991). In studies by Ng et al. (1987, 1992), smoking was not considered to affect the progression of silicosis in granite quarry workers. However, examining the association of silicosis with lung cancer, Ng et al. (1990) concluded that the excess lung cancer risk in silicosis is attributable to smoking, and there appeared to be a synergistic effect between smoking and silica/silicosis regarding the risk of developing lung cancer.

In a study of 562 South African gold miners exposed to low levels of dust with a high (50–70%) silica content, the incidence of chronic bronchitis was higher than in non-dust-exposed controls. Although the percentage of smokers was higher in those with chronic bronchitis in both groups, there was a significant excess in the dust-exposed smokers (Sluis-Cremer et al., 1967). The authors concluded that there was a factor in dust-exposed smokers that increased the incidence of chronic bronchitis above that expected from smoking alone. In a study of 2209 South African gold miners and 483 non-miners on the effect of silica dust and tobacco smoking on mortality from chronic obstructive lung disease, it was found that miners who smoked and were exposed to silica dust were at higher risk of dying from chronic obstructive lung disease than smokers not exposed to silica dust. In South African gold mines about 30% of the respirable dust is free silica. It was concluded that tobacco smoking and silica dust acted synergistically in causing chronic obstructive lung disease (Hnizdo, 1990). Hnizdo et al. (1990) applied additive and multiplicative relative risk models to the same sample and found that departure from additivity increased progressively with the severity of obstructive impairment. They concluded that tobacco smoking potentiated the effect of dust in causing respiratory impairment and that severe respiratory impairment could have been prevented through elimination

of tobacco smoking (Hnizdo et al., 1990). Oxman et al., (1993) analysed the relationship between occupational dust exposure and chronic obstructive lung disease in both gold and coal miners and found a significant association between loss of lung function and cumulative respirable dust exposure, which was greater in gold miners. In this study there was no evidence of interaction with tobacco smoking for gold miners, and the authors suggested that the increased risk of lung function loss was due to exposure to dust having a higher silica content than coal dust. Among iron ore miners in Sweden, Jörgensen et al. (1988) found a strong relationship between chronic bronchitis and smoking, but not with working underground. The two risk factors, silica dust and smoking, appeared to be additive but the smoking effect was far greater than that of silica dust. In a study of small airway disease in patients with silica dust exposure, with and without radiographic evidence of silicosis, and smoking, Avolio et al. (1986) found no differences in lung function and prevalence of small airways disease with silicosis. However, in both groups small airway disease was significantly related to tobacco smoking, indicating that this had a more powerful effect than silicosis.

3.5 Organic chemical agents

Many organic compounds with properties covering a wide spectrum of molecular structure and biological activity are encountered in a variety of industries. The effects of a few compounds, some of which are encountered in specific industries, and smoking have been studied. Where organic compounds occur in both tobacco smoke and the workplace, the effect of smoking becomes one of dose augmentation, although modification of effect can also occur. Some organic compounds would normally not be found in tobacco smoke but are present because workplace materials have contaminated smoking materials and they are then pyrolysed or volatilized during smoking.

3.5.1 *Chloromethyl ethers*

Chloromethyl methyl ether (CMME) and its contaminant bis(chloromethyl) ether (BCME) are used in the synthetic chemical industry, in the manufacture of ion exchange resins and in polymer production. They are carcinogenic when inhaled, BCME more so than CMME. In a long-term study of chemical workers, 93 had exposure

to chloromethyl ethers and 22 died from lung cancer. Of 32 workers who had no exposure, 3 died from lung cancer (Weiss & Boucot, 1975; Weiss, 1976, 1980, 1982). For the 22 cases in of lung cancer in the exposed workers, a dose–response relationship was established. In the groups with heavy occupational exposure, there were fewer heavy smokers (>20 cigarettes per day) than in the groups with lower occupational exposure. This statistically significant shift might be explained by self-selection of heavy smokers out of the high occupational exposure groups because of the bronchial irritation that is caused by the exposure to chloromethyl ethers, or cigarette smoking might have an antagonistic activity (Steenland & Thun, 1986; Thomas & Whittemore, 1988; Weiss & Nash, 1997).

3.5.2 *Tetrachlorophthalic anhydride*

Tetrachlorophthalic anhydride (TCPA) is used as an epoxy resin curing agent. It is respiratory tract sensitizer and causes asthma (Schlueter et al., 1978). In a study using a radio allergosorbent test with a TCPA human serum albumin conjugate, specific IgE antibody was detected in serum from 24 out of 300 factory floor workers exposed to TCPA. Of these 24, 20 (83%) were current smokers, compared with 133 (48%) of 276 without antibody ($p<0.01$), and there was a weaker association with atopy, defined by skin tests with common allergens. Smoking and atopy interacted, the prevalence of antibody being 16% in atopic smokers, 12% in non-atopic smokers, 8% in atopic non-smokers and none in the non-atopic non-smokers. It was concluded that smoking may predispose to, and interact with atopy in the production of specific IgE antibody to this hapten protein conjugate.

3.5.3 *Dyestuffs*

There is an established relationship between bladder cancer and exposure to certain aromatic amines encountered in the dyestuffs industry, e.g., benzidine, 4-aminobiphenyl and 2-naphthylamine (IARC, 1987), and smoking is causally associated with bladder cancer (IARC, 1986; US Surgeon General, 1989). From an analysis of 991 cases by Cartwright (1982), a significant risk of bladder cancer was associated with cigarette smoking, and a dose–response relationship, based on years of employment, was found in workers in dyestuffs manufacturing. The risks were considered to be additive. Overall, there

was a significant risk of bladder cancer associated with cigarette smoking, a risk ratio of 1.8 for males, and there were significant overall risks associated with occupations such as those of process workers in the dye manufacturing industry who had a risk of 2.9 for males. When dye manufacturing process workers who were smokers were compared with non-smoking workers, the risk for smokers was 4.6, while for non-smokers the risk was 1.9.

Boyko et al. (1985) concluded that arylamines in the dyestuffs industry posed a major threat of bladder cancer. However, there was little evidence to support an effect due to smoking or an interaction between smoking and occupational exposure.

In an area of Spain where 44% of the adult population worked in dyeing and printing textile fabrics, there was an increased risk of bladder cancer for smokers (OR 2.3) (Gonzalez et al., 1985). The estimated risks for occupation and for smoking and occupational exposure were OR 5.5 and 11.7, respectively. The observed effect was multiplicative. Tobacco smoke contains many amines, including the bladder carcinogens 4-aminobiphenyl (>9 ng/cigarette) and 2-naphthylamine (54 ng/cigarette) (Patrianakos & Hoffmann, 1979; Pieraccini et al., 1992; Grimmer et al., 1995).

In a study of risk factors for bladder cancer in Spain (Bravo et al., 1987), the results were considered to corroborate previous data that bladder cancer does not have a single cause. Cigarette smoking was considered an important cause but one which was additional to urological disease or occupational exposure, among other factors. In a study of men in Spain (Gonzalez et al., 1989), increased risks of bladder cancer were found for textile workers (OR 1.97), mechanics and maintenance workers (OR 1.86), and workers in the printing industry (OR 2.06). The highest risk was in those who were employed in the textile industry before the age of 25 and prior to 1960. Among mechanics the highest risk was for those who started after the age of 25 and after 1960. The OR for smokers who had also been employed in one of the high-risk occupations was 7.82, which is compatible with a multiplicative effect of joint exposure to tobacco smoke and occupational hazards. In an Italian study (D'Avanzo et al., 1990), risk additivity was found for the interaction between tobacco smoke and several occupations associated with bladder cancer but the occupations were not specified. The bladder cancer risk for smokers of black

tobacco was higher (OR = 3.7) compared with smokers of blond tobacco cigarettes (OR = 2.6). A higher risk for black tobacco than for blond varieties and a protective effect for smokers of tipped cigarettes was also reported in a study in Northern Italy where a multiplicative effect for smoking and high risk occupations was also found (Vineis et al., 1984).

Bartsch et al. (1993) correlated the higher incidence of bladder cancer among smokers of black tobacco with high yield aromatic amines, particularly 4-aminobiphenyl from black tobacco (5 times greater than from blond tobacco). The concentrations of urinary mutagens and of 4-aminobiphenyl adducts in the blood were also higher in smokers of black tobacco.

A Chinese study of bladder cancer incidence and mortality in workers with benzidine exposure found a marked dose response and an elevated risk for both producers and users of benzidine. Workers exposed to benzidine who were smokers had a 31-fold risk, while the risk for exposed workers who were non-smokers was 11-fold, and a multiplicative interaction was suggested (Bi et al., 1992).

3.5.4 Polycyclic aromatic hydrocarbons

Tobacco smoke contains many polycyclic aromatic hydrocarbons (PAHs) (IARC, 1986), a number of which, such as benz(*a*)pyrene and dibenz(*a,h*)anthracene, are known to be carcinogenic (IARC, 1987; Hoffmann & Hoffmann, 1997). PAHs are generated by incomplete combustion of organic matter in many industrial processes and constitute a hazard not only in occupations but also as environmental pollutants, representing primary risk factors as lung and bladder carcinogens. A tobacco smoker can obtain one dose of PAHs from tobacco smoke and another from the industrial or environmental source. Furthermore, an interaction of tobacco smoke and an occupational hazard is a possibility. PAHs in the workplace are often accompanied by many other toxic compounds, particularly irritants, and, in addition to carcinogenic PAHs, tobacco smoke contains co-carcinogens and tumour promoters as well as ciliatoxic agents, irritants and other biologically active species.

PAHs occur in coal gas manufacture, coking oven fumes, aluminium smelting, in the use of tar and asphalt, in oil refining and

the exhaust from internal combustion engines. They are frequently accompanied by irritant fumes or aerosols and potentially harmful particulate matter. There is a lack of smoking data for workers in many of these industries, but it has been assumed that the smoking prevalence is at least as high as the average for blue collar workers. At a Norwegian smelter 69% of workers were smokers when the expected prevalence of smoking was 52% (Abramson et al., 1989). The percentage of smokers and ex-smokers among workers exposed to chemicals and coal tar pitch in a 1982 survey of 800 000 men and women in the USA was 49.9% against 46.1% for the average worker (Stellman et al., 1988).

A Canadian study found a high prevalence of bladder cancer in aluminium smelter workers, particularly among those employed in Söderberg potrooms where carbon electrodes made from a mixture of petroleum pitch and coal pitch are used and PAH levels are high (Thériault et al., 1984). Changing electrodes, breaking the crust that forms on top of the molten metal and cleaning out the "pots" are activities that create air pollution by tar volatiles including carcinogenic PAHs which, measured as benzo(*a*)pyrene, could reach a concentration of 800 $\mu g/m^3$/8 h (Bjorseth et al., 1978). High levels of PAHs were found in urine samples from aluminium plant workers (Haugen et al., 1986). Lung cancer rates among aluminium reduction plant workers are also high (Gibbs & Horowitz, 1979). Tobacco smoke appears to increase the risk. In a study by Thériault et al. (1984), the numbers were too small to determine whether the interaction was additive or multiplicative, but in another study (Bjorseth et al., 1978) there was suggestive, but not conclusive, evidence that the relative risks from combined exposure to tar volatiles and cigarette smoke were multiplicative. In a study in which the preceding data were augmented (Armstrong et al., 1986), the tar volatiles were confirmed as the cause of bladder cancer and the results suggested that a multiplicative risk arose from a combined exposure to tar volatiles and cigarette smoke.

Gullvåg et al. (1985) found that the alveolar macrophage count for workers in the potrooms of an aluminium reduction plant was elevated and for workers who were also smokers the count was further elevated. The conclusion was that smoking and workplace pollution act synergistically in increasing the number of alveolar macrophages.

Workers in coke oven plants have a higher incidence of lung cancer than the general population and a measurable concentration of PAHs in urine, which is higher in smokers than non-smokers (Haugen et al., 1986). Van Schooten et al. (1990) analysed blood samples from coke oven workers for PAH-DNA adducts and urine for 1-hydroxypyrene and compared the results with those of non-exposed workers. Levels were elevated in coke oven workers and in both exposed and control groups the PAH-DNA adduct levels were higher among smokers than among non-smokers.

Professional drivers are exposed to benzene and carcinogenic PAHs and nitroarenes through the exhaust of petrol (gasoline) and, particularly, diesel engines. An excess of lung cancer has been found in this occupational group, with a suggestion of a synergistic interaction between smoking and occupational exposure (Damber & Larsson, 1985a).

Diesel exhaust contains large quantities of carbonaceous particulates with adsorbed PAHs. The association between lung cancer and diesel exhaust and the contributing role of cigarette smoking has been considered to be problematic (Garshick et al., 1987, 1988; Boffetta et al., 1988; Stöber & Abel, 1996; IPCS, 1996). In its evaluation, IARC (IARC, 1989c) considered diesel engine exhaust to be probably carcinogenic to humans (group 2A) and gasoline engine exhaust as being possibly carcinogenic to humans (group 2B).

In most of the workplaces where PAHs contaminate the atmosphere, there are also gases, fumes and aerosols that contain other hazardous materials that act as irritants; they may play a role in the etiology of chronic obstructive lung disease. It is important to include smoking in epidemiological studies. In a study of lung cancer mortality rates and smoking patterns in workers in the motor vehicle industry, proportionate mortality rates were considerably reduced when smoking rates were taken into account. An increased lung cancer risk has been described among foundry workers; PAHs and silica were considered to be possible etiological factors (Sherson et al., 1992). IARC (IARC, 1984, 1985b) considers the following technical products as carcinogenic to humans: coal tar and coal tar pitches, shale oils, soots, effluent aerosols from coal gasification, and emissions from coke ovens. Exposure occurring in the production of aluminium is classified as probably carcinogenic to humans, whereas the exposures

to aerosol emissions from iron and steel foundries are classified as possibly carcinogenic to humans.

3.5.5 Ethanol

Clinical and epidemiological studies have established a strong relationship between smoking and drinking (Istvan & Matarazzo, 1984; Bien & Burge, 1990; Zacny, 1990).

Elevated tobacco and alcohol consumption are regarded as the major risk factors for oropharyngeal and oesophageal cancer in many developed countries (Herity et al., 1982; Tuyns, 1983, 1991; Boyle et al., 1990; Muir & McKinney, 1992; Negri et al., 1992).

It has been difficult to distinguish the separate effects of these agents since many smokers tend to consume alcoholic beverages and *vice versa*. In addition, the consumption of one substance may have an effect on the use of the other substance. The possible interactions (e.g., multiplicative effect) of tobacco smoking and alcohol consumption for cancers of the oral cavity, pharynx and larynx have been evaluated by IARC (1986). IARC (1986) concluded that tobacco smoking was an important cause of oral, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers and combined ethanol consumption increased the risk substantially. In a case control study of 1114 patients with oropharyngeal cancer, Blot et al. (1988) showed that the risk to consumers of tobacco and alcohol was multiplicative rather than additive and increased 35-fold in those who consumed two or more packs of cigarettes and more than four alcoholic drinks per day. The risk was higher in those consuming spirits or beer than in those consuming wine and was lower in lifetime smokers of filter cigarettes.

Alcohol consumption and smoking affect fetal outcome, leading to infants with low birth weight (Wright et al., 1983, 1984; Smith et al., 1986).

In contrast to the many studies in laboratory animals of the interactions of ethanol with tobacco-smoke condensate (TSC) and specific tobacco constituents, e.g., nicotine (receptor studies) (Collins, 1990), (gastric-mucosal damage) (Wong et al., 1986; Cho et al., 1990), tobacco-smoke-specific nitrosamines, e.g., *N*-nitrosonornicotine (metabolism and carcinogenicity) (McCoy et al., 1981; Castonguay et

al., 1983, 1984) and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) (Jorquera et al., 1992; Schüller et al., 1993), there has been a relative paucity of studies involving ethanol and tobacco smoke *per se*. These latter studies have included fetotoxicity in mice (Peterson et al., 1981), gastric mucosal damage (Iwata et al., 1995; Chow et al., 1996), and mechanisms underlying behavioural association between alcohol and tobacco consumption (Zacny, 1990).

In *in vitro* studies on the effect of tobacco smoke condensate on rat buccal mucosa cells following exposure to ethanol, the level of adducts was higher than in controls, suggesting an increased uptake of carcinogens in the condensate (Autrup et al., 1992). Hsu et al. (1991) studied *in vitro* genotoxicity of tobacco smoke condensate in conjunction with 2% and 4% ethanol in human lymphoid cell lines. Ethanol potentiated clastogenicity, measured by frequency of chromosome breaks per cell, in a dose-dependent manner, and the results indicated that ethanol at relatively high doses inhibited DNA and chromosome repair systems.

Swiss Albino mice fetuses prenatally exposed to both tobacco smoke and ethanol had a high resorption frequency, a significant reduction in fetal weight and length, and neonatal growth retardation, indicating that ethanol and tobacco smoke may interact to produce fetotoxicity (Peterson et al., 1981).

Both cigarette smoking and ethanol consumption individually have been associated with gastric and duodenal ulcers in humans and animals. Exposure to cigarette smoke significantly potentiated ethanol-induced gastric mucosal damage in Sprague-Dawley rats (Iwata et al., 1995; Chow et al., 1996).

The effect of smoking on the incidence of cancers of the oral cavity, oropharynx, hypopharynx and larynx is often combined with other factors, principally alcohol, in the Western world. The possibility of interaction between cigarette smoking and alcohol consumption is complex (Burch et al., 1981).

Rothman & Keller (1972) reviewed the effect of joint exposure to tobacco and alcohol with regard to oral cancers alone (based on data published earlier by Keller & Terris, 1965) and concluded that a single

multiplicative function of the relative risks associated with alcohol and tobacco separately provided an adequate summary of their joint effect.

Wynder & Bross (1961) studied etiological factors in cancer of the oesophagus, considered the consumption and effects of tobacco and alcohol separately and together, and considered that the combined effect was multiplicative. Tuyns et al. (1977) reported a similar pattern of joint effect of tobacco and alcohol in a retrospective study of oesophageal cancer in Brittany, France. The relative risk of developing oesophageal cancer increased linearly with daily consumption of alcohol and tobacco independently. The combined effect fitted a multiplicative model.

Wynder et al. (1976) analysed environmental factors in cancer of the larynx and showed a combined effect of tobacco and alcohol. In the presence of smoking, heavy drinking increased the risk of cancer of the larynx, especially for cancer of the supraglottic portion of the larynx. Similar findings were reported by Burch et al. (1981).

In a prospective epidemiological study, the relative risk of incurring a single primary carcinoma of the oral cavity, pharynx, larynx and oesophagus in any one of these sites was increased independently by the duration and intensity of exposure to tobacco or alcohol and sustained exposure enhanced the risk in a multiplicative or synergistic fashion (Schottenfeld et al., 1974). The relative risk of multiple primary cancers in the sub-group with combined exposures to high levels of tobacco and alcohol was 3.9 times that of patients exposed previously to low levels of alcohol and tobacco.

3.5.6 *Other organic compounds*

Exposure situations involving compounds and mixtures of organic compounds for which no definite smoking interactions have been established but which are known to present serious health hazards are summarized in chapter 4.

3.6 Physical agents

3.6.1 *Radiation*

The harmful forms of ionizing radiation that are of concern are α- and β-particles and γ- and X-rays. All cause cellular damage and have

been implicated in carcinogenesis. IARC (1988) classified radon and its decay products as Group 1 (carcinogenic to humans) on the basis of sufficient evidence in humans and in laboratory animals. The interaction of the effects of these radiations with the effects of tobacco smoke has been studied. Radium is present in uranium and other minerals and in all rocks and soils. It emits α- and β-particles and γ-rays and decays to form the chemically inert radioactive gas radon, which is released in tiny amounts into the atmosphere where its concentration is extremely small because of dilution. It can, however, become more concentrated in some locations, particularly in uranium and other mines and in residential buildings. Radon is an inspirable gas and its radioactive decay products are ionized metal atoms, which adhere to inspirable dust particles. These atoms are themselves undergoing radioactive decay and emitting damaging α- and β-particles and γ-rays. In addition to interactions of tobacco smoke with radon in mines and residential situations, other effects of tobacco smoke and radiation interactions have been studied in atom-bomb survivors and in the low energy transfer radiation involved in the use of therapeutic radiation (X-rays).

3.6.1.1 Radon in mines (high linear energy transfer (LET) α-radiation)

Unless mines are well ventilated, the atmospheric concentration of radon becomes significant. The gas and its radioactive decay products, the radon daughters, can be inhaled. The daughters have short half-lives and their decay is proceeding while the particles to which they adhere are resident in the lungs and before they can be removed by normal lung clearance. Thus radiation is delivered directly to the delicate lung tissues where it causes an excess of lung cancer among some miners.

Observations in several mining communities, e.g., among uranium miners in the USA, Czechoslovakia, Canada and France, workers in a niobium mine in Norway, iron ore miners in Sweden, tin miners in China and the United Kingdom, and fluorspar miners in Newfoundland, showed a significant dose-related increase in lung cancer risk with exposure to radon and radon daughter elements (Archer, 1988). In miners who were cigarette smokers, there was an interaction between the radiation exposure and the smoke exposure leading to more than the expected number of cases of cancer. The latent period for induction of lung cancer was longer when the exposure to radioactivity started at a younger age, it was shortened by

high exposure rates and by cigarette smoking, and lung cancers developed at lower levels of exposure to radioactivity in miners who smoked than in those who were non-smokers. In Bulgaria, Michaylov et al. (1995) used sputum cytology to study bronchial cell dysplasia in 334 miners (uranium and metal mines) exposed to ^{222}Rn progeny, and 100 control miners from a metal mine where radon was virtually absent. The dust and silica concentrations and exposure to diesel exhaust and explosion gases were similar. The frequency of bronchial cell dysplasia was significantly higher in radon-exposed miners than in controls and the frequency of dysplasia in smokers was significantly greater than in non-smokers.

The lower prevalence of lung cancer among coal miners than among other underground workers is probably because coal mines are well ventilated to reduce fire and explosion risk, and no build up of radioactivity occurs. Attempts to reduce silicosis by ventilation have achieved a similar effect. In some Swedish mines, because freezing occurred when outside air was used for ventilation, filtration was achieved in the 1920s by circulating the air through old underground mine workings, with the result that the potential for silicosis was reduced. However, an increase in lung cancer was found because radioactive materials built up, a fact that only became evident many years later (Archer, 1988).

The nature of the interaction between radon and cigarette smoke is not clear. In a study by Edling (1982), the effects of smoking and radon were considered to be additive, whereas in another by Damber & Larsson (1985b) the effect was multiplicative. From a long-term study on Swedish iron ore miners (Jörgensen, 1984), it was concluded that tobacco smoke acts as a tumour promoter, an effect that has been demonstrated in almost all animal studies. The concept that radon serves as a tumour initiator and tobacco smoke as the tumour promoter for the induction and development of lung cancer is supported by a sequence of studies. Tobacco contains small amounts of polonium-210 (^{210}Po), which primarily originates from phosphate fertilizers (Tso et al., 1966) and, to a minor extent, from airborne ^{210}Po trapped by the glandular hairs (trichomes) found on the soil-facing surfaces of tobacco leaves (Martell, 1974). ^{210}Po is a decay product of radon -222 and an emitter of α-particles. It is present in cigarette smoke, and the bronchial epithelium of smokers contains 2–10 times more ^{210}Po than is found in these tissues in non-smokers (Harley et al., 1980). The

α-radiation of ^{210}Po damages DNA in the bronchial airways and serves as a tumour inhibitor, and the tar in the tobacco smoke acts as a tumour promoter.

The frequencies of different histological types of lung cancer among miners have varied with working conditions and follow-up time. It has also been shown (Archer, 1988) that the age range of the population under observation can influence the conclusion. Thus, the smoking–radon relationship appears to be multiplicative only for the group aged 35–65 years. Steenland (1994) found the death rates from lung cancer in smoking uranium miners to be intermediate between additive and multiplicative for the two exposures, but, when stratified for age, the multiplicative model fitted well for the youngest and oldest categories but poorly for the middle range. In a comprehensive analysis of data from 11 studies of radon-induced health risks (Lubin et al., 1995), it was concluded that the joint effect of radon progeny exposure and smoking is greater than the sum of the individual effects and for smokers is higher by a factor of at least three. The tobacco of cigarettes contains 0.1–1.0 pCi of ^{210}Po (Cohen et al., 1985; Hoffmann et al., 1986).

The conclusion reached by the US Surgeon General (1985) was that the smoking–radon interaction consists of two parts: an additive effect of the contribution of the two agents on the number of tumours produced and an accelerating effect due to tumour promoters in cigarette smoke. Thus for a miner who smokes, not only is the chance of lung cancer greater but the latent period is shorter and therefore the cancer appears sooner in smokers.

3.6.1.2 *Environmental radon (high linear energy transfer (LET) α-radiation)*

Alpha-radiation from radon daughters in the home or in other situations where there are enclosed spaces with poor ventilation, e.g., where strict energy conservation measures have been adopted, presents an elevated health hazard to occupants, particularly smokers, and is a matter of public health concern. The ease with which ionized radon daughters could be attracted to environmental tobacco smoke particles and the possibility of a higher than additive combined effect of radon progeny and smoke clearly indicate the importance of residential contamination by radon.

The relative risk in the range of exposure experienced by miners has been found to be linear, and it has been suggested from extrapolation that exposures at the lower levels found in homes would carry some risk (Lubin et al., 1995). Steindorf et al. (1995) calculated that 7% of all lung cancer deaths in the western part of Germany may be due to residential radon.

Axelson (1995) reviewed cancer risks from exposure to radon in the home and suggested that cancers other than lung cancer may also be related to indoor radon, especially leukaemia, kidney cancer and malignant melanoma. However, it was acknowledged that studies of radon and miners gave no clear support for this. Alavanja et al. (1995) listed other risk factors as being responsible for lung cancer in lifetime non-smokers and found a small non-significant risk for subjects exposed to domestic radon at median concentrations. In a case-control study of lung cancer in relation to exposure to radon in homes (Letourneau et al., 1994), no increase in the relative risk for any of the histological types of lung cancer was detected in relation to cumulative exposure to radon. On the other hand, Biberman et al. (1993) found an increased risk for small cell lung cancer following residential long-term exposure to radon at a low-dose level. In a large case-control study in Sweden, Pershagen et al. (1994) reported an increased relative risk of lung cancer within the highest exposure group. In an attempt to resolve the conflicting epidemiological data, Lubin & Boice (1997) conducted a meta-analysis of eight large-scale case-control studies of residential radon and lung cancer. This analysis was consistent with an excess lung cancer risk. Furthermore, the slope of the exposure–response curve derived from this meta-analysis was comparable with that obtained from a combined analysis of eleven miner cohorts exposed to radon (Lubin et al., 1997).

The combined analysis of the miner data also confirmed the strong synergistic relationship between radon and tobacco at high levels of exposure to these two agents (Lubin et al., 1997), although it is difficult to determine whether the interaction is closer to additive or multiplicative (Chaffey & Bowie, 1994). When extrapolated to lower levels of exposure, however, the magnitude of this interaction is substantially diminished (Moolgavkar et al., 1993). However, Pershagen et al. (1994) reported some evidence of a synergistic effect between tobacco and residential radon exposure, with the relative risk of radon-induced lung cancer being highest among heavy smokers. In

a case-control study of 982 subjects with lung cancer and 3185 hospital or population control subjects, lung cancer risk was examined in relation to residential radon concentration and length of time that subjects were resident, and adjusted for age, sex and smoking (Darby et al., 1998). The relative risk increased in an exposure-related manner with time-weighted residential radon concentration and fitted the data from studies in miners and the effect of smoking. Regardless of the magnitude of any interaction between tobacco smoking and residential radon, the lung cancer risks due to smoking exceed the risk associated with radon in homes.

3.6.1.3 *Atomic bomb site radiation (low linear energy transfer (LET) radiation)*

In tobacco-smoking survivors of atomic bombing in Hiroshima and Nagasaki, Japan, elevated levels of cancer of several sites have been reported. In the case of lung cancer both additive and multiplicative models fit the data (Prentice et al., 1983; US NRC, 1988).

3.6.1.4 *Therapeutic X-rays (low linear energy transfer (LET) radiation)*

Lung cancer as a possible side effect of the radiation therapy used to treat breast cancer has been studied by Neugut et al. (1993, 1994) and discussed by Inskip & Boice (1994). Neugut et al. (1993) reported that the risk was greater in the ipsilateral than in the contralateral lung. In a second study (Neugut et al., 1994), a three-fold relative risk was found for the effect of radiation therapy among 10-year survivors, a 14-fold risk was associated with smoking alone, and a 33-fold risk was found among irradiated smokers; in each case the effect was most pronounced for ipsilateral lung cancer. A multiplicative interaction was proposed and the implications of the results for the design of treatment of breast cancer in smokers was considered. The increased risk of lung cancer among survivors of Hodgkin's disease(HD) was studied by van Leeuwen et al. (1995). Their overall conclusions were that the risk of lung cancer increased more with increasing radiation dose in HD patients who smoked than among those who did not smoke. Thus, smokers were at greater risk from the radiotherapy than non-smokers. The interaction between the carcinogenic effects of smoking and radiation was significantly stronger than multiplicative, and the low lung cancer rate found among women with HD was attributable to the delayed popularity of smoking among Dutch

women, a fact shown by the male/female lung cancer ratio (13:5) in the Netherlands in 1980.

3.6.1.5 *Nuclear plant*

Ongoing epidemiological studies are being conducted on the workforce exposed to radiation at the Mayak plant in Russia. Of 500 workers examined in a case-control study (Tokarskaya et al., 1995), 162 workers had contracted lung cancer, and the remaining 338 served as radiation-exposed, non-tumour-bearing controls. Both the incidence and duration of smoking was significantly higher in workers contracting tumours compared to combined male and female controls. The strongest smoking-related effect was for squamous cell carcinomas, followed by adenocarcinomas, then small cell carcinomas. However, the findings are complicated by the fact that the great majority of the workforce was male, and there was only one of the 148 "never smokers" among the male lung cancer cases.

3.6.1.6 *Summary*

In summary, miners subjected to chronic exposure throughout a working lifetime to high-LET radiation show a radiation/tobacco smoke interaction greater than additive and sometimes multiplicative. Atomic bomb survivors exposed instantaneously to low-LET radiation show in some cases an additive and in others a multiplicative interaction. The results for residentially exposed smokers, subjected to a lifetime of very low dose exposure, tend to show similar interactions to those for miners. Tobacco-smoking patients subjected to therapeutic radiation (low-LET) show a multiplicative interaction.

3.6.2 *Vibration*

Raynaud's phenomenon is an episodic disorder that produces intermittent attacks of blanching in the extremities and there may be numbness or tingling in the hands and fingers. There are several causes (the term "Raynaud's disease" is applied when the cause is not known). It was first associated with the use of vibrating tools among Italian miners in 1911, and the association has since been reported for a wide range of hand-held vibrating tools such as impact hammers, chipping hammers, grinders, riveters and the motor-driven chain-saws used in forestry. The terms vibration white finger (VWF), vibration

syndrome, traumatic vasospastic disease and dead finger have been used for this condition that begins with numbness and tingling, followed by blanching and can include intermittent episodes of hand and finger pain and flushing. With continuing exposure to vibration the symptoms may become more severe and continue after the cessation of exposure. Damage to digital arteries and narrowing of the lumen has been associated with vibration syndrome (JOM, 1984) and, because nicotine acts as a vasoconstrictor, it has been suggested (JOM, 1984) that limiting smoking could aid blood flow to the extremities and thus reduce the condition. In a survey of forestry workers in Quebec in 1977–1978 (Thériault et al., 1982), a prevalence of Raynaud's phenomenon among 1540 woodcutters was found in 30.5% of chain-saw users and there was a strong association between this and cigarette smoking; the relative risks were 3.60 for non-smokers, 6.55 for smokers and 1.72 for smokers who had not used a chain-saw: corresponding to an additive effect for the two risk factors. From another study of the effect of tobacco use on a cohort of men with VWF, in which the extent of tobacco use was confirmed by blood nicotine and cotinine measurements (Ekenvall & Lindblad, 1989), it was shown that tobacco aggravates the symptoms of VWF. Patients with advanced symptoms were found to use tobacco more frequently and to have higher blood cotinine levels than patients with less advanced disease. In a study of the prognosis of VWF (Petersen et al., 1995), an improvement in the condition occurred when there was no exposure to either vibration or smoking, whereas an aggravation of the condition was most notable in smokers. Whole-body vibration has been associated with persistent severe neck trouble, and smoking was an added predictor for this condition (Viikari-Juntura et al., 1994). Finger temperature changes have been measured after smoking a cigarette; in all cases a reduction in temperature was recorded (Saumet et al.,1986; Bornmyr & Svensson, 1991).

3.6.3 *Noise*

In a study of aviators in 1963 at the US Naval Aerospace Medical Research Laboratory (Thomas et al., 1981), two hearing level groups were identified, one with normal and the other with impaired hearing. The impaired hearing group had smoked more cigarettes for a longer period of time than had those in the normal hearing group. In another study the relationship between cigarette smoking and hearing loss was studied in 2348 noise-exposed workers at an aerospace company and

it was found that smoking was a clear risk factor in noise-induced hearing loss: the OR was 1.27 for "ever smokers" and 1.39 for present smokers, compared with non-smokers (Barone et al., 1987). Vascular insufficiency of the cochlear organ has been cited as the predominant cause of progressive hearing loss that occurs with age. It was suggested that smoking reduces the cochlear blood supply by: a) vasospasm induced by nicotine; b) atherosclerotic narrowing of vessels; and c) thrombotic occlusions (Zelman, 1973). In a study of 1000 subjects at a Veterans Hospital, Zelman (1973) found that whilst age and sex were the most important variables, at all measured frequencies the percentage of loss was greater for smokers, the differences being greater at higher frequencies. From a retrospective analysis of audiograms taken between 1984 and 1990 of a cohort of 119 workers, 78.8% of smokers compared with 25.7% of non-smokers had noise-induced hearing loss (ILO, 1991). Although these studies demonstrated a positive correlation between smoking and hearing loss, Friedman et al. (1969) and Pyykko et al. (1987) were not able to show that smoking was a significant risk factor to hearing loss.

3.6.4 Dupuytren's contracture

Dupuytren's contracture is a contracture of some muscle membranes of the palm of the hand that causes the little finger and ring finger to be drawn into the palm from where they cannot be extended. It is characterized by a retractile sclerosis of the palmar aponeurosis, which may progress to an irreducible flexion of the fingers. Opinions differ on the influence of occupation, handedness and hand injury on Dupuytrens contracture which Dupuytren himself attributed to chronic occupational injury. Some people assert that heavy work always causes the disease, while others claim that it is not responsible. Mikkelsen (1978) studied 901 cases in an epidemiological study of 15 950 and concluded, after isolating hand trauma, that Dupuytren's contracture is caused by heavy work. The contribution made by tobacco has been as contentious as has the cause of Dupuytren's contracture. Hand thermography of affected fingers in Dupuytren's contracture shows a drop in temperature of up to 3 degrees; and hand temperature falls by a similar amount during smoking. In a study of 84 men and 16 women with Dupuytren's contracture, Fraser-Moodie (1976) found no evidence that smoking was connected with the condition, a conclusion also reached by Mackenney (1983). However, cigarette smoking was listed among the

responsible factors for Dupuytren's contracture by Attali et al. (1987), as well as by An et al. (1988), who found that cigarette smoking was linked statistically to Dupuytren's contracture and suggested that it may be involved in its pathogenesis by producing microvascular occlusion and subsequent fibrosis and contracture. An et al. (1988) concluded that cigarette smoking was one of the most significant factors in the development of peripheral vasculopathy Abelin et al. (1990) showed a significant association between Dupuytren's contracture and smoking habits.

3.7 Biological agents

3.7.1 Biological (vegetable) dusts

Uncontrolled exposure to airborne vegetable dusts can affect health and occurs worldwide in many workplaces, e.g., in agricultural operations, textile industries, construction, carpentry and the furniture industry. The population exposed is large, particularly in developing countries where whole families, from young children to the elderly, may engage in agricultural activities and small scale manufacturing operations using vegetable products. These agents can take the form of vegetable dusts, airborne fungal spores and microorganisms, animal danders and feathers, herbicides and pesticides and their residues. Processing of agricultural products, such as cotton, flax, hemp, grain, tobacco, paprika and tea, and the milling of certain varieties of wood are occupations where vegetable dust exposures have been associated with detrimental health effects.

In addition to the irritation and bronchitis that is associated with exposure to almost any dust, biological dusts can cause byssinosis, allergic and immunological responses and, in some cases, nasal and paranasal cancer. All these conditions can be affected in different measure by tobacco smoking.

3.7.1.1 Cotton dust

Byssinosis is a respiratory disease of textile workers. The disease is found in many cotton processing countries. It is more prevalent in the dusty stages of cotton processing, such as carding, than in weaving. Byssinosis, or similar symptoms, and bronchitis have also been found in flax, hemp, jute and sisal workers. The characteristic symptoms are

tightness of the chest and shortness of breath on returning to work after a period of absence. There is the possibility of progression to permanent respiratory disability.

In a study of textile workers in South Carolina, USA, in 1973, the smoking prevalence was almost the same for workers as for controls (Beck et al., 1984). In another study of cotton workers in 1963–1966 (Molyneux & Tombleson, 1970), the percentage of male current smokers was 62.5% and of ex-smokers 16.4%; among females the figures were 33.9% and 6.1%, respectively. Among flax scutchers in Normandy in 1986–1987, 56% were smokers and 18% were ex-smokers; compared with 45% and 15%, respectively, for the controls (Cinkotai et al., 1988a). In 31 Lancashire textile factories (1988) 47.5% of the 4656 workers interviewed were smokers (Cinkotai et al., 1988b). Of 800 000 American workers surveyed (Stellman et al., 1988) for smoking habits in 1982, 5.9% were exposed to textile fibres or dust: 28.5% of these were regular cigarette smokers and 44.9% were former cigarette smokers; compared with 23.5% and 43.5%, respectively, in other occupations not exposed to textiles.

Increases in both byssinosis and bronchitis were attributed to cotton dust exposure and smoking in the cotton industry (Molyneux & Tombleson, 1970; Merchant et al., 1973). From an industrial study of the effects of cotton dust and cigarette smoke, Merchant et al. (1972) concluded that smokers showed an increase in both the prevalence and severity of cotton dust-induced byssinosis and that cigarette smoke also increased the detrimental effect of cotton dust on ventilatory capacity. It was suggested that the impairment of lung clearance mechanisms by cigarette smoke could be responsible for the deleterious effect of cotton dust and that smoking might lower the threshold of susceptibility to the effects of inhaled cotton dust. Additivity and the equal importance of the effects of smoke and cotton dust have been suggested (Beck et al., 1984) but since different lung function parameters are affected it would seem that the two factors affect different sites. The fact that workers who stopped smoking, whilst remaining in the same job, lost their byssinotic symptoms was significant. A survey by Cinkotai et al. (1988a) of workers in 31 textile factories in Lancashire, United Kingdom, showed that byssinotic symptoms (in decreasing order) were related to years in the industry, degree of dust exposure, quality of cotton in use, ethnic origin of workers and smoking habits. Symptoms of chronic bronchitis were

related primarily to smoking habits and then to factors connected with the occupation. In a study of hemp workers (Bouhuys & Zuskin, 1976), decline in ventilatory function was more pronounced in smokers. It was suggested (Cinkotai et al., 1988b) that a surprisingly low prevalence of byssinotic symptoms in 12 flax scutching mills in Normandy may have been due to either self selection of the workforce or to an absence of the causative agent in the dust. Persistent cough and phlegm production were associated with tobacco use.

In textile-related pulmonary disease, smoking as a primary causative factor was reported by Pratt et al. (1980), and a similar conclusion was arrived at from lung function tests carried out over a 3-year period on 153 women (103 smokers, 50 non-smokers) with grades 2 and 3 byssinosis by Honeybourne & Pickering (1986). Cancer deaths in general and lung cancer in particular were lower in workers exposed to cotton dust than in others (Enterline et al., 1985). Kilburn (1989) suggested that the effect of byssinosis on mortality of textile workers from pulmonary disease needed more comprehensive study.

3.7.1.2 *Wood dust*

IARC (1995) evaluated the carcinogenic risk of wood dust and classified it as carcinogenic to humans (Group 1), based on sufficient evidence in humans and inadequate evidence in animals. The risk of developing cancer of the nasal cavity among workers manufacturing wooden furniture has been shown to be up to 100 times greater than for the general population (Rang & Acheson, 1981). The effect is worst in the most dusty areas (Rang & Acheson, 1981; Hayes et al., 1986). The association of risk with certain hardwoods and the finishing of fine furniture, rather than with woodworking in general, suggests that it may be allied to both the chemical and physical nature of the dust. In the study where the nasal cancer incidence was 100 times greater than for the general population, it did not appear to be affected by smoking habits. A similar conclusion was reached in a study in an area of Italy with a large number of cases of nasal cancer among wood and leather workers (Cecchi et al., 1980). An association with smoking was established in other studies, and current and past smoking habits were shown to be a risk factor for developing squamous cell cancer of the sinus in men (Fukuda et al., 1987). A case-control study of 121 male woodworkers who were examined for

cancer of the nasal cavity or paranasal sinus, in British Columbia in Canada between 1939 and 1977 (Elwood, 1981), showed increased relative risks associated with occupations involving exposure to wood (relative risk 2.5) and with smoking (relative risk 4.9). In a study in North Carolina and Virginia in the USA between 1970 and 1980 (Brinton et al., 1984), a major finding was the elevated risk of nasal cavity and sinus cancer among cigarette smokers. However, the nature of any interaction of wood dust and tobacco smoking needs further study because adenocarcinomata appear to be the tumour type associated with wood dust, whereas the relative risks for squamous-cell and small-cell cancers tend to be higher for smokers. The available data do not permit an assessment of the degree of interaction between smoking and wood dust exposure.

3.7.1.3 *Allergic responses*

This type of response can occur in the upper airways, where it is manifest as hay fever, in response to certain types of pollen, or in the bronchi as asthma, or it may appear in both. Some of the dusts that cause allergic airways responses (occupational asthma) are grain dusts from various cereals and their products, wood dusts particularly from red cedar and iroko, and dusts from teas and tobacco. Among asthmatics, environmental cigarette smoke makes the effect of the asthma worse (Shim & Williams, 1986), and smoking effects appear to be additive to that of asthma from other causes (Conolly et al., 1988).

Grain dust exposure and smoking have been found to cause increases in the prevalence of respiratory symptoms and reductions in pulmonary function of grain elevator workers. The effect of smoking was slightly more pronounced; the combined effect of grain dust and smoking appeared to be additive, except in the least exposed workers (5 years or less) where a synergistic effect was observed in tests for peripheral airways dysfunction (Cotton et al., 1983). Chan-Yeung et al. (1985) stated that the effect of grain dust and smoking was additive and not synergistic in causing a decrease in lung function. In 303 workers in the animal feed industry exposed to dusts of grains and cassava, 61 (20%) showed respiratory symptoms; in office staff in the same plant the prevalence was similar. The plant workers had a higher prevalence of smoking than office staff. Current smoking was strongly

associated with respiratory complaints in both groups (Post et al., 1994).

Occupational asthma also occurs in flour, tea, coffee and rice handlers. In Italian bakers and pastry makers De Zotti et al. (1994) found that 54 (23%) of the 226 subjects were atopic. Forty (18%) were skin-test-positive to storage mites, 27 (12%) to wheat flour and 17 (8%) to α-amylase. Skin sensitization to these occupational allergens was significantly associated with atopy, smoking and duration of exposure. In a study of 401 workers in bakeries or flour mills, Cullinan et al. (1994a) found that work-related symptoms of allergy were more common in smokers, with little difference between atopic and non-atopic workers. However, smoking was not independently related to either symptoms or positive skin test.

Zetterstrom et al. (1981) skin-prick-tested 129 workers in a coffee roastery with green coffee bean and castor bean extracts. There was a significantly increased prevalence of positive skin prick tests in smokers. In enzyme detergent workers with occupational asthma, it was found that twice as many smokers as non-smokers exhibited asthmatic symptoms (Greenberg et al., 1970; Mitchell & Gandevia, 1971).

Smokers are more likely to show higher specific antibody production and correspondingly be more susceptible to asthma.

3.7.2 *Other biological agents*

Although many biological dusts are known to have detrimental health effects, there have been few studies of any interaction of smoking with these agents. Extrinsic allergic alveolitis may be caused by spores from a number of fungi which are small enough to reach the pulmonary compartment. There are several forms of allergic alveolitis, of which farmer's lung, bagasse pneumonitis, and bird fancier's lung are examples. These are caused by fungal spores in mouldy hay or mouldy sugar cane or an agent in bird feathers, respectively, and are immunologically mediated (Lancet, 1985). Extrinsic allergic alveolitis is a rare example of a respiratory disease which is more prevalent in non-smokers than in smokers. In one study, 14 of 18 patients (11 with farmer's lung and 7 with bird fancier's lung) were non-smokers, twice the proportion of non-smokers in patients with cryptogenic fibrosing

alveolitis or in the local population (Warren, 1977). Carrillo et al. (1991) investigated IgG response to pigeon serum and its relation to tobacco smoking in 160 pigeon fanciers. The sensitization rate was 31.9%. Pigeon fanciers who were current smokers had significantly lower levels of IgG antibodies to pigeon serum ($P<0.001$). Precipitating antibodies to *Micropolyspora faeni*, a common cause of farmer's lung, were found to be twice as common in the area of non-smokers in farming communities compared with smokers (Morgan et al., 1975). Alveolar macrophage phagocytosis has been shown to be depressed by cigarette smoke and it has been suggested this may explain its apparent protective effect (Hocking & Golde, 1979).

3.7.3 Agents found in factory farming (animal confinement effects)

Factory farming of pigs, where the animals are kept in confined conditions, is common practice in livestock production in many developed countries and it has been found to be accompanied by adverse respiratory symptoms in workers. Donham et al. (1984) summarized the effects as: acute toxicosis and inflammation of the respiratory tract from inhaling hydrogen sulfide; acute asthma-like symptoms; bronchitis; and delayed or hypersensitivity pneumonitis-like symptoms. They found that smoking interacted additively with the bronchitis and obstructive symptoms of the condition. In a study of workers in swine confinement areas, Zuskin et al. (1992) reported similar effects. They also found that smoking aggravated acute and chronic respiratory symptoms and impairment of lung function.

3.7.4 Laboratory animals

Venables et al. (1988b) examined data from three cross-sectional surveys of 296 laboratory workers around 30 years of age exposed to small mammals. Two populations were of pharmaceutical research workers ($N = 133$ and 140) and one of research workers in a tobacco company ($N = 23$). One of the pharmaceutical research worker populations had a laboratory animal allergy (LAA) prevalence rate of over 40% (Venables et al., 1988a). The tobacco company research workers were exposed only to rats while the other two populations were exposed to rats, mice, guinea-pigs and rabbits. Atopy was determined by skin prick test to non-animal aeroallergens. Sensitization to laboratory animals was determined by response to skin prick tests using urinary extracts from the species used in each

laboratory. Radioallergoabsorbent tests (RASTs) were used to measure serum IgE antibody concentration to the urinary extracts in two of the populations.

Atopy in the three populations ranged from 30% to 44%, and positive skin response to urinary extract ranged from 13% to 48%. Pooled data from the three surveys showed an association between smoking and positive skin response to urinary extract. Associations with smoking persisted after stratifying by atopic status, suggesting that smoking was a risk factor for developing laboratory animal allergy.

In other studies of 238 laboratory workers without previous occupational exposure to rats in three institutions specializing in small animal research, atopy was again determined by skin prick test response to non-animal aeroallergens and sensitization to laboratory rats by response to urinary extract. Exposure to total dust and rat urinary aeroallergen was also measured. Allergy to rats was positively related to exposure intensity and this was stronger in atopic subjects. Positive responses to skin prick testing with rat urinary extract were strongly related to atopy and to smoking at all levels of exposure (Cullinan et al., 1994b).

Several studies from Europe have shown an association between ownership of pet birds or pigeons and lung cancer (Holst et al., 1988; Kohlmeier et al., 1992; Gardiner et al., 1992). The relative risk adjusted for smoking was 6.7 (2.2–20.0). However, two community-based case-control studies, one from the USA and one from Sweden, could not confirm an association between pet birds and lung cancer (Alavanja et al., 1996; Modigh et al., 1996). In 1998, a hospital-based case-control study conducted in New York City and Washington, DC, with 887 cases and 1350 controls, did not show an association of keeping pet birds with lung cancer in non-smokers. There was a ten-fold increase of lung cancer among smokers who were not bird keepers over non-smokers, but there was no indication of synergism between smoking and keeping a pet bird (Morabia et al., 1998).

3.7.5 *Schistosomiasis*

In a study carried out in Spain, risk factors for urinary bladder cancer were identified (Bravo et al., 1987). The factors were listed in

order of importance and the first three were total number of cigarettes smoked, history of urological disease and exposure to an occupational risk. Vineis (1992) summarized epidemiological, biochemical and molecular evidence that clearly linked smoking with an increased risk of bladder cancer. Cohen & Johansson (1992) considered smoking to be the most important etiological factor for bladder cancer. They also implicated a variety of occupational exposures and, in some parts of the world, an association with various endemic diseases including schistosomiasis. Schistosomiasis is a waterborne parasitic disease found in many developing countries in Africa, Asia and South America. It is a widespread occupational disease for agricultural workers, and also affects members of the general population.

A phase in the life-cycle of the trematodes responsible for the disease lives in the blood vessels of visceral organs and their eggs are discharged through the bladder or intestine in urine and faeces. Some species live in the mesenteric veins and the eggs are discharged in the faeces but the eggs of *Schistosoma haematobium* mature in the veins of the bladder and are discharged in the urine. The eggs mature in water and the resultant larvae infect freshwater snails. Within the snail the parasites multiply to produce free swimming cercaria larvae which can infect humans via skin penetration and repeat the cycle. *S. haematobium* is found in nearly all countries in the African continent and it has been found that the incidence of bladder cancer is higher in areas with a high prevalence of infection than in areas with a low prevalence. IARC classifies infection with *S. haematobium* as carcinogenic to humans (Group 1) (IARC, 1994b). In Egypt, the most common form of cancer is bladder cancer, accounting for 27.6% of all malignancies encountered (38.5% of cancers in males and 11.3% in females), and these high levels have been attributed to underlying schistosomiasis (Tawfik, 1987). Makhyoun (1974) carried out a case-control study of smoking among Egyptian males with and without a previous history of *S. haematobium* infection. A smoking index was calculated (average number of cigarettes per day x duration of smoking in years) to categorize subjects. The smoking index (intensity and duration of smoking) was higher in all the patients with bladder cancer. In the patients with a previous schistosomiasis infection, 22.7% were moderate or heavy smokers compared with 79.3% of the non-schistosomiasis patients. In the latter there was a good correlation with the smoking index but in the bladder cancer patients with previous schistosomiasis there was no significant difference in

smoking index between patients and matched controls. It was not possible to identify an interaction between smoking and schistosomiasis in the production of bladder cancer.

However, in a review of the role of *S. haematobium* in human bladder cancer, Badawi et al. (1995) referred to several major studies that implicated this infection with the subsequent development of bladder cancer. Badawi et al. (1995) listed examples of a co-carcinogenic effect of parasitic infection in the presence of chemical carcinogens and it has been suggested (Hicks et al., 1980; Hicks, 1982) that schistosomiasis could supply the necessary proliferative stimulus to accelerate cancer growth from latent tumour foci on exposure to carcinogenic nitrosamines. Nitrosamines have been implicated as carcinogens among tobacco chewers and oral snuff users (Hecht & Hoffmann, 1988, 1991; Hoffmann et al., 1991a), nitrosamines have been demonstrated in smoke (Tricker & Preussmann, 1992; Hoffmann et al., 1991b) and nicotine-derived *N*-nitrosamines cause cancer (Hoffmann & Hoffmann, 1991; (IARC, 1991). Some *N*-nitrosamines are excreted as esters via the urinary tract, e.g., *N*-nitroso-di-*n*-butanol or NNK as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. They may hydrolyse in the presence of infectious agents in the bladder, as is the case in schistosomiasis, and thus appear in their precarcinogenic form, thereby increasing the risk for cancer in the urinary tract. Endogenous nitrosation, which is increased by tobacco smoking, chewing and oral snuff use has been demonstrated by monitoring urinary *N*-nitrosamino acids (Tsuda & Kurashima, 1991). Badawi & Mostafa (1993) and Badawi et al. (1995) suggested that the evidence for an association between urinary schistosomiasis and bladder cancer development is sufficient to justify the conclusion that *S. haematobium* infection is a factor in inducing preneoplastic changes in the bladder. Infection can reduce detoxification mechanisms (and thus prolong retention of carcinogens in the bladder), stimulate nitrosamine synthesis, and alter the activity of carcinogen-metabolizing enzymes.

The conclusion is that an interaction is likely between tobacco use and schistosomiasis infection.

3.7.6 *Other urinary tract infections*

Kantor et al. (1984) found that the joint effect of urinary tract infection and cigarette smoking on bladder cancer was slightly beyond

that expected under an additive model and suggested that patients with cystitis may be especially prone to tobacco-derived carcinogens in the urine. La Vecchia et al. (1991) studied cystitis, gonorrhoea and condylomata acuminata and found an interaction between urinary tract infection and tobacco that appeared to be multiplicative, with relative risk 2.4 for "ever smoking", 3.2 for cystitis alone, and 10.3 for combined exposure. It was concluded that a relationship between urinary tract infection (and possibly some genital infections) and bladder cancer indicated a cancer promotion role of infection and a multiplicative smoking interaction. There have been reports of synergism between herpes simplex virus and tobacco-specific *N*-nitrosamines in cell transformation (Park et al., 1991a); an additive interaction between smoking and herpes simplex virus type 2 in the promotion of cervical abnormalities (Mayberry, 1985), and the possibility of an interaction between cigarette smoking and herpes virus infection leading to cancer of the uterine cervix (Winkelstein et al., 1984).

3.7.7 Sarcoidosis

Bresnitz & Strom (1983) reviewed sarcoidosis and concluded that tobacco smoking might have a protective effect for the pathogenesis of sarcoidosis. Sarcoidosis is a generalized granulomatous disease involving the reticulo-endothelial system with lesions predominantly in the lymphatic system. Harf et al. (1986) investigated the smoking habits of 113 cases of histologically confirmed sarcoidosis in a case-control study in Lyon, France. Smoking habits were defined in 101 cases and these were compared with a control group of healthy volunteers. There was a highly statistically significant negative association between sarcoidosis and smoking (OR = 3.8; 95% confidence interval: 2.4, 6.5) in both cases.

3.8 Vector effects

Toxic chemicals, as well as harmless materials that produce harmful chemical agents when they are burnt or vaporized, can be inadvertently transferred to cigarettes or other smoking materials and cause the smoke to be more injurious when it is inhaled.

3.8.1 Polytetrafluoroethylene

Polytetrafluoroethylene (Teflon®) is used in coatings for cooking utensils, for making chemical vessels, gaskets and bearings and in sprays as a mould release agent. Polytetrafluoroethylene and polyvinyl fluoride are inert materials but their thermal decomposition products can be very biologically reactive. Cigarettes can be easily contaminated in the workplace and, when smoked, the polymer burns to form fumes which cause "polymer-fume fever": severe gripping chest pain giving rise to difficulty in breathing; trembling and shaking; elevated temperature; and severe diaphoresis. The symptoms pass after a day or two, but recur on again smoking a contaminated cigarette. Before the cause was recognized a case was recorded of a person, who used the polymer in a mould release spray, having some 40 attacks (Kuntz & McCord, 1974). Another case was a person who referred to the disease as "mould machine pneumonia" (Kuntz & McCord, 1974). Other cases have been reported (Albrecht & Bryant, 1987) and better occupational hygiene and a ban on smoking in the workplace resulted in the disappearance of symptoms in those previously affected.

3.8.2 Mercury

Inorganic mercury occurs in many industries, as elemental mercury in scientific and electrical instruments, as amalgams with many other metals, in paints and pigments and in the chemical industry, as well as in mining and extraction of the metal. Organic mercury compounds are used as antiseptics, disinfectants, fungicides, bactericides and herbicides. Contamination of smoking materials can lead to the inhalation of mercury vapour. Mercury has been detected by neutron activation analysis as a naturally occurring trace element in tobacco (<1.0 ng/g) and in the smoke of cigarettes (4 ng/cigarette) (Schneider & Krivan, 1993; Krivan et al., 1994).

3.9 Effects of tobacco smoking and metabolism of drugs and other chemicals

3.9.1 Oral contraceptive use

In the 1970s it was postulated that an interaction between tobacco use and oral contraceptives increased the risk of myocardial infarction in women. In a study of women less than 45 years of age, a greater

proportion of moderate to heavy smokers were found in oral contraceptive users experiencing myocardial infarction, compared against a control population (Mann et al., 1975, 1976). Sturtevant (1982), however, found no "convincing evidence" for an interaction or synergism between the factors smoking and oral contraceptive use for the major classes of cardiovascular disease. Lidegaard (1993) reported no difference in the proportion of smokers between users and non-users of oral contraceptives in Danish women experiencing a cerebral thromboembolic attack and age-matched controls. Regarding thrombosis, the data of Vessey & Doll (1969) suggest an increased thromboembolism risk from oral contraceptive use for heavy smokers compared to non-smokers. However, other studies reviewed by Sturtevant (1982) and Nevius et al. (1982) are said to be ambiguous regarding a possible interaction between smoking and oral contraceptive use. On balance, there is evidence for certain interactions between smoking and oral contraceptive use: the US Surgeon General (1983a), concluded that "women who use oral contraceptives and who smoke increase their risk of a myocardial infarction by an approximately tenfold factor, compared with women who neither use oral contraceptives nor smoke", and "the use of both cigarettes and oral contraceptives greatly increases the risk for subarachnoid haemorrhage among women."

3.9.2 Drug and chemical metabolism

A number of studies have demonstrated that the metabolism of various drugs and other chemicals is influenced by the smoking status of the individual. This effect is sufficiently noteworthy that the US Surgeon General (1979) report concluded that it is "apparent that cigarette smoking is one of the primary causes of drug interactions in humans". The extensive review of the literature at that time led to the conclusions that, with respect to the influence of smoking on the disposition/metabolism of other compounds: (a) the dominant effect of smoking is enhanced drug disposition caused by the induction of hepatic enzymes; (b) tobacco smoke contains many enzyme inducers, notably polynuclear aromatic hydrocarbons; and (c) smoking can induce the metabolism of various therapeutic agents and their pharmacological and/or clinical effects. The metabolism of chemical carcinogens involves various isozymes of cytochromes P450 and differences in their genotypes or phenotypes may be a main factor responsible for differences among individuals in susceptibility to

carcinogens. Metabolic activation of the procarcinogens such as benzo(*a*)pyrene to the ultimate form is accomplished by cytochrome P450IA1 (Kawajiri et al., 1990; Kawajiri & Fujii-Kuriyama, 1991; Nakachi et al., 1991). Although the most noteworthy effects of smoking cited were related to enzyme induction, it should also be noted that other components of the smoke, such as carbon monoxide, nicotine, cadmium, some pesticides, cyanide and acrolein, may serve to inhibit the function of some enzymes (Jusko, 1978). An example for this phenomenon is the inhibition by nicotine of the P450 isozymes that are involved in the metabolic activation of NNN and NNK (Murphy & Heiblum, 1990). Nicotine levels exceed those of NNN and NNK by more than 500 times. Therefore, it was not surprising that even increasing NNN and NNK levels in snuff ten-fold by adding the synthetic compounds did not alter the carcinogenic potency of snuff in the oral cavity of rats (Hecht et al., 1986).

Miller (1990) reviewed how cigarette smoking affects the pharmacokinetic and pharmacodynamic properties of various drugs. The drugs pentazocine, phenylbutazone and heparin show increased metabolism in smokers. Also in smokers, the metabolism of oestrogen and theophylline is increased. In addition, although smoking does not pharmacokinetically affect the drugs propranolol and pindolol, the nicotine in smoke is associated with elevations in blood pressure, and thus smoking might serve to inhibit the antihypertensive effects of these beta-adrenergic receptor blockers. On the other hand, smoking had no effect on the drug disposition and/or pharmacological effects of various other drugs examined (Jusko, 1978; Miller, 1990).

3.10 Animal studies of the interactions between cigarette smoke exposure and other agents

Fourteen chronic inhalation studies (whole-body or nose-only exposure) with mainstream cigarette smoke in rats and mice were reviewed by Coggins (1998) and the results and histopathological changes contrasted with epidemiological studies in humans. In most of the studies there were epithelial changes in conducting airways and increased numbers of alveolar macrophages, occasionally associated with alveolar metaplasia. Lung adenomas and adenocarcinomas were seen in some of the studies but no statistically significant increase in the incidence of malignant lung tumours was found in either rats or mice. This contrasts with human epidemiology where there is an

increased lung cancer risk. In an invited commentary, Morgan (1998) stated that, based on these differences, rodents may be ineffective models for predicting human health risk, at least for certain inhaled materials, but stressed the interspecies differences in respiratory anatomy and physiology and the need for consideration of the many factors that may lead to differences in the effects of tobacco smoke exposure.

The existing animal toxicology studies regarding interactions between tobacco smoke and other materials do not form a comprehensive body of work on the topic. A number of combinations of exposures between smoke and other agents have been studied. Results are at times inconsistent or contradictory, and the mechanisms by which interactions occur are often not understood. This section provides a brief review of the literature. In general, the existing work: (a) was generally performed using rodents; (b) usually (but not always) examined the effects of cigarette smoking (or components of the smoke) combined with either with specific chemical components of the smoke or with radiation; and (c) usually examined cancer as the biological response end-point of interest. Other studies have focused on the use of cigarette smoke components or condensates, and have used models such as *in vitro* cell systems or mouse skin; a discussion of these studies is beyond the scope of this section.

3.10.1 Non-cancer end-points

Several studies in experimental animals have examined the effects of cigarette smoke administered over short periods of time (from hours to daily exposures over several weeks). The cigarette smoke-induced increase in the number of pulmonary macrophages and leukocytes noted in humans has also been seen in animals such as the guinea-pig, even after short exposures (Rylander et al., 1979). In addition, Morimoto et al. (1993) observed a synergistic increase between mineral fibres and exposure to cigarette smoke in the production of tumour necrosis factor by rat alveolar macrophages. On the other hand, a 10-week tobacco smoke exposure in rats suppressed radiation-induced pulmonary inflammation (Nilsson et al., 1992), and a 12-week exposure of rats to smoke did not influence the lung damage caused by an intratracheal instillation of cadmium (Lai & Diamond, 1992).

Nishikawa et al. (1992) studied in guinea-pigs the effects of combined exposure and single exposure to ozone and cigarette smoke on airway responsiveness and tracheal vascular permeability and found that the combined exposure increased airway responsiveness and vascular permeability to a greater extent in terms of magnitude, but not in duration, than a single exposure. This indicated that combined exposure was more harmful than exposure to either agent alone.

3.10.2 Cancer studies: tobacco (cigarette) smoke plus other chemicals

Mori (1964) studied rats receiving multiple subcutaneous injections of the carcinogen 4-nitroquinoline-1-oxide (NQO) with or without 6–7 month inhalation of cigarette smoke. Six of eight rats had lung carcinomas in the combined exposure group compared to 3 of 9 rats in the NQO-only group, and tumours occurred earlier. Davis et al. (1975) studied Wistar rats receiving single intratracheal instillations of benzo(*a*)pyrene with or without cigarette smoke inhalation for most of the lifespan. Slight elevations of pulmonary squamous neoplasia were noted in the combined exposure group compared with the individual agents alone. However, the effects were not statistically significant.

In mice, inhaled cigarette smoke did not influence the occurrence of lung tumours in (a) B6C3F$_1$ mice pretreated with 3-methylcholanthrene or benzo(*a*)pyrene (Henry & Kouri, 1984), (b) C57BL mice receiving benzo(*a*)pyrene or influenza virus(Harris & Negroni, 1967), (c) A/J mice receiving intraperitoneal injections of the tobacco specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and a 6-month inhalation of smoke using a whole-body mode of exposure (Finch et al., 1996), or (d) A/J mice exposed to sidestream smoke plus the carcinogen 3-methylcholanthrene or urethane (Witschi et al., 1997). On the other hand, a carcinogenic synergism in lung adenoma formation was reported in Strain A mice some 6 months after initiation of treatment with intraperitoneally injected urethane and skin-painted cigarette smoke tar (DiPaolo & Sheehe, 1962). However, the non-pulmonary route of exposure makes it difficult to interpret the relevance of this result.

Several studies in hamsters have combined cigarette smoke exposure with other agents. Dontenwill et al. (1973) combined smoke exposure with a single intratracheal instillation of asbestos, but found no significant differences in laryngeal lesions or tumours in the group

exposed to both materials, compared with the group receiving smoke alone; the asbestos alone was non-tumorigenic. The combination of a single intratracheal administration of dimethylbenz(*a*)anthrene (DMBA) and smoke was found to increase the tumour incidence in the oral cavity, pharynx, trachea and non-pulmonary tissues, compared to the individual agents alone (Dontenwill et al., 1973). A similar synergism between DMBA and smoke in producing laryngeal papillomas and other oral and laryngeal lesions was reported by Hoffmann et al. (1979) and by Kobayashi et al. (1974), and a synergism was also noted between the nitrosamine DENA and smoke (Dontenwill et al., 1973). Hamsters pretreated with a single dose of either 1.0, 3.3 or 10.0 mg of NNK, and subsequently exposed twice daily for up to 72 weeks to diluted cigarette smoke developed significantly more tumours in the respiratory tract than hamsters receiving the identical dosage of NNK and subjected to sham-smoking (Hecht et al., 1983). This supports the concept that tobacco smoke has tumour-promoting activity. A combination of smoke plus benzo(*a*)-pyrene adsorbed onto haematite produced tracheal and laryngeal hyperplasia, whereas either agent alone did not (Hoffmann et al., 1979), but no tumours were produced.

3.10.3 Cancer studies: cigarette smoke plus radiation

Dogs were used to study the potential interactions between radon and cigarette smoke inhalation in producing lung cancer (Cross et al., 1982). The lung tumour incidence in dogs exposed to radon plus cigarette smoke for 4–5 years was decreased compared to that of dogs receiving a mixture of radon, radon daughters, and uranium ore dust.

Studies have examined the potential interactions between tobacco smoke and the alpha-emitters radon or plutonium-239 in rats or mice. In a series of studies, Chameaud et al. (1982) examined the effects of combined exposures to radon and cigarette smoke in Sprague-Dawley rats, as well as the effects of pre-treatment with either radon or smoke exposure. Smoke exposures begun before radon exposure did not influence the radon-induced lung tumour incidence, but this increased by 2- to 3-fold in the combined exposure group receiving radon before cigarette smoke compared to the group receiving radon alone.

Finch et al. (1995a) examined F-344 rats receiving a single inhalation exposure to $^{239}PuO_2$, combined with chronic (up to 30

months) cigarette smoke exposure, and found a synergistic crude tumour incidence in rats receiving both agents, compared with animals receiving the radiation alone. Most of these effects could be explained by a cigarette-smoke-induced retardation of lung clearance of the $^{239}PuO_2$ particles (Finch et al., 1995b). This group is continuing to study the potential combined effects of smoke and X-ray exposure in rats, and the potential effects of smoke combined with either X- or alpha-irradiation in mice (Finch et al., 1995a). Talbot et al. (1987) reported results of a study in which mice inhaled cigarette smoke, $^{239}PuO_2$ or both materials. As in the case of rats, cigarette smoke exposure caused retarded lung clearance and thus led to greater radiation doses in animals receiving both agents.

4. EFFECTS OF EXPOSURE TO TOBACCO SMOKE AND OTHER AGENTS: SEPARATE EFFECTS OR POSSIBLE INTERACTIONS

4.1 Coal mining

4.1.1 Coal dust

Coal miners can suffer from chronic bronchitis, coal workers pneumoconiosis, progressive massive fibrosis, and emphysema. The respiratory impairment appears as radiologically visible and functional changes in the lungs, but although some of these are associated solely with coal dust, some are also closely associated with smoking. In the past it has been difficult to apportion attributable risk to the two causes due to the fact that coalface workers, the group subjected to the highest dust exposure, have a different smoking pattern and perhaps a different daily consumption of smoking materials than non-coalface workers because smoking in the mine is forbidden. With the limitation of dust in modern mining, the effect of the two factors, dust and smoking, is becoming clearer. However, difficulties arise in interpreting data because non-smokers may accumulate more dust, as they have less absenteeism, a different pattern of lung clearance and a longer life (NIOSH, 1995).

In most of the countries surveyed, the prevalence of smoking by miners tends to have been somewhat higher than in either the male population as a whole, or among most other occupational groups, although a distinction is seldom drawn between miners and coal miners except in studies centred on coal mining populations. Between 1963 and 1975 in the United Kingdom, the smoking prevalence fell for the male population (and for miners) from 54% (miners 77%) to 47% (miners 49%) (Lee, 1976). The figures for 1988 and 1990 were 33% and 31% (Bennett et al., 1996) and for face-trained coalminers 35.7% in 1989 (Elliott, 1995). In a study of 8555 American miners from 29 bituminous coal mines (Kibelstis et al., 1973), over 50% were smokers and 25% were ex-smokers. In a United Kingdom study (Love & Miller, 1982), only 13% of 1677 coal miners from 5 British collieries, who were examined in a lung function study, were non-smokers; 66% were regular smokers and the remainder were intermittent or ex-smokers. In a 20 year follow-up study of a population of coal British miners and others (Cochrane & Moore, 1980), 69% of the coal miners

were smokers. These examples typify the smoking prevalence of coal miners prior to the early 1980's. A 1982 survey of 800 000 American men and women in relation to their occupations (Stellman et al., 1988) found that among miners (type unspecified) 29.4% had never smoked regularly, 31.5% were current smokers and 39.1% were former cigarette smokers. This may reflect a general trend in the countries with higher income economies where smoking has been decreasing in many sections of the population.

4.1.2 Bronchitis in coal miners

Kibelstis et al. (1973) found that the prevalence of bronchitis in coal miners who smoked was higher than in non-smoking coal miners. Coalface workers had more bronchitis and more airway obstruction than surface workers and the difference between smokers working at the coalface and non-smoking surface workers showed that the effect of smoking was five times greater than that of coal dust. A German epidemiological evaluation of chronic obstructive bronchitis in 5605 miners, 1276 ex-miners and 3898 individuals who had never worked in a mine showed that smoking has a more serious effect on miners than on other groups (Roth et al., 1985). It is possible that, within a mining community, the other two groups may have a predisposition to the disease and have achieved their status by job selection or job escape. In a study of new entrants into coal mining McLintock (1971) found that those who drop out of mining tend to be less physically fit and more prone to chest problems than those who remain.

Morgan (1982) analysed the effects of cigarette smoking, dust exposure and environmental factors on respiratory disease, and concluded that bronchitis and airways obstruction were two separate responses to cigarette smoking. The airflow obstruction found in smokers is due to small airways disease and an involvement of respiratory bronchioles leading to the development of emphysema. In coal miners, the prevalence of bronchitis among non-smokers is related to the degree of dust exposure. Marine et al. (1988) analysed data from studies on 53 382 coal miners in the United Kingdom and found that smoking miners were at greater risk of developing chronic bronchitis. In a study by Selig & Nestler (1985) of the relationship between chronic bronchitis, smoking and dust (unspecified source), heavy smoking was equated with 20 years of dust exposure. From postmortem examinations of coal mine workers, a correlation was

reported between clinical chronic bronchitis and smoking (Selig & Nestler, 1985).

The chronic bronchitis of coal miners is probably a combination of (a) mucus hypersecretion caused by dust; (b) mucus hypersecretion, mucus modification and clearance impairment caused by tobacco smoke; (c) small airways disease caused by tobacco smoke; and (d) the effect of dust on small airways tissue already inflamed by smoking. Bronchitis due to smoking causes mucus hypersecretion which is much greater than that due to coal dust (Morgan, 1982). Cigarette smoke impairs lung clearance by changing the physical and chemical properties of mucus and causing ciliastasis. Rheological measurement show changes in the viscoelastic properties of mucus; chemically the mucus glycoprotein structure is changed (King et al., 1989) and the irritant gases in smoke cause abnormal mucus secretion and ciliastasis (Holbrook, 1977). Small airways disease and bronchiolitis, leading to emphysema, are due to smoking rather than to dust (Morgan, 1982).

4.1.3 Emphysema and pneumoconiosis in coal miners

Dust in coal mining is considered to be the primary cause of coal workers pneumoconiosis. In a study of coalworkers and non-coalworkers, Cockroft et al. (1982) concluded, after taking any effect of smoking into account, that there was a 7-fold excess of emphysema in coalworkers. Results of postmortem examinations of 866 Australian miners (Leigh et al., 1983) showed a positive correlation between dust exposure and emphysema and pneumoconiosis, with the severity highest in non-smokers. However, smoking and non-smoking coalface workers were not compared. From a postmortem comparison of lungs from 450 coal miners, Rockley et al. (1984) found that emphysema occurred more frequently in smokers (72%) than in ex-smokers (65%) or in non-smokers (42%) and the relative frequency increased with age at death. The study considered the possibility that coal dust might cause emphysema which inhibits clearance and, in turn, promotes fibrosis, or alternatively that fibrosis caused by dust increases the chance of emphysema. However, the findings of a study of South Wales coal miners (Fletcher., 1972) militated against dust-induced emphysema. It has been suggested that differences in emphysema between coalworkers and non-coalworkers can be accounted for by taking into account current smokers in the two groups. Morgan (1982) concluded that the evidence militates against obstructive emphysema

occurring more commonly in coal miners than in the general population, or that more dust inhalation leads to a greater likelihood of emphysema developing. Reviews of small airways disease (SAD) suggested that emphysema proceeds from smoking-induced SAD. Cosio et al. (1980) considered that their observations supported the hypothesis that SAD is causally related to centrilobular emphysema, but not necessarily to panlobular emphysema.

4.1.4 Lung cancer in coal miners

Perhaps as a result of failure to control confounding factors, there has been a lack of consistency among reports on the relationship between coal mining and lung cancer incidence in miners. In a direct evaluation of the relationship between lung cancer mortality and coal mine dust exposure, controlling for smoking status, Ames et al. (1983) found no evidence of a link between coal mine dust exposure and lung cancer risk, nor of an interaction effect, although the expected lung cancer risk in cigarette smokers was observed. From a study of dust exposure, pneumoconiosis and mortality of coal miners (Miller & Jacobsen, 1985) it was found that lung cancer mortality among miners who smoked was 5.5 times higher than in "never smokers" but that the effect was entirely due to smoking.

Radon and radon daughter contamination of the dust in coal mines might be expected to be as prevalent as in all other mines, and thus the apparent very low lung cancer risk in coal mining may seem unexpected. However, because of the explosion risk in coal mines, the ventilation is usually efficient and a build-up of radioactivity is probably less likely than in other types of mine.

4.2 Other mineral dusts

4.2.1 Talc

Talc is a hydrated magnesium silicate, often contaminated with free silica or fibrous asbestos-like minerals such as tremolite and anthophyllite. The only significant difference in the effects on exposed and non-exposed was in the number and severity of cases of dyspnoea in the talc workers, and smoking was considered to be an aggravating factor (Kleinfeld et al., 1973).

4.2.2 Kaolin

Kaolin (pure China clay) is a hydrated aluminium silicate used for ceramics and as a filler in the paper, rubber and paint industries. The dry powder can give rise to fibrotic nodules in the lungs (Seaton et al., 1981; Wagner et al., 1986). Characteristic smoker's inclusions have been seen in transmission electron micrographs of pulmonary alveolar macrophages obtained from cigarette smokers. The contents of these inclusions are heterogeneous and include electron-dense areas, lipid material and needle-like structures. These have properties consistent with the composition of kaolinite. Kaolinite is present in cigarette smoke from different brands, and pulmonary alveolar macrophages are able to ingest this material *in vivo* (Hocking & Golde, 1979).

4.2.3 Alumina

Alumina (aluminium oxide) is extremely hard and is used as an abrasive (corundum). A cross-sectional study of 788 employees of an aluminium production company examined the relationship of radiographic abnormalities to smoking and dust exposure during bauxite and alumina mining and refining (Townsend et al., 1988). Chest radiographs showed a moderate time trend of increasing prevalence of small opacities in non-smokers with high cumulative dust exposures. In most exposure categories, smokers had a higher prevalence of opacities than non-smokers. For cumulative exposures of less than 100 mg/m^3-years, increasing trends with duration of exposure were accentuated in smokers as compared to non-smokers. The stronger effects observed in smokers were attributed to the joint effects of duration of smoking and duration of occupational exposure (Townsend et al., 1988).

4.3 Fibrous minerals

Fibrous minerals have been implicated in pleural thickening, pulmonary fibrosis, mesothelioma and lung cancer in some villages in the Anatolian region of Turkey (Artvinli & Baris, 1979), where fibrous zeolite minerals (chabazite and erionite) are present in volcanic deposits and used in buildings. Erionite has been shown to induce mesothelioma. The symptoms and pathology of the respiratory disorders and malignant disease were similar to those of asbestos. Asbestos-type diseases have also been described in communities

exposed to zeolite minerals and tremolite dust in other similar regions by Baris et al. (1979) and Yazicioglu et al. (1980). Non-asbestos fibrous materials have been associated with pulmonary fibrosis (Stanton et al., 1977). There are no data on any interaction of these minerals with smoking but there appears to be a potential for interaction.

Wollastonite is a fibrous monocalcium silicate, which has been used as a substitute for asbestos, as a filler and flux in ceramics, in grinding wheels, refractory products, building blocks and acoustic tiles. It is weakly fibrogenic. Hanke et al. (1984) studied a small population of workers exposed to wollastonite and attributed significant levels of chronic cough, phlegm and bronchitis to smoking and not to exposure to wollastonite.

4.4 Metals

4.4.1 Antimony

Antimony is chemically similar to arsenic. Arsenic is metalloid, antimony is a metal, both have volatile hydrides and form halogen, oxygen and sulfur derivatives. Compounds of both frequently occur together, particularly in smelter fume. Biological effects are similar to those of arsenic (De Wolff & Edelbroek, 1994; De Wolff, 1995).

The concentrations of antimony, arsenic, cadmium, chromium, cobalt, lanthanum, lead, selenium and zinc measured in lung tissues of deceased smelter workers suggested that lung cancer risk was multifactorial, involving carcinogenic and anti-carcinogenic factors (Gerhardsson & Nordberg, 1993). A 30-year study at an antimony smelter did not specifically implicate antimony as the cause of excess lung cancer because of concurrent exposure to other carcinogens (Jones, 1994). In another study of smelters, the data suggested an increase in lung cancer and non-malignant respiratory and heart disease (Schnorr et al., 1995).

Antimony can have harmful effects on lung tissues, including pneumoconiosis. IARC (1989a) evaluated antimony trioxide and antimony trisulfide and concluded that the trioxide was possibly carcinogenic to humans (Group 2B) and the trisulfide was not classifiable (Group 3). It is likely that the effects of inhalation of

antimony fume/dust and tobacco smoke would be worse than inhaling either separately. The similarities of antimony to arsenic, both chemically and in some biological effects, leads to the conclusion that tobacco smoke and antimony could interact like tobacco smoke and arsenic in producing toxicity.

4.4.2 Cadmium

Most zinc and lead-zinc ores contain small amounts of cadmium. It is used in electroplating, in metal alloys (with copper for overhead wires, and aluminium for casting), in nickel-cadmium dry cells, for pigment manufacture and use, added to silver to prevent staining, and it is a hazard of welding. The main route of exposure for the non-smoking general population is via food, while for exposed workers it enters the body mainly by inhalation. Tobacco is an important source of cadmium in smokers (IPCS, 1992), and the tobacco source affects the level of cadmium exposure (Yue, 1992). Any intake is important because cadmium has an extremely long biological half-life. It was suggested (Hassler et al., 1983) that higher levels of cadmium in the blood and urine of exposed workers could arise both from workplace contamination of cigarettes and transfer as fume during smoking.

Cadmium has various toxic effects, the earliest being impairment of renal tubular function leading to failure of resorption and excretion of low molecular weight protein, glycosuria, aminoaciduria and hypercalciuria (IPCS, 1992; IARC, 1993). It has been associated with some types of lung disorder (emphysema, obstructive pulmonary disease and diffuse fibrosis) (IPCS, 1992) Exposure to cadmium compounds has been associated with cancer of the lung. There is some evidence for an association with prostatic cancer (IARC, 1993). Other epidemiological studies did not confirm an increased risk of prostatic cancer (Kazantzis et al., 1992). The evaluation by IARC (1993) concluded that cadmium and cadmium compounds are carcinogenic to humans (Group 1). The supposition that cadmium in cigarette tobacco or in the workplace may cause lung cancer has been questioned (Lamm et al., 1992; Hertz-Picciotto & Hu, 1994). In a cohort mortality study of cadmium workers in England, an observed increase lung cancer risk could not be attributed strictly to cadmium due to the presence of multiple confounding factors, particularly arsenic (Kazantzis et al., 1992). Lamm et al. (1992) also suggested that arsenic may be responsible for the observed lung cancer increased.

The many elements in the lung tissues of deceased smelter workers (Gerhardsson & Nordberg, 1993) illustrates the difficulty in apportioning a role to one material in a multifactorial environment.

Cadmium affects the myocardium and produces hypertension in animal studies but the induction of cardiovascular disease and hypertension in humans has not been demonstrated in epidemiological studies (Kristensen, 1989; IPCS, 1992)). Blood and urine cadmium levels are higher in smokers than in non-smokers and were found to be considerably elevated in smokers working in an alkaline battery factory (Hassler et al., 1983) and in smelter workers who were also smokers (Kazantzis & Armstrong, 1984; Lilis et al., 1984a,b).

Davison et al. (1988) reported a cadmium dose/effect relationship in functional and radiological evidence of emphysema in 101 subjects. Leduc et al. (1993) described the very rapid development of emphysema in a smoker after exposure to very high levels of cadmium. Smoking by cumulatively increasing the body burden and hindering the lung clearance may have provided an additional cause for the emphysema. However, an additive or synergistic mechanism for the cadmium plus smoking effect could not be inferred in this case because of the high cadmium dose.

4.4.3 Cobalt

Cobalt is used in the production of alloys, tungsten carbide tools, permanent magnets, and in the electrical industry

Cobalt has toxic effects (Beliles, 1994). Cobalt exposure has been linked to various allergic reactions (Shirakawa et al., 1992); hard metal exposure and smoking together arithmetically increased total IgE levels. Interstitial lung disease has been associated with cobalt in susceptible individuals (Sprince et al., 1988), although in a study involving the manufacture of permanent magnets (Deng et al., 1991) abnormalities in pulmonary function and respiratory symptoms were no higher than those of a reference population, except for 4 subjects out of 362, who showed diffuse patches consistent with pneumoconiosis.

4.4.4 Lead

Lead is used in batteries, paint, glass, ceramics, fuel additives and other industrial applications. In lead-using industries the main route of exposure is by inhalation, mainly as dust and fume. Lead has a range of toxic effects on blood, and the renal and nervous systems (IPCS, 1995).

Levels of lead in blood vary from one area to another, between urban, rural and occupationally exposed populations, and between men and women (IPCS, 1995). The tobacco plant absorbs lead from the soil and around 5–6% of that in cigarettes is inhaled in the smoke. Lead concentrations in the smoke from one cigarette were found to range from 0.017 to 0.98 μg (IARC, 1986). Higher blood lead and erythrocyte protoporphyrin levels have been demonstrated in heavy smokers exposed to lead (Williams et al., 1983; Landrigan & Straub, 1985); these could have been partly due to contaminated cigarettes acting as vectors. Other studies on occupationally exposed workers showed a progressive increase in blood lead with an increase in the number of cigarettes smoked (Maheswaren et al., 1993).

The association between lead exposure, tobacco smoke exposure and blood pressure was examined in a cross-sectional study on 809 men occupationally exposed to lead in a battery factory but only a small increase in systolic blood pressure was found (Maheswaren et al., 1993). There was no evidence of interactive effects between smoking and lead exposure, but the absorbed lead from cigarettes added to the body burden.

4.5 Rubber industry

Some of the principal hazards in the industry are fumes, talc, carbon black, chemical additives and organic solvents but the components of the hazard mixture differ between different areas of work. A high risk of pulmonary disease has been reported in the rubber industry. It was elevated for smokers, particularly those employed in areas where there were respirable particulates and/or solvents (Lednar et al., 1977). The data suggested an interaction between smoking and hazards encountered in mixing (particulates), extrusion (solvent sprays and mould release agents), and curing (solvents and rubber reaction products). A problem in epidemiological

studies in the industry arises because of movement of workers between jobs. Some high-risk workers who were also smokers were involved in finishing and inspection but they tended to be older employees who had worked in other areas before moving to this particular job. Emphysema was the principal pulmonary condition leading to premature termination of employment (Lednar et al., 1977).

IARC (1987) classified the rubber industry as Group 1, based on sufficient evidence for carcinogenicity to humans. Excess mortality from cancers of various sites, the site usually being associated with the nature of the work and types of exposure, has been reported with bladder cancer being associated with exposure to aromatic amines (Fox et al., 1974; Monson & Nakano, 1976a,b; Monson & Fine, 1978; Kilpikari, 1982; IARC, 1987; Zhang et al., 1989; Weiland et al., 1996). Lung cancer was associated with curing and inner tube manufacture. The use of talc in the rubber industry has been associated with pulmonary disease (Kleinfeld et al., 1973). In the rubber industry the relative risk of lung cancer for talc-exposed workers was 3.2 for men and 4.4 for women (Zhang et al., 1989), compared with 2.5 times excess lung cancer risk in talc-using industries not associated with rubber manufacture (Thomas & Stewart, 1986). In jobs where very high lung cancer rates were found, smoking levels were also very high, but any possible interaction effect from the two exposures could not be assessed.

Gastrointestinal cancer, bladder cancer and leukaemia were found to be associated with jobs in the rubber industry (Monson & Fine, 1978; IARC, 1987). Possible causes, such as exposure to carbon black, plasticisers, antioxidants, arylamino compounds and benzene have been suggested. Urine samples from rubber workers showed a higher mutagenic activity in the middle of a working week than at the beginning of a week in both smokers and non-smokers, indicating the presence of mutagens in the work environment. In a study involving the analysis of urine from rubber workers for mutagenic factors, a possible synergistic effect of smoking and occupational exposure was found in smokers (Wicklund et al., 1988). There was a relationship between skin contamination and urinary mutagenicity (Bos et al., 1989). Other studies involving the analysis of urine from rubber workers for mutagenic factors also suggested a possible synergistic effect of smoking and occupational exposure among smokers (Falk et al., 1980; Crebelli et al., 1985).

Andjelkovich et al. (1988) carried out a case-control study of lung cancer in workers at a rubber manufacturing plant. There was an association between lung cancer mortality risk and work in certain areas for smokers and non-smokers, and the risk was greater in smokers. Zhang et al. (1989) studied a cohort of 957 men and 667 women employed in a rubber factory. The relative risk of lung cancer for smokers was 8.5 for men and 11.4 for women, and for those exposed to curing agents or talc the relative risk was 3.2 for men and 4.6 for women. Additive and multiplicative models were used to evaluate the interaction between smoking and occupational exposure on lung cancer. The additive interaction term was not statistically significant and the multiplicative interaction was negative. Weiland et al. (1996) were not able to find interactions between smoking and exposure in the rubber industry.

4.6 Petroleum industry

Petroleum refining involves exposure of workers to a large number of chemical compounds occurring in crude oil or encountered in production processes as intermediates, catalysts, additives or in the final products. Because of fire risk, there are sections of the industry where smoking is not permitted. However, in a study of 10 923 male and 624 female employees of the Australian petroleum industry between 1981 and 1984, it was found that the smoking habits did not differ substantially from those of the general population (Christie et al., 1986), and continued surveillance of these workers showed that mortality rates were lower than for the general population (Christie et al., 1987).

IARC (1989b) concluded that there is limited evidence that working in petroleum refineries entails a carcinogenic risk. This limited evidence applies to skin cancer and leukaemia; for all other cancer sites on which information was available, the evidence was inadequate. The overall evaluation, taking account of sufficient or limited evidence in experimental animals for the carcinogenicity of various distillates produced during petroleum refining, was that occupational exposures in petroleum refining are probably carcinogenic to humans (Group 2A).

In a study of 92 men with histologically confirmed renal cell carcinoma (Domiano et al., 1985), it was concluded that there could

be an interaction between long-term gasoline exposure and heavy smoking. In a case-control study of bladder cancer in New Jersey, USA, Najem et al. (1982) found a significantly elevated risk of bladder cancer in patients who had worked in the petroleum industry (OR, 2.5, CI, 1.2–5.5). While the risk was increased in current smokers (OR, 2.6), it was higher in "never smokers" (OR, 5.6) and only slightly elevated in ex-smokers (OR, 1.4). In another hospital-based study in Argentina an association was found between bladder cancer and oil refinery work, along with an elevated risk of lung cancer in smokers, but the numbers were too few for any evaluation of the interaction (Iscovich et al., 1987).

There was no increased mortality from either kidney cancer or leukaemia in employees exposed to gasoline (Wong et al., 1993). A low frequency of bladder cancer among refinery workers was attributed to an assumed lower level of smoking among the group of workers studied (Higginson et al., 1984).

In the study of workers occupationally exposed to gasoline vapour, the sister chromatid exchange (SCE) frequency in peripheral blood lymphocytes was used as an indicator of genotoxic response. Workers employed in gasoline retail outlets were classified according to cigarette smoking habits. The SCE frequency in lymphocytes was unaffected by cigarette smoke or gasoline exposure alone, but increased with combined exposure. The increased SCE frequency observed in smokers occupationally exposed to gasoline vapour could be due to the activation of hepatic enzymes by cigarette smoke, leading to a greater formation of reactive metabolites of gasoline vapour (Edwards & Priestly, 1993).

4.7 Pesticides

A variety of chemical compounds, natural and synthetic, are used as pesticides. The number of individuals exposed during manufacture is relatively small, and processes are usually contained, but the worldwide population of pesticide users is very large. Most of the world's population is exposed to pesticide residues in food and drinking-water (Ecobichon, 1995). There is some information concerning effects on health from interaction of pesticide exposure and smoking.

"Vineyard sprayer's lung", is an occupational disease associated with the spraying of copper-sulfate-based Bordeaux Mixture. In a study of the cytological changes in the respiratory tract of vineyard workers spraying Bordeaux Mixture (Plamenac et al., 1985), the macrophages of control subjects contained no copper whereas copper was detected in 64% of the sprayers. Abnormal cytological changes in the sputum were found in smokers, in sprayers and controls, and atypical squamous metaplasia of the respiratory epithelium was observed in 29% of the sprayers who were smokers.

In a study to evaluate the hypothesis that exposure to lead arsenate resulted in an excess mortality from lung cancer, Wicklund et al. (1988) compared 155 male orchard workers who had died of respiratory cancer with 155 orchard workers who had died of other causes. Two groups of non-orchard workers (620) were used as matched controls. There was no difference in lead arsenate exposure between the orchard worker group. Although cigarette smoking was common among the orchard workers, their smoking habits were similar to the non-orchard worker control groups. In both groups of orchard workers mortality from respiratory cancer was higher in smokers than in non-smokers.

McDuffie et al. (1990) examined the possibility that pesticide use was related to the risk of primary lung cancer. In a case-control study using data from a population-based cancer registry, they interviewed 273 men and 103 women with diagnosed primary lung cancer and compared their occupational exposures, medical history and working characteristics with 187 male community control subjects. There was no correlation of lung cancer risk with exposure to pesticides and adjusting for smoking did not alter this.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

1. Tobacco use, particularly smoking, is the single most important public health hazard in the world today, and a major preventable cause of morbidity and mortality.

2. In addition to the adverse health effects of active tobacco use, adverse health effects have also been demonstrated as a result of exposure to environmental tobacco smoke.

3. The risks from tobacco smoke are demonstrably increased through interactions with certain chemical, physical and biological hazards found in the workplace and general environment.

4. Based on this review of the scientific literature, additional interactive effects, not yet identified, may exist.

5. In addition to synergistic interactions between tobacco smoke and other agents, a few instances of antagonistic interactions were also noted. However, even in these cases, the health risks of tobacco smoke far outweigh any apparent protective effects.

5.2 Recommendations for protection of human health

1. All possible measures should be taken to eliminate tobacco use, particularly smoking.

2. In order to avoid interaction with occupational exposures, and eliminate the risks of exposure to environmental tobacco smoke, smoking in the workplace should be prohibited.

3. Smoking in public places should be strongly discouraged.

4. In order to reduce the risks of exposure to environmental tobacco smoke, particularly for children, smoking in domestic environments should be strongly discouraged. Such action will also avoid possible deleterious interactions between tobacco smoke and residential exposures to other hazards.

5. Awareness-building through active educational programmes on the health hazards of smoking should be undertaken in both developed and developing countries. This should include enhanced communication about deleterious interactions between tobacco and other agents. Governments, industry, health and educational professionals, and the general public should share in this responsibility.

6. Since smoking may result in altered response or adverse reactions to drugs and other therapeutic treatments, appropriate dose adjustments and patient surveillance should be taken into consideration by clinicians.

7. Health professionals should provide assistance to smokers to stop smoking. This may necessitate the allocation of additional resources for this purpose.

6. FURTHER RESEARCH

1. A number of different methodological approaches to investigating interactions currently exist. The feasibility of harmonizing methodologies for the assessment of potential interactions between two or more health hazards should be explored. In the interim, investigators should make every effort to state clearly which methodologies have been used when reporting their results.

2. In many of the observational studies included in this review, exposure data were limited. In order to improve future investigations of interactions among human health hazards, more complete and accurate exposure assessments should be performed.

3. Further epidemiological investigations of potential interactions between tobacco smoke and other hazards in both the occupational and general environments are needed to identify additional populations at risk. Such interactive effects can lead to risks higher than would be predicted by separate analyses of the risks associated with individual hazards.

   Epidemiological investigations in countries where the health effects of tobacco have not been extensively studied previously are of particular importance. This information would be of value in characterizing the morbidity and mortality due to tobacco use in those countries.

4. Additional research is needed to clarify the toxicological mechanisms by which tobacco smoke leads to adverse health effects, and by which tobacco smoke and other agents interact. This information will be of use in the design and interpretation of epidemiological studies on the health effects of tobacco, including interactive effects.

5. Additional epidemiological research on the health effects of passive smoking, particularly carcinogenic, cardiorespiratory and allergic effects, would be of value in characterizing the effects of low levels of exposure to tobacco smoke. Interactions between

environmental tobacco smoke and other health hazards also warrant further investigation.

6. Established biomarker methods should be applied to the monitoring of workers for the early detection of harmful exposures to toxic or carcinogenic agents, and, in many areas, new biomarker methods should be developed to improve hazard identification. Consideration should be given to evaluating the ongoing exposure of workers to active or passive tobacco smoke by monitoring salivary or urinary cotinine, one of the major nicotine metabolites.

7. A comprehensive review of the adverse health effects of environmental tobacco smoke should be undertaken. This review would provide an authoritative summary of the health impacts of environmental tobacco smoke, as well as interactions between environmental tobacco smoke and other health hazards.

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SYNOPSIS

1. Introduction

Le tabac, notamment lorsqu'il est fumé, exerce divers effets nuisibles à la santé; il est directement en cause dans un certain nombre de maladies graves et peut accentuer l'action nocive d'autres agents chimiques, physiques ou biologiques. Les produits chimiques et autres agents présents sur les lieux de travail peuvent, si l'on n'y veille pas suffisamment, provoquer diverses pathologies, des invalidités et des décès prématurés. Il est clair que sur les lieux de travail, des effets indésirables peuvent résulter de la synergie entre le tabagisme et d'autres facteurs de risque. La plupart des interactions entre les constituants nocifs de la fumée de tabac et certaines substances chimiques toxiques se produisent lorsque celles-ci sont présentes dans l'atmosphère, mais le tabagisme peut également, comme on l'a observé, interagir avec des agents toxiques absorbés par voie buccale ou autre.

La consommation de tabac est universelle, des pays économiquement défavorisés aux nations industrialisées les plus riches. Le tabac est consommé par les hommes et les femmes, les enfants et les adultes et des millions de gens sont exposés malgré eux à la fumée de tabac présente dans l'environnement. Il y a de nombreuses explications au tabagisme, mais la raison principale de son universalité tient à la présence, dans les feuilles de toutes les variétés de tabac, de nicotine, une substance qui engendre la dépendance. Cette dernière pénètre dans l'organisme du consommateur en quantité variable, selon le type de tabagisme auquel il s'adonne (Chapitre 2). L'apparition de la cigarette, qui peut être produite en quantités industrielles, qu'il est facile de se procurer à un prix relativement bas et que sa légèreté permet de tenir entre les lèvres en gardant les mains libres, a profondément modifié le comportement des fumeurs, que ce soit dans la vie en général ou sur les lieux de travail.

Il y a beaucoup de pays où fumer est considéré comme très dangereux pour la santé et comme un facteur qui contribue de manière importante à la mortalité résultant d'un certain nombre d'affections courantes. Ces pays ont adopté une législation qui vise à alerter les consommateurs des risques qu'ils courent et ils ont également pris des

mesures pour freiner la consommation, soit par la taxation, soit par la mise en oeuvre de campagnes d'information à destination du grand public qui ont pour but d'attirer l'attention sur les dangers du tabagisme et les avantages qu'il y a à cesser de fumer ou à ne pas commencer du tout. Certains pays n'ont toutefois pas encore pris de mesures décisives pour traiter le problème du tabagisme.

L'activité professionnelle comporte souvent une part de risque. Elle peut être de nature à mettre la santé en danger et à contaminer l'environnement. La culture du tabac elle-même implique l'utilisation de pesticides, la récolte des feuilles peut provoquer des intoxications dues à l'absorption percutanée de nicotine et les diverses opérations auxquelles elles sont ensuite soumises expose les travailleurs à respirer les poussières et les spores de champignons présentes dans l'atmosphère. Dans les zones où sont implantées des manufactures de tabac, on observe une incidence élevée de cancers chez les sujets de sexe masculin. L'air des exploitations minières est chargé de poussières minérales et dans l'agriculture ou les industries qui utilisent des matières premières d'origine biologique, les travailleurs sont exposés à des poussières de même origine. Le soudage donne également lieu à la production de vapeurs, et les gaz, fumées, brouillards etc. produits dans de nombreuses industries sont aussi source de dangers. Une chaleur excessive ou l'exposition aux ultraviolets peuvent nuire au bien-être des travailleurs. On admet désormais que les rayonnements ionisants émis dans les mines ou par certains appareils modernes constituent un risque professionnel. Nombreuses sont les activités professionnelles qui entraînent une exposition à des niveaux de bruit excessifs ou à des vibrations nocives. Toutes ces conditions de travail ont des effets indésirables sur la santé, mais qui peuvent être plus graves pour les fumeurs que pour les non fumeurs. Dans un grand nombre de pays, il est interdit de fumer sur les lieux de travail, essentiellement d'ailleurs en raison des risques d'incendie ou d'explosion. Dans d'autres, cette réglementation n'est pas toujours appliquée. Dans certains pays nouvellement industrialisés, les problèmes sanitaires liés à l'activité professionnelle ne sont pas encore totalement pris en compte et de nombreux employés et ouvriers ne sont pas conscients des risques de leur métier sur le plan sanitaire. En outre, il existe un vaste secteur industriel "non officiel", en particulier dans les pays en développement, où le travail, qui se fait à domicile, peut comporter l'utilisation de produits chimiques (solvants,

résines, colorants de synthèse etc.) auxquels toute la famille va donc se trouver exposée. En outre, il n'existe pas de réglementation qui restreigne l'exposition ou interdise de fumer dans ces circonstances.

Beaucoup moins bien défini est le cas d'effets nocifs résultant de l'action combinée d'une exposition à la fumée de tabac, provenant du courant principal ou de l'environnement, et à des agents présents dans le milieu domestique. On sait toutefois qu'en ce qui concerne l'incidence du cancer du poumon, la courbe dose-réponse obtenue dans le cas d'une exposition domestique au radon est analogue à celle qu'on obtient chez des mineurs exposés à ce gaz, avec un risque plus important chez les fumeurs.

2. Exemples d'effets combinés d'une exposition à la fumée de tabac et à d'autres agents

On est fondé à penser que dans le cas de certains effets toxiques (en l'occurrence le cancer) il existe une synergie entre le fait de fumer et l'exposition à l'arsenic, à l'amiante, à l'éthanol, à la silice et aux rayonnements (radon, bombe atomique, rayons X). D'un autre côté, il y a également lieu de croire à l'existence d'un antagonisme entre le tabagisme et les chlorométhyléthers cancérogènes comme le chlorométhylméthyléther (CMME) et le bis (chlorométhyléther) (BCME) (Hoffmann & Winder, 1976; CIRC, 1986), entre le tabagisme et l'alvéolite allergique ou encore entre le tabagisme et la bérylliose chronique. Fumer accentue les effets nocifs d'une exposition à la poussière chez les mineurs de charbon, ou aux pesticides chez ceux qui en manipulent, et cette accentuation du risque s'observe également dans l'industrie du caoutchouc et du pétrole. Les mineurs de charbon qui fument risquent davantage de contracter une bronchite chronique ou une pneumopathie obstructive, mais pas un emphysème. Les cancers du poumon observés chez les mineurs de charbon sont attribués en totalité au tabagisme. Fumer peut accroître les effets d'une exposition aux poussières végétales qui engendrent des affections respiratoires chroniques, comme la byssinose produite par la poussière de coton et le cancer des fosses nasales provoqué par la poussière de bois.

3. Composition des feuilles et de la fumée de tabac

On a isolé plus de 3040 composés chimiques des feuilles de tabac après transformation (Roberts, 1988). La plupart d'entre eux sont des constituants de la feuille, mais d'autres résultent des conditions de culture (sol et atmosphère de la région) ou encore des produits agrochimiques utilisés et des traitements subis (sauçage, humidification, aromatisation et séchage). On constate des différences selon la région d'origine du tabac, les variétés et les diverses méthodes de séchage et de transformation utilisées. Ces différences peuvent affecter la proportion des divers constituants mais la composition globale ne varie pas. Parmi les importants composés toxiques que l'on a mis en évidence, on trouve, à côté de la nicotine, des nitrosamines cancérogènes qui proviennent de l'action des nitrites, des amines, des protéines et des alcaloïdes d'origine foliaire, des hydrocarbures aromatiques polycycliques formés au cours du séchage, des éléments radioactifs captés dans le sol et dans l'air ainsi que du cadmium dans le cas de tabacs cultivés sur des sols riches en cadmium. Lorsque l'on fume, la combustion du tabac conduit à la formation de nombreux produits de pyrolyse ou résultant d'autres types de réactions.

4. Fumée du courant principal

La fumée de tabac est un aérosol consistant en une phase particulaire constituée de gouttelettes de liquide dispersées dans une phase gazeuse ou vapeur. Lorsque l'on fume une cigarette, il se forme de nombreux composés qui résultent de la pyrolyse du tabac. Ceux-ci peuvent, soit traverser la cigarette dans la fumée constituant le courant principal-certains d'entre eux se condensant légèrement en arrière du cône incandescent-, soit passé dans l'air à partir de l'extrémité incandescente, dans la fumée qui constitue le courant latéral. A chaque bouffée, ces composés se concentrent dans la fumée car les produits qui s'étaient déjà condensés viennent s'y ajouter — la zone de condensation se réduisant à mesure que la cigarette se raccourcit. La nature physicochimique de la fumée dépend du traitement subi par le tabac et de sa combustion, de la porosité et du traitement du papier et du type de bout-filtre (Hoffmann & Hoffmann, 1997). Dans le cas d'une cigarette ou de ce que l'on appelle un "bidi" en Asie (du tabac roulé dans la feuille d'une plante), la composition chimique de la fumée dépend de facteurs tels que les dimensions et la porosité de

l'enveloppe ainsi que des paramètres du fumage : volume, fréquence et durée des bouffées (NIH, 1998). Les variations de composition chimique concernent davantage la proportion des différents constituants que la présence ou l'absence de tel ou tel composé.

La fumée du courant principal est produite à l'intérieur du cône incandescent dans une atmosphère relativement pauvre en oxygène à une température de combustion de 850–950 °C. Au départ, les particules de cette fumée ont un diamètre aérodynamique massique médian (DAMM) de 0,2 à 0,3 μm; toutefois, dès qu'elles pénètrent dans les voies respiratoires, où le degré d'humidité est de 100%, elles s'agrègent pour former des particules de plus grande taille et se comportent alors comme si leur DAMM était de l'ordre du micromètre. Environ 50 à 90% des particules inhalées peuvent être retenues dans les voies respiratoires (Wynder & Hoffmann, 1967; Hinds et al., 1983). Pour des raisons d'ordre dimensionnel, les particules présentes dans l'aérosol, les constituants de la phase gazeuse et les gaz permanents sont capables d'atteindre les alvéoles lors de l'inhalation de la fumée. Le comportement des constituants hydrophiles en présence d'une forte humidité fait que le dépôt dans l'arbre trachéobronchique revêt un caractère complexe, mais de toute manière, la fumée s'insinue dans la totalité des voies respiratoires.

Près de 4000 constituants ont été répertoriés dans la fumée du courant principal à côté d'un nombre indéterminés de substances non identifiées (Roberts, 1988). La fumée du courant principal comporte une phase particulaire et une phase gazeuse. La phase particulaire contient de la nicotine, des nitrosamines telles que la 4-(méthylnitrosamino)-1-(3-pyridyl)-1-butanone (NKK) et la *N*-nitrosonornicotine (NNN), des métaux comme le cadmium, le nickel, le zinc et le polonium-210, des hydrocarbures polycycliques et des amines cancérogènes comme le 4-aminobiphényle. La phase gazeuse renferme du monoxyde et du dioxyde de carbone, du benzène, de l'ammoniac, du formaldéhyde, du cyanure d'hydrogène, de la *N*-nitrosodiméthylamine, de la *N*-nitrosodiéthylamine et un certain nombre d'autres composés. Les composés présents dans la fumée de tabac peuvent, selon leurs effets biologiques, être classés en asphyxiants, irritants, ciliatoxines, mutagènes, cancérogènes, inhibiteurs d'enzymes, neurotoxines ou dérivés dotés d'action pharmaceutique. C'est principalement par les voies respiratoires que

la fumée de tabac pénètre dans l'organisme mais de nombreux constituants, présents en particulier dans la fumée de pipe et de cigare, se dissolvent dans la salive et sont soit avalés, soit absorbés au niveau de la cavité buccale. Les fumeurs de pipe et de cigare n'inhalent généralement pas la fumée, qui demeure dans la cavité buccale où, on vient de le voir, elle se dissout dans la salive et peut être soit absorbée par passage à travers la muqueuse buccale, soit être directement avalée (NIH, 1998). Les boissons alcoolisées, par leur effet solvant sur les constituants de la fumée, en facilitent la résorption.

5. Fumée du courant latéral

La fumée du courant latéral est généralement produite à une température de combustion plus faible (500–600 °C) dans une atmosphère réductrice. Les particules de cette fumée ont, lorsqu'elles sont fraîchement émises, une taille à peu près équivalente à celle des particules du courant principal, avec un diamètre aérodynamique massique médian (DAMM) d'environ 0,2 µm. Quantitativement, la composition de la fumée du courant latéral est analogue à celle de la fumée du courant principal. Certaines substances du courant latéral sont émises à une concentration (rapportée à 1 g de tabac brûlé) plus élevée que les constituants du courant principal. C'est notamment le cas de composés cancérogènes comme la *N*-nitrosodiméthylamine et la *N*-nitrosodiéthylamine ou encore de métaux comme le nickel et le cadmium. Beaucoup de dérivés cancérogènes sont plus concentrés dans la fumée du courant latéral que dans celle du courant principal. Des épreuves biologiques consistant à badigeonner la peau de souris avec un condensant de fumée du courant latéral ont montré que ce dernier est plus cancérogène que celui de la fumée du courant principal (Wynder & Hoffmann, 1967; US Surgeon General, 1986; NIH, 1998).

6. La manière de fumer la cigarette et ses effets sur la toxicité de la fumée

Les cigarettes n'ont pas toutes la même teneur en nicotine et le fumeur "tire" plus ou moins fort en inhalant plus ou moins profondément pour satisfaire son besoin de nicotine. Il s'ensuit qu'en fumant une cigarette à bout-filtre pauvre en nicotine (< 1,2 mg) le fumeur va tirer plus intensément, ce qui ne sera pas sans effet sur la toxicité (NIH, 1998).

7. Résumé des conclusions et des recommandations

La consommation de tabac, notamment en le fumant, constitue un problème de santé publique d'une extrême importance en raison de la morbidité et de la mortalité qui en résultent. Outre les effets nocifs causés par une utilisation active du tabac, on a montré qu'il en existe aussi qui résultent de l'exposition passive à la fumée présente dans l'environnement. Les dangers du tabagisme sont également accrus par la possibilité d'interactions avec certains agents chimiques, physiques ou biologiques présents sur les lieux de travail ou dans l'environnement en général. On connaît certes quelques cas d'interactions antagonistes, mais les risques inhérents au tabagisme l'emportent de très loin sur ses effets protecteurs apparents. Tout doit être mis en oeuvre pour faire cesser la consommation de tabac et en particulier l'habitude de fumer. Il faut s'opposer très vigoureusement au tabagisme sur les lieux publics. En outre, pour éviter des interactions avec d'autres types d'exposition tout en éliminant le risque d'exposition passive à la fumée de tabac, il faut interdire de fumer sur les lieux de travail.

Il faut aussi vivement inciter les gens à ne pas fumer à la maison afin de protéger la santé de la famille et notamment celle des enfants. On évitera ainsi également des interactions potentiellement dangereuses avec d'autres types d'exposition pouvant survenir dans l'environnement domestique. Il est nécessaire d'établir sans attendre des programmes éducatifs sur les dangers du tabagisme pour la santé. Les professionnels de la santé doivent prêter assistance aux personnes qui désirent cesser de fumer. Comme le tabagisme peut entraîner une modification des réactions aux médicaments ou autres formes de traitement, voire susciter à leur encontre des réactions indésirables, les médecins doivent ajuster les doses de leurs patients en conséquence et surveiller leurs réactions.

PANORAMA GENERAL

1. Introducción

El consumo de tabaco, particularmente el hábito de fumar, provoca una serie de efectos nocivos para salud, está directamente relacionado con varias enfermedades graves y puede aumentar los efectos adversos de otros agentes químicos, físicos y biológicos. Si no se controlan, los agentes químicos y de otro tipo pueden producir en el puesto trabajo enfermedades, discapacidades y la muerte prematura. Es evidente que en el lugar de trabajo los efectos adversos pueden deberse a la interacción sinérgica del humo de tabaco con otros peligros. La mayor parte de las interacciones de los constituyentes nocivos del humo de tabaco con sustancias químicas tóxicas se producen cuando estas últimas están en el aire, aunque se han notificado asimismo interacciones del humo con agentes perjudiciales ingeridos y/o absorbidos.

El consumo de tabaco está generalizado en todo el mundo, desde los países de bajos ingresos hasta los industrializados más ricos. Lo utilizan hombres y mujeres, niños y adultos, y millones de personas están involuntariamente expuestas al humo de tabaco en su entorno. Si bien hay numerosas explicaciones del hábito de fumar, la razón principal de su ubicuidad es el efecto adictivo de la nicotina, droga presente en todas las formas de la hoja de tabaco y que llega al consumidor en cantidades variables según los distintos tipos de consumo (capítulo 2). La aparición del cigarrillo, de producción masiva, fácil de obtener, relativamente económico y ligero de peso, de manera que se puede llevar en la boca dejando las manos libres, ha tenido repercusiones importantes en el hábito de fumar, tanto en general como en el puesto de trabajo.

En muchos países se reconoce que el humo de tabaco constituye un peligro grave para la salud y es un factor que contribuye de manera importante a la muerte causada por diversas enfermedades comunes. En esos países se ha aplicado una legislación de alerta sanitaria y medidas impositivas para el control de su consumo, así como programas de educación del público sobre los peligros del tabaco y las ventajas de no comenzar a fumar o de interrumpir el consumo. Sin

embargo, todavía hay países donde no se han puesto en marcha medidas decisivas para abordar el problema del consumo de tabaco.

Son muchas las situaciones laborales que conllevan un elemento de riesgo. El tipo de trabajo puede generar efectos nocivos para salud y las actividades laborales pueden provocar la contaminación de medio ambiente. El propio cultivo del tabaco requiere el uso de plaguicidas, la recolección de la hoja puede ocasionar trastornos debido a la absorción de nicotina a través de la piel y su elaboración expone a los trabajadores a peligros para la salud provocados por el polvo y las esporas de hongos presentes en el aire. Se ha notificado una elevada incidencia de cáncer en el sexo masculino en zonas con industrias tabaqueras. En la minería existe polvo de minerales en el aire y en la agricultura y la industria basadas en materias primas producidas biológicamente hay polvo biológico. Durante las actividades de soldadura se produce humo y en muchas industrias crean peligro los gases, humos, neblinas y vapores cargados de sustancias orgánicas y/o inorgánicas tóxicas. Un calor excesivo o la exposición a luz ultravioleta pueden ser perjudiciales para el bienestar de los trabajadores. Está admitido que las radiaciones ionizantes en la minería y en la tecnología moderna son un peligro en el lugar de trabajo. En numerosas actividades, los trabajadores están expuestos a un ruido excesivo o a vibraciones mecánicas peligrosas. Estas condiciones laborales pueden afectar más negativamente a la salud de las personas fumadoras que a la de las no fumadoras. Son muchos los países en los que está prohibido fumar en el trabajo, fundamentalmente por razones de seguridad en cuanto incendios/explosiones. Sin embargo, en algunos países no siempre se cumple la reglamentación. En varios países recientemente industrializados no se han abordado todavía plenamente los problemas de salud asociados con el trabajo y muchos empleadores y trabajadores desconocen los peligros para la salud de sus actividades. Además, existe un amplio "sector extraoficial" de la industria, particularmente en los países en desarrollo, en que se trabaja en el hogar y se utilizan sustancias químicas (en particular disolventes, resinas y colorantes sintéticos), estando expuesta toda la familia, y no hay restricciones sobre la exposición a los peligros en el trabajo o al humo.

Está mucho menos definida la situación en relación con los efectos adversos en la salud derivados de la exposición combinada al

humo de tabaco — de la corriente principal o del medio ambiente — y a los agentes del entorno doméstico. Sin embargo, la incidencia de cáncer de pulmón y la concentración de radón en los hogares tiene una relación dosis-respuesta similar a la que se produce entre el cáncer de pulmón y la concentración de radón en las minas, y el riesgo es más elevado para los fumadores.

2. Ejemplos de efectos combinados de la exposición al humo de tabaco y a otras sustancias

Está demostrada la existencia de sinergia en la producción de efectos nocivos (cáncer) entre el humo de tabaco y la exposición al arsénico, el amianto, el etanol, el silicio y las radiaciones (radón, bomba atómica, rayos X). Por otra parte, hay pruebas de antagonismo en el caso del humo de tabaco y los clorometiléteres carcinogénicos, es decir, el clorometilmetiléter (CMME) y el bis(clorometil)éter (BCME) (Hoffmann y Wynder, 1976; CIIC, 1986), el humo de tabaco y la alveolitis alérgica y el humo de tabaco y la beriliosis crónica. El humo de tabaco influye en el riesgo para la salud de la exposición en la extracción de carbón, el manejo de plaguicidas y las industrias del caucho y el petróleo. Los trabajadores de las minas de carbón que fuman tienen un riesgo más elevado de contraer bronquitis crónica y enfermedades obstructivas de las vías respiratorias, pero no enfisema. El cáncer de pulmón de los mineros del carbón se ha atribuido totalmente al humo de tabaco. El humo de tabaco puede aumentar el riesgo para salud de la exposición a polvos vegetales que producen trastornos respiratorios crónicos, como la bisinosis debida al polvo del algodón y el cáncer nasal provocado por el polvo de la madera.

3. Composición de la hoja del tabaco y del humo de tabaco

De las hojas de tabaco elaboradas se han aislado más de 3040 compuestos químicos (Roberts, 1988). La mayoría son constituyentes de la hoja, pero la presencia de algunos depende de las condiciones de cultivo, como el suelo y la atmósfera de la zona, mientras que otros se derivan del uso de productos químicos agrícolas, de revestimientos, humectantes y aromatizantes añadidos a las hojas y de los métodos de curado. Las diferentes variedades de tabaco que se cultivan en los distintos países, así como las distintas formas de curado y elaboración,

ponen de manifiesto diversas diferencias. Las proporciones de los distintos constituyentes pueden ser diferentes, pero no la composición general. Entre los compuestos tóxicos importantes identificados, aparte de la nicotina, figuran nitrosaminas carcinogénicas, derivadas de nitritos, aminas, proteínas y alcaloides presentes en la hoja, hidrocarburos aromáticos policíclicos procedentes del proceso de curado, elementos radiactivos absorbidos del suelo y el aire, y cadmio en el tabaco cultivado en suelos ricos en este elemento. Cuando se quema tabaco al fumar, se forman numerosos productos derivados de la pirólisis y de otras reacciones.

4. Corriente principal del humo de tabaco

El humo del tabaco es un aerosol formado por una fase particulada de gotitas de líquido dispersas en una fase de gas/vapor. Al fumar un cigarrillo se forman numerosos compuestos por la pirólisis del tabaco. Éstos pasan a través del cigarrillo en la corriente principal del humo, condensándose algunos a corta distancia detrás del cono de combustión, o bien se emiten en el aire a partir del extremo que se quema como humo lateral. En cada bocanada el humo se hace progresivamente más fuerte, porque se le añade material previamente condensado y porque la longitud del cigarrillo disponible para la ulterior condensación disminuye. Las características fisicoquímicas del humo dependen de la elaboración y la combustión del tabaco, la porosidad y el tratamiento del papel en el que está envuelto y del tipo de filtro (Hoffman y Hoffman, 1997). En el caso de un cigarrillo o "bidi" asiático (tabaco envuelto en hoja vegetal), la química del humo se ve afectada por factores tales como las dimensiones, la porosidad de la envoltura y los parámetros del volumen, la frecuencia y la duración de la bocanada de humo (NIH, 1998). Las variaciones en la química del humo se dan fundamentalmente en la proporción entre sus constituyentes, más que en la presencia o ausencia de compuestos concretos.

El humo de la corriente principal se genera en una atmósfera con un contenido comparativamente bajo de oxígeno a una temperatura de combustión de 850–950 °C en el cono de combustión. Al principio, las partículas presentes en la corriente principal tienen un diámetro aerodinámico medio de la masa (MMAD) de 0,2 a 0,3 micras; sin embargo, en cuanto llegan al tracto respiratorio, con una humedad del

100%, se unen para formar partículas mayores y se comportan como si su MMAD fuera del orden de micras. En el tracto respiratorio se puede retener alrededor del 50–90% de todas las partículas inhaladas (Wynder y Hoffmann, 1967; Hinds et al., 1983). Por lo que se refiere al tamaño, al inhalar el humo pueden llegar a los alvéolos las partículas en aerosol, los constituyentes de la fase de vapor y los gases permanentes. La deposición en el árbol traqueobronquial se ve complicada por el comportamiento de los constituyentes hidrofílicos en condiciones de humedad elevada, pero el humo llega a todas las partes de las vías respiratorias.

El humo de la corriente principal contiene cerca de 4000 sustancias químicas identificadas y un número desconocido de sustancias químicas sin identificar (Roberts, 1988). El humo de la corriente principal se puede dividir en una fase de partículas y otra de gas. La fase de partículas contiene nicotina, nitrosaminas como la 4-(metilnitrosamino)-1-(3-piridil)-1-butanona (NNK) y la *N*-nitrosonornicotina (NNN), metales como el cadmio, el níquel, el zinc y el polonio-210, hidrocarburos policíclicos y aminas carcinogénicas, como el 4-aminobifenilo. La fase de vapor contiene monóxido de carbono, anhídrido carbónico, benceno, amoníaco, formaldehído, cianuro de hidrógeno, *N*-nitrosodimetilamina, *N*-nitrosodietilamina y otros compuestos. Los compuestos del humo de tabaco se pueden clasificar por su actividad biológica como asfixiantes, irritantes, ciliatoxinas, mutágenos, carcinógenos, inhibidores de las enzimas, neurotoxinas o compuestos farmacológicamente activos. El principal punto de entrada del humo del cigarrillo en el organismo es por las vías respiratorias, pero muchos constituyentes, en particular del humo de pipa y de cigarro, se disuelven en la saliva y se absorben en la cavidad bucal o se ingieren. Los fumadores de cigarros y de pipa no suelen inhalar el humo, que permanece en la cavidad bucal, se disuelve en la saliva y se absorbe a través de las membranas mucosas o se ingiere (NIH, 1998). Las bebidas alcohólicas tienen un efecto disolvente de los constituyentes del humo, facilitando su absorción.

5. Humo de tabaco lateral

El humo lateral se forma con una temperatura de combustión más baja (500–600 °C) en una atmósfera reductora. Las partículas del humo lateral fresco son prácticamente del mismo tamaño que las de la

corriente principal, con un diámetro aerodinámico medio de la masa de alrededor de 0,2 micras. Desde el punto de vista cualitativo, la composición del humo lateral es semejante a la del humo de la corriente principal. Algunas sustancias químicas se emiten en el humo lateral con una concentración mayor por gramo de tabaco quemado que en el humo de la corriente principal. Esto es particularmente aplicable a carcinógenos como la *N*-nitrosodimetilamina y la *N*-nitrosodietilamina y a metales como el níquel o el cadmio. Muchos compuestos carcinógenos están más concentrados en el humo lateral que en el principal. En biovaloraciones con aplicación a la piel de ratones se ha demostrado que el humo lateral condensado es más carcinogénico que el principal (Wynder y Hoffmann, 1967; US Surgeon General, 1986; NIH, 1998).

6. Efectos de la manera de fumar los cigarrillos en la toxicidad del humo

El contenido de nicotina de los distintos cigarrillos varía, y el fumador, para satisfacer la necesidad adquirida de nicotina, la ajusta mediante la intensidad con la que fuma y la profundidad de la inhalación. Por consiguiente, el fumador de cigarrillos con filtro y de contenido bajo en nicotina (< 1,2 mg) fuma con mayor intensidad, y esto influye en la toxicidad (NIH, 1998).

7. Resumen de las conclusiones y recomendaciones

El consumo de tabaco, en particular el hábito de fumar, representa un peligro para la salud pública de la máxima importancia y es una causa prevenible importante de morbilidad y mortalidad. Además de los efectos adversos del consumo activo de tabaco para la salud, se han demostrado efectos adversos derivados de la exposición al humo de tabaco presente en el medio ambiente. Los riesgos del hábito de fumar también aumentan como consecuencia de las interacciones con ciertos peligros químicos, físicos y biológicos existentes en el lugar de trabajo y en el medio ambiente general. Hay un pequeño número de casos de interacciones antagonistas, pero los riesgos del humo de tabaco para la salud son muy superiores a cualquier efecto protector aparente.

Se deben adoptar todas las medidas posibles para eliminar el consumo de tabaco, en particular el hábito de fumar, y se ha de

disuadir con firmeza de fumar en lugares públicos. A fin de evitar la interacción con otros tipos de exposición ocupacional y de eliminar el riesgo de exposición al humo de tabaco del medio ambiente, debería prohibirse fumar en el lugar de trabajo.

Con objeto de proteger la salud, en particular la de los niños, se debería desalentar con firmeza el hábito de fumar en el hogar. De esta manera se previenen posibles interacciones perjudiciales entre el humo de tabaco y la exposición a otros peligros en la vivienda. Hay una necesidad imperiosa de programas educativos sobre los peligros del hábito de fumar para la salud. Los profesionales de la salud deberían prestar asistencia para ayudar a los fumadores a dejar este hábito. Debido a que el humo puede provocar una alteración de la respuesta a los medicamentos y otros tratamientos o una reacción adversa a éstos, los médicos deberían estudiar la posibilidad de introducir ajustes apropiados de la dosificación y vigilar a los pacientes.

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