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

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3.2 Interactions between tobacco smoke and other agents

3.2.1 Asbestos

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

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

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

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

Table 5. Smoking prevalence in asbestos-exposed workers

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

3.2.1.1   Asbestos and lung cancer

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

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

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

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

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

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

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

3.2.1.2   Asbestos and pleural mesothelioma

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

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

3.2.1.3 Asbestos and other forms of cancer

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

3.2.1.4 Asbestosis

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

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

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

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

3.3 Non-asbestos fibres

3.3.1 Glass fibre

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