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HEALTH EFFECTS OF INTERACTIONS ARISING FROM TOBACCO USE AND EXPOSURE TO CHEMICAL, PHYSICAL OR BIOLOGICAL AGENTS

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1. HEALTH EFFECTS OF INTERACTIONS ARISING FROM TOBACCO USE AND EXPOSURE TO CHEMICAL OR PHYSICAL AGENTS OR BIOLOGICAL DUSTS

1.1 General introduction

There has been concern for many years concerning the potential of tobacco use to cause a range of adverse health effects, including augmenting the adverse effects of other chemical and physical agents. It is recognized that chemical pollution in the workplace can cause disease, incapacity and early death in many occupations. From observations in the workplace, it has become clear that smoking in the presence of certain chemical/physical agents represents more than an exposure to two types of hazard, one attributable to the agent and the other to tobacco smoke. Adverse health effects can arise sometimes from a combination of effects of tobacco smoke and a hazard or sometimes from a synergistic interaction of the two. Chemical pollution of the environment can present health hazards to the general population. Tobacco use, particularly cigarette smoking, is the principal cause of several major diseases in the general population.

The main purpose of this monograph is to identify interactions between tobacco smoke and other agents, chemical, physical and biological that result in adverse health effects. However, other forms of tobacco use and adverse health conditions associated with tobacco use are included for completeness. The majority of interactions of harmful tobacco smoke constituents with toxic chemicals occur when the latter are airborne although some cases have been reported of interactions of smoking with ingested and/or absorbed harmful agents.

Tobacco use is widespread throughout the world, in countries with low income economies and in the most affluent industrialized nations. Tobacco is used by men and women, by children and adults, and millions of others 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 various methods of tobacco use (Section 5).

During the past 40 years, it has been accepted in many countries that smoking is a serious health hazard and, as a major contributing factor, a cause of death from many common diseases. In countries where the effects of smoking on health are appreciated and the economic costs/losses realized, health warning legislation has been enacted, a measure of control exercised through taxation, and action taken to educate the public both on the dangers of smoking and also on the benefits to be gained from not starting or stopping tobacco smoking. However, there are still countries where the health hazards associated with tobacco use by the population been given no thought and no decisive action taken to deal with the problems 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. There are airborne mineral dusts in mining and biological dusts in farming and industries using biologically produced raw materials. Fume is 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 ultra-violet light can be detrimental to the well being of workers. Ionizing radiation in mining and modern technology are recognized workplace hazards. In many occupations workers are subjected to excessive noise or harmful mechanical vibration. Such working conditions take their toll on well-being and health and it is recognized in some cases, and suspected in others, that their effects are greater when combined with the effects from tobacco smoking.

Tobacco growing involves the use of pesticides. Harvesting can cause sickness due to skin absorption of nicotine, and processing exposes workers to health hazards from airborne dust and fungal spores. However, the greatest impact of tobacco on the health of the total workforce in any country, additional to its effects on the health of the population as a whole, lies in the combined adverse effects of smoking and workplace hazards. Smoking, particularly cigarette smoking, is detrimental to health in a variety of occupations, not only because of the diseases it causes *per se* but because it can adversely affect disease conditions in which other toxic agent(s) may be aetiologically implicated. Toxic substances in the workplace and the hazards associated with smoking in the presence of these materials cannot be considered in isolation. In some situations, smoking increases the severity of a disease beyond what could be expected from smoking alone or the toxic hazard alone.

These considerations may also be relevant to passive smoking in a contaminated atmosphere. In industrialized countries, the hazards of workplaces are recognized, regulations have been formulated and legislation has been enacted to protect workers and provide for their education on the dangers that may arise from the work they do. However, in some countries, implementation of the rules and law is not always strictly imposed and workers sometimes neglect the training they have been given. In some newly industrializing countries where development is progressing swiftly, health problems associated with work have not yet been fully addressed and many workers are ignorant of the dangers to health of their occupations.

In most countries and in many working situations, a combination of the effects of smoking and the effects of other airborne hazards are not fully recognized, or accepted, by governments, employers, unions, or individuals. The dangers of smoking at work or in any other area where

the atmosphere may be contaminated is only given serious attention where smoking presents risks of large scale accidents from fire or explosion.

This review contains the results of a literature survey of human data relating to tobacco use, principally smoking, and potentiation of effects of other exposures. Although interactions have been widely discussed there is convincing evidence in few instances. There are also instances where tobacco use may contribute to adverse effects but there is no evidence for interaction as such.

1.2 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) and antagonism in the case of tobacco smoke and chloromethyl ethers (chloromethyl methyl ether (CMME), its contaminant bis(chloromethyl) ether (BCME), and tobacco smoking and allergic alveolitis, chronic beryllium disease (Section 2), and platinum salt sensitization (Section 3). The effect of tobacco smoking on the health risks of exposures in coal mining, pesticides, and the rubber and petroleum industries is described in Section 3. 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. Exposure to vegetable dusts, principally cotton, produces byssinosis, a chronic respiratory condition, and wood dusts are carcinogenic. Tobacco smoking may compound these risks (Section 2.6.5).

1.3 Composition of tobacco leaf and tobacco smoke

More than 2500 chemical compounds have been isolated from processed tobacco leaf. Most were leaf constituents, but some arise from growing conditions such as the soil and atmosphere in an area and the use of agricultural chemicals, from casings, humectants and flavourings added to the leaves, and from curing methods. Thus different tobacco varieties grown in different countries and processed in different ways will show some differences, however, individual constituents are likely to differ only in balance rather than in their presence or absence. Some compounds identified and known to have toxic effects, other than the nicotine, are certain nitrosamines derived from the amines, proteins and alkaloids present in the leaf, some polycyclic aromatic hydrocarbons for which the method of curing is usually responsible, radioactive elements

absorbed both from the soil and the air, and cadmium in tobacco grown on cadmium-rich soils. Of these, the nitrosamines are the most important carcinogens and not only are their concentration levels far higher than in any other consumer product but they are also being formed whilst the tobacco is being chewed or sniffed. When tobacco is burned in the course of smoking many pyrolysis and other products are formed.

1.4 Mainstream tobacco smoke

Tobacco smoke is an aerosol consisting of a particulate phase composed of liquid droplets dispersed in a gas/vapour phase. When a cigarette is smoked, a large number of compounds are formed by pyrolysis of the tobacco at the burning end from where they are distilled. These either pass down the cigarette as mainstream smoke, some being condensed a short distance behind the burning cone, or are emitted into the air from the burning end as sidestream smoke. With each subsequent puff the procedure is repeated but the smoke becomes progressively stronger because not only is the previously condensed material redistilled and added to the smoke, but the length of cigarette available for further condensation is constantly decreasing. The nature of the smoke depends on the growing and processing and burning of the tobacco. In the case of a cigarette or Asian "bidi" (tobacco wrapped in vegetable leaf) the smoke chemistry is also affected by such factors as dimensions, wrapper porosity and smoking parameters (puff volume, frequency, and duration). However, variations in smoke chemistry are mainly confined to changes in the balance of smoke constituents rather than to 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 0.3 to 0.4 μm; however, as soon as they enter the 100% humidity in the respiratory tract, they coalesce into larger particles and behave as if their MMAD was in the micrometer range. Fifty to 90% of all inhaled particulate matter may be retained in the respiratory tract. Thus, from size considerations, the aerosol particulate matter, along with the vapour phase constituents and the permanent gases, is capable of reaching the alveoli when smoke is inhaled. Deposition in the tracheobronchial tree is complicated by the behaviour of hydrophillic constituents in the high humidity conditions and by some electrostatic precipitation, yet it has been demonstrated that smoke reaches every part of the trachea, bronchi and alveoli.

Mainstream smoke contains more than 4000 identified chemicals and probably an unknown number of as yet unidentified chemicals (IARC, 1986). Mainstream smoke can be

divided into two phases, the particulate phase, i.e., material that is retained on a Cambridge filter when smoke is drawn through it, and the vapour phase. The mainstream smoke particle phase contains nicotine, 1,3 butadiene, certain nitrosamines such as NNK and N-nitrosonornicotine, metals such as cadmium, nickel, zinc and polonium^{210}, polycyclic hydrocarbons and carcinogenic amines. The vapour phase contains CO, CO_2, benzene , ammonia, formaldehyde, hydrogen cyanide, n-nitrosodimethylamine and N-nitrosodiethylamine, among other compounds. The compounds can be classified by chemical structure or grouped according to their biological activity as chemical asphyxiants, irritants, carcinogens, enzyme inhibitors, neurotoxins, and pharmacologically active compounds. The main point of entry into the body by cigarette smoke is the lungs, but many constituents, particularly from pipe and cigar smoke, dissolve in saliva and are absorbed in the buccal cavity or swallowed. Alcoholic beverages also provide a solvent in which compounds are swallowed.

1.5 Cigarette sidestream smoke

Sidestream smoke is generated at lower burning temperature (500 - 600°C) in a reducing atmosphere. Fresh sidestream particles are about the same size as mainstream smoke particles and, within a short time after generation, the MMAD is approximately 0.2 μm. Qualitatively, sidestream composition is similar to the composition of mainstream smoke. However, as a general rule, chemicals in sidestream smoke are emitted at much higher amounts than they are in mainstream smoke; this appears to be particularly true for several carcinogens such as N-nitrosodimethylamine and N-nitrosodiethylamine, or metals such as nickel or cadmium. Many carcinogenic compounds are thus more concentrated in sidestream than they are in mainstream smoke. This has led to the speculation that the sidestream component of environmental tobacco smoke is more carcinogenic than the mainstream smoke mix. Mouse skin painting studies have shown that sidestream condensate is more carcinogenic than mainstream smoke condensate (Mohtashamipur et al., 1990).

1.6 Environmental tobacco smoke

Airborne material in indoor or outdoor air resulting directly from the smoking of tobacco is known as environmental tobacco smoke. It consists of three components: mainstream smoke, i.e., the smoke exhaled by a smoker (approximately 85%), sidestream smoke generated during the active smoking of a cigarette, i.e., vapour phase tobacco constituents diffusing out of the tobacco

through the cigarette wrapping, and sidestream smoke released during puff intervals from the smouldering end of a lit cigarette, consisting of both vapour and particle phases.

Exhaled mainstream smoke is depleted of many of its volatile compounds. Mainstream smoke particles after exhalation lose water and other volatile particle components such as nicotine; MMAD decreases to 0.15-0.2 μm. Accordingly, retention of environmental tobacco smoke inhaled particulate material in the lungs of involuntary smokers is about 10 to 11%, as opposed to an intrapulmonary retention of 50 to 90% of inhaled mainstream smoke particulate material by the active smoker. As far as nicotine is concerned, 10% or less is associated in environmental tobacco smoke with particulate matter. However, there exist substantial quantitative differences between fresh and aged mainstream smoke, fresh and aged sidestream smoke generated under laboratory conditions and the mixture in polluted atmospheres known as fresh or aged environmental tobacco smoke

A wide range of environmental tobacco smoke concentrations, measured mostly as total suspended particulate matter, has been reported to exist in various environments. Exposure of non-smokers to environmental tobacco smoke is difficult to estimate. Particulate matter is a commonly measured indoor air pollutant. It is generated in part from mainstream and sidestream smoke. Indoor measurements show a wide range of total suspended particulates (TSP) and it is usually estimated that in an environment where people smoke that about half of TSP originate from mainstream and sidestream smoke. Indoor air concentrations of TSP may range from 10 to 1000 $\mu g/m^3$; personal exposure of non-smokers to particulate matter associated with environmental tobacco smoke has been estimated to range from 18 to 64 $\mu g/m^3$ (Guerin et al., 1992; Rodgman, 1992; US EPA, 1992). Exposure to airborne nicotine is usually 10 $\mu g/m^3$ or less; however, under special conditions such as in badly ventilated rooms or in motor cars they may be 5 to 10 times higher (Guerin et al., 1992). As far as CO is concerned, it is reasonable to assume that exposures of the general public usually do not exceed 4 ppm. However, such measurements may not provide information for some particularly critical exposures of individuals to environmental tobacco smoke. Infants and small children close to a mother that smokes may receive considerably greater exposure than measured in the general environment of a home, since smoke concentration is likely to increase inversely with the square of the distance from the source.

1.7 Effects of ways of cigarette smoking on smoke toxicity

Physico-chemical analyses are carried out on smoke produced under standard conditions, e.g. 35ml puffs of two seconds duration at one minute intervals down to a specified butt length,

but the constitution of the smoke is sensitive to changes in these parameters which only reflect the way in which anyone smokes in a general way. Furthermore, the way in which the smoke is then used is far from standard. A smoker might light a cigarette but being preoccupied leave it to burn away, whilst another will feverishly puff to the last millimetre of available tobacco. Some draw the smoke into the mouth and then blow it out whereas others inhale each puff into the deepest recesses of the lungs. Some smokers retain a lit cigarette between the lips, seldom taking a definite puff but inhaling a continuous stream of both mainstream and sidestream smoke: a habit often seen among those who need to keep both hands free to perform a task. It is clear that ways of smoking could partly explain why some smokers fall victim to smoking-related disease sooner than others.

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

2.1 Introduction

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.

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.

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, heavy metal elements.

Vector effects. Materials used in the workplace, which 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, methylparathion.

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

2.1.1 Effects of tobacco smoking on lung clearance of particles

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,and slower, deep lung clearance, in which phagocytic cells can remove inhaled particles. These processes are balanced by the solubility of the inhaled particles; relatively insoluble particles can have a substantial residence time in the alveolar portions of the lungs. A longer residence time in the lung would be accompanied by a longer temporal possibility that harmful effects could occur (this might be particularly true, and possibly most quantifiable, for radioactive particles). Both rapid and slow clearance phases are reduced by smoking, although probably by different mechanisms. Cigarette smoking has been demonstrated to retard particle clearance from the lungs. This retardation of clearance has been shown for airway-deposited particles, in which apparently decreased mucous transport velocities slowed this relatively rapid phase of clearance (Lourenco et al., 1971; Chopra et al., 1979).

In addition, several studies have demonstrated that 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 nonsmokers, 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 definitively shown, but may be related to impairment of phagocyte function and/or smoke-induced lung lesions.

2.2 Interactions between tobacco smoke and other agents

2.1.1 Asbestos

Asbestos is a generic name for a group of fibrous silicates that have found widespread use over the past 100 years for their heat, fire, acid and, to some extent, alkali resistant properties. Asbestos types are classified according to their physical characteristics as serpentine or amphibole. Chrysotile is in the first group and consists of long pliable white fibres. Amosite and crocidolite are two varieties in the second group, members of which tend to have shorter and straight needle-like fibres. The long fibre varieties of asbestos can be spun into yarn which can be woven into fabric; shorter fibre varieties are incorporated into cement, board and tiles. Asbestos products have been used in fabric of buildings, for electrical and thermal insulation, for fire and safety

equipment and for the brake linings of cars. Asbestos has found uses in shipbuilding and the glass industry, in domestic electrical and heating equipment and in theatres and cinemas for fire curtains. Just as workers in a wide range of manufacturing industries may be exposed to various forms of asbestos, many others are exposed in maintenance work, in demolition, and in recycling operations; sometimes more intimately than are those using new asbestos products in manufacturing. Workers in mining and separation of the mineral from rock also have high exposure.

A link between airborne asbestos and ill health was first appreciated in 1898 in a patient whose death a year later was found to have been from diffuse pulmonary fibrosis. With the increasing use of asbestos came the growing realization of the health hazards inherent in its uses. Case reports on fibrosis arising from the inhalation of asbestos dust were published in 1924 (Cooke, 1924) and later on pulmonary asbestosis (Cooke, 1927). In the ensuing years the range of asbestos related diseases has been extended to include not only asbestosis (parenchymal and pleural fibrosis) but also lung cancer (Lynch & Smith 1960), pleural mesothelioma (Wagner et al., 1960) and cancer of other sites (Selikoff et al., 1979). Since the differences between the effect of asbestos on the health of smokers and non-smokers were reported, there have been studies specifically aimed at elucidating the combined effects of smoking and asbestos exposure. Studies on the health effects of asbestos must take the possible effect of smoking into account.

Exposure to asbestos is a hazard to household contacts of asbestos workers, who bring home dust on their clothes, and to people living within an area where there is environmental contamination by asbestos dust from industry (Anderson et al., 1979).

The several forms of asbestos differ in their colour and fibre length and in their relative carcinogenic potential. The amphibole varieties - crocidolite and amosite - appear to carry the highest carcinogenic risk. Crocidolite appears to carry greater risk than amosite which in turn is more dangerous than chrysotile, a serpentine variety. Erionite and tremolite are non-asbestos but are fibrous minerals that are used for building materials 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 who may be exposed. 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.

From the information available, it is reasonable to assume that the smoking habits of asbestos exposed workers probably reflect those of blue collar workers in general and are thus higher than national average figures. Table 1 gives examples of smoking prevalence in different groups of asbestos-exposed workers.

Table 1 Smoking prevalence in asbestos-exposed workers

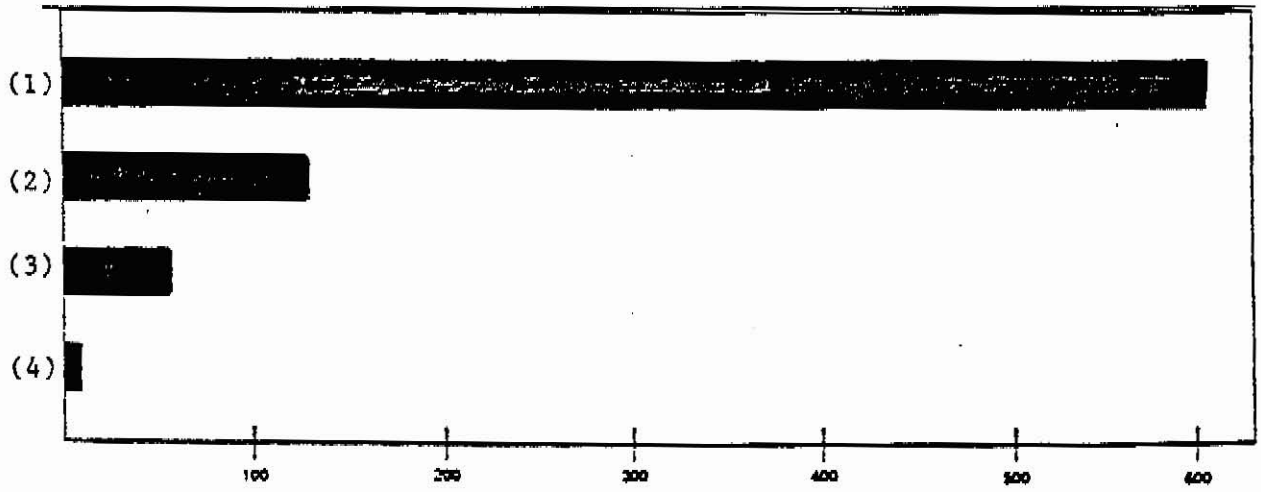
Exposure	Smoking habits	References
Asbestos textile workers	75% smokers 46% cigarette smokers 36% ex cigarette smokers 5.5% pipe/cigar smokers	Weiss (1971)
Electrochemical plant (two areas)	84% to 87% were smokers or ex smokers	Kobusch et al. (1984)
Population in Telemark, Norway	Asbestos exposed: 44.6% 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 (1982)
Lung cancer case-referent study; Swedish industrial city	Men: 95% smokers Women: 78% smokers	Jarvholm (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% (male population average 66%) Women: 49% (female population average 40%)	Newhouse & Berry (1979)

2.2.1.1 Asbestos and lung cancer

Exposure to asbestos dust carries a risk of parenchymal and pleural fibrosis, mesothelioma and lung cancer. In 1968, Selikoff et al. demonstrated that cigarette smoking was an added hazard among asbestos workers. This was a small study with no lung cancer deaths among non-smoking asbestos workers. A similar observation was reported in another small scale study

(Berry et al. 1972). It has become clear that, in combination, the two hazards are in most cases associated with very high lung cancer rates and attempts have been made to understand the nature of the effect. Cigarette smoke and asbestos could act independently, their combined effect being the sum of the individual effects, or there could be interaction between the two with the ultimate effect being a product of the two risk factors. Many studies have been carried out (e.g., Hammond & Selikoff, 1973; Hammond et al., 1979; Martschnig et al., 1977; Acheson et al., 1984; Selikoff et al., 1980; Berry et al., 1985). In some, the effects of smoke and asbestos appear to be additive, in others multiplicative and in others somewhere between the two. However, whatever may be the smoking/asbestos interaction influencing the incidence of lung cancer, the fact remains that there is an extraordinary increase in the risk for the asbestos exposed worker who smokes (Figure 1).

Figure 1
Comparison of lung cancer death rates for (1) cigarette smokers exposed to asbestos; (2) smokers with no asbestos exposure; (3) exposure only to asbestos; (4) no exposure either to cigarette smoke or to asbestos



Modified from: Hammond et al. (1979)

Several reasons for the lack of consistency can be invoked, such as 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 smoking history of the population sampled is important, bearing in mind the changes in smoking materials that have occurred in many countries during the course of this century, the vastly different smoking materials used in different parts of the world and the possible effects of passive smoking in societies where smoking is practised by a large percentage of the population (Cheng & Kong, 1992).

In a historical context, both smoking prevalence and cigarette consumption are difficult to obtain with accuracy, particularly if reliance is to be placed on relatives or friends rather than on information from the individual concerned. Furthermore, over the 25 to 30 year period that individuals who were the subjects of surveys had worked with asbestos, and been smokers, there were considerable changes in the tar and nicotine yields of cigarettes in many countries and, since it is often difficult to compare smoking materials used in different societies, comparisons of results may be open to question. Between 1933 and the late 1940's, the yield from an average cigarette could have varied from 33 mg to 49 mg tar and from less than 1mg to 3 mg nicotine (Todd et al., 1976) whereas, in the 1960's and 1970's, the average yield from cigarettes in Western Europe and the USA had been reduced to around 16mg tar and 1.5 mg nicotine. The average levels today are even lower. This can be compared with the smoke from the "bidi" of many Asian countries which can contain over 40 mg tar while Indian cigarettes can yield up to 28 mg tar, a value as high as US cigarettes before 1960 (Ball & Simpson, 1987). The "kretek" (cigarette of strong tobacco and cloves) of Indonesia can yield up to 71mg tar (WHO, 1985). Several of the smoking materials of northern Thailand (cigarette or cigar of strong tobacco plus various vegetable materials) produce up to four times the amount of tar and nicotine found in the smoke from standard UK cigarettes (Simarek et al., 1977).

In considering the initiation of asbestos and tobacco smoking related lung cancer, account must be taken of the different degrees of interaction between smoking and asbestos exposure that have been reported. These range from a high degree of apparent synergism to other studies in which the effects were less than additive. 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 must also reflect the complex nature of tobacco smoke which contains primary carcinogens and cocarcinogens and other compounds which can influence the multistage carcinogenic process. The ability of rat tissue to metabolize benzo(a)pyrene after exposure to crocidolite has been shown (Brown et al., 1984). It has been suggested that smoking causes mutations in the K-*ras* oncogene in DNA and that asbestos acts as a promoting agent by creating selective growth conditions for the mutated cells (Vainio et al., 1993). Vainio & Boffetta (1994) concluded: "Both tobacco smoke and asbestos fibres can be genotoxic and cytotoxic and cause proliferative lesions in the lungs. Tobacco smoke is known to contain carcinogens that bind to critical genes in DNA and cause mutations. Asbestos fibres may cause chronic inflammation of the lungs, which releases various cytokines and growth factors, and therefore may provide a possible selective growth advantage for mutated cells".

The weight of evidence favours a synergistic or multiplicative model for the interaction of asbestos and smoking. The data from Hammond et al. (1979) clearly indicated a very strong synergistic effect and this was supported by studies in shipyard workers in Italy (Bovenzi et al., 1993), asbestos factory workers in London (Newhouse & Berry, 1979), Finnish anthophyllite miners and millers (Meurman et., 1979), chrysotile workers in China (Zhu & Wang 1993; Cheng & Kong, 1992) and workers exposed to crocidolite in Western Australia (de Klerk et al., 1991). The Chinese study (Cheng & Kong, 1992) gave a lower ratio of non-smoking to smoking lung cancer death rates than reported for other countries: it was 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 their data would fit an additive model but gave a slightly better fit to a multiplicative model. They concluded that the combined relative risk lay somewhere between the two. Both Selikoff (1980), from a study of amosite factory workers, and Berry (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.

Nevertheless, whatever the degree or nature of the asbestos/smoking interaction, there is no doubt that the lung cancer risks are extremely high for anyone who may be exposed to asbestos, either occupationally or environmentally, and who is also a smoker.

2.2.1.2 Asbestos and pleural mesothelioma

The relationship between asbestos exposure and pleural mesothelioma is well known although, in 1983, only amphiboles (crocidolite and to a lesser extent amosite) had been shown to cause malignant mesothelioma and chrysotile was not implicated (Stellman, 1983). However, a subsequent report on shipyard workers "mainly exposed to chrysotile" (Sanden et al., 1992) found an increase in pleural mesotheliomas up to 15 years after cessation of exposure. The risk of lung cancer fell after exposure ceased and it was suggested that this is consistent with asbestos acting as a lung cancer promoter but the residual high risk for mesothelioma long after cessation of exposure indicated that asbestos acted as a complete carcinogen.

Malignant mesothelioma has an extremely long latent period, an average of 43 years has been suggested (Newhouse & Berry, 1976). It is possible that the greater solubility of chrysotile fibres reduces the likelihood of their residing in the tissues for as long a time as the less soluble crocidolite thus lowering their disease potential. This may partly account for chrysotile having initially escaped implication as a cause of pleural mesothelioma (Sanden, 1992).

Although up to 90% of pleural mesothelioma cases have been attributed to asbestos, no evidence has been advanced either directly associating smoking with the disease, or showing that smoking has any influence on the asbestos related incidence (Berry et al., 1985; Dupre et al., 1984; Hughes & Weill, 1991; Sanden & Jarvholm, 1991; Muscat & Wynder, 1991).

2.2.1.3 Asbestos and other forms of cancer

Asbestos fibres have been found in many tissues, other than the lungs, of asbestos workers. Few studies have been carried out, but it appears that an asbestos/smoking interaction increases the incidence of cancer of the oesophagus, pharynx and buccal cavity and larynx, however, as for pleural mesothelioma, smoking has no effect on peritoneal mesothelioma, 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).

2.2.1.4 Asbestosis

Asbestosis is a fibrotic reaction to asbestos in the lungs. The opacities formed differ from those attributable to silica or coal dust. The formation of fibrotic tissue might be expected as a natural reaction of lung tissue to some harmful constituents of tobacco smoke. Some tobacco smoke constituents can damage lung tissue, leading to emphysema. In a review of evidence (histological, animal experimental and X-ray), Weiss (1984) concluded that cigarette smoking can result in diffuse fibrosis similar to that caused by asbestos and that the changes showed a dose response to the duration and degree of smoking. Although the two agents cause apparently similar effects, it was not possible to assess the contribution of each during combined exposure. Most of the prevalence studies are consistent in showing a higher frequency of diffuse small irregular opacities in asbestos workers who were smokers than in those who were non-smokers. It was suggested that the effects may be additive but the mechanism remains unclear. Tobacco smoke can affect lung clearance and hence the retention of asbestos fibres in the lungs. In asbestosis the intensity of fibrosis correlated with the number of asbestos bodies in the lungs. Murai et al. (1994) concluded that a reduction of lung clearance by tobacco smoke could increase the intensity of fibrosis. It was also reported that crocidolite fibres were the most fibrogenic of the various types of asbestos. However, in a study of the effects of crocidolite de Klerk et al. (1991) concluded that while crocidolite multiplied the rates of lung cancer due to smoking, smoking had no measurable effect on asbestosis.

There is evidence that asbestos fibres stimulate alveolar macrophages to generate the inflammatory and fibrogenic mediator, tumour necrosis factor-alpha (TNFα), and this may cause the onset of inflammation and lung fibrosis due to asbestos (Ljungman et al., 1994). Other fibrous materials showed a similar effect *in vitro*.

An interaction between asbestos and smoking leading to 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).

A dose of asbestos capable of producing an excess risk of lung cancer could also produce asbestosis. The conclusions from a prospective mortality study (Hughes & Weill, 1991) were that asbestosis is a precursor of asbestos-related lung cancer but in this study all the cases of lung cancer developing from asbestosis were in smokers and in the absence of data from non-smokers it was not possible to make any assessment of the interaction of tobacco smoking and asbestosis.

2.2.1.5 Conclusion

A summary of the situation on smoking and asbestos is contained in the following quotation (Dupre et al., 1984): "1) the relative risk of contracting lung cancer from asbestos is approximately the same for smokers and non-smokers; 2) the great preponderance of lung cancers, in absolute terms, occurs in asbestos workers who are smokers; 3) asbestos exposure and smoking act synergistically in causing lung cancer, producing an effect that is greater than the sum of their individual contributions; 4) smoking appears to have the more powerful effect on the incidence of lung cancer; and 5) the risk of death in asbestos exposed persons who stop smoking is decreased considerably". Although it is unlikely that smoking initiates the fibrotic process that leads to asbestosis, it may affect it in terms both of the extent to which clinical asbestosis becomes manifest and of its rate of progression.

2.3 Non-asbestos fibres

2.3.1 Fibrous minerals

Fibrous minerals have been implicated in high rates of pleural thickening, pulmonary fibrosis, mesothelioma and lung cancer in some villages in the Anatolian Region of Turkey (Artvinli & Baris, 1979), where no type of asbestos could be found but where fibrous zeolite minerals (chabazite and erionite) are present in volcanic deposits. The materials are used in

building materials and the fibres were found in lung samples of thoracotomy patients. The pleural and pulmonary diseases were less evident in nearby villages where there were no asbestiform minerals in the soil. The symptoms and pathology of the respiratory disorders and malignant disease appeared to be identical to those caused by asbestos. Asbestos-type diseases have also been described in communities exposed to zeolite minerals and tremolite dust in similar regions by Baris et al.(1979) and Yazicioglu et al.(1980). Other non-asbestos fibrous materials have also been associated with pulmonary fibrosis (Stanton et al. 1977). However, there are no data on the effects of any interaction of these minerals with smoking.

2.3.1.1 Wollastonite

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. Exposed workers were studied in 1976 and 1982 (Hanke et al., 1984). Significant levels of chronic cough, phlegm and bronchitis were attributed to smoking and were not affected by exposure to wollastonite. However, the study population was small and interaction between smoking and dust exposure was not considered.

2.3.1.2 Glass fibre

In 1977 Stanton et al. suggested that glass fibre may be carcinogenic, because it can be inhaled in a form with dimensions similar to those of asbestos. 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. However, the matter has been controversial and evidence for conclusions about either exposure to glass fibre alone or with the added effect of smoking has been limited. Enterline et al. (1987) carried out a case control study of 7586 glasswool workers in four plants producing small diameter fibres, less than 3μm in diameter. Smoking histories were obtained for 75%. Analysis of data by logistic regression showed that smoking was a powerful variable and multiplied the any effect of fibre exposure. Chiazze et al. (1992) studied respiratory disease among employees of a glass fibre manufacturing facility and concluded that smoking was the most important risk factor for lung cancer but was not as important for nonmalignant respiratory

disease. Smoking prevalence in the area was at a sufficiently higher level than among the overall population of the country for the authors to suggest that it could account for the excess of lung cancer.

2.3.1.3 Rockwool, slagwool and ceramic fibres

An evaluation by 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. A survey of insulation workers using rock and glass wool (Clausen et al., 1993) concluded that modern insulation materials are associated with increased risk of developing obstructive lung disease. A study in seven European plants manufacturing ceramic fibres concluded that exposure to these fibres is associated with irritant symptoms, similar to those caused by other man made fibres, and cumulative exposure may cause obstruction by promoting the effects of cigarette smoke (Trethowen et al., 1995). Ljungman et al. (1994) demonstrated stimulation of alveolar macrophages to generate tumour necrosis factor-alpha (TNF-α), a potent inflammatory and fibrogenic mediator, by chrysotile A & B, crocidolite, rock wool, slag wool, kaolin ceramic fibre and silicon carbide whiskers. The effect of tobacco smoke was not examined.

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 and Leanderson & Tagesson (1989) found that cigarette smoke potentiated the DNA-damaging effect of man-made mineral fibres (rockwool, glasswool and ceramic fibres).

2.3.1.4 Conclusion

Mineral fibres cause irritation, and mucus hypersecretion; tobacco smoke affects mucus secretion and quality, and ciliary clearance. Some natural non-asbestos fibres have carcinogenic properties similar to those of asbestos and they could interact with tobacco smoke in a similar way. Man-made mineral fibres have been associated with obstructive lung disease and it has been

suggested not only that these fibres behave like asbestos in stimulating a potent inflammatory and fibrogenic agent but that the effect is also synergised by tobacco smoke.

2.4 Other inorganic chemical agents

2.4.1 Arsenic

Compounds of arsenic have been used as pesticides in orchards, tobacco cultivation, viticulture and tomato growing, and as preservatives of wood and leather. They are encountered in gold, tin and uranium mining, in the smelting of non-ferrous metals, particularly copper and lead, and as agents in the production of glass, lead alloys, paints, insecticides, rodenticides and semiconductors. In some operations, particularly non-ferrous smelting, other compounds may also be present in the dust and fume, dependent upon the source of the raw material. Radon progeny are frequently encountered as a contaminant of arsenic. In many parts of the world arsenic occurs in drinking water.

Arsenic and its compounds are recognized carcinogens and have been associated with cancer of several sites (WHO, 1980; IARC, 1987; Tsuda et al., 1990, 1995), particularly skin cancer after ingestion (Tseng et al., 1968) and lung cancer after inhalation by smelter workers or by people living nearby (Welch et al., 1982; Pershagen, 1985; Pershagen et al., 1987) and 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. Arsenic ingested from drinking water and medicinal preparations can cause skin cancer and it has been suggested that arsenic in drinking water may also cause liver, lung, kidney and bladder cancer (Smith et al., 1992) , although extrapolation of these findings from the source of the data (Taiwan) to any US population which may be exposed to arsenic in drinking water has been questioned (Carlson-Lynch et al., 1994).

There appear to be several possible interactions of arsenic and/or its compounds with other potentially toxic materials. The combined effect of arsenic and tobacco smoke has been given most attention although the possibility of additive or synergistic interactions involving arsenic and some of the materials with which it is often encountered in industrial operations have also been considered. 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 the exposure to cadmium particulates, that are considered to be carcinogenic.

It was suggested that there was an interaction between arsenic and smoking among exposed workers in a small Japanese village where arsenic was mined and refined (Tsuda,1990). The village was in a valley, the operations were primitive, the valley was constantly covered by a pall of smoke from the workplace and underground water flowed into the stream which was also polluted by slag disposal. It is, therefore, difficult to assess any interaction in such a situation. Results from a USA study in copper smelter workers (Welch, 1982) indicated that the effect of arsenic was more important than that of tobacco smoke, although caution was advised in interpreting the data. Several studies in Sweden have shown increased lung cancer risks from arsenic exposure at a copper smelter and a multiplicative effect for smoking and arsenic was found in a study of lung cancer mortality among 228 copper smelter workers: age standardized rate ratios were 3.0 for arsenic exposed workers, 4.9 for smokers with no arsenic exposure and 14.6 for arsenic exposed smokers (Pershagen, 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 less intense. In another study of a cohort of 3916 Swedish copper smelter workers (Jarup & Pershagen, 1991), 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.

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). Smoking was considered to be an unlikely explanation for the excess of lung cancer mortality in Ontario gold miners (Kusiak et al.1991) which, it was concluded, was probably due to exposure to arsenic and radon decay products. The same authors reached a similar conclusion regarding mortality from lung cancer in Ontario uranium miners. Part of the excess lung cancer was attributed to exposure to arsenic before 1946 and to exposure to short lived radon decay products. This finding is 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).

The question of whether synergism (an effect greater than additive) between active smoking and exposure to arsenic increases the risk of lung cancer was examined by assembling data from several studies (Hertz-Picciotto et al., 1992). It was calculated that 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. Taken as a whole, the evidence was compelling that arsenic and smoking

act synergistically to cause lung cancer. It has also been found that arsenic induced lung cancer is not limited to exposure to inhaled arsenic. There is evidence of synergism between ingested arsenic and smoking in the development of lung cancer, as well as between inhaled arsenic and smoking (Tsuda et al., 1995).

Bates et al. (1995) found that an association of arsenic exposures with bladder cancer was confined to subjects who had been smokers and suggested that the potentiation of the carcinogenic properties of arsenic by smoking "could provide an insight into why arsenic remains among the few established human carcinogens for which corresponding animal evidence of carcinogenicity has proven elusive". The possibility that inorganic arsenic may require a strong cocarcinogen to manifest any carcinogenic effect was raised. An alternative possibility, that arsenic might be acting as cocarcinogen rather than directly as a carcinogen has also been proposed (Stohrer, 1991; Tsuda et al., 1995).

In considering interactions of arsenic and other toxic materials, account must be taken of the facts that arsenic seldom occurs in situations in which it is not contaminated with other elements and compounds, many of which have themselves been implicated in carcinogenesis, and that tobacco smoke is also a storehouse of biologically active materials. Thus smelter fume may contain antimony, cadmium, chromium, cobalt, lanthanum, lead, selenium (Gerhardsson & Nordberg, 1993) sulphur dioxide (Enterline et al., 1987) nickel and polycyclic aromatic hydrocarbons (Pershagen et al., 1987). The arsenic encountered in tin, gold and uranium mining is often contaminated by radioactive materials (Taylor et al., 1989; Kusiak et al., 1991). Polycyclic aromatic hydrocarbons are likely to be present as atmospheric contaminants from machinery used in many mining operations. Tobacco smoke contains many primary carcinogens such as polycyclic aromatic hydrocarbons and nitrosyl compounds, along with cocarcinogens Thus interactions are likely to be very complex and beyond being considered as simple one-upon-one interactions.

In a study in Sweden (Pershagen et al., 1987) 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. 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). It was difficult to interpret the histological types associated with arsenic and tobacco smoke exposure (Pershagen, 1987). The suggestion (Tsuda et al., 1995) that arsenic may behave as a cocarcinogen needs further consideration.

From studies of the effect of arsenic trioxide in smelter workers, of poisoning by arsine, and of arsenic contamination of drinking water and beer, reviewed by Kristensen (1989), there appears to be a causal relationship between cardiovascular disease (CVD) and arsenic compounds and a dose response has been demonstrated for arsenic and cardiovascular mortality. There have also been reports of a link between high levels of arsenic in drinking water and both heart disease and peripheral vascular disease. The known effects of smoking on all forms of CVD could be expected to contribute additively to any effects from exposure to arsenic compounds but the possibility of a multiplicative effect has not been examined.

2.4.2 Beryllium

Beryllium is a hard, grey and brittle metal and in thin sheets transparent to X-rays. It has a number of uses (IPCS, 1990; IARC, 1993). It was used as a constituent of phosphorescent powders for fluorescent lighting; it is used alloyed with aluminium, copper, nickel and steel and finds special uses in nuclear energy applications and the rocket and aerospace industry. 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. Coarse particles, deposited in the nose or mouth, are swallowed and pass through the alimentary tract without detrimental effect.

Beryllium metal, oxide and some salts can 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, their role in respiratory carcinogenesis remains controversial because in the epidemiological studies carried out 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; McMahon, 1994; Kotin, 1994).

The prevalence of chronic beryllium disease (CBD) appears to be reduced in smokers compared with non-smokers. Although the disease appears to be preceded by the development of beryllium-specific sensitization, it is not known to what extent sensitization leads to clinical

disease. Two separate studies examining different worker populations have shown that prevalence of smoking in populations having clinically diagnosed chronic beryllium disease is lower that in groups that were sensitized but that did not have the disease (Kreiss et al, 1993; Kreiss et al, 1996).

2.4.3 Other inorganic elements and compounds

Coal dust and silica in mining and a wide range of inorganic elements and compounds encountered in mining, smelting, enamelling, electroplating, metal castings, the production of alloys, glass, paints, batteries, semiconductors, or used in the chemical, or petroleum industries and frequently arising in welding operations have detrimental health effects. The nature of these hazards have been frequently recorded and in many cases it has been found that smoking either masks the true nature of the ill health effects or causes a more severe condition. However, interactions between smoking and these chemical agents have not been established. Other health hazards of these exposure situations are considered in Section 3 (3.1-3.5).

2.5 Organic chemical agents

In a large number of very different industries, many organic compounds are encountered with properties covering a wide spectrum of both molecular structure and biological activity. Some may affect lung clearance, or the cardiovascular system, or have neurobehavioural effects; or tissues in the lungs, liver, kidneys, blood, bone, the central nervous system; or processes such as reproduction and cell division, and be tumour initiating or promoting. Likewise, cigarette smoke also contains a large number of organic compounds, many of which can affect tissues and biological processes.

Exposures to organic compounds in industry and exposure due to smoking are different. In most industrial situations, the individual usually encounters only one or perhaps a limited group of compounds whereas cigarette smoke delivers the full chemical storehouse in each of a series of short sharp insults. However, in spite of the many biologically active organic compounds encountered in industry and the prevalence of smoking among workers, little has been reported on the effects on health of the interaction of industrial exposure to organic compounds and tobacco smoke. Nevertheless, the effects of a few compounds, or of some that are encountered in specific industries, have been studied and from the known effects of smoking it is possible to understand some likely effects of a combination of the hazards and to realize the potential for interaction.

There are some organic compounds encountered in industry that have not been detected in cigarette smoke and any combined effect with smoking would be to change the risk associated with the occupational exposure. 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 arise from pyrolysis or volatilization during smoking. Some compounds fall into all three categories.

2.5.1 Chloromethyl ethers

These compounds display an antagonistic interaction with smoking. Chloromethyl methyl ether (CMME) and its contaminant bis(chloromethyl) ether (BCME) are encountered in the synthetic-chemical industry, in the manufacture of ion exchange resins and in polymer production. They are carcinogenic when inhaled, BCME far more so than CMME. Groups of chemical workers who had been exposed to these compounds were studied from 1963 to 1972 (Weiss & Boucot, 1975; Weiss, 1976, 1980, 1982). The results showed a modification of the carcinogenic effect by smoking in that there was a higher rate ratio for non-smokers than for smokers and the effect for smokers was not only less than additive but apparently antagonistic. The study was, however, carried out on a very small number of subjects: only 11 lung cancer deaths occurred in total. The findings have been reviewed (Steenland & Thun, 1986; Thomas & Whittemore, 1988) and several explanations put forward, such as protection by a greater mucus barrier in smokers, or less access to tissues due to constriction of small airways in smokers, and more frequent clearance. However, if this protection is available for the chloromethyl ethers, it should also be available as protection against other carcinogens, and this is not the case.

2.5.2 Dyestuffs

There is a well established relationship between bladder cancer and exposure to certain aromatic amines encountered in the dyestuffs industry, e.g. benzidine and 2-naphthylamine (IARC, 1987). In addition, based on a small number of reports, there is evidence showing a relationship between bladder cancer and smoking (IARC, 1986). 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 author considered the risks 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 pose the major threat of bladder cancer; the risks having decreased with the banning of 2-naphthylamine in 1950 and benzidine in 1962 in the UK. It was considered that there was little evidence to support an effect due to smoking or an interaction between smoking and occupational exposure.

From a survey in an area of Spain where 44% of the adult population work in dyeing and printing textile fabrics (Gonzales et al., 1985), it was clear that there was an increased risk of bladder cancer for habitual smokers. Habitual smokers were found to present a higher risk than non-smokers (OR 2.3) The estimated risks for occupation and for smoking and occupational exposure were OR 5.5 and 11.7 respectively. Tobacco smoke contains many amines and an additive effect for tobacco smoke and exposure to dyes would not be surprising; however, the observed effect in this case was multiplicative.

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 listed as an important cause but one which was additional to urological disease or occupational exposure, among other factors. In a study in men in Spain (Gonzales 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 associated with smoking black tobacco was also considered: for black tobacco smokers OR was 3.7 compared with OR of 2.6 for smokers of blond cigarettes. A higher risk for black tobacco than for blond varieties and a protective effect for smokers of tipped cigarettes was reported in a study in Northern Italy where a multiplicative effect for smoking and high risk occupations was also found (Vineis et al., 1984).

From a Chinese study of bladder cancer mortality and incidence among workers in benzidine exposed jobs in several cities, a marked dose response was found along with 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. A multiplicative relationship between the two carcinogens was suggested (Bi et al., 1992).

2.5.3 Polycyclic aromatic hydrocarbons

Tobacco smoke contains many polycyclic aromatic hydrocarbons (PAH) (IARC, 1986). Most PAHs are known to be carcinogenic, such as benz(a)pyrene and dibenzanthracene (IARC, 1987). PAHs are generated 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 cocarcinogens and promoters as well as 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. It is known that 69% of workers at one Norwegian smelter were smokers when the expected prevalence of smoking was 52% (Abramson et al., 1989) and, although not specific to these industries, the percentage of smokers and ex-smokers among workers exposed to chemicals and coal tar pitch in a survey of 800,000 American men and women in 1982 in relation to their occupation (Stellman 1988) was 49.9% against 46.1% for the average worker.

A Canadian study concluded that the incidence of bladder cancer was unusually high in aluminium smelter workers, particularly among those employed in Söderberg potrooms, where PAH levels are high (Thériault et al., 1984). Lung cancer among aluminium reduction plant workers is also high (Gibbs & Horowitz, 1979). Aluminium is produced by a very high current electrolytic process which involves the use of carbon electrodes made from a mixture of petroleum pitch and coal pitch which is baked to form the carbon electrode. Changing electrodes, breaking

the crust that forms on top of the molten metal and cleaning out the "pots" are activities which create air pollution by tar volatiles including PAHs which, measured as benzo(a)pyrene, can reach a concentration of 800 $\mu g/m^3$/8 hours (Bjorseth et al., 1978): the PAHs were considered to be the carcinogenic factor.

Tobacco smoke appears to increase the risk. Studies of bladder cancer in the aluminium industry have considered the possibility of synergism between cigarette smoking and the exposure to tar volatiles in smelter workers but in the study by Thériault et al. (1984) the numbers involved were too small to distinguish whether the interaction was additive or multiplicative but in another study (Bjorseth et al., 1978) it was considered that there was suggestive but not conclusive evidence that the relative risks from exposure to tar volatiles and cigarette smoke combined multiplicatively. In a more extensive study in which the former 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.

The function of alveolar macrophages(AM) 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 was higher in persons exposed to cigarette smoke than from non exposed persons (Harris et al., 1975; Rylander et al., 1979). Gullvag et al. (1985) found that the AM 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 drawn from these results was that smoking and workplace pollution act synergistically in increasing the number of AM.

Workers in coke oven plants have a higher incidence of lung cancer than the general population and measurable concentrations of PAHs in urine, which is higher for smokers (Haugen et al., 1986); higher levels were also found in urine samples from aluminium plant workers. Van Schooten et al. (1990) analyzed 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. This does not indicate any interaction between PAH from the two sources but shows that each augments the other.

Professional drivers are exposed to PAHs through the exhaust of petrol 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).

In most of the workplaces where PAHs contaminate the atmosphere, there are also gases, fumes and aerosols which contain other hazardous materials which act as irritants, and may play a role in the aetiology of chronic obstructive lung disease. It is important to include smoking in epidemiological surveys. 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 aetiological factors (Sherson et al., 1992).

2.5.4 Ethanol

The International Agency for Research on Cancer has evaluated possible interactions of tobacco smoking and alcohol consumption (IARC, 1986). In the case of cancers of the oral cavity, oropharynx, and hypopharynx there was epidemiological evidence for a multiplicative effect of smoking on cancer risk (Schwartz et al., 1957; Rothman & Keller, 1972). Wynder et al. (1976) and Burch et al. (1981) reported a combined effect of cigarette smoking and alcohol consumption in cancer of the larynx. For oesophageal cancer there was a multiplicative effect (Wynder & Bross, 1961; Tuyns et al., 1977; Breslow & Day, 1980; Keil et al., 1980).

2.5.5 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 Section 3

2.6 Physical agents

2.6.1 Radiation

The harmful forms of radiation of concern are α- and β-particles and γ- and X-rays. All cause cellular damage and have been implicated in carcinogenesis. IARC, 1988, classed radon and its decay products as group 1, carcinogenic to humans, on the basis of sufficient evidence in humans and in experimental animals. The interaction of the effects of these radiations with the effects of tobacco smoke to result in a modification of effect have 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 alpha and beta particles and gamma 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 effects involved in the use of therapeutic radiation (X-rays).

2.6.1.1 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, for example in the USA, Czechoslovakia, Canada and France among uranium miners, workers in a niobium mine in Norway, iron ore miners in Sweden, tin miners in China and the UK 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 are cigarette smokers there is an interaction between the radiation exposure and the smoke exposure leading to more than expected cases of cancer. Several facts emerge: the latent period for induction of lung cancer is longer when the exposure to radioactivity starts at a younger age; it is shortened by high exposure rates and by cigarette smoking; and lung cancers develop at lower levels of exposure to radioactivity in miners who smoke than in those who are 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 by circulating the air through old underground mine workings

with the result that, in the 1920's, the potential for silicosis was reduced but this success was marred by an increase in lung cancer 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 and in another by Damber & Larsson (1985b) the effect was clearly multiplicative. From a long term study on Swedish iron ore miners (Jorgensen, 1984) it was concluded that tobacco smoke acts as a tumour promoter, an effect that has been demonstrated in almost all animal studies. The histological types of lung cancer among miners have been different as working conditions have changed and as the time elapsing between follow-up studies has changed. 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 conclusion reached by the US Surgeon General (1985) was that the smoke-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.

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

The possibility that α-radiation from radon daughters in the home or in other situations where there are enclosed spaces with poor ventilation, as where tight energy conservation measures have been adopted, may present an elevated hazard to smokers is a matter for 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 RR 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) but caution was advocated in interpreting information on miners because of concomitant exposure to other carcinogens by these workers. However, Steindorf et al. (1995) calculated that 7% of all lung cancer deaths in the western part of Germany may be due to residential radon. The suggestion that linearity in mines would permit extrapolation into the domestic environment was not confirmed in a study of the linear no threshold theory for lung cancer induced by exposure to radon (Cohen, 1994).

Axelson (1995) reviewed the situation on cancer risks from exposure to radon in the home and suggested that other cancers may also be related to indoor radon, especially leukaemia, kidney cancer and malignant melanoma but accepted 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 nonsignificant 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. Biberman (1993) on the other hand found an increased risk for small cell lung cancer following residential long term exposure to radon at a low dose level. Pershagen et al. (1994) studied residential radon exposure and concluded that the interaction between radon exposure and smoking with regard to lung cancer exceeded additivity and was closer to a multiplicative effect. However Chaffey & Bowie (1994) concluded that whether the combined effect of smoking and radon exposure is a multiplicative or additive effect remains unclear.

In the case of lung cancer risk it is reasonable to conclude that the interaction between tobacco smoke and radon exposure is greater than additive. There could be a risk from low level radon exposure in the home and any effect would be increased by the interaction with tobacco smoke inhalation but smoking is probably the primary factor in causing lung cancer in any domestic situation where radon concentration is at only a very low level. The matter of lung cancer arising from interactions between residential radon, tobacco smoking, and environmental tobacco smoke remain one for public concern and further study.

2.6.1.3 Atomic bomb site radiation (low linear energy transfer (LET) radiation)

In tobacco-smoking survivors of atomic bombing in Hiroshima and Nagasaki 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; NRC, 1988).

2.6.1.4 Therapeutic X-rays (mainly 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 threefold 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) led to a study of possible responsible factors (van Leeuwen et al., 1995). The overall conclusions were that the risk of lung cancer increased with increasing radiation dose in HD patients who smoked more 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 found among women with HD was attributable to the delayed popularity of smoking among Dutch females, a fact evidenced by the male/female lung cancer ratio (13:5) in the Netherlands in 1980.

2.6.1.5 Nuclear power plant

Ongoing epidemiological studies are being conducted on the workforce exposed to radiation at the Mayak plant in Russia. A total of 500 workers were examined in a case-control study (Tokarskaya et al., 1995); !62 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 smoker" among the male lung cancer cases.

2.6.1.6 Conclusion

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, tending to show similar interactions to those for miners. Tobacco-smoking patients subjected to therapeutic radiation (low-LET) show a multiplicative interaction.

2.6.2 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. An American survey estimated that 1.2 million workers were exposed to hand-arm vibration. 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, and 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).

2.6.3 Noise

Noise is also vibration, usually at a slightly shorter wave length than mechanical vibration. 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 1) vasospasm induced by nicotine, 2) atherosclerotic narrowing of vessels, and 3) 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. However, Pyykko et al. (1987) concluded that in some subjects with vibration white finger syndrome and those with elevated diastolic blood pressure, there was an increased risk of exaggerated hearing loss.

2.6.4 Dupuytren's contracture

Opinions differ on the influence of occupation, handedness and hand injury on Dupuytrens contracture which Dupuytren himself attributed to chronic occupational injury. Some assert that heavy work always causes the disease others that it is never 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. Fraser-Moodie (1976) in a study of 84 men and 16 women with Dupuytren's contracture found no evidence that smoking was connected with the condition, a conclusion also reached by Mackenney (1983). However, cigarette smoking was been listed among the responsible factors for Dupuytren's contracture by Attali et al. (1987), and 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) found a significant association between Dupuytren's contracture and smoking habits but as they were not the primary aim of the study they suggested that the finding should be considered as the basis for hypothesis rather than as being conclusive. .

2.7 Biological agents

2.7.1 Biological dusts

Airborne biological agents which can affect health are encountered in agricultural operations and textile industries worldwide and the population that may be exposed to them 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.

2.7.1.1 Cotton dust

Byssinosis is a respiratory disease peculiar to textile workers. The disease occurs in many cotton processing countries such as Brazil, China, Egypt, India, Israel, the Netherlands, Sweden and Uganda. 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 chest tightness 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 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 1963-66 (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 1986/7, 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). 5.9% of 800,000 American workers surveyed (Stellman et al. 1988) for smoking habits in 1982 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. (1988) of workers in 31 textile factories in the UK 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. 1988) 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 an absence of the causative agent in the dust. Persistent cough and phlegm production were associated with tobacco use.

Estimates vary of the incidence and severity of textile related pulmonary disease: from a study of emphysema and other chronic lung disease in textile workers, Moran (1983) concluded that there was no conclusive evidence to show that textile workers, even after many years of exposure, have more emphysema or other chronic lung disease than the non-textile population and that the increase in emphysema in the periods 1962-1969 and 1970-1980 can be explained by the increase in smoking in years prior to the study and corresponded to an increase in lung cancer during these periods. Smoking as a primary causative factor had been reported by Pratt et al. (1980) and a similar conclusion was arrived at from ventilatory function tests carried out over a three 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

2.7.1.2 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 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 (RR 2.5) and with smoking (RR 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.

2.7.2 Allergic responses

This type of response can occur in the upper airways, where it is manifest as Hay Fever, possibly 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) reported that the effect of grain dust and smoking was additive and not synergistic in causing a decrease in lung function.

Occupational asthma also occurs in grain, tea, coffee and rice handlers. In occupational asthma in enzyme detergent workers it was been found that twice as many smokers as non-smokers exhibited asthmatic symptoms.

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

2.7.2.1 Allergic alveolitis

Although many biological dusts are known to have detrimental health effects, there have been few studies of any interaction of smoking with these agents. There are several forms of allergic alveolitis, of which farmer's lung, bagasse pneumonitis, and bird fancier's lung are examples, caused by fungal spores in mouldy hay or mouldy sugar cane or an agent in bird feathers respectively, and it is immunologically mediated (Lancet 1985). It seems to be more prevalent in non-smokers than in smokers, possibly because of a reduction in alveolar macrophage activity caused by smoke.

2.7.3 Factory farming - animal confinement effects

Factory farming of pigs with animals 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 sulphide; 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.

2.7.4 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. The relative importance of the factors was not assessed, nor were possible interactions discussed.

Schistosomiasis is a waterborne parasitic disease found in many developing countries in Africa,, Asia and South America. It is an extremely widespread occupational disease to which a very large number of agricultural workers are exposed, as well as affecting ordinary members of the general population.

A phase in the life-cycle of the trematodes responsible for the disease live 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 ares with a high prevalence of infection with this parasite than in areas with a low prevalence. IARC classifies infection with S. haematobium as carcinogenic to humans (Group 1) (IARC 1994). In Egypt, the most common form of cancer is bladder cancer. At the National Cancer Institute in Cairo, it accounts 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 on 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 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. Thus, it was not possible to identify an interaction between smoking and schistosomiasis in the production of bladder cancer although both can cause bladder cancer.

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

A basic tenet of toxicology is that studies in animals can be used to understand effects of toxicants in humans. Unfortunately, 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: (1) was generally performed using rodents, (2) 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 (3) usually examined cancer as the biological response endpoint of interest. Numerous other reports 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 reports are beyond the scope of this section.

2.8.1 Non-cancer endpoints

Several studies have examined in animals 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 smoke exposure of rats to smoke did not influence the lung damage caused by an intratracheal instillation of cadmium (Lai & Diamond, 1992).

2.8.2 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 3,4-benzpyrene 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 (1) B6C3F1 mice pretreated with 3- methylcholanthrene or benzo[a]pyrene (Henry & Kouri, 1984), (2) C57BL mice receiving benzo[a]pyrene or influenza virus(Harris & Negroni, 1967), (3) 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 (4) A/J mice receiving exposure to sidestream smoke plus the carcinogens 3-methylcholanthrene or urethan (Witschi, personal communication). 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 urethan and skin-painted cigarette smoke tar (DiPaolo et al, 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). A combination of smoke plus benzo[a]pyrene adsorbed onto hematite produced tracheal and laryngeal hyperplasia whereas either agent alone did not (Hoffmann et al, 1979), but no tumours were produced.

2.8.3 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 dogs receiving a

mixture of radon, radon daughters, and uranium ore dust. The authors speculated that smoke-induced increases in mucous flow might have reduced the radiation dose,but the use of relatively few animals made interpretations difficult.

Several studies have examined the potential interactions between the alpha-emitters radon or 239-plutonium 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, and these investigators also studied the effects of pre-treatment with either radon or the smoke exposure. Smoke exposures begun before radon exposure did not influence the radon-induced lung tumour incidence, but the incidence was increased by two- to three-fold over radon-alone rats the combined exposure group had radon exposure first followed by smoke. Finch et al. (1995a) examined F344 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 this 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 noted above in rats, cigarette smoke exposure caused retarded lung clearance and thus led to greater radiation doses in animals receiving both agents.

3. COMBINATION OF SEPARATE EFFECTS: TOBACCO SMOKE AND OTHER AGENTS

3.1 Coal mining

3.1.1 Coal dust

Chronic bronchitis of coal miners who smoke is probably a combination of mucus hypersecretion due to dust; masked by mucus hypersecretion and impaired lung clearance caused by smoke; along with small airways disease (SAD) caused by smoke; and the effect of dust on small airways inflamed by smoke. Emphysema possibly proceeds from SAD, rather than being primarily caused by dust, and thus there are more cases of emphysema in coal miners who smoke than in non-smokers. Coal workers pneumoconiosis is caused by coal dust. There is no association between coal dust and lung cancer; only between smoking and cancer.

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 because 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 but difficulties arise in interpreting data because non-smokers may accumulate more dust because they have less absenteeism, a different pattern of lung clearance and a longer life.

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 UK, the smoking prevalence fell for the male population (and for miners) from 54% (miners 77%) to 47% (miners 49%) (Lee 1976). The New Zealand population census in 1976 gave the smoking prevalence for the male population as 39%, and for miners 57% (similar to transport workers and labourers). In a report on the 1981 census by the National Heart Foundation of New Zealand (1984), smoking prevalence quoted for males was 35% and for production workers, transport operatives and labourers, (the group which included miners in the earlier census) 43% In a study

of 8555 American miners from 29 bituminous coal mines (Kilbestis et al., 1973), over 50% were smokers and 25% were ex-smokers. In a UK 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 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.

3.1.2.1 Bronchitis in coal miners

Kilbestis 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. Table 2 shows the results of an epidemiological evaluation of chronic obstructive bronchitis in 5605 miners (M), 1276 ex-miners (EM) and 3898 individuals who had never worked in a mine (NM) (Roth et al., 1985)

Table 2 Prevalence of bronchitis by age and smoking status in 8492 bituminous miners

	Non-Miners (3898)		Coal Miners (5605)		Ex-Miners (1276)	
	⟨29 yr	⟩50 yr	⟨29 yr	⟩50 yr	⟨29 yr	⟩50 yr
Chronic bronchitis						
Non-smokers	1.1	20.5	1.6	9.6	0	15.0
Smokers	2.4	28.2	4.8	34.6	3.3	31.5
Obstructive symptoms						
Non-smokers	4.6	10.3	0	10.8	0	12.5
Smokers	6.1	14.2	10.3	16.4	6.6	16.0

These figures show that smoking has a more serious effect on miners than on other groups. 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: from 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) analyzed 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. Bronchitis leads to hypersecretion of mucus and affects the large airways. 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, prevalence of bronchitis in non-smokers is related to the degree of dust exposure. Marine et al. (1988) analyzed data from studies on 53,382 UK coal miners. 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 a continuous series of postmortem examinations of coal mine workers, a correlation was reported between clinical chronic bronchitis and smoking (Selig & Nestler 1985), although there has been considerable debate on this (Morgan 1986).

It is can be concluded that the chronic bronchitis of coal miners is probably a combination of:

- mucus hypersecretion caused by dust;
- mucus hypersecretion, mucus modification and clearance impairment caused by tobacco smoke;
- small airways disease caused by tobacco smoke;
- the effect of dust on small airways tissue already inflamed by smoking.

3.1.3 Emphysema and pneumoconiosis in coal miners

Dust in coal mining is considered to be the primary cause of coal workers pneumoconiosis. Cockroft et al. (1982) in a study of coalworkers and non-coalworkers concluded, after taking any effect of smoking into account, that there was a seven times excess of emphysema in coalworkers. Results of post mortem 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 post mortem comparison of lungs from 450 coal miners Ruckley 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 et al. 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, but not necessarily to panlobular emphysema.

3.1.4 Lung cancer in coal miners

Perhaps due to 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. 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. A hypothesis (Meyer et al., 1980) that increased pulmonary retention of carcinogenic particles as a result of impaired ventilatory function would predispose to lung cancer and that normal ventilatory function, permitting efficient clearance and subsequent swallowing of carcinogens, would lead to stomach cancer among coal miners has been tested (Ames & Gamble, 1983). The results contradicted the hypothesis, suggesting that obstruction may set a condition for stomach cancer and normal lung clearance may set a condition for lung cancer and that the inhaled carcinogenic agent is different for each type of cancer. For miners with airways obstruction or long term smoking, coal dust poses a stomach cancer risk and for miners with normal ventilatory function, current cigarette smoking poses a disproportionately high lung cancer risk. 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 would be expected to be as prevalent as in all other mines and thus the apparent very low lung cancer risk in coal mining is unexpected. However, because of the explosion risk in coal mines, their ventilation is usually efficient and a build up of radioactivity is probably less likely than in other types of mine.

3.2 Silica

Silicosis is the other major fibrosis caused by non-asbestos mineral dust. In some industries it has always been known that there are diseases peculiar to the work: colloquially known by terms such as "potters' rot", "miners' phthisis" and "grinders' asthma". Silica related diseases are not only a hazard of mining. Other examples are 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).

Since silica exposure can occur in many situations it is not possible to generalize on the smoking habits of those exposed. Almost all, however, will be blue collar workers with a smoking prevalence higher than for the general population. Among lifelong underground workers (average 31 years) in a Swedish iron ore mine in 1984 (Jorgensen et al. 1988), 37% were "never smokers" and in a slightly older group (average 34.5 years underground) but now working on the surface, only 23% were never smokers. Ex-smokers in the two groups were 29% and 39% respectively. 25% of surface workers were smokers; 51% were ex-smokers. Among slate workers in North Wales in 1981, 57% were cigarette smokers and only 14.7% were "never smokers" (Oldham et al., 1986). Smoking prevalence was high among Australian gold miners (Holman et al., 1987): in 1985 56.2% were smokers, 18.5% ex-smokers and 25.3% non-smokers. In the survey of the smoking habits of 800,000 American workers in 1982, only 19% of workers exposed to coal or stone dust had never smoked regularly (Stellman et al., 1988).

Mortality rates of silica exposed workers have been consistently higher than for non-exposed workers but the effects of smoking were seldom considered. Occupational silica exposure can be associated with chronic silicosis, which develops after 20 to 40 years of exposure, and acute silicosis which has a more rapid onset. There are also other types of pneumoconiosis

related to the nature of the dust and chronic bronchitis and airways obstruction have been associated with silicaceous dust exposure. The principal complication of silicosis is pulmonary tuberculosis which is said to accelerate fibrosis, respiratory insufficiency and non-specific pulmonary infection. Lung cancer has also been associated with silicosis.

A widely held hypothesis for the pathogenesis of chronic silicosis is that silica particles are phagocytosed by the alveolar macrophages to which they have a marked selective toxicity. Autolysis of the macrophages initiates reactions leading to the formation of collagenous fibres. Acute silicosis arises from the inhalation of more highly reactive silica (Vallyathan, 1988). Although silica is the sole aetiological agent for all forms of silicosis, a study of workers exposed to granite and quartz dust, 30% showed opacities that were considered to be due both to the dust and to smoking. In a study by Ng et al. (1987), however, smoking was not considered to affect the progression of silicosis in granite quarry workers.

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). 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). It was argued that this effect of smoking should be taken into account when an association between silicosis and lung cancer was being considered.

An association between silica exposure and lung cancer has been studied. From an attempt to link gold mining dust with lung cancer (Hnizdo & Sluis-Cremer, 1991) a combined effect of dust and smoking that fitted a multiplicative model for lung cancer was suggested. Amandus et al. (1992) studied lung cancer in males already diagnosed with silicosis and suggested that the evidence was consistent with the hypothesis of an association between the two diseases, but the conclusion drawn from a study of iron foundry workers was that cigarette smoking was a strong predictor of lung cancer whereas silica exposure showed no association with the disease (Andjelkovich et al., 1994).

Another attempt to assess whether silica induces lung cancer was made by comparing pottery workers, tungsten, copper-iron and tin miners. Confounders such as arsenic (As), polycyclic aromatic hydrocarbons (PAH) and radon were taken into account (McLaughlin et al., 1992). It was found that lung cancer risk increased with silica exposure among tin miners but this risk also correlated with arsenic and PAH exposure. Lung cancer risk was related to silica exposure in pottery workers, a form of silica less contaminated by confounding agents. There

was, however, no cancer risk among the group most heavily exposed to silica, namely the tungsten workers. An interaction with smoking was not examined.

From a survey in two Sardinian metal mines, in which the conditions were low dust/high radon in one mine and high dust/low radon in the other (Carta et al., 1994) it was concluded that crystalline silica *per se* does not affect lung cancer mortality but there was a slight association between lung cancer and radon exposure. Impaired pulmonary function was seen as a predictor of lung cancer because of the enhanced residence of inhaled carcinogens such as alpha particles, or PAHs, or tobacco smoke, caused by impaired lung clearance.

In a study of South African gold miners, Sluis-Cremer et al. (1967) concluded that smoking effects overwhelmed the effect of silica dust on bronchitis. In a study of 2209 South African gold miners and 438 non-miners assessing 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. 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) analyzed the relationship between occupational dust exposure and chronic obstructive pulmonary disease and found a significant association between loss of lung function and a cumulative respirable dust exposure, which was greater in gold miners. In gold miners there was no evidence of interaction with tobacco smoking and the authors speculated that the greater risk was due to the occupational dust having a higher silica content than coal dust. In South African gold mines about 30% of the respirable dust is free silica (Hnizdo et al., 1990). Among iron ore miners in Sweden (Jorgensen et al., 1988)) a strong relationship was found 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 functional compromise of small airways by silica and smoking (Avolio et al., 1986) it was concluded that small airways disease due to encroachment of bronchiolar walls by silica deposition is masked by the damage produced by cigarette smoking, even in the presence of radiographic signs of silicosis.

3.3 Other mineral dusts

3.3.1 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).

3.3.2 Kaolin

Kaolin (pure china clay) is a hydrated aluminium silicate which is 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. Smoking effects probably resemble those with silica.

3.3.3 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. Smokers had a significantly higher prevalence of opacities and their trends with time were accentuated, compared to non smokers. The stronger trends were attributed to the joint effects of duration of smoking and occupational exposure.

3.4 Metals

3.4.1 Antimony

Antimony is chemically similar to arsenic. Arsenic is metalloid, antimony is a metal, both have volatile hydrides and form halogen, oxygen and sulphur derivatives. Compounds of both frequently occur together, particularly in smelter fume. Antimony is used in new high technology industries, and medicinally. It is reasonable to expect some biological effects to be similar to those

of arsenic but because the two usually occur together, often with other toxic materials, it is difficult to isolate the hazard posed by antimony alone. The concentrations of antimony, arsenic, cadmium, chromium, cobalt, lanthanum, lead, selenium, and zinc in lung tissues of deceased smelter workers suggested that lung cancer risk is multifactorial, involving carcinogenic and anti-carcinogenic factors (Gerhardsson & Nordberg, 1993). A thirty 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). From another study of smelters the data suggested an increase in lung cancer and nonmalignant respiratory and heart disease (Schnorr et al., 1995). Antimony trisulphide has been implicated in sudden deaths from chronic heart disease, and in electrocardiograph changes in 37 out of 75 of the exposed workers (Kristensen, 1989). Molten antimony fumes have been held responsible for dermatoses (White et al., 1993).

Antimony salts have toxic effects (De Wolff, 1995). Antimony compounds, for example sodium stibogluconate, have been used for treating leishmaniasis but acute pancreatitis (de Lalla et al., 1993), neurotoxicity (Laguna del Estal et al., 1994), and a nephrotic syndrome (Morin et al., 1991) have been associated with using pentavalent antimonials for treating visceral leishmaniasis.

Antimony and may have detrimental effects on lung tissues, including pneumoconiosis. IARC (1989 a) evaluated antimony trioxide and antimony trisulfide and conclude 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, permits the conclusion that tobacco smoke and antimony could act synergistically.

3.4.2 Cadmium

Most zinc and lead-zinc ores contain small amounts of cadmium, which also occurs as the sulphide in mineral form. Cadmium is a hazard of the fume during zinc and lead smelting. 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 is a hazard of welding. The main route of exposure for the non-smoking general population is via food and for exposed workers it enters the body mainly by inhalation. Tobacco is an important source of cadmium in smokers (IPCS, 1992).

The tobacco plant absorbs cadmium from the soil and a high proportion is transferred to the mainstream smoke. Thus the tobacco source can affect cadmium dose (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 effects, most noticeably the impairment of the renal function giving rise to proteinuria and general ill health. It has also 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 and the prostate; the evidence for lung cancer is stronger (IARC, 1993). The evaluation by IARC in 1993 concluded that cadmium and cadmium compounds are carcinogenic to humans (Group 1). Cadmium has effects on 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)). The effects of smoking on cadmium related diseases are not known but blood and urine cadmium levels have been shown to be much higher in smokers than in non-smokers. These levels 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 (Kazantis & Armstrong, 1984; Lilis et al., 1984a,b). The question arose as to whether the higher cadmium levels in smokers were due to the increased burden imposed by smoking or to an impairment of clearance. In these surveys (Hassler et al., 1983; Kazantis & Armstrong, 1984; Lilis et al. 1984a, 1984b) it was found that low levels of cadmium exposure did not impose a health risk either among smokers or non-smokers. In the study of copper smelter workers (Lilis et al., 1984a) neither cadmium nor lead absorption was in the range where an effect on renal function is normally found and neither an additive nor a synergistic effect of absorption of these two nephrotoxic metals could be detected.

The supposition that cadmium in cigarette tobacco or in the workplace may cause lung cancer seems to be untenable (Hertz-Picciotto & Hu, 1994; Lamm et al., 1992). The indications among cadmium exposed workers (Lamm et al. 1992) were that arsenic in the working environment and cigarette smoke, rather than cadmium, may have caused the observed increased rate of lung cancer. 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.

Davison et al. (1988) reported a 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. Blood, urine and lung tissue analyses confirmed massive exposure. Smoking by cumulatively increasing

the body burden and hindering the lung clearance may have provided an additional cause for the emphysema. An additive or synergistic mechanism for the cadmium plus smoking effect could not be inferred because of the huge cadmium doses to which the lungs were exposed. Ten years after the patient stopped working the cadmium levels in lung tissue remained 150 times greater than the values in controls.

3.4.3 Chromium

Chromium and its compounds are encountered in the metallurgical, chemical, electroplating and leather tanning industries. Workers producing ferrochrome alloys or welding stainless steel, or involved in the production or use of chromium salts and pigments and tanning liquors can be exposed. The many uses of chromium and many of its biological effects both in experimental animals and humans have been reviewed by (IARC, 1990).

The principal route of entry to the body is through the lungs. Chromium ulcers and dermatitis from handling chromium products have been reported. The deposition of chromates on mucous membranes may cause ulceration which, in the nasal septum, can lead to perforation (Lindberg & Hedenstierna, 1983: IARC, 1990). There can be an asthmatic reaction to chromium, chromic acid and some chromium compounds. Hexavelant chromium salts have been associated with lung cancer both in experimental animals and in epidemiological studies. After evaluating the available data (IARC, 1990) considered that "there is sufficient evidence in humans for the carcinogenicity of hexavelant chromium compounds as encountered in chromate production, chromate pigment production and chromium plating industries".

There have been no systematic studies of the combined effects of smoking and hexavelant chromium inhalation but there have been several small scale studies (Abe et al., 1982; Langard & Vigander, 1983; Yoshizawa, 1984; Nishiyama et al., 1985) which suggested that workers with chromium compounds who are also smokers may be at greater risk than non-smokers but the numbers were too small for conclusions on any interactions to be drawn.

A follow up of chromium and nickel exposed arc welders in Germany (Becker et al., 1991) confirmed an increased relative risk for all cancers but the slight increase in lung cancer applied equally to turners who were not exposed to fumes. Another study (Moulin et al., 1993) failed to show a higher lung cancer risk for stainless steel welders than for mild steel welders.

Chromium often occurs with other metals in smelter fume but it was concluded (Gerhardsson & Nordberg, 1993) that excess lung cancer risk is probably multifactorial in character, involving the interaction of several factors.

3.4.4 Cobalt

Cobalt is used in the production of tungsten carbide tools and permanent magnets which are made from cobalt, nickel and various rare earth elements. It is also used in the electrical industry and internal combustion engines. With chromium and nickel, is a constituent of hard metal alloy.

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. Barborik & Dusek (1972) suggested that cobalt exposure and cardiomyopathies may have a causal link and, if this were the case, smoking could be expected to contribute additively, but this has not been established.

3.4.5 Lead

Lead is a soft, silvery-grey metal with a range of uses in batteries, paint, glass, ceramics, the petroleum industry as a fuel additive, the chemical industry and in insecticides. In lead-using industries the main route of exposure is by inhalation, mainly as dust and fume. Lead can have a range of toxic effects toxic effects on blood, renal and nervous systems (IPCS, 1995). IARC (1987) concluded that the evidence for the carcinogenicity of lead and inorganic lead compounds in humans was inadequate.

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 is also found in sidestream smoke. In filter tipped cigarettes produced between 1960 and 1980 the mean content of lead was 2,4μg/g (Mussalo-Rauhamaa et al., 1986). Concentrations ranging from 0.017 to 0,98 micrograms in the smoke from one cigarette have been reported (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 showed a gradual increase in the blood lead with an increase in the number of cigarettes smoked (Maheswaren et

al., 1993). The levels in terms of cigarettes per day/micrograms lead per decilitre were 0/28.8, 1-10/30.9, 11-20/31.6, and >20/34.7. There is no evidence of an interaction between smoking and lead exposure, however, the lead transferred to the body in smoke would provide an added burden.

Kristensen (1989) reviewed epidemiological studies of the effect of lead on cardiovascular disease and concluded that there might be a causal relationship. The association between lead exposure, tobacco smoke exposure and raised blood pressure was examined in a cross-sectional study on 809 men occupationally exposed to lead in a battery factory but only a weak effect was found (Maheswaren et al., 1993).

3.4.6 Manganese

Manganese is encountered by miners, workers in the ferromanganese and iron and steel industries, the production of dry cell batteries and the manufacture and use of welding rods. The principal route of entry to the body 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, phagocytosed and absorbed.

Derivatives are present in tobacco leaves and it has been reported (IARC, 1986) that 0.003μg. of manganese appears in the mainstream smoke from one cigarette, equivalent to a daily exposure to 0.06μg. for a smoker of one pack per day. Although only a fraction of the dose received near a blast furnace or from welding fume, it nevertheless represents an added contribution of manganese in the form of the smallest and most dangerous particles.

Long term exposure to manganese damages the central nervous system and impairs mental capacity. It causes lung damage leading to an increased incidence of pneumonia and a higher rate of acute and chronic bronchitis. Data from a study of manganese alloy production workers suggested that the work environment may contribute to the development of chronic lung disease. Those with a history of smoking appeared to be more affected than non-smokers and the relationship between the number of cigarettes smoked and the prevalence of respiratory tract symptoms in the exposed workers suggested that smoking may act synergistically with manganese (Saris & Lucic-Palaic, 1977). In a study of workers producing manganese salts and oxide (Roels et al., 1985), additive effects for smoking and manganese exposure were found. There have been two studies on workers producing iron-manganese alloys, one concerned with chronic bronchitis (Misiewicz et al., 1994) and the other with ventilation disturbance (Misiewicz et al., 1992). In

neither was any relationship found between the occupational environment or the duration of exposure. The chronic bronchitis and ventilatory disturbance were attributed to cigarette smoking.

3.4.7 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 to gaseous nickel carbonyl (IPCS, 1991a).

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: it is possible that some of this could be in the form of nickel carbonyl. Table 3 (WHO, 1987) summarizes the levels of daily intake of nickel by humans who are not likely to have any industrial exposure.

Table 3 Levels of daily nickel intake by humans from different sources

Type/route of exposure (%)	Daily nickel intake (μg)	Absorption (μg)/retention	
Foodstuffs	$\leq$ 300	30	($\leq$ 10)
Drinking water	$\leq$ 10	1	($\leq$ 10)
Ambient air (urban dweller)	$\leq$ 0.4	0.4?	(100)
Ambient air (smoker)	$\leq$ 15.4	7.7	(50)

Adapted from: WHO (1987)

For occupational exposure the daily intake and absorption/retention vary very widely between industries (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). The excess risk of cancer among workers in nickel refineries has been well documented (IARC, 1990). A study covering the period 1953-1971 in Norway showed clearly an increased incidence of cancer of the respiratory tract in nickel refinery workers (Pedersen et al., 1973) and when smoking habits were taken into account there was an increased response. Magnus et al. (1982) considered the interaction to be closer to additive than multiplicative. Histological examination of nasal biopsy specimens from 59 retired nickel workers, 21 of whom were smokers and snuff dippers, showed a higher score of early signs of

carcinogenesis for smokers than for non-smokers and 4 of the subjects with nasal carcinoma were smokers (Boysen, 1984). In a histological method for 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 smokers and non-smokers among the nickel workers.

3.4.8 Platinum

Platinum salt sensitivity (PSS) is well known (IPCS, 1991 b). The complex platinum salt ammonium hexachloroplatinate is an intermediate in the refining of platinum. Inhalation of ammonium hexachloroplatinate was shown to provoke asthmatic responses and to elicit immediate skin test responses in sensitised individuals (Pepys et al., 1972). The incidence of occupational allergy in the platinum refining industry was high in United Kingdom in the mid 1970's. In a cohort study of 91 workers who entered employment in a platinum refinery in the two years 1973 and 1974 (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 smoking was more important than atopy as a predictor of developing a positive skin test reaction. Calverley et al. (1995) associated smoking and intensity of exposure to platinum salts with PSS development but the nature of any interaction was not explored.

3.5 Rubber industry

Some of the principal hazards 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 disability 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, 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 requiring 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, 1976 a,b; Monson & Fine, 1978; Kilpikari, 1982; IARC, 1987; Zhang et al., 1989). Lung cancer was associated with curing and inner tube manufacture in all the references but the agents responsible were not identified. Curing involves using solvent based sprays and, during the process, mixtures of gases and vapours of undefined composition are produced. The use of talc, hence a possible exposure to asbestos-type fibrous minerals, 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 use 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 have been associated with jobs in the rubber industry (Monson & Fine, 1978; IARC, 1987). Possible causes, such as exposure to carbon black, plasticizers, antioxidants, arylamino compounds and benzene have been suggested. The possible role of smoking interactions has not been addressed. Also, information is lacking on the smoking prevalence among workers in the rubber industry but it is probably similar to that of other blue collar workers in the same geographical area.

Urine samples from rubber workers showed a higher mutagenicity midweek than at the beginning of a week in both smokers and non-smokers, suggesting that mutagens are present 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 observed among smokers (Wiklund et al., 1988).

3.6 Petroleum industry

Worldwide, some 500 000 people work in petroleum refining. They may be exposed to a large number of chemical compounds that occur in crude oil or are encountered in production processes, as intermediates, catalysts, additives, or in the final products. Many compounds that occur are peculiar to this industry and many also occur in cigarette smoke. Because of fire risk, there are sections of the industry where smoking cannot be permitted but 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). The surveillance of these workers continued and it was eventually shown that the mortality rates were lower than those for the national population (Christie et al. 1987).

There have been suggestions of an increased risk of renal cancer in the industry. From 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. This form of cancer has been found in other studies among petrochemical workers but any relationship to smoking was not considered. In a case-control study of bladder cancer in New Jersey, USA, Najem et al. (1982) found a significantly raised 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). The two risk factors were demonstrated separately but it is unlikely that together there would be any risk reduction.

Several studies have failed to show any health risks in the petrochemical industry, smoking having been the primary cause of abnormal urinary cytology (Adolphs et al., 1985) and kidney cancer risk (Wen et al. 1984). No increased mortality from either kidney cancer or leukaemia could be detected among employees who were exposed to gasoline (Wong et al., 1993). An unexpectedly low frequency of bladder cancer among refinery workers was surprising and attributed to (an assumed) lower level of smoking among the group of workers studied (Higginson et al., 1984). However, mineral oil has been implicated as an important contributing factor in the development of lung cancer among workers in a Norwegian cable manufacturing company (Ronneberg et al., 1988).

IARC (1989 b) in its evaluation of carcinogenic risks to humans of occupational exposures to petroleum refining, crude oil and major petroleum fuels 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 view of the presence of polycyclic aromatic hydrocarbons in the many products of the petroleum industry, it is surprising that so little cancer has been reported. Perhaps when more studies have been carried out in areas where the more aromatic "heavy" oils are extracted a different pattern may emerge.

3.7 Pesticides

Fungicides, insecticides, herbicides, rodenticides and all other agents that reduce the detrimental effects of life-forms that may harm agricultural production or transmit disease were historically derived from inorganic elements such as copper, lead, arsenic, sulphur and compounds such as lime and chlorates. Many of these materials have now been replaced by complex organic compounds and the number and variety of these, with all their trade variants, is enormous. The number of individuals who may be exposed during manufacture is relatively small but the worldwide population at risk as pesticide users (eg, mixers, applicators, sprayers) is very large. Most of the world population is exposed to pesticide residues. However, little has been published on the effects on health arising from the interaction of pesticide exposure and smoking.

"Vineyard sprayers lung", in which the pleura is often coloured deep blue, a condition not observed in any other pathological condition of the lung, has been described as an occupational disease. In a study of the cytological changes in the respiratory tract of vineyard workers spraying copper sulphate based Bordeaux Mixture (Plamenac et al., 1985) The macrophage cytoplasm of control subjects contained no copper whereas copper was detected in 64% of the vineyard sprayers. This shows the extent to which fungicidal sprays can be inhaled. Abnormal cytological changes were found in smokers among both the sprayers and controls and atypical squamous metaplasia were observed in 29% of smokers who were vineyard workers.

In a study among orchardists, it was found that lead arsenate exposure was associated with an excess mortality from respiratory cancer (Wiklund et al., 1988); it was also found that respiratory cancer mortality among smokers was 4.6 times higher than among non-smokers. That a difference should exist between smokers and non-smokers is not unexpected in view of the effects that have been shown to be attributable to industrial arsenic exposure and the interaction of this with smoking. The data in a population-based tumour registry (McDuffie et al., 1990) showed that farmers comprised 40% to 50% of lung cancer cases, although it was not possible to link the risk to any specific pesticides.

It is likely that many of the complex organic pesticides in current use, in the form of dusts, dispersible powders, and emulsifiable concentrates or solutions for spraying, will be inhaled

during use. In the case of dusts/powders there could be effects due to the carrier dusts *per se* independent of the pesticides. These are primarily bronchitis and SAD, and in smokers the usual overriding effect of smoke induced bronchitis and the effects of the dust on smoke-inflamed small airways. Many of the pesticides have been associated with enzyme inhibition and effects on the respiratory, central nervous, and cardiovascular systems, and carcinogenic properties have been ascribed to some. Effects on smokers have not been specifically studied, nor have any interactive effects

Smoking and burning anti-mosquito coils have been independently associated with risk of nasopharyngeal cancer but any interaction between the two was not considered (West et al., 1993).

There have been studies of the mutagenic potential of pesticides (see Richardson & Gangolli, 1993). The effect of smoking has also been shown to increase chromosomal aberrations. In a study in cotton field workers, a 2- to 3-fold increase in chromosomal aberrations was noted in smokers exposed to pesticides, when compared to non-smoking co-workers exposed to the pesticides and working in the same fields (Rupa et al., 1989). In this study, a high prevalence of aberrations was recorded in a second group of smokers who used pesticides in cotton fields. A relationship between skin contamination with pesticides and urinary mutagenicity has been observed (Plamenac et al., 1985).

The results from several studies have demonstrated a positive association between insecticide exposure and Parkinson's Disease: insecticide exposure (OR 5.75), residence in a fumigated house (OR 5.25) and herbicide exposure (OR 3.22), on the other hand the disease has been inversely associated with smoking but no studies of interaction effects have been carried out (Stern et al., 1991; Wechsler et al., 1991; Butterfield et al., 1993; Hubble et al., 1993).

Analyses of hand washings from pesticide sprayers and tobacco leaf pickers have provided evidence of significant pesticide contamination of skin (Izmirova et al., 1988). Thus smoking could act as a vector for pesticide intake.

4. HEALTH RISKS FROM TOBACCO USE

4.1 Responses to mainstream smoke (and other chemicals)

4.1.1 Acute Responses

The initial response to any inhaled chemical insult is irritation of the upper respiratory tract (URT), nasal and paranasal sinus inflammation, sore throat and bronchial oedema. Pulmonary oedema may follow if the irritants penetrate to the lower respiratory tract. The longer term effects are the initiation and augmentation of chronic disease. Acute irritation of the URT usually follows inhalation of highly soluble gases such as ammonia. Slightly less soluble gases such as sulphur dioxide cause URT and bronchial irritation. Chlorine, a less soluble gas than sulphur dioxide, can not only affect the URT but can penetrate more deeply, to cause bronchial constriction. Gases such as the oxides of nitrogen and ozone are relatively insoluble and as a result their effects are delayed and they can build up a concentration in the alveoli that leads to pulmonary oedema.

Cigarette smoke contains many compounds with irritant properties which can affect all parts of the lung. It would seem reasonable to assume that the least that a combination of smoking with inhalation of other irritants could have would be an enhancement of effect.

4.1.1.1 Acute bronchitis

Acute bronchitis consists of an inflammation of the bronchial mucous membrane, initially accompanied by a dry painful cough and followed by mucopurulent expectoration which becomes free as the inflammation subsides. The cause may be infectious agents or physical/chemical agents such as dusts, fumes, vapours, or gases. Allergic factors may also be important. Tobacco smoke is a frequent cause of the condition.

4.1.1.2 Asthma

Asthma is a form of paroxysmal dyspnoea due to bronchial obstruction produced by a combination of spasm of the bronchial musculature, with swelling of the mucous membranes and the production of viscid mucus. It arises as a response to a specific agent, at a concentration below that at which the agent may cause a nonspecific irritant response in normal individuals.

Many chemical agents, including mixtures like tobacco smoke, can induce asthma but many cases remain undetected because an asthmatic individual quickly recognizes an unpleasant effect, associates it with a cause and avoids any further exposure. In some situations, frequent minute doses of a causative agent can result in sensitization after a period of symptomless exposure. Smoking enhances the effect of other agents and can reduce the latent period from first exposure to onset of sensitization.

4.1.2 Chronic responses

4.1.2.1 Chronic Obstructive Lung Diseases (COLD).

Poor social conditions, inadequate nutrition, overcrowding and excessive atmospheric pollution were the social and environmental factors responsible for widespread bronchitis in nineteenth century England. Bronchitis was, however, ill defined and the definition varied between countries. With the amelioration of working and living conditions, levels of chronic bronchitis should have decreased, but the cigarette boom of the twentieth century has ensured a high prevalence of the disease throughout the world. It is now classified as one of several diseases under the collective heading of Chronic Obstructive Lung Diseases (COLD). The other members of the group are: small airways disease, toxic bronchiolitis obliterans (other forms of this condition occur but are less important in the present context), emphysema and fibrosis.

4.1.2.2 Chronic Bronchitis

For the purposes of considering the effects of smoke and other toxic compounds a definition of "Industrial Bronchitis" is relevant, namely "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" (Morgan, 1982). In smokers' lungs the effect of dust is overwhelmed by the irritant constituents of tobacco smoke which not only cause hypersecretion of mucus and alter it's physical properties and chemical structure, but also impair the mucociliary clearance mechanism. Mineral dusts, particularly those encountered in mining, cause bronchitis, as do many biological dusts, irritant vapours and gases and inorganic and organic chemical dusts and sprays. Morgan (1983) considered that bronchitis in nonsmoking coal miners was related to dust exposure but in smokers the effects of dust were overwhelmed and obscured by those of smoke.

4.1.2.3 Small Airways Disease (SAD)

Small airways disease 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 can be associated with environmental and industrial pollutants, but it arises mainly as an injury caused by smoking. When dust is deposited in membranous bronchioli, it can induce fibrosis.

Toxic bronchiolitis obliterans, an extreme form of SAD is caused by the inhalation of toxic gases and fumes, such as phosgene, oxides of nitrogen, sulphur dioxide, and smoke from fires, and it leads to widespread bronchiolar obliteration.

4.1.2.4 Emphysema

Emphysema is defined as an enlargement of the air spaces distal to the terminal non-respiratory bronchioli, accompanied by destructive changes in the alveolar walls. It tends to be prevalent in older age groups and follows small airways disease. Macrophages which 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 recognized which vary with the nature of the insult to the tissues. For purposes of post mortem examination of lung slices of miners, Ruckley (1984) defined emphysema as the presence of air spaces of 1 mm or more in size.

4.1.2.5 Pulmonary fibrosis

Pulmonary fibrosis is the abnormal formation of fibrous or scar tissue is the response of bronchiolar tissue to deposition therein of an inhaled inciting agent. Different types of particles, such as coal dust, silica or asbestos, cause different types of reaction by the lung tissue. The various types of radiological changes seen in early stages of these fibroses are associated with relatively minor pulmonary impairments, but continuous exposure leads to a greater degree of fibrosis and to progressive massive fibrosis in some subjects. On histological, animal experimental and roentgenographic evidence, Weiss (1984) concluded that cigarette smoking was also capable of causing diffuse fibrosis.

4.1.2.6 Conclusion

Tobacco smoking, and even exposure to environmental tobacco smoke, increases susceptibility to pulmonary infections. Some data also exist regarding the effects of smoking on systemic immunity. Studies in rats indicate that nicotine induces impaired responses of systemically-distributed B- and T-lymphocytes to antigen-induced signalling (Geng et al,1995). Other results in humans are reviewed in IARC (!986); smoking impairs aspects of both humoral and cellular immunity. Through this effect on immune responses, tobacco smoking could indirectly alter either systemic or local immune responses to other chemicals.

It could be argued that the Chronic Obstructive Lung Diseases (COLD) diseases, although perhaps not the most dramatic in the public's eye, are probably among the most important of the pulmonary diseases caused by smoking and/or chemical pollution, not only from the health aspect but also because of their negative economic impact on a community. In a study by Simecek et al. (1986) of 215,229 adults in a region of Czechoslovakia, smoking was the most important risk factor. 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.

4.1.3 Cancer

Many forms of cancer have been associated with inhaled particulate matter, vapours, fumes and gases. Lung cancer is probably the commonest.

Despite many examples of an association between lung cancer and industrial materials, "the vast majority of the evidence available at the present time suggests that (only) around 4 to 5% of all lung cancer is related to occupational exposure" (Morgan, 1982). It seems that occupational and any other form of exposure to chemical compounds are of limited importance in the aetiology of lung cancer overall: smoking is the cause of 90%. It is possible that occupational and other sources of exposure to carcinogenic chemical compounds also make only a limited contribution to some other forms of cancer.

"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 in some regions of India (Reddy & Rao, 1957; Mehta et al., 1971; Pindborg et al, 1971; Reddy, 1974; Bhonsle et al., 1976).

4.1.4 Cardiovascular Disease

In countries where cigarette smoking has been a long established custom the major cardiovascular diseases (CVD) are responsible for around 25% of deaths. Since, in many of these countries, about 45% of all deaths are caused by CVD, compared with up to 8% of all deaths being due to lung cancer, it follows that, of the two, most smoking related deaths are attributable to CVD.

Two components of tobacco smoke, nicotine and carbon monoxide, appear to share most responsibility for the harmful cardiovascular effects (Lakier 1992). Nicotine from cigarette smoke is rapidly and completely absorbed in the lungs. From pipe and cigar smoke, or chewing tobacco and snuff, it is slowly absorbed from the buccal mucosa. Nicotine causes increases in heart rate and blood pressure; stimulates structures, such as the central nervous system, that are activated by acetylcholine release; causes an increased mobilization of free fatty acids in the serum; and enhances platelet adhesiveness. These effects are responsible for more cardiac work (which for individuals with some forms of heart disease will not be met by increased coronary blood flow), an interference with metabolic exchange across capillary walls, ischaemic episodes and an initiation of 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 a great affinity for myoglobin and may interfere with oxygen uptake by the myocardium. "Bidi" smoke contains higher concentrations of both nicotine and carbon monoxide than the smoke from cigarettes (Ball & Simpson, 1987). Higher levels of nicotine are obtained from most of the many Asian preparations where non-porous wrappers and dark tobacco types are used (Simarak et al., 1977; WHO, 1985). High nicotine and carbon monoxide are also obtained from many dark tobacco cigarettes and from cigars. "Sheesha" smoke contains only small amounts of nicotine but it is high in carbon monoxide and the carboxyhaemoglobin concentration in "sheesha" smokers is distinctly 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) since it was first described in 1908, and its effects are alleviated by smoking cessation. It is "an inflammatory obliterative, non-atherosclerotic, vascular disease that affects the small- and medium-sized arteries, veins and nerves. The disease usually becomes quiescent if the patient stops smoking cigarettes, otherwise amputation commonly results" (Olin, 1994). It was considered to be very rare in women but during the past decade a dramatic increase has been observed; and ascribed to the increased use of tobacco by young women (Yorukoglu et

al., 1993). The effect of cigarette smoking on the peripheral microvascular system can be demonstrated by hand thermography and by measurable reductions in skin temperature. "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). It is possible that hydrogen cyanide, the oxides of nitrogen and some of the several inorganic elements such as arsenic, cadmium and lead, present in tobacco smoke, might contribute to CVD.

Cardiovascular disease has been associated with exposure to some external stimuli which can be classified as physical, chemical and biological, and with occupation or life-style. Physical exposures include extremes of barometric pressure, vibration, noise, temperature and humidity. Chemical agents, which may be absorbed by inhalation, skin absorption, or ingestion, can produce cardiovascular toxicity by directly affecting the myocardium, by impairing the oxygen carrying capacity of the blood and causing anoxic damage to the vascular system, or by enzyme inhibition. Biological agents may be encountered in laboratories, hospitals or in endemic areas. Lifestyles encompass dietary factors and many aspects of behaviour: they may be sedentary or involve great physical activity and within their spectrum the "personality type" can influence the incidence of cardiovascular disease.

The combination of smoking with any additional potentially harmful exposure will predispose to an increased detrimental cardiovascular effect. The anoxia concomitant with working at high altitude along with reduced oxygen carrying capacity of the blood due to carboxyhaemoglobin from cigarette smoke will act in concert to cause anoxic damage and oxygen debt. The normal bodily reactions to heat and humidity or to cold and submersion will be changed by the effects of nicotine on vasodilation and vasoconstriction. Chemical agents which may be encountered from an external source such as the atmosphere, which also occur in cigarette smoke and which are known to have cardiovascular effects, will exert a greater effect when accumulated from the two sources. Interaction effects can be expected when the cardiovascular system, itself affected by hazardous materials from one source, is stressed to overcome toxicity or impaired physiological activity arising elsewhere in the body because of agents from another source.

The many interactions causing cardiovascular disease, whether occupational, dietary, hereditary, or due to life-style and physical activity, complicate any understanding of the effects which result in the high levels of morbidity and mortality attributable to smoking and the combined effects of smoking with other toxic materials on CVD have not been extensively studied in the way that the interactions between smoking and COPD or cancer have.

4.2 Effect of tobacco smoking on the metabolism of drugs and other chemicals

A number of studies have demonstrated that the metabolism of various drugs and other chemicals are influenced by the smoking status of the individual. This effect is sufficiently noteworthy such that the U.S. Surgeon General's 1979 report concluded that it is "apparent that cigarette smoking is one of the primary causes of drug interactions in humans" (Surgeon General, 1979). 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, (1) the dominant effect of smoking is enhanced drug disposition caused by the induction of hepatic enzymes, (2) tobacco smoke contains many enzyme inducers, notably polynuclear aromatic hydrocarbons, and (3) smoking can induce the metabolism of various therapeutic agents and their pharmacologic and/or clinical effects. Although the most noteworthy effects of smoking cited were related to enzyme induction, it should also be stated 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)

One notable interaction that has been apparent since the 1970s is that between tobacco use and oral contraceptives in increasing 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). When all smoking classifications were considered together, smoking significantly increased the risk of myocardial infarction, although the authors cautioned that the numbers of observed cases were relatively small.

Miller (1990) reviewed how cigarette smoking affects the pharmacokinetic and pharmocodynamic 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 within 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).

4.3 Environmental tobacco smoke

In 1986 the US Surgeon General issued a report designed to alerted the public to the adverse health effects of "passive" or "involuntary smoking", i.e., exposure to environmental tobacco smoke (US Surgeon General, 1986)). A review published in 1987 provided a thorough analysis of the toxicological principles that might make environmental tobacco smoke a human health risk (Remmer, 1987). One early and major conclusion was that children living in homes with smokers are a major population group at risk. Epidemiological studies, going as far back as the 1970s clearly show that bronchitis and pneumonia are substantially increased during the first year in infants exposed to second hand smoke. Later in life, there may be an increased tendency to develop asthma. Since exposure to the mother's active smoking, rather than the father's, correlates best with pulmonary problems in children, both *in utero* and postnatal exposure appear to be determinants for development of adverse health effects. The issue has been discussed in several recent reviews that all came to the conclusion that adverse respiratory effects in children represent the most serious and most widespread health hazard due to the involuntary exposure to tobacco smoke. (US Surgeon General, 1986; Spitzer et al., 1990; Witschi et al., 1991; Samet, 1992; US EPA, 1992).

It also has become obvious that environmental tobacco smoke may produce numerous additional adverse health effects in children and in adults. Cancer of the respiratory tract is considered to be the most serious consequence of involuntary smoking. Epidemiological studies show that non-smokers married to smokers have a statistically significant increased risk to develop lung cancer (Pershagen, 1994; Tredaniel et al., 1994c). In 1992, the US Environmental Protection Agency conducted a meta-analysis of 11 US epidemiological studies and concluded that environmental tobacco smoke might be responsible for approximately 3000 lung cancers in non-smokers aged 35 and over (US EPA, 1992). In 1994, the US Department of Labor determined that among nonsmoking American workers exposed to environmental tobacco smoke in the workplace there would be between 144 and 722 lung cancer deaths and the excess lung cancer rate in the workplace would be approximately 1 in 1000 (US OSHA, 1994). The numbers are significant since it is at the workplace, rather than at home, where it will be possible to reduce risk form environmental tobacco smoke by a ban on smoking. Finally there is the possibility that exposure to environmental tobacco smoke of the fetus or of young children eventually will increase the development of cancers in various sites later in adulthood. At present, the evidence does not yet appear to be conclusive, although such an association has biological plausibility (Tredaniel et al., 1994a).

A second major impact on human health attributable to environmental tobacco smoke may be cardiovascular disease. Steenland (1992) estimated that in 1992 in the USA passive smoking might account for 35,000 to 40,000 annual excess heart-disease deaths among "never smokers" and former smokers exposed to environmental tobacco smoke. Plausible biological mechanisms were offered by Glantz & Parmley (1992, 1995). The American Heart Association, in a position paper, concluded that environmental tobacco smoke is a major preventable cause of cardiovascular morbidity and mortality (Taylor et al., 1992). To what extent environmental tobacco smoke contributes over-all to chronic obstructive lung disease in adults appears to remain, for the time being, rather uncertain (Tredaniel et al., 1994b). In a recent large epidemiological study it was found that, in adults, an association exists between passive smoke exposure at the workplace and chronic respiratory symptoms such as wheezing and cough; the severity of the signs was dependent upon hours per day of smoke exposure (Leuenberger et al., 1994).

Other epidemiological studies have pointed to several additional adverse health effects that might be caused by exposure to environmental tobacco smoke. Involuntary smoking during pregnancy may result in a small, although significant reduction of birth weight (Rubin et al., 1986; Martin & Bracken, 1986). Some data suggest that to smoke in the same room where small infants are kept appears to increase the risk of sudden infant death syndrome (Klonoff-Cohen et al., 1995). It also has been speculated that tobacco smoke may compromise immune function; to what extent environmental tobacco smoke may do so, appears to be less certain (Johnson et al., 1990). Therefore, a growing body of evidence suggests that environmental tobacco smoke may adversely affect the health of a large number of non-smokers and thus represents a substantial public health problem.

The conclusions drawn by public health officials and governmental regulatory agencies concerning the ill effects of environmental tobacco smoke have not gone unchallenged. According to documents recently made public, the tobacco industry apparently determined already in the mid 1970s that cigarette sidestream smoke was an irritant and contained many toxic substances, some of them known animal or human carcinogens (Barnes et al., 1995). Nevertheless, the conclusions drawn by the US EPA who labelled environmental tobacco smoke a known human carcinogen (US EPA, 1992), were severely criticized (Smith et al., 1992; Mantel, 1992; Huber et al., 1993, Gori, 1995). It was emphasized that concentrations of environmental tobacco smoke constituents in homes or in the workplace were far too low to produce a substantial toxicological risk and actually were considerably lower than threshold limit values (TLVs) (Rodgman, 1992)). It also was maintained that epidemiological studies did not show an increased risk at the workplace for environmental tobacco smoke induced lung cancer (LeVois & Layard, 1994) or that many of the

epidemiological studies suffered from errors in classification of the study subjects (Witschi et al., 1995). However, in view of the large number of people exposed worldwide to environmental tobacco smoke it certainly remains good public health policy to reduce exposure to the most possible extent.

4.3.1 Environmental tobacco smoke and respiratory tract infections in children

Perhaps the most obvious untoward effects of passive smoking are found in children (US EPA, 1992). Children, at least small ones, are not active smokers, but may suffer considerable exposure to second hand smoke (environmental tobacco smoke) when living in homes with parents that are active smokers. Numerous epidemiological studies have conclusively shown that the population most at risk from environmental tobacco smoke exposure are neonates, young children and possibly already the fetus while *in utero*. The issue has been reviewed (Witschi et al., 1991; Samet, 1992) and in the following only a few illustrative examples of possible interactions in children exposed to other factors are discussed.

Infants of mothers who smoke require significantly more admissions to hospitals for infections of the lower respiratory tract, most notably bronchitis or pneumonia, and will on the average stay longer in the hospital. This is not only true for infants in the first year of life (Harlap & Davies, 1974), but also in children aged up to 5 years (Rantakallio, 1978) and even in children at the ages of 6 to 12 (Ekwo et al., 1983). A clear cut dose-response relationship, expressed as the number of cigarettes smoked by the mother, is often apparent (Harlap & Davies, 1974). It is ironic that children of smoking mothers, and who are regularly brought to day care centres, appear to develop less wheezing and lower tract respiratory illnesses than do children who have the "benefit" of staying home (Wright et al., 1991).

The commencement of exposure to smoke constituents may be an important determinant in the development of environmental tobacco smoke induced untoward health effects in children. Exposure early in childhood or even in utero is a critical determinant. Cunningham et al. (1994) pointed out that *in utero* exposure, i.e., maternal smoking during pregnancy, produces a more severe persistent deficiency in pulmonary function later in life than would be expected by exposure to environmental tobacco smoke after birth . It may be speculated that tobacco smoke constituents, inhaled by the mother, absorbed and eventually crossing the placenta, adversely affect the developing bronchial tree; the issue needs further investigation. A recent study strongly emphasizes that paternal smoking is a most important risk factor for the development of wheezing bronchitis in children and that interactions between environmental tobacco smoke exposure and

with atopic heredity, recurring upper respiratory tract infections and short breast feeding period is most pronounced in children under 18 months of age (Rylander et al., 1993).

To what extent maternal as opposed to paternal smoking influences the development of adverse health has been repeatedly examined. Most studies find a strong association with maternal rather than with paternal smoking (Rylander et al., 1993; Ware et al., 1984) and smoking by other household members appears to be of little, if any significance (Wright et al., 1991). The observation does not necessarily imply that maternal smoking constitutes a special risk. Rather, it might be a consequence of exposure, small children having the tendency to be longer together with their (smoking) mother and possibly being also closer to her than to the father or other smoking household members.

Interactions between environmental tobacco smoke and specific agents resulting in the development of respiratory illness in small children are most of the time not easily identifiable. One study stipulates that smoking may seriously aggravate respiratory syncytial virus bronchiolitis in infancy (Sims et al., 1978). In another study it was found that the association between exposure to environmental tobacco smoke in a household with one or more cigarette smokers and respiratory syncytial virus infection was not stronger than it was for other lower respiratory tract infections, making it unlikely that there was a specific association between smoking and viral infection (Hall et al., 1984). It was also thought that the exposure to common air pollutants might play a role in enhancing pulmonary disease in children exposed to environmental tobacco smoke. When examined in an appropriate study, no additive effects on illness incidence was found in children living in polluted urban areas as compared to children in cleaner rural areas (Forastiere et al., 1992). On the other hand, signs of home dampness tended to increase the risk to develop asthma already increased by exposure to environmental tobacco smoke (Lindfors et al., 1995). It was also postulated that exposure to environmental tobacco smoke might enhance the risk to atopic sensitization from animal domestic furry pets (Lindfors et al., 1995).

The question was also repeatedly asked whether gender might play a role in susceptibility to environmental tobacco smoke and the associated risks. The issue seems not to have a clear cut answer. In one study maternal smoking primarily seemed to affect girls where environmental tobacco smoke exposure resulted in lower flow rates in pulmonary function tests (forced expiratory volume; (Vedal et al., 1984)). In another study, a persistent, but mild and non progressive impairment of the FEV_1/VC ratio was only observed in males, but not in females exposed to parental smoking (Sherrill et al., 1992). It was speculated that passive smoking might particularly increase the risk to develop asthma in boys (Martinez et al., 1988). A large-term

follow up of children up to the age of 18 failed to detect significant gender differences (Wang et al., 1994).

Biomarkers of exposure to tobacco smoke constituents are readily identified in the blood of pre-school children of smoking mothers; plasma cotinine and polycyclic aromatic hydrocarbon - albumin adducts are significantly correlated between mothers who smoke and their children (Crawford et al., 1994). It was pointed out, however, the collection of urinary cotinine measurements did not really offer an advantage of the more common practice of gathering exposure data by questionnaire (Lindfors et al., 1995)

4.4 Smoking - 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 far more injurious when it is inhaled.

4.4.1 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. This polymer, 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, also 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) and other cases have been reported (Albrecht & Bryant 1987). In the early cases there appeared to be no long term effect, but in the case mentioned above, after the 40 attacks and following about 18 months of well-being, the subject began to complain of shortness of breath. Post mortem examination of the lungs, after death from an unrelated condition, revealed interstitial pulmonary fibrosis. It has been suggested that polymer-fume fever should be regarded as a potentially serious disorder (Williams, 1974).

4.4.2 Fluorocarbons

Fluorocarbons frequently occur as volatile vapours in aerosols and refrigerants and some occur as liquid solvents and in plastics. When burnt, they produce hydrofluoric acid which is an intense irritant.

4.4.3 Methylparathion

This is one of a group of organophosphorus compounds used as pesticides which are rapidly absorbed into the body, particularly when entering by inhalation, and which cause a wide range of unpleasant and debilitating symptoms at low concentrations and severe illness at higher concentrations.

4.4.4 Dinitro-o-cresol (DNOC)

DNOC is used in agriculture as a herbicide and pesticide, and as an intermediate in the dyestuffs industry. It can enter the body by inhalation and causes several conditions from intoxication, excessive sweating, thirst, fatigue, and fever which may lead to rapid deterioration and death.

4.4.5 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, leading to bronchitis, bronchiolitis and pneumonitis. A wide range of conditions can arise from long term exposure at low levels.

4.4.6 Cadmium

Cadmium is present in tobacco and is transferred to mainstream smoke. Contamination of smoking materials in workplaces where cadmium is present could increase the amount present in mainstream smoke and thus increase the amount inhaled.

4.4.7 Chlorinated hydrocarbons

Chlorinated hydrocarbons are found in many industries and workplaces where they are used for cleaning, degreasing, destaining, in leather finishing, as solvents, in paints and resins, in printing, tar and wax making and wool scouring, to name but a few. The majority when burnt form carbonyl chloride, also known as phosgene, which causes upper respiratory tract irritation and in larger doses dyspnea and respiratory failure. Smoking materials could act as vectors.

In all cases where smoking materials act as vectors for toxic chemicals, there can be added hazards from interactions between the effects of the tobacco smoke and the foreign chemical compounds.

4.5 Health risks from smokeless tobacco use

4.5.1 Introduction

Snuff use and chewing had their heydays in the 18th and 19th centuries in Europe and the USA. Information on their effects at that time is scant, although detrimental aspects of the habits had been noted (Redmond, 1970). In more recent times, however, there have been many reports linking oral cancers with oral tobacco habits in the USA, Sweden and the Indian subcontinent. In India and other Asiatic countries where chewing habits are common there are high rates of oral cancer but tobacco is often only one constituent of the material chewed and this complicates an evaluation of its role. The fact that chewers may also smoke allows for the possibility of a combination of factors, particularly from the strong smoke from the "bidi", "chutta", or "dhumti" and when "reverse smoking" may be practised. Nevertheless, chewing of materials containing tobacco has been isolated from other habits and shown in some cases to be a primary cause of oral cancer (Shanta & Krishnamurthi, 1959; Jussawalla & Deshpande, 1971).

The consequences of chewing can be reactional keratosis, irreversible gingival recession, periodontitis, oral dysplasia and leukoplakia, cancer and certain cardiovascular effects (Chakrabarti et al., 1991; Guggenheimer, 1991).

4.5.2 Cancer

Leukoplakia and oral cancer are the most widespread reported result of oral tobacco use, particularly in the countries of Asia. Simarak et al. (1977) reported a strong association between

betel chewing and oral cancer in Chiang Mai (Northern Thailand) but found no association of the cancer with "miang" chewing (miang does not contain tobacco). Sankaranarayanan et al.(1989 & 1990) associated oral cancers in Kerala, southern India, with "pan"-tobacco chewing. Chakrabarti et al. (1991) are among many who have demonstrated much higher levels of premalignant 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 potentially carcinogenic tobacco nitrosamines (Nair et al., 1989).

4.5.3 Cardiovascular disease

The effect of tobacco chewing on cardiovascular disease has received less attention but any adverse consequences of nicotine absorption would be expected whether the alkaloid were obtained by smoking or chewing. Although Eliasson et al. (1991) found no significant elevation of diastolic blood pressure in young snuff users, 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 with a tendency towards a greater overall cardiovascular effect with the use of smokeless tobacco. Nanda & Sharma (1988) also recorded incremental increases in heart rate and blood pressure following tobacco chewing. Bolinder et al. (1994) found an excess risk of death from cardiovascular and cerebrovascular disease among smokeless tobacco users. 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 in women who smoke (Lehtovirta & Forss, 1978). Tobacco chewing also has detrimental effects on pregnancy (Krishna, 1978) which, in the absence of any anoxia due to carbon monoxide found in smokers, could be due to nicotine induced vasoconstriction.

O'Dell et al. (1987) reported a case of Buerger's disease in a 38-year-old man that was clearly 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 whole of the Indian subcontinent (Jindal & Patel,1992); a region of the world with an enormous use of tobacco and a multiplicity of ways of using it. In a report on the disease in Bangladesh, the one woman with the disease (it is uncommon in women) was a tobacco chewer (Grove & Stansby,1992).

Little consideration has been given to interactions arising between the effects from oral tobacco use and other hazards but it is reasonable to assume that the effect of nicotine absorbed during chewing will augment the effect of conditions that contribute to cardiovascular disease. Thus effects of chewing on peripheral vascular disease could affect hearing acuity, Reynaud's syndrome and Dupuytren's disease, in ways comparable to the effects of smoking. Although the interactions occurring between smoke and industrial hazards that affect lung function and cause respiratory disease are unlikely as a result of chewing tobacco in the presence of other inhaled hazards, the fact that chewing tobacco is, like smoke, a source of toxic chemical compounds suggests that systemic effects can be expected, such as synergistic effects on bladder cancer.

5. TOBACCO AND ITS USES

5.1 Introduction

The genus *Nicotiana*, a member of the plant family *Solanaceae*, is represented by about 100 species and sub-species (Cromwell, 1955) widely distributed throughout the world. The cultivars *N. tabacum L.* and *N. rustica L.* are the principal sources of tobacco, the former being the most widely used. The primary intention in using tobacco is to obtain the alkaloid nicotine but the it is unclear why, once the habit has been established, nicotine appears to fulfil both a pharmacological and psychological need.

It is generally accepted that tobacco and its uses were unknown outside America before its discovery by Columbus. Wilbert (1987), in a description of tobacco use among some 300 South American tribes, used information from European explorers who tried to explain the unusual uses and effects of this plant and described its many ritual uses. In addition to inhaling the smoke through tubes and from rolls of the leaf, in ways like those now used worldwide, smoke was inhaled through the nostrils using a Y-shaped tube, swallowed and belched back, blown from one person to another, and blown into the eyes. Leaves were chewed, alone or mixed with ash or powdered shells and sometimes honey, or held in the mouth and sucked to allow the juices to trickle down the throat. Infusions were drunk or a concentrated infusion licked or even used as an enema. Wilbert (1987) referred to the use of snuffs as a peculiarly South American custom which spread with the use of tobacco to the rest of the world. Many ways of preparing and taking snuff among different tribes were reported.

Wilbert (1987) described six types of tobacco use by internal application: chewing, drinking, licking, rectal, snuffing and smoking. Smoking was by far the most common, while rectal application was only used occasionally. There were two forms of external application, ocular and smoke blowing. All methods of use were linked to religious shamanistic rituals

The rest of the world adopted tobacco use in the forms of smoking, chewing and snuffing; smoking has been the most popular. Ways of smoking are legion but are all based on burning the leaf, perhaps mixed with fragrant additives, in some form of pipe or hand-rolled tube. Cigarette smoking has largely replaced other methods in developed countries.

Cigarettes appeared in Europe, possibly as an imitation of "papyrosi" after the Crimean War, and records dating back as far as the 1880's detail cigarette consumption in France and the UK. The reasons for their popularity in Europe and the USA were probably related to availability following the invention of large scale manufacturing machinery, their greater convenience over

other forms of tobacco use, particularly in the exigencies of wartime, and to fashion. By the end of the second world war, cigarette smoking had become established as a socially acceptable habit for both men and women in most developed countries where, for a period during the 1950's, there may have been more smokers than non-smokers. In these 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 among the more affluent classes.

5.2 Tobacco smoking

Smoking prevalence data and most studies into the effects of smoking have concentrated on cigarette smoking, yet only about 55% of tobacco cited in international production statistics is used for cigarettes. The rest, along with 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. Tobacco consumption data are more difficult to interpret than are those for cigarettes but they can give an insight into tobacco related disease in some parts of the world, as can information on other ways of smoking.

Differences in smoke chemistry occur with different tobacco cultivars and curing methods. Essentially, curing removes moisture so that the leaf can be stored without fermenting or rotting, however, the time and temperature of curing also control enzyme reactions such as deamination and oxidation as well as the content of oils and resins. Traditions and climate govern the variety of tobacco grown and its curing. Air-, fire-, sun-, and flue-curing are the principal methods and each produces distinctive tobaccos which are frequently most suitable for smoking in a specific way or to suit a particular preference.

In Bangladesh, Pakistan India and Nepal, the "Bidi" (or "Beedi") is the most frequently encountered smoking device. In 1991, about 80 billion" bidis" but only 13 billion manufactured cigarettes were sold in Bangladesh. In India, the world's third largest tobacco market, producing and consuming some 7% of world tobacco (US DA, 1990), less than 30% of non-industrial use is as cigarettes; 50% is smoked as "bidis"; 10% is smoked in other ways; and 10% is used for chewing. "Farm-gate" sales and home grown tobacco augment the non cigarette uses. A "Bidi" consist of tobacco flakes, loosely packed and hand rolled in a tendu or temburni leaf (*Diospyros melanoxylon*). The weight of a random sample was 0.35g, compared with 0.89g for a cigarette (Ramakrishnan et al., 1995); the tobacco contents were 0.223g and 0.782g respectively. The "bidi" tobacco contained up to 8.2% nicotine compared with up to 3.7% in the cigarette tobacco. An analysis of "bidi" smoke has shown a range of 23 to 41 mg tar and 1.74 to 2.92 mg nicotine.

Popular brands of Indian cigarette gave 18 to 28 mg tar and 1.0 to 1.8 mg nicotine; levels which compare with American cigarettes prior to 1960 and are high compared with US cigarettes today (Ball & Simpson, 1987). "Bidi" smoke has a higher carbon monoxide content than cigarette smoke.

Turkey ranks fifth in world tobacco production, the number of cigarettes manufactured is increasing, imports are greater than exports, contraband imports are high, per capita consumption is high, smoking prevalence is high (63% M; 24% F) and the tar yields of cigarettes are relatively high (11.8 mg to 29.3 mg) (IARC, 1986).

Many cigar-like devices are smoked throughout Asia. The "Chutta" is made from tobacco flakes rolled in a tobacco leaf; it may be smoked conventionally or in the reverse manner (Reddy, 1974). The "Dhumti", also used for "reverse smoking", is made by rolling tobacco in the leaf of a jackfruit tree (*Artocarpus integrifolia*), banana leaf (*Musa paradisiaca*) or hansali leaf (*Grewia microcos*) (Bhonsle et al., 1976). "Reverse smoking" is a practice in which a "chutta", "dhumti", or "bidi", is smoked with the burning end inside the mouth. It seems to be more popular among females than among males.

Tobacco additives enhance the fragrance or taste of smoke: sugars, aromatic substances and humectants are often applied to tobacco before cutting and flavouring essential oils, resins and plant extracts are added after cutting. These will affect the smoke chemistry to some extent, but in some societies very large amounts of tobacco additive have very significant effects. The "kretek" is an Indonesian cigarette containing up to 50% ground cloves mixed with strong tobacco. A range of values from 41 to 71 mg tar and 1.2 to 3.2 mg nicotine have been found in smoke analyses of different brands (WHO, 1985). "Kretek" sales represent 75% of all cigarette sales in Indonesia. Because of the large amount of clove powder, the smoke contains a significant amount of eugenol, a local anaesthetic that can cause severe gastroenteritis when ingested but the effects of inhalation are not known. Indonesia has many primary industries and interactions between kretek smoke and industrial hazards may have important health implications.

Several types of cigarette/cigar found in Thailand have been described by Mounge et al (1982). "Khi Yo" of northern Thailand contain strong tobacco and up to 50% of a mixture of koi bark (*Streblus asper)*; dry tamarind pod (*Tamarindus indica*); khai bark (*Homonoia riparia, Euphorbiaceae*); Mu'at bark from a tree not clearly identified and Areca palm bark (*Areca catechu*) rolled in a banana leaf. "Tra Kai" of central Thailand are small cigars made from local tobacco and fragrant additives such as sandalwood. These and other cigar-like devices give very high yields of both tar and nicotine (Simarek et al., 1977): frequently more than four times the yield from standard U.K. cigarettes.

Many shapes and sizes of smoking pipes are found worldwide. They consist of a bowl made from clay, porcelain, wood, meerschaum etc. in which the tobacco burns and from which the smoke is drawn through a tube. Various types of tobacco are used and the smoke can range from mild to very strong. Analyses of smoke from these are difficult to make and standardize.

A variant of the pipe, used throughout North and Sub-saharan Africa, the Eastern Mediterranean, Middle East and many parts of Asia, is the "sheesha". It is a device in which tobacco is kept alight by pieces of glowing charcoal and the smoke is drawn through water before being inhaled. The pipes, known by many names, vary in size from the small Egyptian "goza" to the large "'narghile" of the Persian Gulf countries. "Sheesha" tobacco may be locally grown "tombac" or "hemmaya", or "maasel" made by adding molasses to a blended mixture of tobacco. Blending achieves flavour and aroma and ensures that the mixture can absorb molasses whilst remaining friable. Another mixture is "jirak" (or "jurak") which is tobacco molassed with black honey and date juice dates and left to ferment with a mixture of ripe fruits and absorb the flavour. Smoking with these pipes involves inspiring a tidal volume of smoke directly into the lungs; the smoke is mild, any acrid 'bite' having been lost in bubbling through the water but a hidden danger is the high level of carbon monoxide, in part from the charcoal that keeps the tobacco burning, and smokers have high carboxyhaemoglobin levels (Zahran et al., 1985, 1988). "Sheesha" smoking reduced FEV1 by 8.5% in females and 45% in males compared with 9%in females and 27% in males for cigarette smoking (Zahran et al., 1988).

Smoking is often a relaxed social event which may last for several hours, the bowl of tobacco being replaced several times. The mouthpiece may be passed from one smoker to another, facilitating the transmission of infectious diseases.

5.3 Tobacco chewing and snuffing

Tobacco chewing and snuffing are two other methods of tobacco use. Their popularity has varied in Europe and the USA. In the 19th century, chewing was popular among pioneers in North America and more tobacco was chewed than smoked but the habit and its social acceptability declined as education, health awareness, hygiene legislation and the use of cigarettes increased. Although their popularity had declined the habits have seen a resurgence in recent years. In many less developed countries oral uses have maintained popularity. Nasal inhalation of finely powdered tobacco leaf, 'snuff', was originally the most common practice but gave way to the oral application of snuff. Snuff made for this purpose may be dry or moist and is placed either between the gum and lip, or gum and buccal mucosa. A wide range of tobacco containing

mixtures are also used orally throughout Asia by being placed between the gum and cheek or lips, or under the tongue. Chewing tobacco comes in several forms; "plug" consists of leaves pressed together to form a bar, "twist" is tobacco leaves coiled together as in a rope, and some "loose" chewing tobaccos have flavour added from syrups, liquorice, and brandy. Snuff takers are catered for by dry snuff, moist snuff, fine cut tobacco and small tobacco bags, like tea bags.

Tobacco chewing has retained its followers in some groups and is preferred by many US workers in heavy industry such as steel and mining and in the petroleum industry where the inflammability of the environment precludes smoking. It is uncommon in the UK, although it is found among coal miners at the coal face, and in other European countries except Sweden. In Sweden oral tobacco habits have remained more common but the preference is for moist snuff rather than chewing tobacco; 17% of the population are users of moist snuff. In India oral tobacco use is common among men and women, in all age groups, at every income level and among all castes and most creeds. Oral tobacco use in developing countries could decline because it is mainly in rural areas and among old people whereas growing urban populations and younger age groups are smoking cigarettes.

In other parts of the world a variety of tobacco-containing mixtures are chewed. The most widespread habit," betel-quid" chewing, is found throughout Asia and in many African countries. It predates the introduction of tobacco by centuries and it is not clear for how long tobacco has been an ingredient; in fact, a "betel-quid" need not include tobacco. It has been estimated (Burton-Bradley, 1979) that there are 200 million "betel-quid" users worldwide. The basic contents of a quid are slices of areca nut (*Areca catechu*), lime, and tobacco, wrapped in a betel pepper leaf (*Piper betle*). "Pan" is often a more complex form of betel-quid which may also contain dried dates, menthol and spices such as cardamom, clove, coriander, mace, and cinnamon. "Pan Masala" is predominantly Indian and is an attractively packed form of pan, even considered a status symbol and its offering a sign of hospitality.

Other preparations for oral use vary in composition between countries and regions but often have lime, or calcium carbonate, or sodium carbonate or some form of ash added to powdered tobacco and flavouring materials may be present: the lime etc. doubtless assists the release of nicotine. These powders are usually retained in some part of the mouth, some may be used for cleaning the teeth. A few examples are "ashammah" (Saudi Arabia/Yemen), "gazare" (Pakistan/ Afganistan frontier region), "khaini" (India/Nepal), "mainpuri" (Pakistan), "makla" (Algeria), "mishri" (India), "nass" (Iran/Central Asian USSR), "naswar" (Pakistan)(containing indigo), "neffa" (Tunisia), "seffa" (Sudan) and "zarda" (Nepal).

In Europe, the use of nasal snuff is mainly in Germany, followed by the UK and then France. Smaller quantities are used in a other parts of Europe, and in South Africa, India and Pakistan.

Trade statistics can give a measure of the extent of the habits in many countries but in others where statistical data may be less precise and where they are affected by extensive cross border and contraband traffic, by farm gate and local market sales and by home production of tobacco, the nature and extent of all forms of tobacco use cannot be assessed with any accuracy.

REFERENCES

Abe S, Ohsaki Y, Kimura K, Tsuneta Y, Mikami H, & Murao M (1982) Chromate lung cancer with special reference to its cell type and relation to the manufacturing process. Cancer, 49(4):783-787.

Abelin T & Segmuller H (1990) Tobacco and alcohol consumption as risk factors of Dupuytren's contracture. The Global War. Proceedings of the 7th World Conference on Tobacco and Health, Perth, Western Australia, :449-450.

Abramson MJ, Wlodarczyk JH, Saunders NA, & Hensley MJ (1989) Does aluminium smelting cause lung disease. Am Rev Respir Dis, 139:1042-1057.

Acheson ED, Gardner MJ, Winter PD, & Bennett C (1984) Cancer in a factory using amosite asbestos. Int J Epidemiol, 13(1):3-10.

Adolphs HD, Hildebrand G, Schwabe HW, & Vahlensieck HW (1985) Urinary cytology in workmen engaged in the petrochemical industry with reference to non-industrial risk factors. Urolol Res, 13(2):61-65.

Alavanja MC, Brownson RC, Benichou J, Swanson C, & Boice JD (1995) Attributable risk of lung cancer in lifetime nonsmokers and long-term ex-smokers (Missouri, United States). Cancer Causes and Control, 6(3)209-216.

Albrecht WN & Bryant CJ (1987) Polymer-fume fever associated with smoking and use of a mold-release spray containing polytetrafluoroethylene. J Occup Med, 29(10):817-819.

Amandus HE, Castellan RM, Shy C, Heineman EF, & Blair A (1992) Reevaluation of silicosis and lung cancer in North Carolina dusty trades workers. Am J Indust Med, 22(2):147-153.

Ames RG & Gamble JF (1983) Lung cancer, stomach cancer, and smoking status among coal miners. A preliminary hypothesis. Scand J Work Environ Health, 9:443-448.

Ames RG, Amandus H, Attfield M, Green FY, & Vallyathan V (1983) Does coal mine dust present a risk for lung cancer? A case-control study of US coal miners. Arch Environ Hlth, 38(6):331-333.

An HS, Southworth SR, Jackson WT, & Russ B (1988) Cigarette smoking and Dupuytren's contracture of the hand. J Hand Surg, 13A:872-874

Anderson HA, Lilis R, Daum SM, & Selikoff IJ (1979) Asbestosis among household contacts of asbestos factory workers. Ann NY Acad Sci, 330:387-399.

Andjelkovich DA, Shy CM, Brown MH, Janszen DB, Levine RJ, & Richardson RB (1994) Mortality of iron foundry workers. III. Lung cancer case-control study. J Occup Med, 36(12):1301-1309.

Archer VE (1988) Lung cancer risk in underground miners: cohort case-control studies. Yale J Biol Med, 61:183-193.

Armstrong BG, Tremblay CG, Cyr D, & Theriault GP (1986) Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminium smelter workers. Scand J Work Environ Health, 12:486-493.

Artvinli M & Baris YI (1979) Malignant mesotheliomas in a small village in the Anatolian Region of Turkey: An epidemiologic study. J Natl Cancer Inst, 63(1):17-20.

Attali P, Ink O, Pelletier G, Vernier C, Jean F, Moulton L, & Etienne JP (1987) Dupuytren's contracture, alcohol consumption, and chronic liver disease. Arch Int Med, 147:1065-1067

Avolio G, Cacciabue M, Rolla G, Caria E, Oliaro A, Carlino F, Pepino E, Polizzi S, & Bucca C (1986) [Functional compromise of the small airways in subjects exposed to SiO_2]. Minerva Medica, 77(45-46):2183-2185 (in Italian).

Axelson O (1995) Cancer risks from exposure to radon in homes. Environ Hlth Perspect, 103 Suppl 2:37-43

Ball J & Simpson D (1987) Round the World: India. Tobacco and ill health. Lancet, July 18:149

Barborik M & Dusek J (1972) Cardiomyopathy accompanying industrial cobalt exposure. Br J Indust Med, 34:113.

Baris Y, Artvilini M, & Sahin AA (1979) Environmental mesothelioma in Turkey. Ann NY Acad Sci, 330:423-432.

Barnes R (1983) Compensable asbestos related disease in New South Wales. Med J Austral, 2(5):221-224.

Barnes DE, Hanauer P, Slade J, Bero LA & Glantz SA (1995) Environmental tobacco smoke. The Brown and Williamson documents. J Am Med Assoc, 274:248-253.

Barone JA, Peters JM, Garabrant DH, Bernstein L & Krebsbach R (1987) Smoking as a risk factor in noise-induced hearing loss. J Occup Med, 29(9):741-745

Bates MN, Smith AH, & Cantor P (1995) Case-control study of bladder cancer and arsenic in drinking water. Am J Epidemiol, 141(6):523-530.

Beaumont JJ & Weiss NS (1981) Lung cancer among welders. J Occup Med, 23(12):839-844.

Beck GJ, Maunder LR, & Schachter EN (1984) Cotton dust and smoking effects on lung function in cotton textile workers. Am J Epidemiol, 119(1):33-43.

Becker N, Chang-Claude J, & Frentzel-Beyme R (1991) Risk of cancer for arc welders in the Federal Republic of Germany: results of a second follow up (1983-8). Br J Indust Med, 48:675-683.

Benowitz NL, Porchet H, Sheiner L & Jacob P (1988) Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison will cigarettes and nicotine gum. Clin Pharmacol Ther, 44(1):23-28

Berry G, Newhouse ML, & Antonis P (1985) Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Indust Med, 42:12-18.

Berry G, Newhouse ML, & Turok M (1972) Combined effects of asbestos exposure and smoking on mortality from lung cancer in factory workers. Lancet, 2:476-479.

Bhonsle RB, Murti PR, Gupta PC, & Mehta FS (1976) Reverse dhumti smoking in Goa: an epidemiologic study of 5,499 villagers for oral precancerous lesions. Ind J Cancer, 13(4):301-305

Bi W, Hayes RB, Feng P, Qi Y, You X, Zhen J, Zhang M, Qu B, Fu Z, Chen M, et al. (1992) Mortality and incidence of bladder cancer in benzidine- exposed workers in China. Am J Indust Med, 21(4):481-489.

Biberman R, Lusky A, Schlesinger T, Margaloit M, Neeman E, & Modan B (1993) Increased risk for small cell lung cancer following residential exposure to low dose radon: a pilot study. Arch Environ Hlth, 48(4):209-12

Bignon J, Laurent P, de Cremoux H, & Kouzan S (1986) Critical review on small airway dysfunction. Eur J Respir Dis, 69 (Suppl. 146):345-358.

Bjorseth A, Bjorseth O, & Feldstad PE (1978) Polycyclic aromatic hydrocarbons in the work atmosphere; I. Determination in an aluminium reduction plant. Scand J Work Environ Health, 4:212-223.

Bohning DE, Atkins HL, & Cohn SN (1982) Long-term particle clearance in man: normal and impaired. Ann Occup Hyg, 26:259-271.

Bolinder G, Alfredsson L, Englund A, & de Faire U (1994) Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am J Public Health, 84(3):399-404

Bolinder G & Alfredssen L (1995) Comment and response to smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am J Public Health, 85:118-119.

Bornmyr S & Svensson H (1991) Thermography and laser-Doppler flowmetry for monitoring changes in finger skin blood flow upon cigarette smoking. Clin Physiol, 11(2):135-141

Bouhuys A & Zuskin E (1976) Chronic respiratory disease in hemp workers. Ann Internal Med, 84:398-405.

Bovenzi M, Stanta G, Antiga G, Perruzzo P, & Cavallieri F (1993) Occupational exposure and lung cancer risk in a coastal area of northeastern Italy. Int Arch Occup Environ Health, 65(1):35-41.

Boyko RW, Cartwright RA, & Glashan RW (1985) Bladder cancer in dye manufacturing workers. J Occup Med, 27(11):799-803.

Boysen M (1984) Histological changes, rhinoscopical findings and nickel concentration in plasma and urine in retired nickel workers. Acta Oto-Laryngologica, 97(1/2):105-115.

Bravo MP, Del Rey Calero J, & Conde M (1987) Risk factors of bladder cancer in Spain. Neoplasma, 34(5):633-637.

Breslow NE & Day NE (1980) Statistical Methods in Cancer Research. Vol I, The Analysis of Case-Control Studies, IARC Scientific Publications No. 32. Lyon, International Agency for Research on Cancer, pp 122-159.

Brinton LA, Blot WJ, Becker JA, Winn DM, Browder JP, & Farmer JC Jr (1984) A case-control study of cancers of the nasal cavity and paranasal sinuses. Am J Epidemiol, 119(6):896-906.

Burch JD, Howe GR, Miller AB, & Semenciw R (1981) Tobacco, alcohol, asbestos, and nickel in the etiology of cancer of the larynx: A case-control study. J Natl Cancer Inst, 67:1219-1224.

Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, & Nutt JG (1993) Environmental antecedents of young-onset Parkinson's disease. Neurology, 43(6):1150-1158.

Calverley AE et al (1995) Platinum salt sensitivity in refinery workers: incidence and effects of smoking and exposure. Occup Environ Med, 52:661-666.

Carlson-Lynch H, Beck BD, & Boardman PD (1994) Arsenic risk assessment [comment]. Environ Hlth Perspect, 102(4):354-6.

Carta P, Cocco P, & Picchiri G (1994) Lung cancer mortality and airways obstruction among metal miners exposed to silica and low levels of radon daughters. Am J Indust Med, 25(4):489-506.

Cartwright R (1982) Occupational bladder cancer and cigarette smoking in West Yorkshire. Scand J Work Environ Health, 8(suppl.1):79-82.

Cecchi F, Buiatti E, Kriebel D, Nastasi L, & Santucci M (1980) Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy (1963-77). Br J Indust Med, 37:222-225.

Chaffey CM & Bowie C (1994) Radon and health - an update [Review]. J Pub Hlth Med, 16(4):465-470.

Chakrabarti RN, Dutta K, Sikdar S & Ghosh K (1991) Smokeless tobacco and premalignant and malignant lesions of the oral cavity. Ind J Med Sci, 45(10):273-275

Chameaud J, Perraud R, Chretien J, Masse R, & Lafuma J (1980) Combined effects of Inhalation of Radon Daughter Products and Tobacco Smoke. In: Pulmonary Toxicology of Respirable Particles. Vol. CONF-791002; Sanders CL et al., eds. Technical Information Center, U.S. Department of Energy, 551-557.

Cheng WN & Kong J (1992) Retrospective mortality cohort study of chrysotile asbestos products workers in Tianjin 1972-1987. Environ Res, 59(1):271-278.

Chiazze L Jr, Watkins DK, & Fryar C (1992) A case-control study of malignant and non-malignant respiratory disease among employees of a fibreglass manufacturing facility. Br J Indust Med, 49(5):326-331.

Chopra SK, Taplin GV, Elam D, Carson SA, & Golde D (1979) Measurement of tracheal mucociliary transport velocity in humans - smokers versus non-smokers. Am Rev Resp Dis, 119(4);205 (Abstract).

Christie D, Gordon I, & Robinson K (1986) Smoking in an industrial population. An analysis by birth cohort. Med J Austral, 145:11-14.

Christie D, Robinson K, Gordon I, Webley C, & Bisby J (1987) Current mortality in the Australian petroleum industry: the healthy worker effect and the influence of life-style factors. Med J Austral, 147:222-225.

Cinkotai FF, Rigby A, Pickering CAC, Seaborn D, & Faragher E (1988a) Recent trends in the prevalence of byssinotic symptoms in the Lancashire textile industry. Br J Indust Med, 45:782-789.

Cinkotai FF, Emo P, Gibbs ACC, & Jouany JM (1988b) Low prevalence of byssinotic symptoms in 12 flax scutching mills in Normandy, France. Br J Indust Med, 45:325-328.

Clausen J, Netterstrom B, & Wolff C (1993) Lung function in insulation workers. Br J Indust Med, 50(3):252-256.

Cochrane AL & Moore F (1980) A 20-year follow-up of a population sample (aged 25-34) including coal-miners and foundry workers in Stavely, Derbyshire. Br J Indust Med, 37:230-233.

Cockroft A, Seal RME, Wagner JC, Lyons JP, Ryder R, & Andersson N (1982) Post-mortem study of emphysema in coalworkers and non-coalworkers. Lancet, 2(8298):600-603.

Cohen BL & Colditz GA (1994) Tests of the linear-no threshold theory for lung cancer induced by exposure to radon. Environ Res, 64(1)65-89.

Cohen D, Arai SF, & Brain JD (1979) Smoking impairs long-term clearance from the lung. Science, 204:514-517.

Conolly CK et al (1988) The relationship between age and duration of asthma and the presence of persistent obstruction in asthma. Postgrad Med J, 64(752):422-425.

Cooke WE (1924) Fibrosis of the lungs due to the inhalation of asbestos dust. Br Med J, II:147.

Cooke WE (1927) Pulmonary asbestosis. Br Med J, 2:1024.

Cosio MG, Hale KA, & Niewoehner DE (1980) Morphologic and morphometric effects of prolonged cigarette smoking on the small airways. Am Rev Respir Dis, 122:265-271.

Cotton DJ, Graham BL, Li KYR, Froh F, Barnett GD, & Dosman JA (1983) Effects of grain dust exposure and smoking on respiratory symptoms and lung function. J Occup Med, 25(2):131-141.

Crawford FG, Mayer J, Santella RM, Cooper TB, Ottman R, Tsai WY, Simon-Cereijido G, Wang M, Tang D & Perera FP (1994) Biomarkers of environmental tobacco smoke in preschool children and their mothers. J Natl Cancer Inst 86:1398-1402.

Cromwell BT (1955) Modern Methods of Plant Analysis, Volume IV: The Alkaloids. Berlin, Gottingen, Heidelberg, Springer-Verlag, pp367-516

Cross FT, Palmer RF, Filipy RE, Dagle GE, & Stuart BO (1982) Carcinogenic effects of radon daughters, uranium ore dust and cigarette smoke in beagle dogs. Health Phys, 42(1): 33-52.

Cunningham J, Dockery DW & Speizer FE (1994) Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol 139:1139-1152.

D'Avanzo B et al (1990) Cigarette smoking and bladder cancer. Eur J Canc, 26(6):714-718.

Damber L & Larsson LG (1985a) Professional driving, smoking and lung cancer: a case referent study. Br J Indust Med, 42:246-252.

Damber L & Larsson LG (1985b) Underground mining, smoking and lung cancer: a case-control study in the iron ore municipalities in Northern Sweden. J Natl Cancer Inst, 74(6):1207-1213.

Davison AG, Fayers PM, Taylor AJ, Venables KM, Darbyshire J, Pickering CA, Chettle DR, Franklin D, Guthrie CJ, Scott MC, et al (1988) Cadmium fume inhalation and emphysema. Lancet, 663-667.

De Klerk NH, Musk AW, Armstrong BK, & Hobbs MS (1991) Smoking, exposure to crocidolite, and the incidence of lung cancer and asbestosis. Br J Indust Med, 48(6):412-417.

De Lalla F, Pellizzer G, Gradoni L, Vespigiani M, Franzetti M, & Stecca C (1993) Acute pancreatitis associated with the administration of meglumine antimonate for the treatment of visceral leishmaniasis [letter]. Clin Infect Dis, 16(5):730-71.

De Wolff FA (1995) Antimony and health. Br Med J, 310(6989):1216-7.

Deng JF, Sinks T, Elliot L, Smith D, Singal M, & Fine L (1991) Characterisation of respiratory health and exposures at a sintered permanent magnet manufacturer. Br J Indust Med, 48:609-615.

DiPaolo JA & Sheehe PR (1962) The combined carcinogenic effect of cigarette smoke condensate and urethan. Cancer Res, 22: 1058-1060.

Domiano SF, Vena JE, & Swanson MK (1985) Gasoline exposure, smoking and kidney cancer. J Occup Med, 27(6):398-399.

Dontenwill W, Chavalier H-J, Harke H-P, Lafrenz U, Rechzeh G, & SchneiderB (1973) Investigations on the effects of chronic cigarette-smoke inhalation in Syrian Golden Hamsters. J Natl Cancer Inst, 51(6): 1781-1832.

Dupre JS et al (1984) Report of the Royal Commission on matters of health and safety arising from the use of asbestos in Ontario. Toronto, Ontario Ministry of Government Services, Publications Services Branch, .

Edling C (1982) Lung cancer and smoking in a group of iron ore miners. Am J Indust Med, 3(2):191-199.

Eisenbud M (1993) Lung cancer incidence among patients with beryllium disease, J Natl Cancer Inst, 85(2):1697-1698.

Ekenvall L & Lindblad LE (1989) Effect of tobacco use on vibration white finger disease. J Occup Med, 31(1):13-16

Ekwo EE, Weinberger MM, Lachenbruch PA & Huntley WH (1983) Relationship of parental smoking and gas cooking to respiratory disease in children. Chest 84:662-668.

Eliasson M, Lundblad D & Hagg E (1991) Cardiovascular risk factors in young snuff-users and cigarette smokers. J Int Med, 230(1):17-22

Elwood MJ (1981) Wood exposure and smoking: association with cancer of the nasal cavity and paranasal sinuses in British Columbia. Can Med Assoc J, 124:1573-1577.

Enterline PE, Sykora JL, Keleti G, & Lange JH (1985) Endotoxins, cotton dust, and cancer. Lancet, 2(8461):934-935.

Enterline PE, Marsh GM, Henderson V, & Callahan C (1987a) Mortality update of a cohort of US man-made mineral fibre workers. Ann Occup Hyg, 31:625-656.

Enterline PE, Marsh GM, Esmen NA, Henderson VL, Callahan CM, & Paik M (1987b) Some effects of cigarette smoking, arsenic, and SO_2 on mortality among US copper smelter workers. J Occup Med, 29(10):831-838.

Finch GL, Nikula KJ, Barr EB, Bechtold WE, Chen BT, Griffith WC, Hahn FF, Hobbs CH, Hoover MD, Lundgren DL, & Mauderly JL (1995a) Effects of combined exposure of F344 rats to radiation and chronically inhaled cigarette smoke. ITRI-146, 1994-1995, Inhalation Toxicology Research Institute Annual Report, December, 1995. Springfield, VA, NTIS.

Finch GL, Nikula KJ, Chen BT, Barr EB, Chang I-Y, & Hobbs CH (1995b) Effect of chronic cigarette smoke exposure on lung clearance of tracer particles inhaled by rats. Fundam Appl Toxicol, 24: 76-85.

Finch GL, Nikula K, Belinsky S, Barr EB, Stoner G, & Lechner J (1996) Failure of cigarette smoke to induce or promote lung cancer in the A/J mouse. Cancer Lett, 99: 161-167.

Fletcher CM (1972) Coal workers pneumoconiosis [letter]. Br Med J, 3:116.

Forastiere F, Corbo GM, Michelozzi P, Pistelli R, Agabiti N, Brancato G, Ciappi G & Perucci CA (1992) Effects of environment and passive smoking on the respiratory health of children. Int J Epidemiol, 21:66-73.

Fox AJ, Lindars DC, & Owen RI (1974) A survey of occupational cancer in the rubber and cablemaking industries: results of five-year analysis, 1967-71. Br J Indust Med, 31:140-151.

Fraser-Moodie A (1976) Dupuytren's contracture and cigarette smoking. Br J Plastic Surg, 29:214-215

Friedman GD, Siegeland AB & Seltzer CC (1969) Cigarette smoking and exposure to occupational hazards. Am J Epidemiol, 98:175-183

Fukuda K, Shibata A, Harada K (1987) Squamous cell cancer of the maxillary sinus in Hokkaido, Japan: a case-control study. Br J Indust Med, 44:263-266.

Geng Y, Savage SM, Johnson LJ, Seagrave J, & Sopori ML (1995) Effects of nicotine on the immune system. I. Chronic exposure to nicotine impairs antigen receptor-mediated signal transduction in lymphocytes. Toxicol Appl Pharmacol, 135:268-278.

Glantz SA & Parmley WW (1992) Passive smoking causes heart disease and lung cancer. J Clin Epidemiol 45:815-819.

Glantz SA & Parmley WW (1995) Passive Smoking and Heart Disease. Mechanisms and risk. J Am Med Assoc, 273:1047-1053.

Gori GB (1995) Policy against science: the case of environmental tobacco smoke. Risk Anal, 15:15-21.

Guerin MR, Jenkins RA & Tomkins BA (1992) The Chemistry of Environmental Tobacco Smoke: Composition and Measurement. Indoor Air Research Series. Boca Raton, FL, Lewis Publishers.

Gerhardsson L & Nordberg GF (1993) Lung cancer in smelter workers - interactions of metals as indicated by tissue levels. Scand J Work Environ Health, 19(Suppl.1):90-94.

Gibbs GW & Horowitz I (1979) Lung cancer mortality in aluminium reduction plant workers. J Occup Med, 21(5)347-353.

Gonzalez CA, Lopez-Abente G, Errezola M, Castejon J, Estrada A, Garcia-Mila M, Gili P, Huguet M, Serrat M, Soler F, & Rodriguez C (1985) Occupation, tobacco use, coffee and bladder cancer in the county of Mataro (Spain). Cancer, 55:2031-2034.

Gonzalez CA, Lopez-Abente G, Errezola M, Escolar A, Riboli E, Izarzugaza I, & Nebot M (1989) Occupation and bladder cancer in Spain: a multi-centre case control study. Int J Epidemiol, 18(3):569-577.

Grove WJ & Stansby GP (1992) Buerger's disease and cigarette smoking in Bangladesh. Ann Royal Coll Surg Engl, 74:115-118

Guggenheimer J (1991) Implications of smokeless tobacco use in athletes [Review]. Dent Clin North Am, 35(4):797-808

Gullvag B, Mylius E, & Nilsen A (1985) Counting alveolar macrophages from expectorate samples of exposed workers as a test for lung irritation from occupational exposure. Bull Environ Contam Toxicol, 34:702-708.

Gutzwiller F (1985) Epidemiology of chronic bronchitis. J Respir Dis, 66 (Suppl. 139):19-20.

Hall CB, Hall WJ, Gala CL, MaGill FB & Leddy JP (1984) Long-term prospective study in children after respiratory syncytial virus infection. J Pediatr 105:358-364.

Hammond EC & Selikoff IJ (1973) Relation of cigarette smoking to risk of death of asbestos associated disease among insulation workers in the United States. Biological Effects of Asbestos. Lyon, IARC Scientific Publication No.8, pp 312-317.

Hammond EC, Selikoff IJ, & Seidman H (1979) Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci, 33:473-489.

Hanke W, Sepulveda MJ, Watson A, & Jankovic J (1984) Respiratory morbidity in wollastonite workers. Br J Indust Med, 41:474-479.

Harding JJ (1995) Cigarettes and cataract: cadmium or a lack of vitamin C? [Editorial]. Br J Ophthalmol, 79:199-201.

Harlap S & Davies AM (1974) Infant admissions to hospital and maternal smoking. Lancet 1:529-532.

Harris RJC, Negroni G, Ludgate S, Pick CR, FC Chesterman FC, & Maidment BJ (1974) The incidence of lung tumors in C57BL mice exposed to cigarette smoke: air mixtures for prolonged periods. Int J Cancer, 14: 130-136.

Hassler E, Lind B, & Piscator M (1983) Cadmium in blood and urine related to present and past exposure. A study of workers in an alkaline battery factory. Br J Indust Med, 40:420-425.

Haugen A, Becher G, Benestad C, Vahakangas K, Trivers GE, Newman MJ, & Harris CC (1986) Determination of polycyclic aromatic hydrocarbons in the urine, benzo(a)pyrene diol epoxide-DNA adducts in lymphocyte DNA, and antibodies to the adducts in sera from coke oven workers exposed to measured amounts of polycyclic aromatic hydrocarbons in the work atmosphere. Cancer Res, 46(8):4178-4183.

Hayes RB, Gerin M, Raatgever JW, & de Bruyn A (1986) Wood-related occupations, wood dust exposure, and sinonasal cancer. Am J Epidemiol, 124(4):569-577.

Henry CJ & Kouri RE (1984) Chronic exposure of mice to cigarette smoke. Final Report, the Council for Tobacco Research - USA, Inc., Contract CTR-0030. New York, Field, Rich and Associates, Inc.

Hertz-Picciotto I & Hu SW (1994) Contribution of cadmium in cigarettes to lung cancer: an evaluation of risk assessment methodologies. Arch Environ Hlth, 49(4):297-302.

Hertz-Picciotto I, Smith AH, Holtzman D, Lipsett M, & Alexeef G (1992) Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. Epidemiology, 3(1):23-31.

Hertz-Picciotto I & Smith AH (1993) Observations on the dose-response curve for arsenic exposure and lung cancer. Scand J Work Environ Health, 19:217-226.

Hessel PA, Sluis-Cremer GK, & Lee SL (1991) Distribution of silicotic collagenization in relation to smoking habits. Am Rev Respir Dis, 144(2):297-301.

Higginson J et al (1984) The epidemiology of renal carcinoma in humans with a note on the effect of exposure to gasoline. In: Mehlman MA, Hemstreet GPIII, Thorp JJ, & Weaver NK, eds. Advances in Modern Environmental Toxicology, Vol. III, Renal Effects of Petroleum Hydrocarbons. Princeton, NJ, Princeton Scientific Publishers, pp 203-226.

Hilt B (1987) Non-malignant asbestos disease in workers in an electrochemical plant. Br J Indust Med, 44:621-626.

Hilt B, Langard S, Lund-Larsen PG, & Lien JT (1986) Previous asbestos exposure and smoking habits in the county of Telemark, Norway - A cross-sectional population study. Scand J Work Environ Health, 12:561-566.

Hnizdo E (1990) Combined effect of silica dust and tobacco smoking on mortality from chronic obstructive lung disease in gold miners. Br J Indust Med, 47:656-664.

Hnizdo E & Sluis-Cremer GK (1991) Silica exposure, silicosis, and lung cancer: a mortality study of South African gold miners. Br J Indust Med, 48(1):53-60.

Hnizdo E, Baskind E, & Sluis-Cremer GK (1990) Combined effects of silica dust exposure and tobacco smoking on the prevalence of respiratory impairments among gold miners. Scand J Work Environ Health, 16:411-422.

Hoffmann D, Rivenson A, Hecht SS, Hilfrich J, Kobayashi N, & Wynder EL (1979) Model studies in tobacco carcinogenesis with the Syrian Golden Hamster. Prog Exp Tumor Res. 24: 370-390.

Holman CD, Psaila-Savona P, Roberts M, & McNulty JC (1987) Determinants of chronic bronchitis and lung dysfunction in Western Australian gold miners. Br J Indust Med, 44:810-818.

Honeybourne D & Pickering CAC (1986) Physiological evidence that emphysema is not a feature of byssinosis. Thorax, 41(1):6-11.

Hornung RW, Deddens J, & Roscoe R (1995) Modifiers of exposure-response estimates for lung cancer among miners exposed to radon progeny [Review]. Environ Hlth Perspect, 103 (Suppl.2):49-53.

Hubble JP, Cao T, Hassanein RE, Neuberger JS, & Koller WC (1993) Risk factors for Parkinson's disease. Neurology, 43(9):1693-1697.

Huber GL, Brockie RE & Mahajan VK (1993) Smoke and mirrors. The EPA's flawed study of environmental tobacco smoke and lung cancer. Regulation, 3:44-54.

Hughes JM & Weill H (1991) Asbestos as a precursor of asbestos related lung cancer: results of a prospective mortality study. Br J Indust Med, 48:229-233.

Hull CJ, Doyle E, Peters JM, Garabrant DH, Bernstein L, & Preston-Martin S (1989) Case control study of lung cancer in Los Angeles county welders. Am J Indust Med, 16(1):103-12.

Humerfelt S, Gulsvik A, Skjaerven R, Nilsen S, Kvale G, Sulheim O, Ramm E, Eilertsen E, & Humerfelt SB (1993) Decline in FEV1 and airflow limitation related to exposures in men of an urban community. Eur Respir J, 6(8):1095-1103.

IARC (1986) International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans:Tobacco Smoking; Volume 38. Lyon, International Agency for Research on Cancer, 421 pp.

IARC (1987) International Agency for Research on Cancer. Overall evaluations of carcinogenicity; updating of IARC Monographs, Vols 1-42. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7. Lyon, International Agency for Research on Cancer, 440 pp.

IARC (1988) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Man-made Mineral Fibres and Radon; Volume 43 Lyon, International Agency for Research on Cancer, 300 pp.

IARC (1989 a) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint manufacture and Painting; Volume 47. Lyon, International Agency for Research on Cancer, pp 291-305.

IARC (1989 b) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Petroleum refining; Crude Oil and Major Petroleum Fuels; Volume 45. Lyon, International Agency for Research on Cancer, pp 109-110.

IARC (1990) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Chromium, Nickel and Welding; Volume 49. Lyon, International Agency for Research on Cancer, pp 257-445.

IARC (1993) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry; Volume 58. Lyon, International Agency for Research on Cancer, 444 pp.

IARC (1994) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Schistosomes, Liver Flukes and Helicobacter Pylori; Volume 61. Lyon, International Agency for Research on Cancer, pp 45-119.

IARC (1995) International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Wood Dust and Formaldehyde; Volume 62. Lyon, International Agency for Research on Cancer, pp 191-194.

ILO (1991) Smoking contributes to noise-induced hearing loss. ILO Contribution to WHO - World No Tobacco Day, 1992. Geneva, International Labour Organisation .

IPCS (1990) International Programme on Chemical Safety. Beryllium: Environmental Health Criteria 106. Geneva, World Health Organization, pp 40-53.

IPCS (1991a) International Programme on Chemical Safety. Nickel: Environmental Health Criteria 108. Geneva, World Health Organization, pp 48-67.

IPCS (1991b) International Programme on Chemical Safety. Platinum: Environmental Health Criteria 125. Geneva, World Health Organization, pp 79-80.

IPCS (1993) International Programme on Chemical Safety. Cadmium: Environmental Health Criteria 134. Geneva, World Health Organization, 280 pp.

IPCS (1995) International Programme on Chemical Safety. Inorganic lead: Environmental Health Criteria 165. Geneva, World Health Organization, pp 93-98.

Inskip PD & Boice JD (1994) Radiotherapy-induced lung cancer among women who smoke. Cancer, 73(6):1541-1543

Iscovich J, Castelletto R, Esteve J, Munoz N, Colanzi R, Coronel A, Deamezola I, Tassi V, & Arslan A (1987) Tobacco smoking, occupational exposure and bladder cancer in Argentina. Int J Cancer, 40:734-740.

Izmirova N, Kaloianova F, Kalinova G, & Simeonov P (1988) A new approach to setting hygienic pesticide standards. Problemi na Khigienata, 13:98-109, (in Bulgarian).

Jarup L & Pershagen G (1991) Arsenic exposure, smoking and lung cancer in smelter workers - A case-control study. Am J Epidemiol, 134(6):545-551.

Jarvholm B, Larsson S, Hagberg S, Olling S, Ryd W, & Toren K (1993) Quantitative importance of asbestos as a cause of lung cancer in a Swedish industrial city: a case-referent study. Eur Respir J, 6(9):1271-5.

Jindal RM & Patel SM (1992) Buerger's disease and cigarette smoking in Bangladesh. Ann Royal Coll Surg England, 74(6):436-437

Johnson JD, Houchens DP, Kluwe WM, Craig DK, & Fisher GL (1990) Effects of mainstream and environmental tobacco smoke on the immune system in animals and humans: a review. Crit Rev Toxicol 20:369-395.

JOM (1984) Vibration syndrome in chipping and grinding workers. J Occup Med, 26(10):765-788

Jones RD (1994) Survey of antimony workers: mortality 1961-92. Occup Environ Med, 51(11):772-776.

Jorgensen HS (1984) Lung cancer among underground workers in the iron ore mine of Kiruna based on thirty years of observation. Ann Acad Med Singapore 13(Suppl. 2):371-377.

Jörgensen HS, Kolmodin-Hedman B, & Stjernberg N (1988) Follow-up study of pulmonary function and respiratory tract symptoms in workers in a Swedish iron ore mine. J Occup Med, 30(12):953-957.

Jusko WJ (1978) Role of Tobacco Smoking in Pharmacokinetics. J. Pharmacokinetics and Biopharmaceutics, 6:7-39.

Jussawalla DJ & Deshpande VA (1971) Evaluation of cancer risk in tobacco chewers and smokers: an epidemiological assessment. Cancer, 28(1):244-252

Kazantis G & Armstrong BG (1984) Renal function in relation to low levels of cadmium exposure in a group of smelter workers. Environ Hlth Perspect, 54:193-199.

Keil S, Tuyns A, & Lowenfels AB (1980) Esophageal cancer; a study of risk factors by subsite. NY Med Q, 2:38-40.

Kibelstis JA, Morgan EJ, Reger R, Lapp NL, Seaton A, & Morgan WK (1973) Prevalence of bronchitis and airway obstruction in American bituminous coal miners. Am Rev Respir Dis, 108(4):886-893.

Kilburn KH (1989) Byssinosis, emphysema, and mortality of American textile workers. [Editorial]: Arch Environ Hlth, 38(5):277.

Kilpikari MD (1982) Mortality among male rubber workers in Finland. Arch Environ Hlth, 37(5):295-299.

Kleinfeld M, Messite J, & Langer AM (1973) A study of workers exposed to asbestiform minerals in commercial talc manufacture. Environ Res, 6:132-143.

Kobayashi W, Hoffmann D, & Wynder EL (1974) A study of tobacco carcinogenesis, XII. Epithelial changes induced in the upper respiratory tracts of Syrian Golden Hamsters by cigarette smoke. J Natl Cancer Inst, 534: 1085-1089.

Kobusch AB, Simard A, Feldstein M, Vauclair R, Gibbs GW, Bergeron F, Morissette N, & Davis R (1984) Pulmonary cytology in chrysotile asbestos workers. J Chron Dis, 37(8):599-607.

Klonoff-Cohen HS, Edelstein SL, Lefkowitz ES, Srinivasan IP, Kaegi D, Chang JC & Wiley KJ (1995) The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. J Am Med Assoc, 273:795-798.

Kotin P (1994) The epidemiological evidence on the carcinogenicty of beryllium. J Occup Med, 36(1):25-26.

Kreiss K, Wassermann S, Mroz MM, & Newman LS (1993) Beryllium disease screening in the ceramics industry. J Occup Med, 35:16-25.

Kreiss K, Mroz MM, Newman LS, Martyny J & Zhen B (1996) Machining risk of beryllium disease and sensitization with median exposures below 2$\mu g/m^3$. Am J Indust Med, 30:16-25.

Krishna K (1978) Tobacco chewing in pregnancy. Br J Obst Gynaecol, 85:726-728

Kristensen TS (1989) Cardiovascular disease and the work environment. A critical review of the epidemiological literature on chemical factors. Scand J Work Environ Health, 15:245-264.

Kuntz WD & McCord CP (1974) Polymer-fume fever. J Occup Med, 16(7):480-482.

Kusiak RA, Springer J, Ritchie AC, & Muller J (1991) Carcinoma of the lung in Ontario gold miners: possible aetiological factors. Br J Indust Med, 48:808-817.

Kusiak RA, Ritchie AC, Muller J, & Springer J (1993) Mortality from lung cancer in Ontario uranium miners. Br J Indust Med, 50(10):920-928.

Laguna del Estal P, Calabrese S, Zabala JA, & Martin T (1994) [Neurological toxicity from pentavalent antimonials during the treatment of visceral leishmaniasis (letter)].Medicina Clinica, 102(7):276-277 (in Spanish).

Lai YL & Diamond L (1992) Cigarette smoke exposure does not prevent cadmium-induced alterations in rat lungs. J Toxicol Environ Health, 35(1): 63-76.

Lakier JB (1992) Smoking and cardiovascular disease. Am J Med, 93(Suppl.1A):8-12

Lamm SH, Parkinson M, Anderson M, & Taylor W (1992) Determinants of lung cancer risk among cadmium-exposed workers. Ann Epidemiol, 2(3):195-211.

Lancet (1985) Smoking, occupation, and allergic lung disease. Lancet, 1(8435):965.

Landrigan PJ & Straub WE (1985) Occupational lead exposure aboard a tall ship. Am J Indust Med, 8(3):233-239.

Langard S & Vigander T (1983) Occurrence of lung cancer in workers producing chromium pigments. Br J Indust Med, 40(1):71-74.

Leanderson PO & Tagesson C (1989) Cigarette smoke potentiates the DNA-damaging effect of manmade mineral fibers. Am J Indust Med, 16:697-706

Lednar WM, Tyroler HA, McMichael AJ, & Shy CM (1977) The occupational determinants of chronic disabling pulmonary disease in rubber workers. J Occup Med, 19:263-268.

Leduc D, de Francquen P, Jacobovitz D, Vanderweyer R, Lauwerys R, & De Vuyst P (1993) Association of cadmium exposure with rapidly progressive emphysema in a smoker. Thorax, 48:570-571.

Lee P N (ed) (1976) Statistics of smoking in the United Kingdom. Tobacco Research Council, Research Paper 1, 7th edition. London, Tobacco Research Council.

Lehtovirta P & Forss M (1978) The acute effect of smoking on intervillous blood flow of the placenta, Br J Obst Gynaecol, 85:729-731

Leigh J, Outhred KG, McKenzie HI, Glick M, & Wiles AN (1983) Quantified pathology of emphysema, pneumoconiosis, and bronchitis in coal workers. Br J Indust Med, 40:258-263.

Letourneau EG, Krewski D, Choi NW, Goddard MJ, McGregor MJ, Zielinsky JM, & Du J (1994) Case-control study of residential radon and lung cancer in Winnipeg, Manitoba, Canada. Am J Epidemiol, 140(4):310-322.

Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandli O, Braun P, Bron C, & Brutsche M (1994) Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Am J Respir Crit Care Med 150:1221-1228.

LeVois ME & Layard MW (1994) Inconsistency between workplace and spousal studies of environmental tobacco smoke and lung cancer. Regul Toxicol Pharmacol 19:309-316.

Liddell FD, Thomas DC, Gibbs GW, & McDonald JC (1984) Fibre exposure and mortality from pneumoconiosis, respiratory, and abdominal malignancies in chrysotile production in Quebec, 1926-1975. Ann Acad Med Singapore, 13(Suppl.):340-344.

Lilis R, Valciukas JA, Weber JP, Malkin J, & Selikoff IJ (1984a) Epidemiological study of renal function in copper smelter workers. Environ Hlth Perspect, 54:181-192.

Lilis R, Valciukas JA, Weber JP, Fischbein A, Nicholson WJ, Campbell C, Malkin J, & Selikoff IJ (1984b) Distribution of blood lead, blood cadmium, urinary cadmium, and urinary arsenic levels in employees of a copper smelter. Environ Res, 33:76-95.

Lindberg E & Hedenstierna G (1983) Chrome plating: symptoms, findings in the upper airways and effects on lung function. Arch Environ Hlth, 38(6):364-374.

Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, & Nordvall SL (1995) Indoor environmental risk factors in young asthmatics: a case-control study. Arch Dis Child 73:408-412.

Ljungman AG, Lindahl M, & Tagesson C (1994) Asbestos fibres and man made mineral fibres: induction and release of tumour necrosis factor- from rat alveolar macrophages. Occup Environ Med, 51:777-783

Lourenco RV, Klimek MF, & Borowski CJ (1971) Deposition and clearance of 2μm particles in the tracheobronchial tree of normal subjects - smokers and nonsmokers. J Clin Invest, 50:65-83.

Love RG & Miller BG (1982) Longitudinal study of lung function in coal-miners. Thorax, 37:193-197.

Lubin JH, Boice JD, Edling C, Hornung RW, Howe GR, KunzE, Kusiak RA, Morrison HI, Radford EP, Samet JM, et al (1995) Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. J Natl Cancer Inst, 87(11):817-827.

Lynch KM & Smith WA (1960) Pulmonary asbestosis. III. Carcinoma of the lung in asbesto-silicosis. Am J Cancer, 24(1):56-64.

Mackenney RP (1983) A population study of Dupuytren's contracture. Hand, 15(2):155-161

MacMahon B (1994) The epidemiological evidence on the carcinogenicity of beryllium in humans. [Review]. J Occup Med, 36(1):15-24.

Magnus K, Andersen A, & Høgetveit AC (1982) Cancer of respiratory organs among workers at a nickel refinery in Norway. Int J Cancer, 30:681-685.

Maheswaren R, Gill JS, & Beevers DG (1993) Blood pressure and industrial lead exposure. Am J Epidemiol, 137(6)645-653.

Makhyoun NA (1974) Smoking and bladder cancer in Egypt. Br J Cancer, 30:577-581.

Mallen M (1986) Toxicokinetics of toluene in occupationally exposed volunteers. Scand J Work Environ Health, 12:588-593.

Mann JI, Vessey MP, Thorogood M, & Doll R (1975) Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice. Brit. Med. J. 2:241-245.

Mantel N (1992) Dubious evidence of heart and cancer deaths due to passive smoking. J Clin Epidemiol, 45:809-813.

Marine WM, Gurr D, & Jacobsen M (1988) Clinically important respiratory effects of dust exposure and smoking in British coal miners. Am Rev Respir Dis, 137:106-112.

Martin TR & Bracken MB (1986) Association of low birth weight with passive smoke exposure in pregnancy. Am J Epidemiol, 124:633-642.

Martinez FD, Antognoni G, Macri F, Bonci E, Midulla F, De Castro G, & Ronchetti R (1988) Parental smoking enhances bronchial responsiveness in nine-year-old children. Am Rev Respir Dis, 138:518-523.

Martischnig K M, Newell DJ, Barnsley WC, Cowan WK, Feinmann EL, & Oliver E (1977) Unsuspected exposure to asbestos and bronchogenic carcinoma. Br Med J, 1(6063):746-749.

Masironi R & Rothwell K (1988) Tendances et effets du tabagisme dans le monde. World Health Statistics Quarterly, 41:228-241 (in French).

McDuffie HH, Klaassen DJ, & Dosman JA (1990) Is pesticide use related to the risk of primary lung cancer in Saskatchewan? J Occup Med, 32(10):996-1002.

McLaughlin JK, Chen JQ, Dosemeci M, Chen RA, Rexing SH, Wu Z, Hearl FJ, McCawley MA, & Blot WJ (1992) A nested case-control study of lung cancer among silica exposed workers in China. Br J Indust Med, 49(3):167-171.

McLaughlin RF & Tueller EF (1971) Anatomic and histologic changes of early emphysema. Chest, 59:592-599.

McLintock JC (1971) The selection of juvenile entrants to mining. Br J Indust Med, 28:45-51.

Mehta FS, Pindborg JJ, & Hamner JE (1971) Oral cancer and precancerous lesions in India. Copenhagen, Munksgaard.

Melkild A, Langård S, Andersen A, & Tønnessen JNS (1989) Incidence of cancer among welders. Scand J Work Environ Health, 15(6):387-394.

Menzel DB (1992) Antioxidant vitamins and prevention of lung disease. Ann NY Acad Sci, 669:141-155.

Merchant JA, Kilburn KH, O'Fallon WM, Hamilton JD, & Lumsden JC (1972) Byssinosis and chronic bronchitis among cotton textile workers. Ann Intern Med, 76:423-433.

Merchant JA, Lumsden JC, Kilburn KH, O'Fallon WM, Ujida JR, & Germino VH (1973) An industrial study of the biological effects of cotton dust and cigarette smoke exposure. J Occup Med, 15(3):212-221.

Meurman LO, Kiviluoto R, & Hakama M (1979) Combined effects of asbestos exposure and tobacco smoking on Finnish anthophyllite maners and millers. Ann NY Acad Sci, 330:491-495.

Meyer MB, Luk GD, Sotelo JM, Cohen BH, & Menkes HA (1980) Hypothesis: The role of the lung in stomach carcinogenesis. Am Rev Respir Dis, 121:887-892.

Mikkelsen OA (1978) Dupuytren's disease-the influence of occupation and previous hand injuries. Hand, 10(1):1-8

Miller BG & Jacobsen M (1985) Dust exposure, pneumoconiosis, and mortality of coalminers. Br J Indust Med, 42(11):723-733.

Miller LG (1990) Cigarettes and Drug Therapy: Pharmacokinetic and Pharmacodynamic Considerations. Clinical Pharmacy, 9:125-135.

Misiewicz A, Radwan K, Karmolinski M, & Dziewit T (1992) [Degree of ventilation disturbances in persons with occupational exposure to manganese]. Wiadomosci Lekarskie, 45(23-24):890-893, (in Polish).

Misiewicz A, Radwan K, Karmolinski M, Dziewit T, & Matysek A (1994) [Chronic bronchitis in workers producing iron-manganese alloys]. Wiadomosci Lekarskie, 47(7-8):257-261, (in Polish).

Mohtashamipur E, Mohtashamipur A, Germann PG, Ernst H, Norpoth K, & Mohr U (1990) Comparative carcinogenicity of cigarette mainstream and sidestream smoke condensates on the mouse skin. J Cancer Res Clin Oncol 116:604-608.

Molyneux MKB & Tombleson JBL (1970) An epidemiological study of respiratory symptoms in Lancashire mills, 1963-66. Br J Indust Med, 27(3):225-234.

Monson RR & Nakano KK (1976a) Mortality among rubber workers. 1. White male union employees in Akron, Ohio. Am J Epidemiol, 103(3):284-296.

Monson RR & Nakano KK (1976b) Mortality among rubber workers. 2. Other employees. Am J Epidemiol, 103(3):297-303.

Monson RR & Fine LJ (1978) Cancer mortality and morbidity among rubber workers. J Natl Cancer Inst, 61(4):1047-1053.

Moran TJ (1983) Emphysema and other chronic lung disease in textile workers: An 18-year autopsy study. Arch Environ Hlth, 38(5):267-276.

Morgan WKC (1982) Occupational Bronchitis. Eur J Respir Dis, 63(Suppl. 23):117-127.

Morgan WKC (1986) On dust, disability and death. [Editorial] Am Rev Respir Dis, 134:639-641.

Mori K (1964) Acceleration of experimental lung cancers in rats by inhalation of cigarette smoke. Gann, 55: 175-181.

Morimoto Y, Kido M, Tanaka I, Fujino A, Higashi T, & Yokosaki Y (1993) Synergistic effects of mineral fibres and cigarette smoke on the production of tumour necrosis factor by alveolar macrophages of rats. Br J Indust Med, 50:955-60

Morin D, Dumas ML, Valette H, & Dumas R (1991) [Transitory acute kidney insufficiency and insulin-dependent aftertreatment of kala-azar with pentamidine and N-methylglucamine antimony]. Archives Francaises de Pediatrie, 48(5):349-351 (in French).

Mougne C, Maclennan R, & Sirirat Atsana (1982) Smoking, chewing and drinking in Ban Pong, Northern Thailand. Society, Science and Medicine, 16:99-106

Moulin JJ, Wild P, Haguenoer JM, Faucon D, De Gaudemaris R, Mur JM, Mereau M, Gary Y, Toamain JP, Birembaut Y, Blanc M, Debiolles MP, Jegarden D, Laterrière B, Léonard M, Marini F, Massardier C, Moulin M, Reure M, Rigal L, Robert G, & Viossat M (1993) A mortality study among mild steel and stainless steel welders. Br J Indust Med, 50:234-243.

Murai Y, Kitagawa M, Matsui K, Koizumi F, & Miwa A (1994) Asbestos fibre analysis in seven asbestosis cases. Arch Environ Hlth, 49(1):67-72.

Muscat JE & Wynder EL (1991) Cigarette smoking, asbestos exposure, and malignant mesothelioma. Cancer Res, 51(9):2263-2267.

Mussalo-Rauhamaa H, Salmela SS, Leppanen A, & Pyysalo H (1986) Cigarettes as a source of some trace and heavy metals and pesticides in man. Arch Environ Health, 41: 49-55.

Naeslund PE & Hoegstedt P (1982) Welding and bronchitis. Eur J Respir Dis, 2118(Suppl):69-72.

Nair J, Pakhale SS & Bhide SV (1989) Carcinogenic tobacco-specific nitrosamines in Indian tobacco products. Fd Chem Toxicol, 27(11):751-753O

Najem GR, Louria DB, Seebode JJ, Thind IS, Prusakowski JM, Ambrose RB, & Fernicola AR (1982) Life time occupation, smoking, caffeine, saccharin, hair dyes and bladder carcinogenesis. Int J Epidemiol, 11:212-217.

Nanda PK & Sharma MM (1988) Immediate effect of tobacco chewing in the form of 'paan' on certain cardio-respiratory parameters. Indian J Physiol Pharmacol, 32(2):105-113

Nandakumar A, Thimmasetty KT, Sreerameredy NM Venugopal TC, Rajanna, Vinutha AT, Srinivas N & Bhargava MK (1990) A population-based case-control investigation on cancer of the oral cavity in Bangalore, India . Br J Cancer, 62:847-851

National Heart Foundation of New Zealand (1984) Technical Report Series, Report No.40, February 1984. Auckland, National Heart Foundation of New Zealand.

Nery LE, Sandoval PR, Jardim JR, Bagatin E, & Alonso G (1988) The effects of smoking and silica exposure on pulmonary epithelial permeability: a radioaerosol study with 99mTc-DTPA. Brazilian J Med Biol Res, 21(2):223-232.

Neugut AI, Murray T, Santos J, Amols H, Hayes MK, Flannery JT & Robinson E (1994) Increased risk of lung cancer following breast cancer radiation therapy in cigarette smokers. Cancer 73:1615-1620

Neugut AI, Robinson E, Lee WC, Murray T Karwoski K & Kutcher G (1993) Lung cancer after radiation therapy for breast cancer. Cancer, 71:3054-3057

Newhouse ML & Berry G (1976) Predictions in mortality from mesotheliomial tumours in asbestos factory workers. Br J Indust Med, 33:147-151.

Newhouse ML & Berry G (1979) Patterns of mortality in asbestos factory workers. Ann NY Acad Sci, 330:53-60.

Ng T-P, Chan S-L, & Lam K-P (1987) Radiological progression and lung function in silicosis: A ten year follow up study. Br Med J, 295(6591):164-167.

Niewoehner DE, Kleinerman J, & Rice DB (1974) Pathologic changes in the peripheral airways of young cigarette smokers. New Eng J Med, 291:755-758.

Nilsson K, Hendriksson R, Cai YQ, Hellstrom S, Hornqvist-Bylunds S, & Bjermer L (1992) Effects of tobacco smoke on radiation-induced pneumonitis in rats. Int J Radiat Biol, 62: 719-727.

Nishiyama H, Yano H, Nishiwaki Y, Kitaya T, Matsuyama T, Kodama T, Suemasu K, Tamai S, & Takemoto K (1985) Lung cancer in chromate workers - analysis of 11 cases. Jpn J Clin Oncol, 15(3):489-497.

O'Dell JR, Linder J, Markin RS, & Moore GF (1987) Thromboangiitis obliterans (Buerger's disease) and smokeless tobacco. Arthritis-Rheum 30(9):1054-1056

Oldham PD, Bevan C, Elwood PC, & Hodges NG (1986) Mortality of slate workers in North Wales. Br J Indust Med, 43:550-555.

Olin JW (1994) Thromboangiitis obliterans. Curr Opin Rheumatol, 6(1):44-49

Osterman JW, Greaves IA, Smith TJ, Hammond SK, Robins JM, & Thériault G (1989) Respiratory symptoms associated with low level sulphur dioxide exposure in silicon carbide production workers. Br J Indust Med, 46(9):629-635.

Oxman AD, Muir DC, Shannon HS, Stock SR, Hnizdo E, & Lange HJ (1993) Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. Am Rev Respir Dis, 148(1):38-48.

Pedersen E, Hogetveit AC, & Andersen A (1973) Cancer of respiratory organs among workers at a nickel refinery in Norway. Int J Cancer, 12:32-41.

Pepys J, Pickering CAC, & Hughes EG (1972) Asthma due to inhaled chemical agents - complex salts of platinum. Clin Allergy, 2:391-396.

Pershagen G (1985) Lung cancer mortality among men living near an arsenic-emitting smelter. Am J Epidemiol, 122:684-94.

Pershagen G (1994) Passive Smoking and Lung Cancer. In Epidemiology of Lung Cancer, ed. Samet JM. New York, Marcel Dekker, pp 109-130.

Pershagen G, Wall S, Taube A, & Linnman L (1981) On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. Scand J Work Environ Health, 7:302-309.

Pershagen G, Bergman F, Klominek J, Damber L, & Wall S (1987) Histological types of lung cancer among smelter workers exposed to arsenic. Br J Indust Med, 44:454-458.

Pershagen G, Akerblom G, Axelson O, Clavensjo B, Damber L, Desai G, Enflo A, Legarde F, Mellander H, Svartengren M, & Swedjemark GU (1994) Residential radon exposure and lung cancer in Sweden. New Engl J Med, 330(3):159-164.

Petersen R, Andersen M, Mikkelsen S, & Nielsen SL (1995) Prognosis of vibration induced white finger: a follow up study. Occup Environ Med, 52(2):110-115

Philipson K, Falk R, Gustafsson J, & Camner P (1996) Long-term lung clearance of ^{195}Au-labeled Teflon particles in humans. Exptl Lung Res, 22:65-83.

Pindborg JJ, Mehta PS, Gupta PC, Daftary DK, & Smith CJ (1971) Reverse smoking in Andhra Pradesh, India. A study of palatal lesions among 10,169 villagers. Brit J Cancer, 25: 10-20

Plamenac P, Santic Z, Nikulin A, & Serdarevic H (1985) Cytologic changes of the respiratory tract in vineyard spraying workers. Eur J Respir Dis, 67:50-55.

Pratt PC, Vollmer RT, & Miller JA (1980) Epidemiology of pulmonary lesions in nontextile and cotton textile workers: A retrospective autopsy study. Arch Environ Health, 35:133-138.

Prentice RL, Yoshimoto Y, & Mason MW (1983) Relationship of cigarette smoking and radiation exposure to cancer mortality in Hiroshima and Nagasaki. J Natl Cancer Inst, 70:611-622

Pyykko I, Pekkarinen J, & Stark J (1987) Sensory-neural hearing loss during combined noise and vibration exposure. Int Arch Occup Environ Hlth, 59:439-454

Rantakallio P (1978) Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. Acta Paediatr Scand, 67:621-631.

Remmer H (1987) Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. Arch Toxicol 61:89-104.

Rodgman A (1992) Environmental tobacco smoke. Regul Toxicol Pharmacol, 16:223-244.

Rubin DH, Krasilnikoff PA, Leventhal JM, Weile B, & Berget A (1986) Effect of passive smoking on birth-weight. Lancet, 2:415-417.

Rylander E, Pershagen G, Eriksson M & Nordvall L (1993) Parental smoking and other risk factors for wheezing bronchitis in children. Eur J Epidemiol, 9:517-526.

Ramakrishnan S, Sulochana KN, Selvaraj T, Abdul-Rahim A, Lakshmi M, & Arunagiri K (1995) Smoking of beedies and cataract: cadmium and vitamin C in the lens and blood. Br J Ophthalmol, 79:202-206.

Rang EH & Acheson ED (1981) Cancer in furniture workers. Int J Epidemiol, 10(3):253-261.

Rao NM, Patel TS, Raiyani CV, Aggarwal AL, Kulkarni PK, Chatterjee SK, & Kashyap SK (1992) Pulmonary function status of shopkeepers of Ahmedabad exposed to autoexhaust pollutants. Ind J Physiol Pharmacol, 36(1):60-64.

Reddy DJ & Rao KV (1957) Cancer of the palate in coastal Andhra due to smoking of cigars with burning end inside the mouth. Ind J Med Sci, 11: 791-798.

Reddy CRRM (1974) Carcinoma of hard palate in India in relation to reverse smoking of chuttas. J Natl Cancer Inst, 53(3):615-619

Redmond DE (1970) Tobacco and cancer: The first clinical report, 1761. New Engl J Med, 282(1):18-23

Reith AK, Reichborn-Kjennerud S, Aubele M, Jutting U, Gais P, & Burger G (1994) Biological monitoring of chemical exposure in nickel workers by imaging cytometry (ICM) of nasal smears. Anal Cell Pathol, 6(1):9-21.

Richardson M & Gangolli S, eds. (1993) The Dictionary of Substances and their Effects; Vols. 1-7. Cambridge, Royal Society of Chemistry.

Roels H, Sarhan MJ, Hanotiau I, de Fays M, Genet P, Bernard A, Buchet JP, & Lauwerys R (1985) Preclinical toxic effects of manganese in workers in a Mn salts and oxides producing plant. Sc Total Environ, 42:201-206.

Ronneberg A, Andersen A, & Skyberg K (1988) Mortality and incidence of cancer among oil exposed workers in a Norwegian cable manufacturing company. Part 2. Mortality and cancer incidence 1953-1984. Br J Indust Med, 45(9):595-601.

Roth J, Mahrlein W, Kummer G, & Krause M (1985) [Results of an epidemiological analysis concerning the pathogenesis of chronic obstructive bronchitis in miners]. Zeitschrift für Erkrankungen der Atmungsorgane, 164(3):277-279, (in German).

Rothman K & Keller A (1972) The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chron Dis, 25:711-716.

Ruckley VA, Gauld SJ, Chapman JS, Davis JM, Douglas AN, Fernie JM, Jacobsen M, & Lamb D (1984) Emphysema and dust exposure in a group of coal workers. Am Rev Respir Dis, 129:528-532.

Rupa DS, Reddy PP, & Reddi OS (1989) Frequencies of chromosomal aberrations in smokers exposed to pesticides in cotton fields. Mutat Res, 222:37-41.

Rylander R, Sjostrand M, & Bergstrom R (1979) Free lung cell response after combined exposure to cigarette smoke and industrial dusts. Toxicology, 12: 211-220.

Samet JM (1992) Environmental Tobacco Smoke. In Environmental toxicants. Human Exposures and Their Health Effects, ed. Lippmann, M. New York: Van Nostrand Reinhold, pp. 231-265.

Sanden A & Jarvholm B (1991) A study of predictors of mesothelioma in shipyard workers exposed to asbestos. J Occup Med, 33(7):770-773.

Sanden A, Jarvholm B, Larsson S, & Thiringer G (1992) The risk of lung cancer and mesothelioma after cessation of asbestos exposure: a prospective cohort study of shipyard workers. Eur Respir J, 5:281-285.

Sankaranarayanan R, Duffy SW, Day NE, Nair MK, & Padmakumary G & Day NE (1989) A case control investigation of cancer of the oral tongue and floor of the mouth in southern India. Int J Cancer, 44(4):617-621

Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE & Padmanabhan TK (1989) Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. Br J Cancer, 60(4):638-643

Saris M & Lucic-Palaic S (1977) Possible synergism of exposure to airborne manganese and smoking habit in occurrence of respiratory symptoms. In: Inhaled Particles IV. Oxford and New York, Pergamon Press.

Saumet JL, Leftheriotis G, Dittmar A & Delhomme G (1986) Relationship between pulse amplitude and thermal exchange in the finger: the effect of smoking. Psychopharmacology-Berlin, 92(1):118-121

Schnorr TM, Steenland K, Thun MJ, & Rinsky RA (1995) Mortality in a cohort of antimony smelter workers. Am J Indust Med, 27(5):759-770.

Schwartz D, Denoix P-F, & Anquerra G (1957) [Search for sites of cancer associated with tobacco and alcohol factors in humans]. Bull Assoc Fr Etude Cancer, 44:336-361, (in French).

Selig R & Nestler K (1985) [Epidemiology of chronic bronchitis from the viewpoint of occupational medicine]. Zeitschrift fur Erkrankungen der Atmungsorgane, 164(3):273-276, (in German).

Selikoff IJ & Frank AL (1983) Keynote address. Potential of in vitro tests in asbestos-related problems. Environ Hlth Perspect, 51:1-4.

Selikoff IJ, Hammond EC, & Churg J (1968) Asbestos exposure, smoking and neoplasia. J Am Med Assoc, 204(2):106-112.

Selikoff IJ, Hammond EC, & Seidman H (1979) Mortality experience of insulation workers in the United States and Canada. Ann NY Acad Sci, 330:91-116.

Selikoff IJ, Seidman H, & Hammond EC (1980) Mortality effects of cigarette smoking among amosite asbestos factory workers. J Natl Cancer Inst, 65:507-513.

Shanta V & Krishnamurthi S (1959) A study of aetiological factors in oral squamous cell carcinoma. Br J Cancer, 13(3):381-388

Sherrill DL, Martinez FD, Lebowitz MD, Holdaway MD, Flannery EM, Herbison G P, Stanton WR, Silva PA, & Sears MR (1992) Longitudinal effects of passive smoking on pulmonary function in New Zealand children. Am Rev Respir Dis, 145:1136-1141.

Sherson D, Sigsgaard T, Overgaard E, Loft S, Poulsen HE, & Jongeneelen FJ (1992) Interaction of smoking, uptake of polycyclic hydrocarbons, and cytochrome P450IA2 activity among foundry workers. Br J Indust Med, 49(3):197-202.

Shim C & Williams MH (1986) Effect of odors in asthma. Am J Med, 80(1):18-22.

Shirakawa T, Kusaka Y, & Morimoto K (1992) Combined effects of smoking habits and occupational exposure to hard metal on total IgE antibodies. Chest, 101(6):1569-1576.

Simarak S, de Jong UW, Breslow N, Dahl CJ, Ruckphaopunt K, Scheelings P, & Maclennan R (1977). Cancer of the oral cavity, pharynx/larynx and lung in Northern Thailand: case-control study and analysis of cigar smoke. Br J Cancer, 36:130-140

Simecek C et al (1986) [Evaluation of the role of smoking in the development of chronic bronchitis after elimination of other supporting factors]. Studia Pneumologica et Phthiseologica Czechoslovaca, 46(3):168-170 (in Czech).

Sims DG, Downham MA, Gardner PS, Webb JK, & Weightman D (1978) Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. Br Med J, 1:11-14.

Sjogren B, Hedstrom L, & Ulfvarson U (1983) Urine chromium as an estimate of air exposure to stainless steel welding fumes. Int Arch Occup Environ Hlth, 51(4):347-354.

Sluis-Cremer GK, Walters LG, & Sichel HS (1967) Chronic bronchitis in miners and non-miners: an epidemiologic survey of a community in the gold mining area in the Transvaal. Br J Indust Med, 24:1-12.

Smith AH, Hopenhayn-Rich C, Bates MN, Goeden HM, Hertz-Picciotto I, Duggan HM, Wood R, Kosnett MJ, & Smith MT (1992) Cancer risks from arsenic in drinking water. Environ Hlth Perspect, 97:259-67.

Smith CJ, Sears SB, Walker JC, & DeLuca PO (1992) Environmental tobacco smoke: current assessment and future directions. Toxicol Pathol, 20:289-303.

Spitzer WO, Lawrence V, Dales R, Hill G, Archer MC, Clark P, Abenhaim L, Hardy J, Sampalis J, & Pinfold SP (1990) Links between passive smoking and disease: a best-evidence synthesis. A report of the Working Group on Passive Smoking. Clin Invest Med, 13:17-42.

Sprince NL, Oliver LC, Eisen EA, Greene RE, & Chamberlin RI (1988) Cobalt exposure and lung disease in tungsten carbide production. A cross-sectional study of current workers. Am Rev Respir Dis, 138:1220-1226.

Stanton MF, Layard M, Tegeris A, Miller E, May M, & Kent E (1977) Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. J Natl Cancer Inst, 58:587-603.

Steenland K (1992) Passive smoking and the risk of heart disease. J Am Med Assoc, 267:94-99.

Steenland K (1994) Age specific interactions between smoking and radon among United States uranium miners. Occup Environ Med, 51(3):192-194.

Steenland K & Thun M (1986) Interaction between tobacco smoking and occupational exposures in the causation of lung cancer. J Occup Med, 28(2):110-118.

Steenland K & Ward E (1991) Lung cancer incidence among patients with beryllium disease: a cohort mortality study. J Natl Cancer Inst, 83(19):1380-1385.

Steenland K & Ward E (1993) Passive smoking and the risk of heart disease. J Natl Cancer Inst, 85(2):1698-1699.
Steindorf K, Lubin J, Wichman HE, & Becher H (1995) Lung cancer deaths attributable to indoor radon exposure in West Germany. Int J Epidemiol, 24(3)485-492.

Stellman SD, Boffetta P, & Garfinkel L (1988) Smoking habits of 800,000 American men and women in relation to their occupations. Am J Indust Med, 13:43-58.

Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, Gollomp S, & Stolley P (1991) The epidemiology of Parkinson's disease. A case control study of young-onset and old-onset patients. Arch Neurol, 48(9):903-907.

Stjernberg N (1985) Prevalence of bronchial asthma and chronic bronchitis in a community in northern Sweden. Eur J Respir Dis, 67:41-49.

Stohrer G (1991) Arsenic: opportunity for risk assessment. Toxicology, 65:525-531.

Talbot RJ, Morgan A, Moores SR, & Matulionis DH (1987) Preliminary studies of the interaction between $^{239}PuO_2$ and cigarette smoke in the mouse lung. Int J Radiat Biol, 51: 1101-1110.

Tawfik HN (1987) Carcinoma of the urinary bladder associated with schistosomiasis in Egypt: the possible causal relationship. International Symposium Princess Takamatsu Cancer Research Fund, 18:197-209.

Taylor AE, Johnson DC, & Kazemi H (1992) Environmental tobacco smoke and cardiovascular disease. A position paper from the Council on Cardiopulmonary and Critical Care, American Heart Association. Circulation 86:699-702.

Taylor PR, Qiao YL, Schatzkin A, Yao SX, Lubin J, Mao BL, Rao JY, McAdams M, Xuan XZ, & Li JY (1989): Relation of arsenic exposure to lung cancer among tin miners in Yunan Province, China. Br J Indust Med, 46:881-886.

Thériault G, de Guire L, Gingras S, & Laroche G (1982) Raynaud's phenomenon in forestry workers in Quebec. Can Med Assoc J, 126:1404-1408

Thériault G, Tremblay C, Cordier S, & Gingras S (1984) Bladder cancer in the aluminium industry. Lancet, 947-950.

Thomas DC & Whittemore AS (1988) Methods for testing interactions, with applications to occupational exposures, smoking and lung cancer. Am J Indust Med, 13:131-147.

Thomas GB, Williams CE & Hoger NG (1981) Some non-auditory correlates of the hearing threshold levels of an aviation noise-exposed population. Aviation Space Environ Med, 531-536

Thomas TL & Stewart PA (1986) Mortality from lung cancer and respiratory disease among pottery workers exposed to silica and talc. Am J Epidemiol, 124:530.

Todd G F et al (1976) Cohort analysis of cigarette smoking and of mortality from four associated diseases. Tobacco Research Council Occasional Paper No.3. London, Tobacco Research Council.

Tokarskaya ZB, Okladnikova ND, Belyaeva ZD, & Drozhko (1995) The influence of radiation and nonradiation factors on the lung cancer incidence among the workers of the nuclear enterprise Mayak. Health Phys, 69:356-366.

Townsend MC, Sussman NB, Enterline PE, Morgan WK, Belk HD, & Dinman BD (1988) Radiographic abnormalities in relation to total dust exposure at a bauxite refinery and alumina-based chemical products plant. Am Rev Respir Dis, 138:90-95.

Tredaniel J, Boffetta P, Little J, Saracci R, & Hirsch A (1994a) Exposure to passive smoking during pregnancy and childhood, and cancer risk: the epidemiological evidence. Paediatr Perinat Epidemiol, 8:233-255.

Tredaniel J, Boffetta P, Saracci R, & Hirsch A (1994b) Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. Eur Respir J, 7:173-185.

Tredaniel J, Boffetta P, Saracci R, & Hirsch A (1994c) Exposure to environmental tobacco smoke and risk of lung cancer: the epidemiological evidence. Eur Respir J, 7:1877-1888.

Trethowan WN, Burge PS, Rossiter CE, Harrington JM, & Calvert IA (1995) Study of the respiratory health of employees of seven European plants that manufacture ceramic fibres. Occup Environ Med, 52(2):97-104.

Tricker AR, Mostafa MH, Spiegelhalder B & Preussman R (1991) Urinary nitrate, nitrite and N-nitroso compounds in bladder cancer patients with schistosomiasis (bilharzia). IARC Scientific Publications No. 105. Lyon, International Agency for Research on Cancer, pp178-181.

Tseng WP, Chu HM, How SW, Fong JM, Lin CS, & Yeh S (1968) Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst, 40:453-463.

Tsuda T, Nagira T, Yamamoto M, & Kume Y (1990) An epidemiological study on cancer in certified arsenic poisoning patients in Toroku. Indust Hlth, 28:53-62.

Tsuda T, Babazono A, Yamamoto E, Kurumatani N, Mino Y, Ogawa T, Kishi Y, & Aoyama H (1995) Ingested arsenic and internal cancer: A historical cohort followed for 33 years. Am J Epidemiol, 141(3):198-209.

Tuyns AJ, Péquignot G, & Jensen OM (1977) [Oesophageal cancer in Ille and Vilaine in relation to alcohol and tobacco consumption. Multiplicative risks]. Bull Cancer, 64:45-60, (in French)

USDA (1990) World Tobacco Situation, United States Department of Agriculture Foreign Agricultural Service. Circular Series FT 4-90

US EPA (1992) Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders, Report No.EPA/600/6-90/006F. Washington, DC, Office of Health and Environmental Assessment US EPA.

US OSHA (1994) Occupational Safety and Health Administration. Indoor Air Quality, Proposed Rule. Federal Register 59:15968-16038.

US Surgeon General (1979) . Smoking and Health: A Report of the Surgeon General. US Department of Health, Education and Welfare. Washington DC. DHEW Publication No: (PHS) 79-50066.

US Surgeon General (1985) Report of the Surgeon General, The Health Consequences of Smoking: Cancer and Chronic Lung Disease in the Workplace. Rockville, Maryland, US Dept. of Health and Human Services, PHS, pp443 et seq.

US Surgeon General (1986) The health consequences of involuntary smoking. A report of the Surgeon General. US Dept. of Health and Human Services, Centers for Disease Control, pp 8387-8398.

Vainio H & Boffetta P (1994) Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer [Review]. Scand J Work Environ Health, 20(4):235-242.

Vainio H, Husgafvel-Pursiainen, Anttila S, Hackman P & Partanen T (1993) Interaction between smoking and asbestos in human lung adenocarcinoma: role of K-ras mutations. Environ Hlth Perspect, 101(Suppl.3):189-192.

Vallyathan V, Shi XL, Dalal NS, Irr W, & Castranova V (1988) Generation of free radicals from freshly fractured silica dust. Am Rev Respir Dis, 138:1213-1219.

Van Leeuwen, Klokman WJ, Stoval M, Hagwenbeek A, van den Belt-Dusebout AW, Noyon R, Boice JD, Burgers MV, & Somers R (1995) Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst, 87(20):1530-1537

Van Schooten FJ, van Leeuwen FE, Hillebrand MJ, de Rijke ME, Hart AA, van Veen HG, Oosterink S, & Kriek E (1990) Determination of benzo(a)pyrene diol epoxide-DNA adducts in white blood cell DNA from coke-oven workers: the impact of smoking. J Natl Cancer Inst, 82(11):927-933.

Vedal S, Schenker MB, Samet JM, & Speizer FE (1984) Risk factors for childhood respiratory disease. Analysis of pulmonary function. Am Rev Respir Dis 130:187-192.

Venables KM, Dally MB, Nunn AJ, Stevens JF, Stephens R, Farrer N, Hunter JV, Stewart M, Hughes EG, & Newman Taylor AJ (1989) Smoking and occupational allergy in a platinum refinery. Br Med J, 299:939-942.

Viikari-Juntura E, Riihimaki H, Tola S, Videman T, & Mutanen P (1994) Neck trouble in machine operating, dynamic physical work and sedentary work: a prospective study on occupational and individual risk factors. J Clin Epidemiol, 47(12):1411-1422

Vineis P, Estève J, & Terracini B (1984) Bladder cancer and smoking in males: types of cigarettes, age at start, effect of stopping and interaction with occupation. Int J Cancer, 34:165-170.

Wagner LC, Sleggs CA, & Marchand P (1960) Diffuse pleural mesothelioma and asbestos exposure in North Western Cape Province. Br J Indust Med, 17:260-271.

Ware JH, Dockery DW, Spiro A, Speizer FE, & Ferris BGJ (1984) Passive smoking, gas cooking, and respiratory health of children living in six cities. Am Rev Respir Dis 129:366-374.

Witschi HP, Pinkerton KE, & Joad JP (1997) The Toxicology of Environmental Tobacco Smoke. Annu Rev Pharmacol Toxicol, (accepted for publication).

Witschi HP, Pinkerton KE, Coggins CRE, Penn A, & Gori GB (1995) Environmental tobacco smoke: experimental facts and societal issues. Fundam Appl Toxicol, 24:3-12.

Wright AL, Holberg C, Martinez FD, & Taussig LM (1991) Relationship of parental smoking to wheezing and nonwheezing lower respiratory tract illnesses in infancy. Group Health Medical Associates. J Pediatr 118:207-214.

Wang X, Wypij D, Gold DR, Speizer FE, Ware JH, Ferris BGJ, & Dockery DW (1994) A longitudinal study of the effects of parental smoking on pulmonary function in children 6-18 years. Am J Respir Crit Care Med 149:1420-1425.

Wechsler LS, Checkoway H, Franklin GM, & Costa LG (1991) A pilot study of occupational and environmental factors for Parkinson's disease. Neurotoxicology, 12(3):387-392.

Weiss W (1971) Cigarette smoking, asbestos and pulmonary fibrosis. Am Rev Respir Dis, 104:223-226.

Weiss W (1976) Chloromethyl ethers, cigarettes, cough and cancer. J Occup Med, 18(3):194-199.

Weiss W (1980) The cigarette factor in lung cancer due to chloromethyl ethers. J Occup Med, 22(8):527-529.

Weiss W (1982) Epidemic curve of respiratory cancer due to chloromethyl ethers. J Natil Cancer Inst, 69(6):1265-1270.

Weiss W (1984) State of the Art - Cigarette smoke, asbestos and small irregular opacities. Am Rev Respir Dis, 130(2):293-301.

Weiss W & Boucot KR (1975) The respiratory effects of chloromethyl methyl ether. J Am Med Assoc, 234(11):1139-1142.

Welch K, Higgins I, Oh M, & Burchfiel C (1982) Arsenic exposure, smoking and respiratory cancer in copper smelter workers. Arch Environ Hlth, 37:325-335.

Wen CP et al (1984) Epidemiologic studies of the role of gasoline (hydrocarbon) exposure in kidney cancer risk. Adv Modern Environ Toxicol, 7:245-257.

West S, Hildesheim A, & Dosemeci M (1993) Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case control study. Int J Cancer, 55(11):722-727.

White GP Jr, Mathias CGT, & Davin JS (1993) Dermatitis in workers exposed to antimony in a melting process. J Occup Med, 35(4):392-395.

WHO (1980) Recommended Health-Based Limits in Occupational Exposure to Heavy Metals. Technical Report Series 647. Geneva, World Health Organization, pp 21-35.

WHO (1985) World Health Organization, South East Asian Region. Regional Workshop on the Control of Tobacco-related Diseases, New Delhi, 22-26 July, 1985. New Delhi, World Health Organization.

WHO (1986) Recommended Health-Based Limits in Occupational Exposure to Selected Mineral Dusts. Technical Report Series 734. Geneva, World Health Organization.

WHO (1987) Air Quality Guidelines for Europe. WHO Regional Publications, European Series No.23. Copenhagen, World Health Organization.

WHO (1996) Tobacco or Health: First Global Status Report. Geneva, World Health Organization.

Wicklund KG, Daling JR, Allard J, & Weiss NS (1988) Respiratory cancer among orchardists in Washington State, 1968 to 1980. J Occup Med, 30(7):561-564.

Wilbert W (1987) Tobacco and shamanism in South America (Psychoactive plants of the world). New Haven and London, Yale University Press, 294 pp.

Williams MK, Walford J, & King E (1983) Blood lead and the symptoms of lead absorption. Br J Indust Med, 40(3):285-292.

Williams N (1974) Polymer-fume fever: Not so benign. J Occup Med, 16(8):519-522.

Wong O, Harris F, & Smith TJ (1993) Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States. Environ Hlth Perspect, 101(Suppl.6):63-76.

Wynder EL & Bross IJ (1961) A study of etiological factors in cancer of the oesophagus. Cancer, 14:389-413.

Wynder EL, Covey LS, Mabuchi K, & Mushinki M (1976) Environmental factors in cancers of the larynx. A second look. Cancer, 38:1591-1601.

Yazicioglu S, Ilcayto R, Balci K, Sayli BS, & Yorulmaz B (1980) Pleural calcification, pleural mesotheliomas and bronchial cancers caused by tremolite dust. Thorax, 35:564-569.

Yorukoglu Y, Ilgit E, Zengin M, Nazliel K, SalmanE & Yucel E (1993) Thromboangiitis obliterans (Buerger's disease) in women (a reevaluation). Angiology. 44(7):527-532

Yoshizawa K (1984) [Clinicopathological analysis of lung cancer and epithelial changes of the bronchus in chromate workers]. Shikoku Acta Medica, 40(1):123-134, (in Japanese).

Yue L (1992) Cadmium in tobacco. Biomed Environ Sci, 5(1):53-6.

Zahran FM, Ardawi MSM, & Al-Fayez SF (1985) Carboxyhaemoglobin concentrations in smokers of sheesha and cigarettes in Saudi Arabia. Br Med J, 291:1768-1770

Zahran FM, Ardawi MSM, & Attallah AA (1988) Hazards of smoking sheesha in Saudi Arabia. Directorate of Scientific Research, King Abdul Aziz City for Science & Technology. Riyadh, Directorate of Scientific Research, pp237

Zelman S (1973) Correlation of smoking history with hearing loss. J Am Med Assoc, 223(8):920

Zhang Z-F, Yu S-Z, Li W-X, & Choi BCK (1989) Smoking, occupational exposure to rubber and lung cancer. Br J Indust Med, 46:12-15.

Zhu H & Wang Z (1993): Study of occupational lung cancer in asbestos factories in China. Br J Indust Med, 50(11):1039-1042.

Zober A & Wettle D (1985) Cross-sectional study of respiratory effects of arc welding. J Soc Occup Med, 35(3):79-84.