

Physical Carcinogens

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Broadly, *physical carcinogens* includes a wide range of agents: electromagnetic radiations of different kinds, corpuscular (alpha and beta) radiations, low and high temperatures, mechanical traumas, and solid and gel materials. More restrictively, however, the term is ordinarily used to define solid and gel materials, water-insoluble or slightly soluble, that are capable of producing cancer. Both *physical carcinogens* and *solid carcinogens* have been widely used in an oversimplified manner to identify agents that produce cancer mainly, if not exclusively, through their physical properties and physical effects, rather than through their chemical properties and actions, as opposed to *chemical carcinogens*. Physical carcinogens include hard and soft materials, fibrous particles, nonfibrous particles, and gel materials.

The first scientific demonstration of the carcinogenic capacity of physical agents was made by Turner, who found that Bakelite disks, implanted in rats, provoked local fibrosarcomas.¹ Anecdotal cases of tumors that arose around foreign bodies (including bullets in wartime) were reported earlier.

The identification of physical carcinogens is based on epidemiologic and/or experimental data. The extrapolation of experimental results to humans is improved by the use of experimental models as closely equivalent to human situations as possible. Experimental intratissue inserts of metallic alloys or plastics may well reproduce the situations in which allogenic prostheses are implanted surgically in the human body; conversely, the inhalation of particulate materials may correctly reproduce the exposure of laborers working in a dusty occupational environment. In the preamble of the Reports on Carcinogens of the US National Toxicology Program (NTP), it is stated that (1) known carcinogens are “those substances for which there is sufficient evidence of carcinogenicity from studies in humans to indicate a causal relationship between the agent and human cancer;” and (2) substances reasonably anticipated to be carcinogens to humans are “those substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals.”²

KNOWN PHYSICAL CARCINOGENS

HARD AND SOFT MATERIALS The category of hard and soft materials includes metals and metallic alloys, synthetic products, and other natural materials, in the form of disks, squares,

films, and foams. The studies performed in this field are nearly exclusively experimental, and the majority have been made on rats by intratissue implantations, mainly in the subcutaneous tissues, and more infrequently in other sites. The experiments of Oppenheimer and colleagues and of Nothdurft on squares and disks of metals and plastics are classic.³⁻⁶ For other references see Hueper,⁷ Maltoni and Sinibaldi,⁸ and Maltoni and colleagues.⁹

Table 21-1 presents the most relevant available experimental data on the carcinogenicity of these materials. The observed tumors arise around implants and are sarcomas of different types: fibrosarcomas (Figure 21-1), rhabdomyosarcomas (Figure 21-2), and osteosarcomas.

Studies on the sequence of changes taking place at the site of implants, for reconstructing the histogenesis of sarcomas, have shown that the implanted material induces a fibrous reaction that remains apparently unchanged for several months, and may even undergo hyalinization. After several months the cells in the more internal layer of the fibrous capsule, in direct contact with the implanted material, may start to proliferate (Figure 21-3) and then evolve to the formation of sarcomas. These changes and their sequence take place independently from the nature of the implanted material.¹⁰

Various investigators have shown that intact films of certain polymers have more potent carcinogenic effects than perforated films of the same polymer and of the same shape, and are considerably more potent than powdered films. Other investigators, studying a different material, have been unable to confirm such a specific relationship between physical form and carcinogenesis. Testing vitallium in the form of intact disks, perforated disks of the same diameter and thickness, and fragments (in the amount equivalent to the weight of the intact disks), the fragmentation effect has been confirmed, but not that of perforation: such disks proved to be as carcinogenic as intact disks (Table 21-2).⁹

Surgical prostheses of metals, metallic alloys, and polymers are widely used. Only a few cases of human sarcomas around surgical implants of metals and plastics have been reported in the literature.¹¹ More information on the potential carcinogenic risks of surgically implanted hard and soft materials could be provided by programmed long-term follow-up of implanted patients.

Table 21-1 Hard and Soft Materials, of Different Shape and Dimension, Found to Be Carcinogenic When Implanted in Rodents

Metals
Gold
Platinum
Silver
Steel
Tantalum
Nickel
Metallic alloys
Vitallium (chromium, cobalt, molybdenum)
Water-insoluble polymers
Hydrocarbon polymers (synthetic)
Polyethylene (Polythene)
Polymethylmethacrylate (Lucite)
Polyvinylbenzol (Polystyrol)
Cross-linked polyvinyl alcohol (Ivalon)
Polyester condensate of terephthalate and ethylene glycol (Dacron)
Phenol-formaldehyde condensate (Bakelite)
Halogenated-hydrocarbon polymers (synthetic)
Polyvinyl chloride (PVC, Igelit, Vestolit, Vinnol)
Polyvinylidene chloride (Saran)
Polyfluor(chlor)-olefine (Teflon)
Polymethylmethacrylate chloride (Pliofilm)
Copolymer of vinyl chloride and acrylonitrile (Vinyon N, Dynel)
Aminized hydrocarbon polymers (polyamides) (synthetic)
Polyhexamethylene diamine adipanide (nylon)
Poly-ε-caprolactam, polyurethane (Perlon)
Hydrocarbon polymers (semisynthetic and natural)
Processed latex gum (rubber)
Processed polyglucose (cellulose) (cellophane)
Processed cellulose (linen, parchment paper)
Natural organic materials (silk, keratin, ivory)
Silicon polymers (synthetic)
Processed polydimethylsiloxanes (silicone rubber) (Silastic)
Mixture of different siloxanes (silicone gel for prostheses)

FIBERS Natural and synthetic mineral fibers have been investigated by epidemiologic and/or experimental studies for possible oncogenicity.

Asbestos Among the fibrous materials, asbestos has attracted the most attention because of its industrial and commercial relevance (about 3,000 uses), and its diffusion in the occupational and general environment, and because of the early detection of its pathogenicity and carcinogenicity. Six fibrous silicates are currently char-



Figure 21-1 Fibrosarcoma around an implant of a perforated vitallium disk, in a female Sprague-Dawley rat. Hematoxylin and eosin stain; original magnification $\times 200$.

acterized as asbestos: the fibrous serpentine mineral chrysotile (white asbestos), and the amphiboles actinolite, amosite, anthophyllite, crocidolite (blue asbestos) and tremolite. The most commercially important minerals of asbestos are chrysotile, amosite, and crocidolite. Chrysotile is produced in the largest amounts and is the most widely used and diffused into the environment. In the last several decades asbestos has been mined at the rate of 3 to 8 million tons per year worldwide. Asbestos is mainly used in insulating buildings, furnaces and pipes, in the paper industry, maritime and railway carriers, and in the clutch and brake industry. Its wide use for insulation is the major cause of environmental and occupational exposure.

Because of its great production, numerous uses, and its practical indestructibility, asbestos may be considered ubiquitous. It is present in workplaces, the general environment, and the family environment, where it is brought by exposed workers on their clothes and in their hair. It is found in air, and traces of the mineral have been detected in water (including drinking water), in foods and drugs, and in a variety of consumer products. The following worker categories must be considered as exposed to asbestos: miners and millers of the mineral; manufacturers of asbestos products; laborers who repair, maintain, and clean structures and

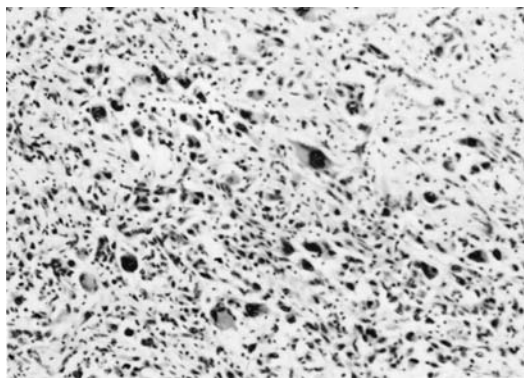


Figure 21-2 Rhabdomyosarcoma around an implant of an intact vitallium disk, in a female Sprague-Dawley rat. Hematoxylin and eosin stain; original magnification $\times 200$.

materials containing asbestos; workers handling waste made of, or contaminated with asbestos; and workers and citizens operating/living in an environment polluted by asbestos fibers.

The possible association between asbestos and cancer was suspected for the first time in 1935, when Lynch and Smith described a lung carcinoma in a patient with asbestosis (fibrosis of the lung caused by the inhalation of asbestos dust).¹² The carcinogenic effect of asbestos fibers of different types on various tissues and organs, both in humans and in experimental animals, is now definitively established by a large number of clinical, epidemiologic, and experimental studies. Several comprehensive reviews on asbestos carcinogenicity are available.¹³⁻¹⁶

The major route of exposure in humans is inhalation. In animals (mainly rats, but also mice and hamsters) asbestos has been tested by inhalation, by intraperitoneal, intrapleural, and subcutaneous injection, and by ingestion. Table 21-3 lists the tumors observed following exposure to asbestos fibers in humans and in experimental animals. Mesothelioma in its different sites (mainly pleura and peritoneum) is the tumor most specifically connected to asbestos, both in humans and in animals (Figures 21-4 and 21-5). Mesotheliomas in humans have been found after occupational, environmental, and family exposure.

The time of latency of asbestos-correlated tumors is long. In general, tumors start to appear 20 years after start of exposure.

Although its rarity makes mesothelioma the tumor most specifically related to asbestos exposure in terms of public health, lung cancer is the neoplasm to which asbestos-exposed workers are at greatest risk. In the case series of Selikoff and Seidman,¹⁷ dealing with deaths among 17,800 insulation workers in the United States and Canada in the period 1967 to 1987, compared to 458 deaths caused by mesothelioma, 899 more deaths caused by lung cancer were registered than expected.

Lung carcinomas and mesotheliomas in people exposed to asbestos may be preceded by or associated with lung fibrosis and pleural plaques. These changes may represent a marker of asbestos exposure.

However, epidemiologic studies on asbestos-exposed workers enable us to state that lung cancer should not necessarily be related to the presence of pleural plaques (or pleural asbestosis).¹⁸ Many lung cancers are diagnosed without any previous diagnosis of pleural plaques. This is partly a result of the lung parenchyma and parietal pleura being anatomically and histopathologically different. Furthermore, when pleural plaques and lung cancer are diagnosed simultaneously, it is very difficult to establish which pathology arose first.¹⁸

Other studies show that the relative risk of lung cancer is higher in patients with asbestosis,¹⁹ although lung cancer may be caused by a relatively low exposure to asbestos, and may arise independently of parenchymal fibrosis.²⁰⁻²²



Figure 21-3 Cellular proliferation in a fibrous capsule 15 months after implantation of an intact vitallium disk. The edge of the cavity containing the implant represents results of direct contact with the disk. Male Sprague-Dawley rat. Hematoxylin and eosin stain; original magnification $\times 200$.

The absence of a sequential relationship between asbestosis and lung cancer obliges us to include smokers with a limited exposure to these mineral fibers in our examination of the role of asbestos in the onset of this tumor.¹⁹

Outstanding epidemiologic studies show that tobacco smoke enormously increases the carcinogenic effect of asbestos on the lung, as indicated by Table 21-4. On the basis of available knowledge, tobacco smoke does not influence the mesothelioma risk due to asbestos.²³

The number of occupational groups at risk of asbestos cancer has been growing, and the incidence of asbestos-correlated tumors in some occupational categories has also been increasing in recent years. A clear example of new risk groups, with an increasing frequency of asbestos-correlated tumors, is represented by the mortality due to mesothelioma among workers exposed to asbestos used in the railroads (Table 21-5),²⁴⁻²⁷ among sugar refinery workers exposed to asbestos used in their factories as a heat insulator (Table 21-6),²⁸⁻³⁰ among asbestos-cement industry workers,^{31,32} and among shipyard workers.³³⁻³⁵ Considering the extent of the railroad network worldwide, there are reasons to anticipate that asbestos-related cancer among railroad workers may significantly increase.

Likewise increasing are the reports of mesotheliomas because of family contact with asbestos (see Tables 21-5 and 21-6). Mesothe-

Table 21-2 Results of Long-term Carcinogenicity Bioassays of Vitallium, in Different Forms, Implanted into Subcutaneous Tissues of Sprague-Dawley Rats

Treatment	No. of Animals	No. of Animals in Which Sarcomas Developed at Site of Implantation
Intact disks	30	13
Perforated disks	30	15
Fragments	30	2
None (controls)	30	0

Reproduced with permission from Maltoni C et al.⁹

liomas caused by environmental asbestos pollution may become a major problem. Three cases of mesothelioma have been reported to arise in housekeepers whose house and neighboring buildings had roofs of corrugated asbestos-cement,³⁶ which deteriorate under atmospheric corrosion, releasing asbestos fibers. An increase in the risk of malignant mesothelioma has been observed among people who have never been engaged in the asbestos-cement industry, but were living within 1,000 meters of the factory.³⁷

In experimental systems, the various asbestos minerals (including the serpentine chrysotile) show a similar carcinogenic potency (Table 21-7).³⁸ There is evidence that each of the major non-neoplastic and neoplastic diseases associated with asbestos in humans is produced by all the different forms of the mineral, the amphiboles as well as the serpentine (chrysotile).³⁹

The diffusion of asbestos minerals in the environment, the number of people exposed, and the high degree of carcinogenicity of these materials make asbestos carcinogenicity a major worldwide problem of public health. This clearly emerges from a comparison of the mortality caused by mesothelioma in males in certain European countries in the period 1970 to 1994, and by the figures available on the mesothelioma mortality trends in some Western European countries, which indicate that a peak of deaths will not be reached until 2015.⁴⁰

Erionite Erionite is a fibrous zeolite, whose fibers are similar in dimension to asbestos fibers. Zeolites are crystalline aluminosilicates, in which the primary structures are tetrahedral consisting of either silicon or aluminum atoms surrounded by four oxygen atoms. These tetrahedral structures combine, linked together by oxygen bridges and cations, to yield an ordered three-dimensional framework. Although there are more than 30 known natural zeolites, only four are fibrous (chabazite, clinoptilolite, erionite, mordenite). Zeolite minerals are found as major constituents in numerous sedimentary volcanic tuffs, especially where these were deposited and have been altered by saline lake water. Many hundreds of occurrences have been recorded of zeolite deposits in more than 40 countries.

Natural zeolites have many commercial uses, most of which are based on the ability of these minerals to adsorb molecules from air or liquids

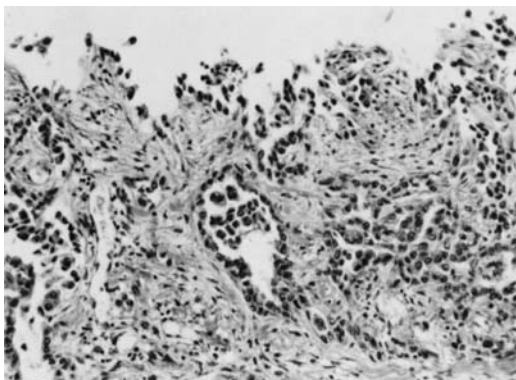


Figure 21-4 Tubular epitheliomorphic mesothelioma of the pleura in an Italian railroad machinist. Hematoxylin and eosin stain; original magnification $\times 200$.

selectively. The exposure of humans can be occupational or environmental.

A vast excess of mortality due to pleural and peritoneal mesotheliomas, both in males and females, constituting 71% to 88% of the cancer deaths and 35% to 51% of all deaths, has been reported in remote Anatolian villages in the same area where erionite occurs. Lung cancer also appeared to be excessive.⁴¹ The high incidence of mesothelioma and lung cancer is attributed to the presence of erionite in the soil, road dust, and building stones of the villages.^{42,43} Asbestos is not more common in erionite villages than in control villages where the excess of mesothelioma was not found.

It is significant that the registered increase of mesotheliomas in Sweden is partly a result of cases of this neoplasia appearing in Turkish migrant workers, probably exposed to erionite at an early age in their own country of origin.⁴⁴

A striking predilection to develop mesothelioma from erionite exposure was discovered in the disproportionate representation of certain human leukocyte antigens (HLA) among malignant pleural mesothelioma (MPM) patients as compared to nonaffected village residents, and also as compared to a referent healthy population (kidney donors). Among MPM patients, HLA B-41 antigen was present in 19.4% compared to 0.8% of villagers and 1.7% of donors (odds ratios [OR] 28.3 and 13.9, respectively). HLA B-58 was also significantly higher (OR 8.6 and 8.5), as was HLA DR-16. These data imply specific risk for certain genotypes and a potential screening tool for special avoidance of fibrous zeolites.⁴⁵ Similar studies have not been reported for asbestos-exposed populations.

The hypothesis that erionite is the causative agent of the Turkish mesotheliomas, and therefore that it is a human carcinogen, is supported by experimental evidence. Following inhalation exposure and intraperitoneal and intrapleural injection, erionite causes the onset of peritoneal and pleural mesotheliomas in rats and mice.^{38,43,46,47} In rats, erionite has been shown to be the most powerful mesotheliomatogenic agent for pleura (Table 21-8).³⁸

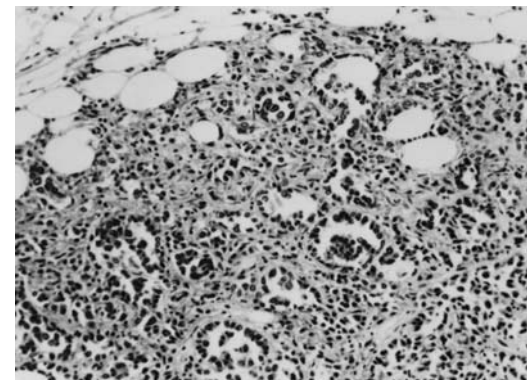


Figure 21-5 Tubular epitheliomorphic mesothelioma of the peritoneum of a male Sprague-Dawley rat injected with 25 mg of Canadian chrysotile, in 1 mL of H₂O. Hematoxylin and eosin stain; original magnification $\times 200$.

The demonstration of the carcinogenic effect of erionite is also of particular relevance considering the large amount and diffusion of natural fibrous and nonfibrous zeolites, their widespread industrial uses, which are expected to increase, and the production of zeolites for several industrial applications (as detergents, and as catalysts in the petrochemical and refining industries). A systematic and integrated project of long-term carcinogenicity bioassays of natural and man-made fibrous and non-fibrous zeolites was begun several years ago at the Bologna Institute of Oncology.

Other Natural and Synthetic Mineral Fibers Other natural fibers include wollastonite (a fibrous silicate), attapulgite (a fibrous silicate) and the asbestiform fibers present in commercial talc. Other synthetic fibers include glass wool, rock wool and slag wool (produced by blowing, centrifuging, and drawing molten rock or slag), and ceramic fibers.

Data on the carcinogenicity of natural and synthetic fibers is of great public interest because of the various industrial uses (the large majority as asbestos substitutes). At present, more than 5 million tons of synthetic mineral fibers are produced annually in more than 100 factories located throughout the world. Glass-fiber products comprise more than 50% of the total.

Most of the carcinogenicity data comes from experimental studies, and only to a limited extent from epidemiologic investigations. The experimental bioassays on carcinogenicity have been performed on rodents, mostly rats, but also mice and hamsters, in which the materials were administered by inhalation and/or intrapleural

Table 21-3 Tumors Related to Asbestos Exposure in Humans and Experimental Animals

Cancer Type	In Humans	In Experimental Animals
Lung cancer	+	+
Pleural mesothelioma	+	+
Peritoneal mesothelioma	+	+
Other-site mesothelioma and possibly sarcoma	+	+
Pharyngolaryngeal cancer	+	
Gastrointestinal cancer	+	
Kidney cancer	+	

Table 21-4 Synergistic Effect of Asbestos Exposure and Cigarette Smoking on Lung Cancer Risk

Asbestos	Cigarette smoking	Lung cancer risk
-	-	1
+	-	5
-	+	11
+	+	53

From Hammond EC et al.²³

Table 21-5 199 Cases of Mesothelioma in Italy Caused by Asbestos Used in Railroads: Distribution According to the Category of Population Exposed and Site of Neoplasia

Category of Population Exposed	No. of Cases of Mesothelioma					
	Pleural	Pericardial	Peritoneal	Pleuroperitoneal	Unspecified site	Total
Asbestos exposure due to job assignments						
Workers of the FS, especially machinists	85	1	0	1	0	87
Rolling-stock machinists and workers engaged in the repair and demolition of the rails, of workshops not belonging to the FS	79	0	7	0	9	95
Subtotal	164	1	7	1	9	182
Asbestos exposure because of workplace pollution						
Personnel working on rolling-stock, not employed by the FS	3	0	0	0	0	3
Asbestos exposure because of general environmental pollution	3	0	1	0	0	4
Asbestos exposure because of family contact						
Family members of exposed workers of the FS and of workshops not belonging to the FS	9	0	1	0	0	10
Total	179	1	9	1	9	199

^a FS = Ferrovie dello Stato (Italian State Railroads).
Reproduced with permission from Maltoni C et al.²⁷

and intraperitoneal injection/implantation. The data on the carcinogenicity of these fibers have been extensively reviewed.^{2,13,43,48,49}

Results of the epidemiologic and experimental studies are shown in Table 21-9.⁵⁰⁻⁵² Fibrous glass (glass wool) carcinogenicity deserves comment. This material is the most widely used substitute for asbestos. Yet on the basis of the available information, both experimental and epidemiologic, glass wool should reasonably be anticipated to be carcinogenic for humans. The International Agency for Research on Cancer stated that "at least 13 studies demonstrate biologically plausible and statistically significant increases in the incidence of lung cancer and mesothelioma in rats and hamsters exposed to glass wool by various routes using standard scientific methods: intrapleural injection, intrapleural implantation, intraperitoneal injection, and intratracheal instillation."⁴⁸ Three epidemiologic studies on workers employed in fibrous glass manufacturing facilities, one in Canada (one factory),⁵³ one in the United States (17 factories),^{54,55} and one in Europe (13 factories),⁵⁶ allow the conclusion that glass wool fibers play a role in causing the excess of lung cancer risk observed among those employees.⁵⁷ Consequently, fibrous glass production and use should be regulated and prompt measures of prevention should be undertaken.

Dacron vascular grafts, although highly oncogenic in rodents, have only rarely been associated

with angiosarcomas and malignant fibrous histiocytomas in humans. Because thousands of such grafts have been inserted in the past four decades, it is unlikely that they exert equal oncogenicity across species.⁵⁸ Given the serious problems for which grafts have been used, the oncogenic risk is tolerable. Sarcoma should be entertained in the differential diagnosis of any mass or thromboembolic event associated with a vascular prosthesis.

NONFIBROUS PARTICULATE MATERIALS Nonfibrous particulates include powdered metallic cobalt and nickel, and crystalline silica.

Particles of pure metallic cobalt (ranging from $3.5 \times 3.5 \mu\text{m}$ to $17 \times 12 \mu\text{m}$) with large numbers of long, narrow particles on the order of $10 \times 4 \mu\text{m}$, and clumps of particles measuring up to $100 \times 100 \mu\text{m}$, when injected into rat thigh muscles, cause the onset of sarcomas (mainly rhabdomyosarcomas), at the site of injection.⁵⁹

After intrafemoral or subcutaneous introduction into rats, particles of pure metallic nickel, ranging in diameter from 2 to $50 \mu\text{m}$ (with a mode between 10 and $30 \mu\text{m}$) have been shown to produce sarcomas of different histotypes in approximately 28% of implanted animals.⁷

Various forms and preparations of crystalline silica (quartz, cristobalite, and tridymite), have been tested for carcinogenicity. Quartz, with particle sizes in the respirable range, administered by inhalation or by intratracheal instillations in rats,

produces adenocarcinomas and squamous cell carcinomas of the lung in three of five experiments. When injected in the pleural and peritoneal cavities, quartz of several types, with particles in the respirable range, resulted in thoracic and abdominal malignant lymphomas, primarily of the histiocytic type. Cristobalite and tridymite, with particles in the respirable range, resulted in malignant lymphomas, primarily of the histiocytic type, when injected in the pleural cavity.⁴³

PARTICULATE AIR POLLUTION Particulate matter (PM) is the general term used for a mixture of solid particles and liquid droplets found in the air. PM stems from a variety of sources, including diesel trucks, power plants, wood stoves, and industrial processes. The chemical composition and physical properties of these particles vary widely.

Particles less than or equal to $2.5 \mu\text{m}$ in diameter, or $\text{PM}_{2.5}$, are known as "fine" particles. Fine particles result from fuel combustion (from motor vehicles, power generation, industrial processes), residential fireplaces, and wood stoves. Fine particles can also be formed in the atmosphere from gases such as sulfur dioxide, nitrogen oxides and volatile organic compounds.

Particles larger than $2.5 \mu\text{m}$ in diameter but less than or equal to $10 \mu\text{m}$ are known as PM_{10} . They are generally emitted from sources such as vehicles traveling on unpaved roads, material handling, and crushing and grinding operations, and windblown dust.

Both $\text{PM}_{2.5}$ and PM_{10} can accumulate in the respiratory system and are associated with adverse health effects. Fine particles are thought to pose a particularly great risk to health because they are more likely to be toxic than larger particles and can be breathed more deeply into the lung.⁶⁰

Although most recent epidemiologic research has focused on the effects of short-term exposure, several studies suggest that long-term exposure may be more important in

Table 21-6 17 Cases of Mesothelioma in Italy Caused by Asbestos Used in Sugar Refinery Plants: Distribution According to Category of Population Exposed and Site of Neoplasia

Category of Population Exposed	No. of Cases of Mesothelioma		
	Pleural	Peritoneal	Total
Asbestos exposure because of job assignments	15	1	16
Asbestos exposure because of family contact	1	0	1
Total	16	1	17

Reproduced with permission from Maltoni C et al.³⁰

Table 21-7 Results of Long-term Carcinogenicity Bioassays of Sprague-Dawley Rats Injected into the Peritoneal Cavity with Various Asbestos Minerals^a

Test material	No. of Animals	No. of Animals Bearing Peritoneal Mesotheliomas
Amosite	40	36
Anthophyllite	40	33
Chrysotile (California)	40	29
Chrysotile (Canada)	40	32
Chrysotile (Rhodesia)	40	33
Crocidolite	40	39
H ₂ O (controls)	150	0

^a A single injection of 25 mg in H₂O was used.
Reproduced with permission from Maltoni C and Minardi F.³⁸

terms of overall public health, with particular reference to cancer risk.

In one epidemiologic study conducted in California, a positive correlation was found between long-term ambient concentration of PM₁₀ and the incidence of lung cancer.⁶¹ This result was consistent with those previously found by other scientists.^{62,63} More recently, it was reported that long-term exposure to combustion-related fine particulate air pollution might be associated with an increase in lung cancer mortality and that each 10 µg/m³ elevation in fine particulate air is related with approximately an 8% increased risk of lung cancer mortality.⁶⁴

Experimental studies performed on rats treated by intratracheal instillation of dust have shown an increase in lung tumors.⁶⁵ Long-term inhalation studies on the effects of diesel exhaust on F344 SPF rats have shown an increase in lung cancer and lymphoma.⁶⁶

On the basis of the present scientific information, further epidemiologic and experimental studies are needed to assess whether the permitted limit values of exposure to particulate air pollution are sufficient to protect people.

GEL MATERIALS Two types of silicone gel used for breast prostheses have been tested by subcutaneous implantation in male and female Sprague-Dawley rats by Dow-Corning. Tumors, the large majority of which are fibrosarcomas, developed at the site of implantation in 22% to 32% of the animals in the treated groups.⁶⁷ The introduction of silicone gels, used for mammary implants, in the peritoneal cavity of susceptible strains of mice, cause the onset of plasmocytomas of the peritoneum.⁶⁸

The relevance of these findings for the public health could be large, considering that silicone implants were widely used for mammary prostheses. According to the United States Food and Drug Administration (FDA), 130,000 silicone gel breast prostheses were implanted annually until 1995, and there are approximately 2 million implanted women to date. Of the breast prostheses implanted, 85% were for cosmetic augmentation purposes; the remainder were for breast reconstruction following mastectomy. Silicone gel implants were also used for testicular prostheses.

Although the silicone gel is encased in a silicone envelope when used in breast prostheses, there is good evidence that silicone gel sometimes “bleeds” through the envelope and can thus get into surrounding tissues and to other distant places in the body. A carcinogenic risk could therefore be not only local but also at distant anatomic sites. There are no data supporting this possibility, however. The withdrawal of silicone prostheses from the marketplace by the FDA was predicated on uncontrolled and anecdotal reports of lupus-like disease associated with their use. Controlled prospective analyses here failed to substantiate these allegations, and the Institute of Medicine, after systematic inquiry, has declared that there is no relationship to connective tissue disease.⁶⁹ In the course of these studies, no excess sarcomagenesis nor breast carcinogenesis was found.

MECHANISMS OF CARCINOGENESIS

It has been hypothesized that physical carcinogens produce cancer by some physical mechanisms rather than by chemical reaction. Such physical mechanisms have been regarded as a mere nonspecific irritative effect of hypothetical surface factors on cells, which could cause cellular proliferation, selection of spontaneously occurring transformed clones, and, finally, neoplasias. Several observations and considerations favor this view. The ratio between length and diameter of the fibers seems to be crucial in the carcinogenicity of asbestos and synthetic mineral fibers.^{16,49} For example, the incidence of pleural mesothelioma in rats following a single intrapleural implantation ranged from 0 of 28 to 20 of 29, and correlated with fiber size rather than with physicochemical properties: the most carcinogenic fibers were those > 8 µm in length and < 1.5 µm in diameter^{70,71}; the form of implanted hard and soft materials, such as polymers and metallic alloys, also appeared to be crucial in some experiments—the carcinogenic effects of these materials is maximal when they are implanted in the form of intact disks, and

Table 21-8 Comparative Mesotheliomatogenic Effects on Rat Pleura of Erionite and Asbestos (Crocidolite and Chrysotile) Following Injection in the Pleural Cavity

Material	No. of Animals	No. of Animals Bearing Pleural Mesotheliomas
Erionite	40	35
Crocidolite	40	18
Chrysotile (Canada)	40	26
H ₂ O (controls)	150	0

^aA single injection of 25 mg in H₂O was used.
Reproduced with permission from Maltoni C and Minardi F.³⁸

they seem to decrease sometimes when the disks are perforated, or when the material is fragmented. It is hypothesized that the fibrous reaction observed around implanted disks, squares, and films, would “immunologically protect” the transformed clones formed in the core of the capsule, in contact with the implants, therefore favoring the formation of tumors. The physical hypothesis comes from the assumption that solid carcinogens are inert.

There are, however, other facts that oppose the physical hypothesis as the unique carcinogenic mechanism of physical carcinogens, and support a possible contribution of chemical mechanisms. Many plastic polymers (the most specific example of inert material), embedded in tissues undergo progressive deterioration at varying rates, indicating some chemical interaction between the xenobiotic material and biologic substrates. The leaching of microquantities of soluble material out of the physical carcinogens into the body may be sufficient to transform cells that are in intimate contact; the perforation effect has not been confirmed by other investigators nor by us, in the course of vitallium disk carcinogenesis. The discrepancy between these experimental results may be explained by different experimental conditions in various laboratories (eg, the duration of experiments), particu-

Table 21-9 Results of Long-term Carcinogenicity Bioassays and Epidemiologic Investigations on Natural (Other than Asbestos and Erionite) and Synthetic Mineral Fibers

Fibrous Material	Tumors in Experimental Animals	Tumors in Humans
Wollastonite	Pleural “sarcomas”	
Attapulgit	Mesotheliomas	
Talc containing asbestiform fibers	Mesotheliomas ^a	Lung cancer mesotheliomas ^b
Glass wool	Lung tumors	Lung cancer mesotheliomas
Rock wool	Mesotheliomas ^c	
Slag wool	(Equivocal findings)	
Rock wool + slag wool		Lung cancer
Ceramic fibers	Lung tumors ^b Mesotheliomas ^d	

^a Adapted from Minardi F et al.⁵⁰

^b The evidence is still limited.

^c Adapted from Minardi F and Maltoni C.⁵¹

^d Adapted from Minardi F and Maltoni C.⁵²

larly when one is analyzing experiments performed many years ago, when standards of good laboratory procedures may not have been uniform. The fragmentation effect may be explained by the fact that fragments or powders, after insertion, usually tend to form a compact spherical mass in the body tissues, with less surface of interaction with the biologic substrate greater than the surface area of a disk. Therefore the chemical mechanism cannot be discarded; recent data show that asbestos (crocidolite and chrysotile) is mutagenic per se (T Hei, C Waldren, personal communication). Moreover, chrysotile fibers have the ability to introduce plasmid deoxyribonucleic acid (DNA) into cells, and that this DNA is able to function in both replication and gene expression. The introduction of exogenous DNA into eukaryotic cells could cause mutations in several ways and thus contribute to asbestos-induced carcinogenesis.⁷²

The mechanisms of the action of physical carcinogens are not only scientific puzzles; they also have specific practical implications: a chemical mechanism would imply a possible mutagenic effect and therefore a nonthreshold dose. This is a topic that deserves further research.

ELECTROMAGNETIC FIELDS

Extremely low frequency electromagnetic fields (ELFEMF) have been the subject of much controversy. Recent extensive studies of electric utility workers show a minimal increase in relative risk of brain tumors (1.12) and of leukemia (1.09) per 10 μ T years of exposure, although both risk had 95% confidence intervals (CI) that spanned 1.0.⁷³

A meta-analysis of all available studies of childhood leukemia, none of which was individually significant, showed a slight but consistent elevation of OR for association of leukemia with residential magnetic field exposure.⁷⁴ In addition there are two recent pooled analyses. In one, based on nine well-conducted studies, Ahlbom and colleagues⁷⁵ observed a twofold excess risk for exposure above 0.4 μ T. In the other, based on 16 studies, Greenland and colleagues⁷⁶ observed a relative risk of 1.7 for exposure above 0.3 μ T. The two studies are closely consistent.

A study of ELFEMF exposure during pregnancy and postnatally on the incidence of acute lymphoblastic leukemia up to the age of 14 was carried out retrospectively by interview with 640 mothers and 640 mothers of matched control children. The OR for use of an electric blanket or mattress pad during pregnancy was 1.59 and during childhood was 2.75, both with CI above 1.0. Risk rose with increasing hours of television watching, but, paradoxically, there was no relationship to usual distance from the screen. Similar inconsistencies existed in other multiple comparisons. In a companion study, measured 60-Hz magnetic fields and wire category coding showed no effect.

Indeed, those living in the highest wire-code category homes had an OR of 0.88 when compared to the lowest category. The authors from the Division of Cancer Epidemiology and

Genetics of the National Cancer Institute caution that these contrary residential data must be considered before ascribing causality to the observed effects of household exposure to electromagnetic fields.^{77,78}

Using a different approach, childhood cancer patients were compared to controls for measured ELFEMF exposure from ground currents, which are often found in homes with uninterrupted metallic plumbing paths to other houses. The OR for high magnetic exposure was 3.0 (CI 1.3 to 68) in children who had lived in the same houses throughout the study period, suggesting a positive effect.⁷⁹

The most recent and largest study lends no support to the proposition, however. In the United Kingdom, 3,838 cases of childhood cancer of all kinds were compared with 7,629 randomly selected age and sex matched controls. Interviews were conducted in all, and ELFEMF measurements made at home and often at school for 2,226 matched pairs. For lymphoblastic leukemia, all leukemia, central nervous system tumors and all tumors, there was no evidence of greater mean exposure to electromagnetic fields.⁸⁰

Studies conducted in the 1980s and early 1990s among workers exposed to ELFEMF show a possible increased risk of leukemia, brain tumors, and male breast cancer. Interpretation of these studies is difficult, mainly because of methodologic limitations and lack of appropriate measurements.⁸¹

Up to now, the results of the numerous epidemiologic researches carried out on children resident in houses in the vicinity of electricity power lines and occupationally exposed workers have indicated a potential carcinogenic risk from electricity-generated electromagnetic fields. However the epidemiologic evidence is insufficient to provide qualitative and quantitative data for use as guidelines for development and operative intervention to safeguard public health. For this purpose we need suitable experimental data.

Long-term carcinogenicity bioassays on extremely low frequency magnetic fields (ELFMF) have been conducted in Canada,⁸² Japan,⁸³ and the United States.⁸⁴

The studies performed in Canada and Japan cannot be considered adequate to show the carcinogenicity of ELFMF.

The most comprehensive study to date to evaluate the potential carcinogenicity of ELFMF was conducted in the United States by the NTP. The results of the study were reported by Boorman and colleagues.⁸⁴ In this study, conducted following Good Laboratory Practices (GLP), groups of 100 Fischer 344 rats and 100 B6C3F1 mice of each sex were exposed to one of several magnetic field conditions: 2, 200, or 1,000 μ T continuously or 1,000 μ T intermittently (1 h on/1 h off), 60-Hz linearly polarized magnetic fields; one group received sham exposure. Exposure began when the animals were 6 to 7 weeks of age and continued for 18.5 h per day for 2 years. After two years of exposure, the animals still alive were sacrificed. The report concluded that there was

equivocal evidence for the carcinogenic activity of 60 Hz magnetic fields in Fischer 344 rats on the basis of the increased incidence of thyroid gland C-cell neoplasms in males exposed to 2 or 200 μ T. There was no evidence of carcinogenicity in female rats, or in male and female mice.

In a recently published monograph on ELFEMF, the International Agency for Research on Cancer classified ELFEMF as *possibly carcinogenic to humans (Group 2B)*.⁸¹

The avalanche of conflicting data means that this controversial topic will continue to command attention, and clearly the question of causality needs to be solved. For this purpose more adequate experimental studies should be performed, using larger groups of animals exposed for their whole life span from the embryo state on, as are being conducted at the Cancer Research Center laboratory of the European Ramazzini Foundation.

TRAUMA

The literature contains many data on the onset in humans of various kinds of tumor, in various organs and tissues, following trauma or wounding. With rare exceptions, such reports concern few or even isolated cases.

Nowadays the knowledge available on the possible role of trauma in the process of carcinogenesis induces us to think that trauma may affect the onset of tumors in different ways: (1) as the only causal factor—in this case trauma must be persistent and the effect may be evident after a long latency period; and (2) as a contribution to tumor onset, by acting on a tissue/organ already “predisposed” by exposure to carcinogenic agents, or as the site of preneoplastic lesions. In this case, the latency period may be shorter.

As far as the primary action of trauma is concerned, in 1932, Masson⁸⁵ induced tumors in the peripheral nerves of rabbits simply by severing them surgically. Hollander and van Rijssel⁸⁶ were able to induce intramandibular carcinomas in mice by single traumas to the enamel epithelium of incisors.

Concerning the promoting action of trauma, the historical experience of Rous should be mentioned: he and his coworkers^{87,88} demonstrated by a series of experiments that trauma caused the onset of skin carcinoma in rabbits pretreated with known carcinogenic agents (tar, aromatic hydrocarbons), even at doses insufficient per se to produce malignant tumors. Other studies performed by Haran-Ghera and colleagues⁸⁹ demonstrated that surgical incision of the abdominal wall of rats treated by ionizing radiation caused an increase in the incidence of rhabdomyosarcomas and a decrease in their latency time in comparison with rats treated only by surgical incision or ionizing radiation.

Skin cancer may arise in humans as an outcome of burns, scars, sinuses, and fistulas, or at sites of chronic infection and inflammation.⁹⁰ A classic example of relationship between repeated burns and skin cancer is kangri cancer occurring in Kashmir where people use a warmer (kangri)

kept close to the abdominal skin.⁹¹ A similar situation is observed in Japan, where kairo cancer is produced by a light metal warmer (kairo) containing embers and ash, kept close to the abdomen.⁹² Some data from the literature point to an association between rhabdomyosarcoma and trauma in humans.^{93–95} Other data indicate a relationship between esophageal stenosis caused by the ingestion of caustic substances and esophageal cancer.⁹⁶

CONCLUSIONS

Physical carcinogenesis may be considered an important public health, economic, and social problem, because of the wide use of particulate nonfibrous and fibrous industrial materials in the general and domestic environment and in workplaces, and the frequent and increasing use of xenobiotic implants, in plastic, orthopedic, vascular, dental, and other types of surgery.

The dramatic carcinogenic effect of asbestos, the data available on other environmental industrial and mineral fibers, the expected introduction of new types of fibrous and nonfibrous materials in the environment, and the expanding use of alloplastic surgery, all call for more systematic and critical studies of physical carcinogenesis. When such studies prove positive, control measures will mainly aim at prevention.

Similarly, and perhaps more acutely, a critical or definitive study is still awaited to resolve the controversy over electromagnetic fields and oncogenesis.

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