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Proceedings of an
International Symposium/Workshop

Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke

Held at the Battelle Seattle Conference Center
April 10-14, 1988, Seattle, Washington

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Winston-Salem, NC 27102

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Electric Power Research Institute
Palo Alto, CA 94303

Biological Interactions: Important Things We Do Not Know

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KEY WORDS: animal models, biological interactions, tobacco smoke, mineral fibers, asbestos, lung neoplasia

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ABSTRACT

Human mortality data suggest that, on average, smoking increases the risk of death from lung cancer by a factor of 10. Inhalation exposure to asbestos increases the risk by a factor of 5, and a combination of smoking and asbestos exposure increases the risk by a factor of 50. This implies multiplicative interaction between smoking and asbestos but throws no light on the mechanisms involved. It has been suggested that the basis of the interaction is "physical": that the adsorption of genotoxic carcinogens from cigarette smoke onto asbestos particles leads to prolonged contact between DNA-damaging electrophiles and lung cells. Alternatively, it has been suggested that one of the two agents (probably in cigarette smoke) is a genotoxic initiator, while the other (probably the asbestos) acts as a promoter because it causes prolonged cellular proliferation. Many experiments involve the introduction, by intratracheal instillation, of particulate material (e.g., ferric oxide, carbon black, as a surrogate for asbestos particles) along with benzo[a]pyrene or another carcinogen (as a surrogate for cigarette smoke) into the lungs of laboratory rodents. These studies have been undertaken on the assumption that the presence of supposedly inert particles in the lung is necessary for and/or greatly increases the chances of tumor development in response to the carcinogen. In fact, the evidence for this is somewhat equivocal. A second problem is that the neoplastic lung lesions most commonly produced in rodents (e.g., nonfatal, peripherally located bronchioloalveolar adenomatous lesions or highly keratinized, seemingly

benign, squamous lesions) may have little relevance to the undoubtedly malignant, often centrally arising, and usually fatal lung cancers of man. A third problem is that cigarette smoke is itself largely composed of particulates. Therefore, why should one expect the presence of other particulate matter in the lungs to enhance its carcinogenic activity? So far, attempts to enhance respiratory tract carcinogenesis in smoke-exposed rodents by prior or concomitant exposure to asbestos or other particulate materials have not produced impressive evidence of multiplicative interaction comparable with that seen by epidemiologists for human lung-cancer mortality.

A critical reevaluation is needed of the results of animal studies and of the likely relevance of producing particular kinds of lesions in the lungs of laboratory rodents to mechanisms involved in human lung carcinogenesis. Only then can one hope to obtain meaningful answers to the many topical and important questions concerning the physical and chemical characteristics of fibrous materials which determine whether or not they contribute to lung-cancer risk in smokers and nonsmokers.

Even if one accepts the epidemiological evidence for a multiplicative interaction between tobacco smoke and asbestos in relation to lung cancer risk, many important questions remain. Must exposure be concomitant, or is an ex-smoker more susceptible to asbestos-induced lung cancer than a lifelong nonsmoker? Also, is a retired asbestos worker more likely than a retired office worker to develop lung cancer if he takes up smoking for the first time? Can we exclude the possibility that irritants in the vapor phase of tobacco smoke (e.g., oxides of nitrogen) may have the effect of enhancing pulmonary carcinogenesis by asbestos? Does smoking enhance the retention of radon more in the lungs of asbestos workers than in those of other workers? These and many other questions apply not only to risks from asbestos exposure but also to risks from exposure to other fibrous dusts.

INTRODUCTION

The starting point of this symposium is the widely held view that cigarette-smoking and exposure to asbestos fibers by inhalation act synergistically in relation to lung-cancer risk in man. Table 1, based on the findings of Hammond et al. (1979), illustrates the epidemiological basis for this view. According to Berry et al. (1985), the observed relative risk of developing lung cancer (after allowing for smoking) that is associated with asbestos exposure is greater in nonsmokers than in smokers. However, Doll and Peto (1985) thought that this might be due to methodological defects, the most important of which is the misclassifying of some current or

ex-smokers as nonsmokers. Presently, the position is that the carcinogenic effects of asbestos dust and cigarette-smoking on the human lung are approximately multiplicative.

Table 1. Mortality ratios based on age-standardized death rates from lung cancer in cigarette smokers and nonsmokers, with or without occupational exposure to asbestos dust (from Hammond et al., 1979).

Asbestos Exposure	Cigarette-Smoke Exposure	Mortality Ratios
+	+	53
+	-	5
-	+	11
-	-	1

Laboratory evidence that particulate matter enhances lung-cancer induction by known carcinogens has tempted some investigators to assume that an animal model exists for asbestos/smoking interaction in humans. They therefore apply the terms tumor initiator and tumor promoter to asbestos dust and cigarette smoke. This symposium provides, among other opportunities, the chance to review the appropriateness of using such terms in light of the available evidence.

LACK OF A SUITABLE ANIMAL MODEL

A serious hurdle in investigating the basis of the synergism between asbestos dust and cigarette-smoking in relation to lung-cancer risk in man is the lack of any really suitable animal model for inducing lung cancer by tobacco-smoke inhalation. In the absence of such a model, a variety of far less appropriate model systems that depend on surrogates have been used. However, surrogation can easily be pushed beyond the point of credibility, particularly when multiple surrogates are incorporated into a single model system. Some of the surrogates that have been used are:

- rat, mouse or hamster lung for human lung
- intratracheal instillation of tobacco tar or suspended dust for inhalation exposure

- intrapleural injection instead of inhalation exposure
- carcinogenic polycyclic aromatic hydrocarbons for cigarette smoke
- a seemingly inert dust (e.g., ferric oxide, India ink) for a biologically active dust (e.g., asbestos)
- doubtful neoplastic end points arising in alveoli or bronchioles instead of the squamous or small-cell carcinomas that arise mainly in large airways
- short-term *in vitro* studies with non-neoplastic end points (e.g., chromosomal aberrations) instead of long-term *in vivo* studies with neoplastic end points.

POSSIBLE MECHANISMS

There is, in fact, no dearth of possible explanations for the interaction between asbestos dust and smoking in the genesis of lung cancer. As an armchair exercise, I have listed some of them. Following are factors that may be determinants of lung-cancer risk in response to a potential carcinogen:

- genetic susceptibility
- dose (airborne concentration, respiratory rate, period of exposure)
- time since first exposure
- particle size, deposition and distribution
- penetration from surface into lung tissue
- clearance rate
- metabolic activation
- detoxification
- tissue damage (irritation, necrosis, cell turnover)
- repair of tissue damage
- immune competence
- other diseases
- nutrition (calories, fat, vitamin A).

In the following list, I postulate a variety of ways in which inhaled cigarette smoke may enhance response to a particulate carcinogen, such as asbestos:

- effect on particle deposition or distribution

- effect on particle penetration into tissues
- effect on particle clearance (e.g., because of ciliotoxicity, destruction of cilia, replacement of ciliated epithelium by squamous epithelium, blockage of lymph drainage, etc.)
- induction of metabolically activating enzymes or inhibition of detoxifying enzymes
- stimulated proliferation of mutant cells (tumor promotion)
- interference with immune competence
- effect on nutritional (including vitamin) status.

Listed below are various ways in which chemically inert non-genotoxic particles that are retained in the lungs may enhance carcinogenesis by cigarette smoke:

- adsorption of smoke carcinogens onto particles might increase the number of cells with which they interact and/or delay their clearance
- effect on clearance of smoke carcinogens in the absence of adsorption onto particles
- proliferation of target cells when exposed to smoke carcinogens
- stimulated proliferation of smoke-damaged mutant cells (tumor promotion)
- Interference with immune competence.

These lists are by no means exhaustive, and another philosopher, sitting in another armchair, could doubtless add to all three lists. The point is that, given the wide variety of possibilities, it would be unwise to plump for one without excluding the others. And it would be very unwise to assume that any of the available animal models is reliable for predicting human lung-cancer risk from exposure to tobacco smoke or dusts such as asbestos.

Among the more popular theoretical causes advanced to explain asbestos/tobacco-smoke interaction in lung carcinogenesis are: (1) the adsorption onto asbestos particles of carcinogens present in tobacco smoke; (2) the slowing of asbestos particle clearance by cigarette smoke; and (3) the slowing of smoke-particle clearance by asbestos. The first two of these explanations seem unlikely, insofar as all observers agree that smoking is wholly without effect on the incidence of mesotheliomas in persons exposed to asbestos. This is not what one would expect if asbestos adsorbed smoke carcinogens, and there is no reason why slowing the clearance of asbestos particles from the lung should not result in an increased risk of mesotheliomas along with the increased risk of lung cancer. Since smoking

is not, by itself, associated with increased risk of mesothelioma, the third of these three possible explanations is the only one that is at all plausible.

IF THE TWO-STAGE THEORY OF CARCINOGENESIS APPLIES, WHICH IS THE INITIATOR AND WHICH IS THE PROMOTER?

According to the two-stage theory of carcinogenesis, a genotoxic (initiating) agent and a nongenotoxic, hyperplasia-stimulating (promoting) agent may operate sequentially in causing neoplasia. However, for each of the two kinds of agent to complement the activity of the other in this way, exposure to the genotoxin must either precede or occur at the same time as exposure to the promoter.

In the case of the combined effects of cigarette smoke and asbestos, most investigators have looked to cigarette smoke to provide the genotoxins, because asbestos has proved inactive in virtually all laboratory tests for genotoxicity. In other words, asbestos is usually cast in the role of tumor promoter, with cigarette smoke possessing all the initiating activity and, perhaps, contributing to the promoting activity as well. Notwithstanding this, Kobayashi et al. (1974) claimed to have shown that inhaled tobacco smoke acted as a tumor promoter and/or co-carcinogen for the upper respiratory tract, including the larynx, of hamsters previously given a large dose of 7,12-dimethylbenz[a]anthracene (DMBA).

In recent years, the two-stage theory of carcinogenesis has been increasingly questioned (Iversen and Astrup, 1984). However, whether it is true or not, the following question arises: For asbestos dust and cigarette smoke to interact in causing lung cancer, does exposure have to be concomitant or in a particular sequence? Thus, are ex-smokers more likely than nonsmokers to develop lung cancer if they are subsequently exposed to asbestos dust? Also, are persons who have previously been exposed to asbestos dust more susceptible than persons who have not if they take up smoking later in life? At present, the answers to these questions are not known, and no one seems to be seeking the answers.

DO NOT LET US FORGET THAT TOBACCO SMOKE IS PARTLY PARTICULATE

It is interesting to compare theories about tobacco-smoke/asbestos interaction and environmental tobacco-smoke/radon interaction in relation to lung-cancer risk. In the case of the former, asbestos is the particulate material which, perhaps, adsorbs carcinogens from tobacco smoke so that they are not so readily cleared from the lungs.

However, in the case of radon and environmental tobacco smoke, it is the latter that is cast in the role of the particulate material onto which genotoxic radon is adsorbed! The foundations of both theories would seem to be a little shaky, to say the least!

IS ENHANCING PENETRATION OF ASBESTOS PARTICLES INTO LUNG TISSUES BY TOBACCO SMOKE IMPORTANT?

Simani et al. (1974) demonstrated that cigarette smoke opens up intercellular junctions in the tracheal epithelium of guinea pigs, thereby allowing relatively large particles to penetrate between epithelial cells and find their way more deeply into the epithelium. Although it seems unlikely that this is an important mechanism in lung carcinogenesis induced by combined exposure to asbestos and cigarette smoke, I am not sure that evidence exists to disprove the theory.

DO ASBESTOSIS, FIBROSIS AND/OR SCARRING OF THE LUNG PREDISPOSE TO LUNG CANCER

According to many groups of investigators, asbestosis is not a prerequisite for the development of lung cancer in persons exposed to asbestos (Selikoff et al., 1964; Enterline, 1965; Jacob and Anspach, 1965). However, Parkes (1974) pointed out that, in many cases, this conclusion was based simply on the absence of radiological evidence of asbestosis (Edge, 1976) and was not backed-up by postmortem data.

Several investigators have reported that lung cancers arising in persons exposed to asbestos tend to occur in the lower lobes, that is to say, the parts of the lung most affected by the deposition of dust and by the consequent fibrosis (Jacob and Anspach, 1965). However, the fact that dust deposition, fibrosis, and cancer development tend to take place in the same area of the lung does not establish that fibrosis predisposes to cancer risk in the case of asbestos.

The picture is confused; firstly, by historical epidemiological data for asbestosis and lung cancer, secondly, because of conflicting data for the association between lung cancer and other pneumoconiotic diseases; and thirdly, by the reported association between local scarring in the lung and cancer development.

A strong association has long been known to exist between asbestosis and lung cancer. Thus, Merewether (1949) reported that 14.7% of workers with asbestosis later developed lung cancer. By 1963, the percentage had, according to Buchanan (1965), risen to over 50. A plausible explanation of this steep rise was that a decrease in

ambient asbestos dust concentrations led to delayed and slower development of asbestosis. In these circumstances, men had more time to develop lung cancer before they died of asbestosis. In any case, evidence of association is not evidence of causation, so that even a 50% risk of lung cancer in a person with asbestosis does not establish that asbestosis predisposes to lung cancer in a causal sense.

The absence of any apparently increased risk of lung cancer in association with pneumoconiotic fibrosis due to other dusts (e.g., coal, amorphous silicates, talc, etc.) suggests that pulmonary fibrosis *per se* is, in fact, not a risk factor for lung cancer. On the other hand, there is good evidence that, in the lung, cancers tend to arise in the vicinity of localized scars (e.g., secondary to tuberculosis), and when they do so, they are mostly adenocarcinomas (Auerbach et al., 1979; Carroll, 1962).

Laboratory studies have not really resolved the matter. Wagner et al. (1974) reported increased incidences of both adenocarcinoma and squamous carcinoma of the lung in rats exposed to asbestos. They stated that there was a positive association between asbestosis and lung tumors. However, all their rats were heavily exposed to asbestos dust, and it remains unclear whether the asbestosis was a prerequisite for tumor development.

There would seem, therefore, still to be some unanswered questions concerning the association between fibrosis, scarring, and lung-cancer risk.

ARE THE LUNG CANCERS THAT ARISE IN RESPONSE TO ASBESTOS AND CIGARETTE SMOKE SIMILAR IN PATHOGENESIS AND HISTOLOGICAL TYPE?

According to Auerbach et al. (1956, 1961), the beginnings of most smoking-associated lung cancers in men are to be found in the epithelium of main airways in the form of basal cell hyperplasia, loss of cilia, nuclear atypia, squamous metaplasia and carcinoma *in situ*. Progression from these changes results in the development of mostly squamous and small-cell cancers that arise, for the most part, close to the center of the chest, near the tracheal bifurcation. Originally, it was thought that the risk of adenocarcinoma development from small airways or from alveolar epithelium, more peripherally in the lung, was only rarely associated with smoking. However, it is clear now, especially in women, that this is not true. By contrast, a seemingly greater proportion of the lung cancers arising in men exposed to asbestos dust are adenocarcinomas than in men not so exposed. If this is so, then it suggests that fibrosis and scarring may really be of some importance.

Kannerstein and Churg (1972) compared 50 cases of asbestos-associated lung cancer and 50 cases of lung cancer not associated with exposure to asbestos. In the former cases, they confirmed that a majority of the cancers arose in the lower lobes, where the asbestosis was most severe. They also recorded more severe pleural involvement in the asbestos-associated cases. However, they saw no significant difference between the two groups in the location of cancers within lung lobes (i.e., central versus peripheral), in the incidence of different types of lung cancer (squamous, small cell, adenocarcinoma, etc.), or in the incidence or pattern of metastasis. They regarded their findings as consistent with asbestos being a weak carcinogen which augments the effect of another potent carcinogen, namely, cigarette smoke.

All in all, it seems likely that the answer to the question posed in the heading of this section is yes. However, whether it is reasonable to regard asbestos as a weak carcinogen and cigarette smoke as a potent carcinogen is certainly open to debate, as is the question as to which agent augments the other.

ASBESTOS, SMOKING, AND CANCER OF THE LARYNX

It is easy to think of possible mechanisms for the interaction of asbestos dust and smoking in relation to lung-cancer risk, even if the plausibility of some of the proposed mechanisms is reduced by the lack of evidence of interaction in relation to mesothelioma, as discussed before. On the other hand, claims that asbestos and smoking interact in the genesis of cancer of the larynx (U.S. Surgeon General, 1979) are more difficult to reconcile with any plausible mechanism. A direct carcinogenic effect of cigarette smoke on the risk of cancer of the larynx has been demonstrated both epidemiologically (U.S. Surgeon General, 1979) and experimentally, in hamsters (Dontenwill et al., 1973). However, no effect of asbestos dust alone on the larynx has ever been described either in man or animals, and it is difficult to imagine what sort of biological activity asbestos dust could exhibit at this site.

Kobayashi et al. (1974) demonstrated that cigarette smoke exacerbates epithelial changes in the larynx of hamsters exposed to DMBA by intratracheal instillation. This adds confusion rather than enlightenment, insofar as tobacco smoke was cast by these investigators in the role of tumor promoter. (See also Kannerstein and Churg, 1972, who considered tobacco smoke a potent carcinogen.)

DATA BASE FOR EFFECTS OF MINERAL DUSTS OTHER THAN ASBESTOS IN RELATION TO ENHANCEMENT OF LUNG-CANCER RISK BY SMOKING

In 1987, the International Agency for Research on Cancer (IARC, 1987) reviewed the available data from animal and epidemiological studies for exposure to silica and various silicates. Unfortunately, none of the data reviewed shed any light on mineral-dust/smoking interactions in relation to lung-cancer risk.

Marked fibrosis as well as lung cancers have been induced in rats, but not in hamsters, by inhalation exposure to crystalline silica (e.g., quartz). However, there is no information on whether exposure to tobacco smoke, in addition, enhances the risk of cancer development. For exposure to amorphous silica, the position is even more unsatisfactory. The epidemiological evidence for increased lung-cancer risk in ore miners, quarriers, coal miners, and persons working in the ceramics industry is either equivocal or negative. Coal miners with pneumoconiosis are seemingly not at as much increased risk of developing lung cancer as asbestos workers with asbestosis. A higher than expected incidence of lung cancer in granite workers and others in the stone-cutting industry might well be due to exposure to radon rather than to silicates. Overall, there seems to be a somewhat higher incidence of lung cancer among persons with silicosis, but even this is not certain because of the failure to collect information about smoking habits. Particularly for this reason, it is impossible to assess whether there is any interaction between exposure to silica and smoking in the causation of lung cancer.

In the case of talc, there is evidence of increased lung-cancer risk for workers exposed to talc that is contaminated with asbestos, but not for workers exposed to talc that is not so contaminated. In the former, there is no information on whether smoking enhances the risk, and no informative inhalation studies in animals have been performed.

Erionite, a fibrous aluminosilicate dust, produces fibrosis of the lung and mesotheliomas in high incidence following exposure by inhalation, both in humans and in laboratory animals. Lung-cancer risk, however, is seemingly not influenced and, in the case of humans, there is no evidence to suggest that smoking has any influence.

DOES INHALED PARTICULATE MATTER REALLY ENHANCE LUNG-CANCER RISK UNDER CONDITIONS OF PRIOR, SIMULTANEOUS, OR SUBSEQUENT EXPOSURE TO GENOTOXIC CARCINOGENS?

This question is fundamental to the subject of this symposium. Although it is traditional to think that inhaled or intratracheally

instilled particulate matter enhances the risk of lung cancer in animals exposed, by the same route, to carcinogens such as DMBA or benzo[a]pyrene (BaP), the evidence is, in fact, equivocal (Farrell and Davis, 1974). Certainly it is not true that a particulate vehicle is *necessary* for experimental lung carcinogenesis induced by carcinogenic polycyclic aromatic hydrocarbons (Staub et al., 1965; Feron, 1972).

Pylev et al. (1969) reported that asbestos particles significantly increased the retention of radioactivity in the lungs of hamsters 21 days after the intratracheal instillation of a 10% aminosol vitrum* suspension of [3H] BaP mixed with asbestos dust, as compared with a suspension of [3H] BaP in 10% aminosol vitrum only. The inclusion of asbestos in the instilled material was associated with an increase in the number of macrophages that could be recovered from the lungs. However, the radioactivity per macrophage was higher in hamsters given BaP only.

Davis et al. (1975) reported that the repeated intratracheal instillation of BaP in infusine gave rise to more squamous neoplasms in the lungs of rats than did the repeated intratracheal instillation of BaP plus carbon-black particles in infusine. In other words, the addition of the particulate matter to the instillate *reduced* the risk of lung-tumor development. These findings were in line with those of Herrold and Dunham (1962), Feron et al. (1973) and Henry et al. (1973, 1974), who reported that a particulate vehicle is not necessary for lung-tumor production by instilled BaP in hamsters.

Wehner et al. (1975a) exposed male hamsters either to chrysotile asbestos dust alone, cigarette smoke alone, or both asbestos dust and cigarette smoke. Lung disease, diagnosed as asbestosis, led to early death in the asbestos-exposed animals. This may explain why the animals exposed to both asbestos and cigarette smoke exhibited a lower incidence of laryngeal lesions than was seen in animals exposed to cigarette smoke only. The incidence of lung adenomas was slightly but not significantly higher (7/51) in the asbestos-plus-smoke-exposed group than in the asbestos-only group (3/51). There were no lung adenomas in hamsters exposed to smoke only (0/51) and only one in a control animal (1/51).

In similar studies involving the exposure of male hamsters to nickel oxide dust and/or cigarette smoke (Wehner et al., 1975b), the main effects of exposure to cigarette smoke alone were reduced body-weight gain, delayed onset of amyloid disease, prolonged survival, and an increased incidence of various pathological changes in the larynx. Exposure to nickel oxide only also increased the

*An aqueous preparation of 10% amino acid and low-molecular-weight peptide derived by enzymatic hydrolysis of animal proteins and marketed by the Vitrum Company, Stockholm, Sweden.

incidence of laryngeal lesions. However, there was no evidence of synergism in animals exposed to both agents. A variety of effects on the lungs, though no lung tumors, were seen in animals exposed to nickel oxide dust, but exposure to tobacco smoke in addition had little or no effect on the incidence or severity of these lesions.

The answer to the question posed in the heading of this section seems to be sometimes yes and sometimes no. The size and composition of particles clearly are important, but so are the chemical and physical natures of genotoxic carcinogens. *Clearly, the results of experiments involving combined exposure to a particular genotoxic carcinogen and a particular dust is not a reliable model for any other carcinogen or any other dust.*

CONCLUSIONS

There is persuasive evidence that smoking and occupational exposure to asbestos act in a multiplicative way in increasing the risk of lung cancer in humans. However, there is no meaningful animal model for investigating the mechanism underlying this phenomenon. Attempts to explain the synergism in terms of the two-stage hypothesis are based on muddled thinking and a lack of persuasive supportive evidence. It is not clear whether the multiplicative effect depends on concomitant exposure to both agents, or whether it would be seen in a retired asbestos worker who took up smoking or in an ex-smoker whose exposure to asbestos dust began only in later life.

In the absence of a better understanding of mechanisms, it is uncertain whether the multiplicative effect applies to very low levels of exposure to both agents. There is persuasive evidence that the long thin shape of asbestos particles, coupled with their other physical and chemical characteristics, is highly relevant to their biological activity. However, the part played by physical and chemical characteristics other than shape is still uncertain (Pott, 1987). Thus, it is not possible to predict, with any confidence, how combined exposure to other dusts and to cigarette smoke might interact in relation to lung-cancer risk.

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