# III. BIOLOGIC EFFECTS OF EXPOSURE

## Extent of Exposure

The manufacture of fibrous glass began in the 1930's and since then has increased to the extent that it is used in over 30,000 individual product applications [1-3]. "Fibrous glass" refers to groups of individual glass fibers combined in any of a variety of forms in the process of manufacture [4]. A glass fiber is defined as a glass particle with a length-to-diameter ratio of at least 3:1.

Fibrous glass operations are usually classified by the industry as textile or wool operations [1]. Textile fibers are generally formed as continuous filaments and are usually greater than 3.0 μm in diameter. In contrast, fibers produced by wool-forming methods may be as small as 0.05 μm in diameter and less than 1 μm in length [5]. Most glass fibers have diameters ranging from 1 to 15 μm. The percentage of fibrous glass with diameters less than 3.5 μm has not been reported. Fibers less than 1 μm in diameter are estimated to comprise less than 1% of the glass fiber market produced. These smaller diameter fibers are manufactured for high performance thermal and acoustical insulation for aircraft and space vehicles and for high efficiency filtration media [2].

Fibrous glass is manufactured by a few basic processes, although there are many subtle variants from operation to operation. The various manufacturing processes utilize different ways of putting large amounts of mechanical energy into the molten raw material stream to cause it to form filaments that are subsequently air-cooled to form fibers [6]. The glass in fibrous glass solidifies from the molten state without crystallization [7].

Most fibrous glass is now produced from borosilicate and low alkali silicate glasses that contain varying amounts of silica, soda, lime, alumina, and titania. Some types of fibers contain as much as 96% silica as silicon dioxide. In fibrous glass, silicon dioxide molecules are arranged in a nonperiodic, random molecular arrangement defined as amorphous [7]. This arrangement is different from the fixed pattern found in crystalline or free silica [8]. The silicon dioxide molecule has a tetrahedral configuration consisting of a central silicon ion surrounded by four oxygen ions. The three-dimensional network of silica terahedra is the basis for the various and unusual properties of glass. By the addition of modifying ingredients such as metallic oxides, which may either become part of the silica network or disrupt it, the properties of the amorphous glass can be varied and adjusted to various levels of performance [7]. Beryllium oxide has been added to glass in some cases to enhance its tensile strength. The compositions of some typical glass fibers are presented in Table XV-1.

Properties of fibrous glass such as chemical resistance, high tensile strength, and its ability to insulate against heat and sound are the bases for its use in thermal, electrical and acoustical insulation, filtration media, weather-proofing, plastic reinforcement, and in structural and textile materials. A few physical properties of some commercial fibrous glasses are presented in Table XV-2.

The majority of fabricated fibrous glass products contain binders, lubricants, and coatings such as those listed in Table XV-3. These surface treatments may present varying degrees of occupational health problems [1]. Surface treating of fibrous glass is performed to bind fibers together, to

protect them, and to increase resistance to impact and friction [2,4,7].

The variety of uses of fibrous glass presents many opportunities for occupational exposure; NIOSH estimates that 200,000 persons in the US may be exposed occupationally to fibrous glass.

In addition to occupational exposure, workers may be further exposed to small amounts of fibrous glass in ambient air and at home. There is a small but measurable amount of fibrous glass in ambient air, presumably contributed by the many fibrous glass products used in our society [9]. Small concentrations, ranging from less than 1,000 to 10,000 fibers/cu m of air, have been found in urban air and concentrations of 30-130 fibers/cu m have been found even in remote rural areas. These concentrations are as much as 10,000 times lower than concentrations of fibrous glass in occupational environments [9]. Fibrous glass used in the lining of ventilating ducts is a potential source of glass fibers in the air in buildings [10], but quantitative studies have shown that concentrations of such fibers in air are extremely low, around 1,000 fibers/cu m of air [11,12].

## Historical Reports

The initial reports of biologic effects of fibrous glass appeared in the early 1940's [13-15]. Siebert [15] reported that between 1939 and 1941 a small but unspecified number of workers in a fibrous glass manufacturing plant experienced transitory mild skin irritation, usually at the beginning of employment or upon returning from vacation. Gardner [14,13] in 1940 and 1941 reported on a study in which rats were exposed by inhalation to glass wool. After 19 months of exposure at "as high a concentration as could be

maintained," no glass fibers were found in the animals' lungs. Slight amounts of chronic inflammation due to glass wool dust accumulation were observed and considered insignificant by the investigator [14]. The rats inhaled glass fibers specified as "short" lengths and under 3 μm in diameter. Gardner [14] suggested that inhalation of fibrous glass was impeded because the fibers tended to form felt-like masses on any surface with which they came in contact.

Effects on Humans

(a) Skin, Eyes, and Mucous Membranes

Extensive data on the effects of occupational exposure to fibrous glass is not available, but an indication of the frequency of reported health effects comes from a study performed in California [16]. Over a 30-month period during 1960-1962, 653 out of 691 cases attributed to fibrous glass involved effects on the skin and eyes. The nature of these effects was not reported. These cases were extracted from summaries of 30,000 cases of occupational disease regularly collected by a state agency.

One of the earliest studies of fibrous glass was performed by Sulzberger et al [17] in 1942. These investigators [17] reported a study of the reactions of 10 human volunteers who were rubbed with glass wool for 10 minutes daily for 7 to 19 days. This produced erythema, localized swelling, and pinhead papules, accompanied by some pain. The effects decreased with rubbing with glass wool on successive days, but there was scaling and thickening of the skin. Repeated rubbing, after a 2-week period without treatment, indicated no definite evidence of sensitization, confirming the findings noted in guinea pigs and rabbits (see Animal

Toxicity) [17]. Microscopic examination of skin sections showed a superficial inflammation.

Other observers have described itching of the skin, dermatitis, and changes in the mucous membranes of the eyes and upper respiratory tract occurring in people working with fibrous glass [18-26]. Although eye irritation has been reported as a result of fibrous glass exposure, such reports are rare [25]. Schwartz and Botvinick [21] noted 25 cases of industrial dermatitis during a 6-month period in a plant that employed 2,000 workers in the manufacture of glass wool for insulation and thread. These investigators [21] found that the binder material used on glass fibers also had effects on the skin. Seven workers with dermatitis were patch tested with binder and three showed positive reactions. The binder was a mixture of starch, polyvinyl alcohol, and a substituted pyrazine. The investigators [21] concluded that the results of the patch tests and the history of onset of dermatitis after several weeks of exposure indicated that the binder was a sensitizing agent rather than a primary irritant.

Erwin [24] stated that at one time practically all 120 workers handling fibrous glass in an aircraft manufacturing plant had mild skin irritations which subsided after better work practices were instituted. Nine employees who developed persistent eczematoid dermatitis while working with fibrous glass were described; they had to be transferred to jobs where there were no fibrous glass or binder exposures. The effects noted could not be reliably attributed by the author [24] to either the binders or the fibrous glass.

One of the earliest reported attempts to define the relationship between fiber dimensions and cutaneous response was that of Heisel and Mitchell in 1957 [27]. They studied skin reactions obtained by patch testing and rubbing fibrous glass on the skin of 92 fibrous glass production workers and of 50 white female volunteers not occupationally exposed to glass fibers. Glass fiber of four different diameters, less than 0.7, 8.8-10.1, 17.7-18.1, and 38.1 μm, was tested. The patch test reactions consisted of small, isolated, erythematous papules, some of which were capped with tiny pustules. Coarse fibers (17.7-18.1 μm and 38.1 μm) produced more skin reactions than did fine ones (0.7 μm and 8.8-10.1 μm), and fibers cut to 3-5 mm lengths were more irritant than fibers 2 cm in length. The coated fibers with starch produced no change in the skin effects. The investigators [27] were unable to develop any evidence of sensitization, but tests carried out 3 weeks apart showed that two individuals with dermographism had urticarial responses to glass irritation.

In 1968 Heisel and Hunt [28], continuing work on fiber dimensions and skin reactions, tested fibers of 2.5-4.5 μm, 3.6-5.8 μm, and 5.3-6.3 μm diameter. The tests included daily skin rubbings with fibrous glass for 45 seconds on 5 consecutive days and patch tests that remained in place for 48, 96, or 168 hours. Their conclusion was that fibers with diameters 5.3 μm or greater would cause transient mechanical irritation, whereas those with diameters less than 4.5 μm would not [27,28].

More serious epidermal responses to glass were reported by McKenna et al [29] in a survey of 126 operators engaged in the manufacture of continuous filament glass fibers in an environment described as hot and

humid. In this operation, the employees' hands were wet a great deal of the time. The authors noted 8 cases of paronychia (inflammation around the fingernails) with abnormal nail formation, 14 cases of folliculitis of the feet, lower legs, forearms, or hands, and 63 instances of maceration of the fourth interdigital space of the foot. No information was provided on the intensity of exposure to fibrous glass, fiber sizes, or the prevalence of similar findings in other populations not exposed to glass but to hot, humid environments. The combination of irritation from glass and favorable opportunities for infection appeared to produce an unusual prevalence of dermal effects in this group.

Possick et al [30] evaluated fibrous glass manufacturing operations and found skin irritation similar to that reported by McKenna et al [29] among the workers although none were found to have disabling dermatitis. In their 1970 review of fibrous glass dermatitis, the investigators [30] stated that skin irritation occurred mainly in new workers who developed burning, itching, or prickling of the skin, associated with papules and papulovesicles. The manifestations were worse in warm and humid weather and usually stopped within a week or so after exposure began, but some workers would quit working with fibrous glass because of the experience. Skin penetration by a fiber was reported to be directly proportional to fiber diameter and inversely proportional to fiber length. The investigators [30] recommended that prospective employees (5% approximately) with dermographism be identified and not allowed to work closely with fibrous glass. They stated that some individuals with atopic dermatitis may not tolerate contact with fibrous glass because of their low itch threshold [30].

The occurrence of itching and dermatitis resulting from the wearing of garments which had been washed at the same time or in the same washing machine as fibrous glass fabrics has been the subject of several reports [31-34]. Such occurrences have led to a rule by the Federal Trade Commission [35], which became effective January 2, 1968, requiring that fibrous glass curtains and draperies and their component fabrics be labeled to advise purchasers that skin irritation may result from either handling such products or from body contact with clothing and other articles which have been washed along with such products.

The potential for eye injury from fibrous glass was illustrated by a case history reported by Longley and Jones [36]. A woman who worked 1 day a week for 8 to 9 months with electrical cables insulated with fibrous glass had recurring itching of the skin, especially of the scalp and eyelids, and then developed acute conjunctivitis and keratitis with a sterile corneal abcess. The absence of ocular effects in other employees doing similar work was attributed to their wearing glasses while the patient did not. This report of Longley and Jones [36] is notable because it is one of the few reports which provide information on airborne dust concentration, reported to be 1.5 mg/cu m. The methods of sampling and analysis were not given. One cannot be certain that glass fibers were not introduced directly into the eye by clothing or hands, or that a clump of airborne fibrous glass was not involved [36].

(b) Respiratory Tract

Isolated case reports appeared between 1944 and 1961 describing severe acute pulmonary reactions associated with fibrous glass inhalation [37-41]. Tara [37] described asthma in a woman who manufactured fire-

resistant clothing. After working with asbestos for 1 year and fibrous glass for 3 years, she developed severe asthmatic attacks, which were diagnosed by physical examination, and eosinophils in the sputum. The asthma disappeared after she stopped working with fibrous glass. Kahlau [38] reported fatal pneumonia in an upholsterer after exposure to dust from a synthetic material containing glass wool. It was interpreted as an acute dust reaction complicated by bacterial infection. Bezjak [39] noted a somewhat similar case in which a man inhaled glass wool (presumably as a plug) during the repair of an incubator, and developed a severe cough followed 3 weeks later by pneumonia in the lower lobe of the right lung. The plug of glass wool was coughed up and there was complete recovery after chemotherapy for the pneumonia. A fourth case was reported in 1961 by Murphy [40] who described pulmonary disease in an electrical worker who had been dismantling fibrous glass-insulated appliances, such as hot water heaters. After several months of repeated exposures, the worker noticed a dry cough, loss of weight, eye smarting, shortness of breath, and hemoptysis. Bronchoscopy led to a tentative diagnosis of bronchiectasis of the right lung. The right lower lobe was removed. Upon examination of the lobe, multiple focal abscesses, involving the terminal bronchioles and the peribronchial parenchyma, were found. The particulate matter found was reported as being identical to that of the insulating material, the glass fibers varying in size from 1 $\mu$m to 14 $\mu$m in diameter and up to 60 $\mu$m in length. Pulmonary fibrosis was reported as slight. The patient recovered and continued to work with fibrous glass employing respiratory protective measures and was considered to be well 3.5 years after the operation.

Trumper and Honigsberg [41] reported acute pharyngeal irritation in a sheet metal worker after he had cut an overhead hatchway through 2 inches of fibrous glass. Glass fibers were found imbedded in the mucosa of his throat, which were located by painting the area with a fluorescent dye. After the fibers were removed, his distress was relieved.

In 1948, Cirla [23] described the findings in 25 workers exposed to fibrous glass in a plant manufacturing electrical conductors. The workers complained of irritation of the upper respiratory tract but no clinical evidence of lung disease was found.

During 30 months in 1960-1962, 691 instances of occupational disease attributed to fibrous glass exposure were reported in California, which annually receives over 30,000 case reports of occupational disease [16]. Of the 691 cases, 38 were primarily respiratory tract irritation. There were 28 additional reports of respiratory tract irritation in a 13-month period in 1967 and 1968 [16]. Occupational designations showed that most complaints were made by individuals who were working directly with fibrous glass or fibrous glass plastics, especially in cutting, sanding, or machining, but some worked only in areas outside the locations where the dust was generated. Roentgenographic evaluations were performed in 13 of the 28 reports, but none showed clear-cut roentgenographic changes attributable to the glass. Three of the more severe cases involved maintenance employees who had removed fibrous glass insulation from steam pipes. The effects were listed as sore throat, nasal congestion, laryngeal pain, and cough as well as itching. Physicians' reports in the 66 cases indicated bronchitis in 66%, pharyngitis in 25%, rhinitis in 20%, asthma in 6%, laryngitis in 4%, sinusitis in 3%, and nosebleed in 1 case. There were

no reports of permanent disability in any individual but the extent of follow-up was not reported [16].

Epidemiologic Studies

Diseases of the respiratory system are the subjects of most epidemiologic studies involving fibrous glass. These studies were usually cross-sectional prevalence studies, many of which were comprised of workers from the same plant. A knowledge of the smoking histories of exposed workers or controls is important in the evaluation of epidemiologic studies. Unless otherwise stated, no information on smoking histories has been provided in the following reports.

In 1960, Mungo [42] studied all 13 workers in a plant manufacturing electrical parts who had handled plastic laminates with fibrous glass reinforcement for 2 to 4 years. All 13 workers were found to have irritation of the skin and of the mucous membranes of the upper respiratory tract. Twelve had normal chest roentgenographs; one (aged 20 years) had accentuation of the bronchovascular markings. One total dust count of 64,000,000 particles/cu m (64 particles/cc) of air as taken with a "midget impinger apparatus" was reported, but the percent of particles that were fibers and the size of the fibers were not mentioned.

Bjure et al [43] in 1964 performed cardiopulmonary evaluations of six insulators who had worked for 8 to 29 years with glass wool and rock wool and compared the results with those of eight men who had worked from 7 to 30 years largely with asbestos-insulating materials. The average length of exposure was 14 years for the group exposed to glass wool and 18 years for the group exposed to asbestos; average ages were 39 and 44.5 years,

respectively. There was no quantification of exposure data. The asbestos-exposed group showed significant ($P < 0.01$) reductions in vital capacity, forced expiratory volume, and diffusion capacity as compared with the fibrous glass-exposed group. Pleural thickening was found in all eight of the group exposed to asbestos and in none of those exposed to fibrous glass. In spite of prolonged exposure to glass wool and rock wool, no impairment was found in the cardiopulmonary functions studied. However, neither group was compared with unexposed controls.

Wright [44] in 1968 reported a roentgenographic survey conducted in 1963 of employees in the plant that had been studied by Siebert [15] in 1939-1941 and which, by 1968, had been engaged in the manufacture of glass wool for approximately 30 years. He studied employees who had worked for 10 years or more in the plant. The distribution of length of service was not given, but it was stated that some had been employed for as many as 25 years. Wright [44] stated that all workers in the factory area currently on the payroll, except those who had spent more than a year in sections where free crystalline silica was present, were included. Male clerical and management staff were also studied. In all, Wright [44] reviewed roentgenographs of 1,389 employees, classified as clerical workers, factory workers, or unclassified, and divided into four exposure catagories, from light to heavy. Concentrations of airborne dust and glass were determined in samples collected by electrostatic precipitators, membrane filters, and midget impingers [44,45]. Total dust concentrations varied from 0.93 mg/cu m to 13.3 mg/cu m throughout the plant, with an average of 2.24 mg/cu m. Complete chemical analysis of the dust was not made. Particle concentrations, based on area averages, ranged from 3.2 to 11.3 million

particles/cu m [0.09 to 0.32 million particles/cubic foot of air (mppcf)], with an average of 0.22 mppcf. It was reported that fibers made up less than 1% of the total particles counted [44,45]. The median diameter of the fibers was 6 μm, with 85% ranging from 2 to 10 μm and 9% less than 3 μm in diameter. The averaged data from samples throughout the plant indicated that 16% of the fibers were less than 40 μm in length and 6% were less than 20 μm.

Wright [44] stated that there had been extensive installation of exhaust and ventilation equipment and that the population described had been exposed to higher concentrations in the past than at the time of the study. No distinctive roentgenographic patterns were observed nor were there increased bronchovascular markings or nodulations occurring in unusual numbers or primarily in the heavily exposed groups. No pleural calcifications were found, but six instances of pleural thickening were seen in lightly exposed individuals. Intrapulmonary and hilum calcifications were observed in about 50% of each group studied. The investigator [44] assumed that such a high percentage of calcifications represented the healed phase of primary tuberculosis or endemic histoplasmosis. Small calcified nodules in the lungs are not an unusual finding for either of these diseases. Wright [44] reported that the design of the experiment and the duration of exposure did not permit any conclusions regarding neoplastic potential.

Pulmonary function studies in a group of workers were reported in 1968 by Utidjian [46] and in 1970 by Utidjian and deTreville [47]. The studies were conducted in the same plant that Wright [44] had studied. Forced expiratory volume in 1 second (FEV 1) and in 3 seconds (FEV 3) and

maximum mid-expiratory flow (MMF) determinations were made on 232 men and categorized into age groups, ie, under 30 years, 30-49 years, and 50 years or over. Each age group was further subdivided into categories (I-III) based on jobs and estimated dust concentrations. Category I represented the least exposure, II represented medium exposure and III represented the highest exposure. No environmental concentrations of fibrous glass were reported. Symptoms of cough, bronchitis, dyspnea, wheezing, and chest illnesses were not more frequent in those with higher exposures, but prevalence of most symptoms did increase with age. Deviations from predicted vital capacity values also did not correlate with exposures. In the report by Utidjian and deTreville [47], the authors noted no apparent effect from fibrous glass dust when they compared employees with the greatest and the least exposure.

A more detailed evaluation of 30 individuals in the highest exposure group who were over 50 years of age, 15 from the least exposure group, and 15 from the highest exposure group was reported by deTreville and coworkers [48]. The study included general histories, respiratory disease questionnaires, physical examinations, fluoroscopy of the chest, electrocardiograms, hematologic tests, pulmonary ventilatory tests, and tests for diffusing capacity (CO steady state method). There were no more ventilation or diffusion abnormalities found in the heavily exposed group than in the lightly exposed one. The results from both groups were compared with predicted values derived from the Veterans Administration Army Cooperative Study of Pulmonary Function [49] and no difference was found. The study of pulmonary function [49] involved healthy people selected from hospital personnel and patients.

In another study related to the work force of the previously described fibrous glass production plant [44-48], Gross et al [50] in 1971 described post-mortem findings in 20 fibrous glass workers who had been exposed for 16 to 32 years and compared the findings with those from 26 urban (Pittsburgh) dwellers with no known occupational exposures to fibrous glass. The inclusion of exposed or unexposed individuals in the study was the choice of the investigators and not the result of random sampling. Both groups studied were generally the same with regard to histopathologic findings. Enlargement of air space within the lungs by alveolar destruction was found in 13 of 20 fibrous glass workers and in 19 of the 26 comparison group. Significant thickening of the walls of small and medium size vessels with luminal narrowing was found in 5 fibrous glass workers and 10 comparisons. Fibers of similar size and number were found in the lungs of fibrous glass workers and in the comparison group but the identity of these fibers was not known. Cholak et al [45] had previously reported that 9% of the airborne fibers in the factory where the workers were employed had been less than 3 $\mu$m in diameter (weighted average). A comparison of the dimensions and amount of the dust in the lungs in the two groups showed no significant differences [50]. Average fiber diameter in glass workers was 2.3 $\mu$m and the average length was 27 $\pm$ 6 $\mu$m. There was an average of 96,000 fibers/g of dry lung in the exposed workers.

Nasr et al [51] in 1971 reviewed roentgenographs of workers in the same plant previously discussed [45-47]. Nasr's analysis was based on 2,028 male fiber glass production workers. Of these, 1,832 were production workers and 196 were office workers; 1,571 (62.67%) had been employed 10 or more years, 1,022 (50%) 15 or more years, 665 (33%) 20 or more years, and

391 (12%) for 25 or more years. Roentgenographic abnormalities of the chest were found in 329 workers (16.22% of the total), the most prevalent changes being increased lung markings, abnormal aorta, abnormal heart configuration, and emphysema. No difference in prevalence of all these chest abnormalities was detected between production and office workers. Nodular opacities were found in 9 of the 2,028 workers, and questionable nodularity was suspected in 17 others. Whether these abnormalities were in the office workers or production workers was not stated. While the data enable a comparison of the prevalence of total abnormalities in production workers with that in office workers, sufficiently detailed information is not provided on specific abnormalities, such as pleural thickening, increased lung markings, fibrosis, or suspected pneumoconiosis, as related to type or duration of exposure [51].

In 1973 Hill et al [52] reported on the comparison of pulmonary function in 70 fibrous glass production workers in England employed for an average of 19.85 years with that of an unexposed, matched control group. Study of roentgenographs, pulmonary function tests, and physical examinations revealed no differences between the two groups. In a follow-up examination 5 years later [53], Hill re-examined 53 of the original study members. The health status of the other 17 workers was not investigated. Roentgenograms revealing pleural thickening in some of the 53 cases led to a review of the original control group. Pleural thickening was equivalent in both groups. Environmental investigations involving sampling with membrane filters and microscopic examination indicated that total dust in the operators' breathing zones ranged from 0.4 to 12.7 mg/cu m. Of this, counts of respirable size dust (less than 5.5$\mu$m in diameter)

ranged from 1,000,000 to 4,800,000 fibers/cu m (1.0 to 4.8 fibers/cc). The "general atmosphere" at the time of the investigation contained an average number of 900,000 fibers/cu m (0.9 fibers/cc). Respirable size dust counts at the dust source 2 feet from an operator's breathing zone ranged from 3,400,000 to 10,700,000 fibers/cu m (3.4 to 10.7 fibers/cc). The high proportion of heavier fibers accounts for the rapid fall-off in fiber count between the dust source and the operator's breathing zone, approximately 2 feet above the source. Fibers collected at the site of emission for sizing purposes indicated that approximately 75% were less than 4 μm and 35% were less than 2 μm in diameter. Fifty percent of the fibers were longer than 50 μm.

In 1975, Enterline and Henderson [54] reported a study of retired workers from six plants engaged in the manufacture of fibrous glass insulation. A total of 617 workers retired between 1945 and 1972; of this group only 416 males who had reached age 65 were studied. The health status of the 201 workers excluded from the study was not known and could have been significant in the data analysis. These included 144 workers who had not attained age 65 (41 who died before age 65 and 103 who had not attained age 65 by December 31, 1972). The remaining 57 workers were women and were not included due to what was considered to be the small number involved and because the authors believed the women would have to be studied separately, since their expected mortality differs from that of men [54].

The mortality experience of the 416 men was compared with the expected mortality based on the cause, age, and time-specific mortality rates of the population of all white men living in the US. A modified life

table method of analysis was used, involving computation of years of life lived by the cohort in five age groups: 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years, and 85 years and over during 5 time periods: 1945 to 1952, 1953 to 1957, 1958 to 1962, 1963 to 1967, and 1968 to 1972. Expected deaths were calculated by applying the age-cause-specific white male death rates for the entire US from every fifth year from 1950 to 1970. The standard mortality ratios (SMR's) were computed by calculating the ratios of observed to expected for selected causes of death including cancers, heart, and respiratory diseases [54].

SMR's were reported for all 416 retirees and for 276 of that group who had normal retirements. The SMR's for all retirees generally showed no excess of observed deaths by any disease cause. The SMR's for the 276 normal retirees showed a slight excess of observed deaths for the categories "all other heart disease" and "nonmalignant diseases of the respiratory system." When 35 workers who had reached age 65 but had retired earlier due to disability were studied, the SMR for all causes of death was 118.6. This represents 18.6% more deaths in the study group than in the general population. In these workers retiring from disability, chronic bronchitis was observed in 3 workers and expected in 0.5 workers. This difference may be important but the small numbers do not allow substantial conclusions to be made. None of the excesses of death were statistically significant [54].

Bayliss et al [55] in 1976 reported a retrospective cohort analysis of mortality patterns among a cohort of fibrous glass production workers in the oldest facility in the US. The study cohort consisted of 1,448 white males with 5 or more years of employment. All members of the cohort were

initially employed between 1940 and 1949. Follow up of all members of the study cohort was accomplished from the time of termination of employment to June 1, 1972, with all persons accounted for. Comparison was made between the observed number of deaths in the study cohort and the number expected on the basis of age, calendar time, and cause-specific mortality rates for the white male population of the United States.

The analysis indicated an excessive risk for one cause-of-death category, that of "nonmalignant respiratory diseases," where 19 deaths were observed and only 10.04 were expected. This category excluded influenza and pneumonia. Bronchiectasis was observed at autopsy in 6 of the 19 cases. (D Bayliss, written report, 1977). The excess of observed nonmalignant respiratory disease deaths was statistically significant ($P<0.05$). Although the role of prior employment in industries other than fibrous glass production cannot be totally evaluated in the etiology of this excessive nonmalignant respiratory disease risk, note should be made that the authors [55] stated "several employees had incidental periods of employment in dusty trades." When the mortality comparisons were made on the basis of interval.since the start of employment, the ratio of observed to expected deaths was significantly greater ($P<0.05$) for those who died after 5 or more years the since start of employment and highly significant ($P<0.01$) for those who died after 10 or more years. The results of this study are presented in Tables XV-4 and XV-5. The exposures in the plant were estimated from an industrial hygiene survey conducted by the same investigators in 1975 [5,55]. An average fiber count of 80,000 fibers/cu m of air (0.08 fibers/cc) was observed, and the average total dust concentration was 0.3 mg/cu m. The collected glass fibers had a median

diameter of 1.8 μm and a length of 28 μm. A more detailed discussion of the environmental data is presented in Chapter IV. Due to limited dust measurements, the lifetime exposure for persons in the cohort study was not determined; however, the investigators [55] stated that historic low exposure levels in the plant had not changed significantly. The length and diameter of airborne glass fibers may have been larger in the past, as indicated by the previous industrial hygiene survey of the same plant by Cholak et al [45] in 1963.

Bayliss et al [55] performed a second study when it was learned that some members of the original cohort might have been exposed to smaller diameter glass fibers than those being produced in the 1970's at the facility under study. During 1941 to 1949 a pilot operation in the facility used a flame attenuation process that produced bulk fibers ranging from 1 μm to 3 μm in diameter. The pilot operation was conducted concurrently with the regular production of fibrous glass insulation.

A case-control study was performed to evaluate the potential health hazard of the smaller glass fibers to the exposed workers [55]. Each death due to malignant or nonmalignant respiratory disease among workers at the plant, or in which respiratory disease was mentioned as a contributory cause, was matched with that of a control selected sequentially from an alphabetized list of the remaining study group members. The 49 cases and 49 controls were matched according to birth date, race, and sex. All subjects had been initially employed in fibrous glass production between 1940 and 1949. Of the 49 cases with respiratory disease, 9 were presumed to have worked with and had been potentially exposed to the smaller diameter fibrous glass on the basis of their work with the flame

exposed to the smaller diameter fibrous glass on the basis of their work with the flame attenuation process. However, not all nine could be paired with controls who had similar exposure. In contrast, of the 40 respiratory disease cases without potential exposure to small-diameter fibrous glass, only 2 matched controls had potential exposures to small-diameter fibrous glass. The results of the study are shown in Table XV-6.

Analysis of the differences between cases and controls by the McNemar Chi-square method for matched pairs showed that exposure to small-diameter fibrous glass was associated with malignant respiratory disease ($0.05 < P < 0.10$) at a level which was stated by the authors [55] to be of borderline significance.

Animal Toxicity

(a) Dermal Effects

In 1942, Sulzberger et al [17] studied the effect of fibrous glass on the skin of animals. In one study, 16 rabbits were rubbed with fibrous glass or other material, for 2 minutes each, on 6 depilated areas 4.5 cm in diameter. Rubbings occurred 5 days a week for 1 month. Two types of fibrous glass, two types of unspecified competing material and two cotton controls were applied to the depilated skin of each rabbit. Twenty-six guinea pigs were rubbed at 8 similiar sites with two fibrous glass textile materials. Skin reactions in both species resulted from the mechanical action of the fibers on the skin. The rabbits' skin had a faint redness, scaling, and superficial yellow crusting. Reactions in guinea pigs were similar but more intense than those of the rabbits with more erythema and crusting.

Similar results in guinea pigs have been reported by Pellerat and Coudert [22]. These investigators also measured the amount of histamine in the blood of guinea pigs and found that it was increased as a result of rubbing the skin with fibrous glass.

(b) Inhalation

In 1955 Schepers and Delahant [56] conducted a study of 100 guinea pigs continuously exposed to glass wool for 20 months and to what was called glass cotton for 20 subsequent months. The glass wool had a nominal diameter of 6 μm. Exposures occurred in a dust chamber measuring 8 x 8 x 8 feet. The dust concentrations of glass wool as determined by electrostatic precipitator measurements ranged from 5.0 to 5.2 mg/cu m (0.143 to 0.146 mg/cu ft). Impinger readings ranged from 49.4 to 77.7 million particles/cu m (1.4 to 2.2 mppcf) as measured by light field count. After 20 months of exposure to these conditions, the glass wool was replaced by glass cotton with a maximum diameter of 3 μm and at a concentration of 0.03 to 0.07 mg/cu ft (1.1 to 2.5 mg/cu m). A series of 50 white rats were likewise exposed to the glass wool in the same chamber for 20 months and subsequently to glass cotton until the end of the 24th month. No controls were provided. Seventeen of 100 guinea pigs and 20 of 50 rats died during the experiments. Deaths were attributed to pneumonia. Microscopic examination of guinea pigs killed during the 18th day of exposure revealed glass wool dust in their bronchi. After 4 months of exposure, there was considerable epithelial hyperplasia and cellular desquamation in the smaller bronchioles and cellular infiltration of alveolar walls, with hyperplasia of parenchymal pulmonary lymph nodes. Atelectatic areas were visible. Dust reaction foci were detectable by macroscopic examination at

the 40th week of exposure and the investigators related these to the atelectatic areas seen at 4 months. Lung abscesses were found in 10% of the rats but there was little evidence for dust pigmentation or tissue reaction. Fibrosis was not evident in either rats or guinea pigs.

In 1960 Gross et al [57] reported a number of experiments with nonfibrous glass dust that was ball-milled from glass flakes. Ninty-five percent of the dust particles were less than 1 μm in diameter. Three groups of 40 rats each and 3 groups of 15 guinea pigs each were exposed either to glass dust (18 mg/cu m), quartz dust (24 mg/cu m), or Kaolin dust (27 mg/cu m) dust for 6 hours/day, 5 days/week for 1 year. The animals were allowed to live for 1 year following the 12-month exposure. Macroscopic examination at autopsy revealed no significant changes from controls in either species. Microscopic examination of guinea pig tissues revealed widely scattered and relatively small foci of clustered alveoli which contained massed dust cells. The lymph nodes also contained dust cells in the form of small, loosely scattered foci. Interstitial pulmonary fibrosis, associated with prominent basophilia of elastic tissue, and calcifications were found in four guinea pigs. In the rats the indication of dust exposure consisted of widely scattered small foci of clustered alveolar macrophages.

The most significant study of the effects of fibrous glass by inhalation was performed by Gross et al [58] who exposed rats and hamsters to fibrous glass at 100 mg/cu m, for 6 hours/day, 5 days/week for 24 months and reported the results in 1970. The average glass fiber diameter was 0.5 μm and the average length was 10 μm. Of the airborne dust, 70-76% was found to be fibrous by means of collection on a membrane filter and

evaluation with phase contrast microscopy. The rats and hamsters were divided into 3 groups of 30 animals of each species. Another group of 20 animals of each species served as controls. One group of animals was exposed to fibrous glass coated with phenol-formaldehyde resin, a second group was exposed to fibrous glass coated with a starch binder, and the third group was exposed to uncoated fibrous glass. Five rats and five hamsters from each group were killed after 6 months and a similar number were killed after 12 months of exposure. The exact number of animals that were killed at 24 months after exposure was not specified [58].

No differences in tissue reactions between the three groups were detected; however, there were differences between the exposed anz the control animals. In the exposed rats, pneumonia and endemic chronic bronchitis and its sequelae were found at a higher, but unspecified, rate than in unexposed rats. Pneumonia, however, is a normal finding in aged laboratory rats. Exposed rats showed an accumulation of dust-filled macrophages within alveoli. A few foci of septal collagenous fibrosis were seen in some rats, but there was no other evidence of fibrosis. A large amount of dust in some of the satellite lymph nodes was found in rats after 2 years of exposure. In the hamsters, macrophage-containing alveoli clustered around respiratory bronchioles. Alveolar ducts contained dust-filled macrophages. Ferruginous bodies were observed. In contrast to the satellite lymph nodes of rats, those of hamsters were not enlarged even at 24 months [58].

Botham and Holt [59], in 1971, investigated the production of ferruginous bodies after inhalation of glass fibers and described their evolution in some detail. Eighteen male guinea pigs were exposed once for

24 hours to glass fibers that were mostly 20 μm in length or shorter and less than 3 μm diameter, mostly less than 1 μm. Fibers measuring 40 μm in length were noted rarely. The exposure concentration was described only as "high." The animals were killed and examined at various intervals after exposure. In the lungs most of the fibers that were visible with the light microscope were less than 20 μm in length; fibers longer than 40 μm were rarely observed. Fibers retained in the lungs deposited initially in the bronchioles. Some fibers moved inward to the alveoli, where they were taken up by macrophages, some of which then combined to form giant cells. The presence of fibers was associated with the escape of erythrocytes from alveolar capillaries. Erythrocytes had been cleared from the respiratory regions and some were seen in bronchiolar debris and others apparently had been ingested by macrophages. Ferroproteins were produced in the cytoplasm of these macrophages. Where glass fibers and ferroproteins occurred in the same cell, the ferroproteins deposited on the longest fiber while other fibers in the cell invariably remained uncoated. The coating then underwent a change until it attained a beaded form. Eventually these structures broke between the beads allowing for clearance by the macrophages.

In the same study, Botham and Holt [59] compared the fate of glass fibers inhaled by guinea pigs with that of inhaled anthophyllite absestos fibers. They found that the sequences of fiber coating and fragmentation were similar but occurred in a shorter time with tne glass fiber. Ferruginous bodies developed as early as 2 to 5 days after exposure to fibrous glass and to asbestos and some could still be found even at 18 months after exposure.

Botham and Holt [60] repeated the experiment using nonfibrous glass dust that was chemically similar to the glass fibers of their earlier experiments. The dust particles were irregular in shape, most having maximum dimensions less than 10 μm, but longer particles (up to 100 μm in length) were found occasionally. Ten guinea pigs were exposed at "high" but unspecified concentrations, killed at various intervals up to 28 days, and examined. The effects of the inhalation of glass dust differed from those observed after inhalation of glass fibers in that fewer erythrocytes escaped from capillaries, very few giant cells were produced, and erythrocytes and intercellular glass particles were cleared more readily because junctions between respiratory and terminal bronchioles were not blocked by giant cells. Intracellular granules containing positive iron staining (Perls-positive) material did not appreciably increase in number or intensity of staining during the month, and particles were not coated with Perls-positive material during the time required to form pseudo-asbestos bodies from glass fibers.

(c) Intratracheal

In 1955, Schepers and Delahant [56] described the results of three intratracheal experiments with glass wool in guinea pigs. In these experiments, fibers of three different dimensional batches were used. Batch A had average diameters of 6 μm, with a range from 3 μm to 8 μm. Batch B was approximately 3 μm in diameter and batch C measured 3 μm or less in diameter with a large proportion around 1 μm. All fibers were 20 to 50 μm in length. The glass fibers in suspensions in saline were introduced intratracheally in three doses of 0.5 ml each with 1-week intervals between doses. Batches A and B were 5% suspensions and batch C

3 μm to 8 μm. Batch B was approximately 3 μm in diameter and batch C measured 3 μm or less in diameter with a large proportion around 1 μm. All fibers were 20 to 50 μm in length. The glass fibers in suspensions in saline were introduced intratracheally in three doses of 0.5 ml each with 1-week intervals between doses. Batches A and B were 5% suspensions and batch C was a 0.5% suspension by weight in isotonic saline. The investigators found that atelectasis was more prevalent in the animals that received the fibrous glass with the smaller diameters than in those that received the largest diameter material. No fibrosis was observed.

Wenzel et al [61] studied the effects of two different sizes of glass fibers administered intratracheally to rats. The finer fibers, 3 μm in diameter and 5-15 μm in length, were administered to 25 female rats and the coarser fibers, 30 μm in diameter and 30-100 μm in length, were administered to 24 female rats. Each group of rats was given one administration of 50 mg, the animals being killed and examined 90, 180, 270, or 360 days later. No control animals were reported. Examination of animals from both groups, killed 3 months after administration, showed widespread uniform distribution of fibers in all lung sections. Intratracheal administration of the finer glass fibers produced desquamation of alveolar epithelium after 3 months and hyperplasia of the mucous membrane. Glass fibers were imbedded in the interstitium (interlobar, interlobular, intracinar, intraductular, and intraalveolar septal connective tissue). Six months after exposure, extensive formation of fibroblasts, fibrocytes, and "glass fiber nodules" were seen. Extensive emphysema and chronic bronchitis were seen at 6 months and were increasingly prevalent at 9 and 12 months after administration. At 12

months atelectases were evident and the bronchioles were hyperplastic [61].

The administration of the coarse fibers resulted in different and less severe tissue reactions than that of fine fibers in the first 9 months. During this time fibers were imbedded in the interstitium and surrounded by connective tissue. At 6 months, the number of fibers present in lung sections was reduced when compared with that in sections at 3 months. The lesions present after 9 months included chronic bronchitis, stenoses of the bronchial lumen with hyperplasia of the peribronchial lymphatic tissue, and atrophic emphysema and atelectasis in the adjacent lung tissue [61].

Gross et al [62] studied a variety of fibrous materials including uncoated glass fibers, ceramic aluminum silicate, silicon carbide whiskers, cosmetic talc, attapulgite, and chrysotile. When the fibers were introduced intratracheally, ferruginous bodies were produced in hamsters in response to all the fibers except attapulgite. Though not indicative of pathogenic potential, the finding is of interest in interpreting epidemiologic studies on ferruginous body content of human lungs. Gross et al [62] observed that while ferruginous bodies have been determined experimentally in animals, there do not seem to be any reported findings of ferruginous bodies in the sputa of workers who inhaled fibrous glass, as so commonly occurs with asbestos exposures [62].

In another report Gross et al [63] compared the lesions in rats produced by intratracheal injections of fibrous quartz, asbestos, talc, and synthetic chrysotile, silicon carbide whiskers, fibrous ceramic aluminum silicate, five varieties of fibrous glass, and brucite. The fibrous glass averaged about 1 $\mu$m in diameter and either had various coatings, no

coatings, or was etched. A dose of 10.5 mg was given. All types of fibers produced proliferative inflammations in the smaller bronchi and bronchioles that were attributed to mechanical trauma from the method of introduction.

The main pulmonary response produced by fibrous glass, brucite, silicon carbide whiskers, and aluminum silicate was the mobilization of dust-filled macrophages which occupied the alveoli evaginating from respiratory bronchioles. The walls of these alveoli were thickened by a combination of surface cell enlargement and proliferation of the septal argyrophilic stroma. The investigators [63] stated that these lesions were reversible and did not affect the anatomic integrity of air spaces or produce proliferation of collagen [63].

In 1974, Kuschner and Wright [64] studied the effects of intratracheal instillation of glass fibers of different dimensions in guinea pigs. Groups of 30 guinea pigs were given intratracheal administrations of one of six possible categories of glass fibers that were differentiated according to dimension. The dimensions of the fibers are shown in Table III-1.

TABLE III-1

TYPES OF GLASS FIBERS USED IN INTRATRACHEAL ADMINISTRATION TO GUINEA PIGS

| Fiber Description | Fiber Dimensions | |
|---|---|---|
| | Diameter, μm | Length, μm |
| Very thin and short | <0.3 | <5 |
| Very thin and long | <0.3 | >10 |
| Thin and short | <1 | 7%>10 |
| Thin and long | <1 | 7%<10 |
| Thick and short | 2 | 88%<10 |
| Thick and long | 2 | 75%>10 |

Adapted from Kuschner and Wright [64]

The fibers were administered in a series of two to six injections [64]. The total amounts injected into each animal ranged from 3 to 25 mg. The animals were killed at 6 months, 1 year, and 2 years after the last administration.

The first two categories studied consisted of thin fibers, most with diameters less than 1 μm. Short thin fibers, of which only 7% were longer than 10 μm, and long thin fibers, of which only 7% were shorter than 10 μm, caused different tissue reactions. No fibrosis was found after exposure to

short fibers but alveoli filled with macrophages and fibers within macrophages in the lymph nodes were observed. Exposure to long fibers resulted in interstitial reaction at areas around respiratory bronchi and proximal alveoli 6 months after exposure. At 1 year after exposure, peribronchiolar interstitial fibrosis was observed [64].

Thinner fibers, most with diameters less than 0.3 μm and lengths less than 5 μm or greater than 10 μm, produced reactions similar to those induced by the previous set of long and short thin fibers. The very thin, long fibers caused a fibrotic reaction whereas the very thin, short fibers did not [64].

Thick fibers, with diameters averaging 2 μm, with 88% shorter than 10 μm or 75% longer than 10 μm, were compared. The short, thick fibers resulted in some interstitial fibrosis after 2 years. This may have been due to the presence of the 12% of fibers in that group longer than 10 μm. The long, thick fibers caused focal areas of interstitial fibrosis at 6 months after exposure [64].

The investigators [64] also studied various sizes of asbestos fibers by the method described and found a markedly greater degree of fibrosis with the longer fibers. They theorized that the marked quantitative difference between fibrous glass and asbestos was a consequence of the lesser durability of a long glass fiber as compared with the durability of asbestos. In the experiments in which long glass fibers were introduced, a "surprisingly" large number of short fibers appeared in the lymph nodes.

The mechanism which Kuschner and Wright [64] believed best explains the commonality of response to a variety of asbestos fibers and to glass is one that has been determined for granulocytes [65] and has been extended to

macrophages [66,67]. Cells attempting to engulf long fibers are involved in incomplete or "frustrated" phagocytosis. The process, known as exocytosis, results in leakage of tissue-damaging enzymes from the cell without being specifically toxic to the phagocyte. The resultant tissue damage is presumed to be the ultimate inciter of fibrosis.

(d) Intraperitoneal

A study of the effects of two sizes of fibrous glass, injected intraperitoneally, was performed by Pott et al [68]. In one type of fibrous glass, identified as MN104, 50% of the fibers measured less than 0.2 μm in diameter and had lengths less than 11 μm. In the other type of fiber, identified as MN112, 50% of the fibers were less than 1 μm in diameter and shorter than 28 μm. Wistar rats received various injected doses up to 25 mg of the fibrous glass. Also, some animals received Union Internationale Contra Cancer (UICC) crocidolite or granular corundum for comparison. The MN104 glass was administered to three different groups of 80 rats each in doses of 2, 10, and 25 mg given twice. Tumor rates of 27.4, 53.2, and 71.4%, respectively, corresponded to the three dose levels. Animals that received 20 mg of MN112 glass had a tumor incidence of 37.8%. This was comparable to the 38.5% occurrence found in the group of rats that received 2 mg of crocidolite. The other comparison group received two 25-mg doses of granular corundum and had a tumor rate of 8.0% Mesotheliomas in the abdomen or thorax were the most frequently encountered tumors, followed by spindle cell sarcomas. More than 70% of all tumors were classified as mesotheliomas (F Pott, written report, February 1976).

In an earlier phase of the study, Pott and Friedrichs [69] compared intraperitoneally administered doses of chrysotile, fibrous glass,

hematite, and nemalite as well as relatively nonfibrous materials such as actinolite and talc. At the end of 530 days, 16 to 25 tumors were found in groups of 40 rats injected with 25 mg of the materials on a weekly basis for 4 weeks. Only five tumors were found in rats given milled chrysotile and no tumors occurred in any group of the rats receiving any of the nonfibrous materials. Abdominal tumors were mainly found in animals with a considerable amount of abdominal fibrosis. The investigators [69] concluded that fiber dimension rather than chemical action was responsible for the tumors. These reports [68,69] support the contention that the dimensions of fibrous materials rather than their chemical composition may be more important in dust pathogenicity.

Davis [70] injected a dose of 10 mg of glass fibers, 0.05 $\mu$m in diameter and as long as 100 $\mu$m, into the peritoneal cavity of 25 Balb/C mice. An unspecified strain of rats also received the same size glass fibers but at a dose level of 25 mg. All animals were left for their full life span or until there were signs of tumor development. Davis found 3 tumors (12%) in mice and 3 tumors (16%) in rats. In some of the advanced tumors, the cells adopted a spindle cell pattern very similar to a fibrosarcoma. Electron microscope studies suggested that most tumors arose from undifferentiated mesenchymal cells in the submesothelial tissues. Davis [70] concluded that the tumors produced by glass fibers appeared to be structurally identical to those produced in the peritoneal cavities of rats and mice by injection of crocidolite asbestos.

(e) Intrapleural

Wagner et al [71] studied the effects in Wistar rats of intrapleural innoculations of glass fibers having different diameters. The fibers used

were of two sizes designated as fine and coarse. In the fine sample, 99% of the fibers had diameters less than 0.5 μm. The median length was 1.7 μm, and only 2% of the fibers were more than 20 μm in length. In the coarse sample, only 17% had diameters less than 1 μm, and the median fiber diameter was 1.8 μm, median length was 22 μm, and 10% of the fibers were longer than 50 μm. Ninety-six rats, 48 of each sex, were randomly allocated to one of three treatment groups consisting of coarse or fine fibrous glass or saline given as the control. The dose/rat of 20 mg in 0.4 ml of normal saline was given once to each animal. Mesotheliomas were diagnosed in 4 of 32 animals ($P<0.01$) that received the fine diameter fibrous glass, whereas none occurred in the group receiving either the coarse fibers or the controls. The altered morphology in the mesothelial cells of the rats that were exposed to fibrous glass was assessed on a 7-point scale ranging from no change to mesothelioma. In addition to the four identified mesotheliomas, there were seven rats with "marked" cellular hyperplasia. Only one rat injected with fine fibrous glass showed no signs of hyperplasia compared with 12 of those injected with coarse glass fibers. These data are summarized in Table XV-7. Table XV-8 is a list of the percentage of rats that developed mesotheliomas after exposure to various fibrous materials in earlier experiments.

Davis [69] studied the effects of injecting various fibrous materials, including fibrous glass, into the pleural and peritoneal cavities of Balb/C mice. Two different diameters, 0.05 μm and 3.5 μm, and two different lengths, mostly "several hundred" μm and less than 20 μm, of borosilicate glass were studied. Samples of fibrous glass belonging to these four dimensional categories were administered to groups of 25 mice in

single doses of 10 mg/mouse. Animals were killed between 2 and 18 months after injection. All the glass samples produced granulomas within the pleural cavity but these differed markedly in their sizes and structures. Short fiber samples of both large (3.5 $\mu$m) and small (0.05 $\mu$m) diameter glass produced very small, compact granulomas which never formed adhesions between the lungs, heart, and chest wall. The longer fibers produced many large granulomas, which often filled a greater part of the pleural cavity and formed firm adhesions between the lungs, diaphragm, heart, and chest wall. Small amounts of collagen were present within the granular tissue 2 weeks after injection and continued to increase, developing a level of fibrosis as severe as that produced by similar doses of chrysotile or crocidolite asbestos [69].

Stanton et al [72] described a technique in which a thin pledget of fibrous glass, coated with heat cured phenol-formaldehyde resin, was used to hold asbestos fibers suspended in gelatin against the pleural and pericardial surfaces of rats. The fibrous glass pledgets themselves produced no neoplasms. The pledgets impregnated with the asbestos mineral crocidolite, however, produced what were described as "mesothelial sarcomas" in 22 of 30 rats (74%).

Stanton and Wrench [73] reported an extension of their earlier work in which they included several experiments with fibrous glass. Specific pathogen free (SPF) female Osborne-Mendel rats, 30 in each exposure group, were used. The asbestos minerals (amosite, chrysotile, and crocidolite) in 40-mg doses led to mesothelial tumors in 58% to 75% of rats surviving the operation for at least 1 year. Reduced doses of crocidolite were associated with correlative reductions of tumor incidence. Intact fibrous

glass pledgets resulted in no tumors in 58 animals. Partially pulverized material containing fibers in the 1 to 20-$\mu$m length range was associated with a low incidence, about 4%, whether coarse pledget material, fibrous Pyrex glass under 10 $\mu$m in diameter, or old glass wool 1 to 15 $\mu$m in diameter, was used. When partially pulverized AAA fibrous glass, less than 3 $\mu$m in diameter, was tested, the tumor incidence was 12% for uncoated and 18% for coated material. Whereas two types of fibrous glass with fibers of larger size (up to 25 $\mu$m in diameter) produced only 4 mesotheliomas among 91 rats (4.4%). The authors concluded that carcinogenicity of fibrous glass was related more to the dimensions of the materials than to their physicochemical properties. They calculated that the tumor incidence correlated reasonably well with the theoretical number of microfibers (defined as fibers in the mean diameter range of 1.25 by 3.75 $\mu$m) present in the lesions, irrespective of whether the material was asbestos or fibrous glass [73].

Continuing this line of investigation, Stanton and his colleagues [74] analyzed data from the foregoing and conducted additional experiments with particular reference to the lengths and diameters of fibers. When tested for oncogenic activity on the pleura of rats, asbestos, fibrous glass, and aluminum oxide were most active when composed predominantly of fibers between 0.5 and 5 $\mu$m in diameter and shorter than 80 $\mu$m in length. The authors [74] regarded these results as reflecting physical structure rather than physiocochemical properties in producing the neoplastic response. However, their previous paper [73] had showed that powdered crocidolite and chrysotile, with quite similar distributions of sizes of particles, produced mesotheliomas in 75 and 58%, respectively, of the

pleura of rats to which they were applied.

In 1973, Maroudas et al [75] reported the results from a series of in vitro studies undertaken to determine whether there were any known properties of living cells that would cause them to react to the dimensions of foreign bodies, such as glass fibers. Fibroblasts, except under special conditions, require the support of a solid substrate for growth, a property which has been termed "anchorage dependence." Growth in suspension reportedly does not occur unless the cells can attach to solid particles above a critical dimension. On the basis of the results from a series of cell suspensions, the investigators [75] noted that particles shorter than 20 $\mu$m did not induce growth in vitro nor, on the basis of the animal studies of Stanton and Wrench [73], induce mesothelioma in vivo. The investigators [75] postulated that fibers induce two basic types of cellular reaction according to length, an anchorage-dependent growth at 40 to 320 $\mu$m and phagocytosis of fibers shorter than 20 $\mu$m.

Stanton et al [76] studied 17 different dimensional configurations of fibrous glass to determine their comparative ability to induce pleural sarcomas in rats. Sixteen groups, each containing 30 Osborne-Mendel SPF female rats, were exposed to various configurations of fibrous glass. A control group consisted of 130 rats and only received the pledget vehicle which was made of coarse fibrous glass. The exposures were achieved by pleural implantation of coarse 45-mg fibrous glass pledgets that contained 40-mg of test glass fibers chosen on the basis of diameter and length and, in some cases, wholeness. Estimation of particle size distribution for each sample was made by optical and electron microscopy, the fibers being categorized into 34 dimensional ranges. Calculations were made for the

number of particles of a given size in the standard 40-mg dose and the percent weight occupied by particles of a given size. The rats were exposed at 12 to 20 weeks of age. Survivors were allowed to live until the 25th month, when they were killed and examined microscopically.

During the 17 experiments, 89 pleural sarcomas were observed; none were seen in the controls. The investigators [76] estimated the probability of tumor induction for each group using standard actuarial life table methods to adjust for deaths of animals without tumors before the end of the experiment. The estimates of tumor probabilities for each dimension category are shown in Table XV-9. The rank order of tumor probabilities coincides with tumor incidence except for one case. The higher tumor probabilities were associated with concentrations of relatively long (> 8 $\mu$m) and thin (< 2.5 $\mu$m) fibers.

Using regression techniques, two nonoverlapping size categories, used individually, showed highly significant relationships with tumor probability. The first of these categories included fibers longer than 8 $\mu$m and with diameters less than or equal to 0.25 $\mu$m. The other category was comprised of fibers longer than 64 $\mu$m and with diameters between 0.25 $\mu$m and 1.5 $\mu$m.

The estimated probabilities of pleural sarcoma ranged from 85.3% to zero. However, analysis of the standard deviations of the probabilities of pleural sarcomas indicates that only three categories of response were distinguishable--high, intermediate, and low risk [76].

Stanton et al [76] noted than an apparent correlation exists between the amount of collagen in the lesion and the probability of pleural sarcoma. Collagen deposition, induced by fine, long fibers, appears to be

similar to the tissue capsule or envelope that develops around various types of implanted foreign bodies [76,77].

Brand et al [77] reviewed the factors and mechanisms involved in sarcoma development upon implantation in tissue of various types of foreign bodies presumed to be chemically inert. Fibrous glass can be considered a foreign body in organisms. There is much evidence that the physical presence of an implanted material alone is responsible for tumorigenesis [72-76]. Foreign body tumorigenesis is reported to be a multistage developmental process. Some of the salient features of the process are: monoclonal origin from mesenchymal stem cells of the micro-vasculature, origination of neoplastic destination and specific tumor determinants in cells distant from the implant during the earliest stage of the tumorigenic process, the regular finding of varied aneuploidies, the importance of fibrosis and macrophage inactivity during the preneoplastic maturation process, and direct contact with the foreign body surface as the terminal requirement for preneoplastic cells to attain neoplastic autonomy. Whether all these stages occur with fibrous glass is not known.

The literature reviewed by Brand [77] indicates that the size and shape of foreign bodies has a strong influence on tumorigenic potential. This finding has been supported by many studies involving fibrous glass [64,70-76]. Rodents are also quite susceptible to foreign body implants and show a sarcomatous response [77]. Most of the animal studies with fibrous glass involved rodents.

(f) Fiber Aerodynamics and Deposition

Timbrell [78,79] described the findings of a variety of experiments conducted to determine the aerodynamic characteristics of fibrous particles

and their penetration and retention in animal lungs. These experiments were performed by exposing rats to asbestos and subsequently to fibrous glass, by simulation using hollow casts of porcine lungs, and by use of various size-selective elutriators and gravitational spectrometers.

In 1965 Timbrell [78] concluded that the behavior of fibers in air is determined primarily by the diameter of the fibers; the length of fibers has only a limited effect. The behavior of fibers in air, indicated by falling speed, compared to the behavior of a reference spherical particle of unit density is described by the term, "aerodynamic diameter." The aerodynamic diameter determines what happens to particles brought within the breathing zone. Those particles with falling speeds greater than the velocity of air entering the nostrils are not taken into the respiratory system. Those particles with a falling speed equal to the velocity of air entering the nostrils can either be collected at various points in the respiratory passages or penetrate to the alveoli. Timbrell [78] found that the ratio of the aerodynamic diameter to the absolute diameter in very long fibers has been found to be, on the average, three [78]. The largest compact particles found in human and rat lungs had aerodynamic diameters of 10 $\mu$m; for these particles the absolute diameter was about 3.5 $\mu$m. Fibers larger than about 3.5 $\mu$m would usually deposit in the nasopharynx or tracheobronchial regions of the respiratory system. Fibers less than about 3.5 $\mu$m in diameter would likely escape deposition in the upper regions and penetrate deeply into the lung, especially into the alveoli. The maximum alveolar penetration occurs with fibers 2 $\mu$m in diameter and decreases to a minimum of about 20% with fibers 0.4 $\mu$m in diameter [79].

Harris [80] and Harris and Fraser [81] in 1976 developed a mathematical model for estimating lung deposition of straight fibers such as fibrous glass. The model indicated that slightly over 30% of fibers, 25 μm in length and depending on their diameters, might be deposited in alveoli. Further, the amount of deposition would decrease to 1-3% as fibers increased in length up to 200 μm.

Lippmann et al in 1974 [82] presented some experimental deposition data obtained by using a hollow bronchial cast of the human airway, and comparing this data with predicted depositions for the same airways. The predicted depositions were based on experimental data on the deposition of spherical particles. The investigators [82] found that equations for deposition of fibers would not accurately predict what would occur in a cast of the human respiratory system at flowrates greater than 30 liters/minute because of underestimation of the deposition in larger bronchi.

Brain et al [83] in 1976 reported on a study that compared the deposition of particulate matter in the lung as a result of aerosol inhalation or intratracheal instillation. This study did not involve fibrous glass but it is illustrative of differential particle deposition resulting from two different routes of exposure. Radioactively labeled nonfibrous particles were administered to hamsters and rats. It was found that the distribution of intratracheally instilled particles differed considerably from that produced following inhalation of comparable particles. Quantitative techniques indicated that the distribution of these particles was more even with inhalation than with intratracheal instillation, so that there was less concentration in particular sites

within the lung after the inhalation method than after the intratracheal method. Whether these same patterns of deposition occur with fibrous particles has not been determined [83].

Correlation of Exposure and Effect

The literature on fibrous glass indicates that fibers of differing size exert different biologic effects [27,28,56,58,61,64,76,78]. The dimensions of glass fibers rather than the chemical composition have been assumed to be the etiologic factors in biologic activity. This assumption has been based on the results of the comparative studies of different sized fibrous materials, expecially fibrous glass, along with comparisons of differential biologic effects of fibrous and nonfibrous glass [64,66,68,70-72,76]. Fibrous aerosols having the same concentration as measured by fiber count but markedly differing in diameter, length, or other configuration of the fibers may affect different regions of the respiratory system. After simulating fiber behavior with a mathematical model Harris [80] reported a decreasing probability of fiber deposition in airways distal to the terminal bronchioles with increasing aerodynamic diameter, with increasing length, and with increasing interception as the cross-section of the airway decreased. This may be interpreted generally to mean that larger fibers would be less likely to deposit in alveoli than smaller fibers. Exposure conditions in occupational or experimental situations often include aerosols or workroom atmospheres that contain particles of differing lengths and diameters [5,58,78,79].

Most epidemiologic studies of workers exposed to glass fibers 2-10 $\mu$m in diameter demonstrated no excess of roentgenographic abnormalities,

pulmonary dysfunction, or malignancy [44,46-48,50,79]. These were all cross-sectional prevalence studies conducted among current employees. Such studies gave no indication of the health of those who had ceased employment prior to the study or the individual lengths of exposure. Most of these epidemiologic studies investigated the workforce of the oldest fibrous glass production plant in the US [44]. Cholak et al [45] characterized the exposure conditions in this plant in 1963. Samples were taken using midget impingers and dust counts made using a microscope technique. Total dust concentrations ranged from 0.93 to 13.3 mg/cu m. The number of particulates ranged from 3.2 to 11.3 million particles/cu m (0.09 mppcf to 0.32 mppcf). Of these particles, only 1% or 0.002 mppcf (70,000 fibers/cu m) were found to be fibrous and 85% of these were between 2 and 10 μm in diameter (median, 6 μm). Average plant values indicated that 16% of the fibers were less than 40 μm in length and 6% were less than 20 μm.

Bayliss et al [55] performed a retrospective cohort study on former employees of the same plant. This study involved a cohort of 1,448 men, 376 of whom had died between January 1, 1940 and June 1, 1972. Using life table methods of analysis, 404 deaths were expected to occur. Only one cause-of-death category indicated a possible excess of disease; this was "nonmalignant respiratory disease exclusive of influenza and pneumonia." Environmental investigations indicated a mean airborne fibrous glass concentration of 80,000 fibers/cu m (0.08 fibers/cc) with 85% of the fibers counted being equal to or less than 3.5 μm in diameter. When Cholak et al [45] studied the conditions of the plant in 1963 the median diameter of fibers was 6 μm with average fiber counts of 70,000 fibers/cu m. Hence, the retrospective cohort study of Bayliss et al [55] indicated that fibers

3 to 6 μm in diameter or larger were correlated with an increased risk of deaths due to nonmalignant respiratory diseases exclusive of influenza and pneumonia. Of 19 deaths due to nonmalignant respiratory disease 6 were found at autopsy to be due to bronchiectasis.

Enterline and Henderson [54] studied the mortality and morbidity experience of 416 retired fibrous glass insulation production workers who were at least 65 years old. No statistically significant excess of observed versus expected deaths for any cause was found. The size concentration of glass fibers that these workers were exposed to was not reported. However, most fibrous glass insulation is greater than 4 μm in diameter although smaller diameter fibers are known to exist in the air of insulation production plants [5]. When the experience of 276 workers with normal retirements (as opposed to disability and early retirements) was studied, slight excesses of observed vs expected deaths for the categories "all other heart disease" and nonmalignant "diseases of the respiratory system" were detected. There was also a slight excess of deaths from all causes in a group of 35 workers who had reached age 65 after retiring earlier due to disability. Among the total of 127 workers who retired early because of disability, chronic bronchitis was observed six times more than was to be expected but the number of workers involved was very small. The design of this study excluded workers with significant effects due to fibrous glass exposure if they died before they reached age 65; on the other hand, the mean followup period from the first exposure was about 30 years.

Hill et al [52] found no difference in pulmonary function between 70 fibrous glass production workers (mean exposure, 19.8 years) and an

unexposed matched control group. Examination of roentgenographs, pulmonary function tests and physical examinations also revealed no differences between the two groups. In a followup study 5 years later, Hill et al [52] re-examined 53 of the original 70 study members and an unreported number of the control group and found equivalent amounts of pleural thickening. The fates of the unexamined 17 other workers were not reported. Environmental investigations in the production plant revealed that total dust in the operators' breathing zones ranged from 0.4 to 12.7 mg/cu m. Mean fiber counts in the breathing zones of operators sampled were 1,400,000 to 5,500,000 fibers/cu m (ranged from 1.4 to 5.5 fibers/cc). Of the fibers, 75% were less than 4 $\mu$m in diameter and 34% were less than 2 $\mu$m [52].

The epidemiologic and case studies except for that of Bayliss et al [55] indicate a dearth of pathologic reactions in populations exposed to fibrous glass with diameters of 2 to 10 $\mu$m. Many of the studies were limited in their ability to detect significant abnormalities in the health of exposed workers. These limitations included the designs of studies that excluded workers previously, but not currently, employed. Thus far human exposures to smaller diameter fibrous glass have not been of a sufficient extent or duration for adequate study, so that the animal studies with small fibers are of special importance.

Animals have been exposed to fibrous glass by various routes such as inhalation, intratracheal, intraperitoneal, and intrapleural administrations. No neoplastic response and only slight fibrosis was observed as a result of inhalation exposures [58] whereas fibrosis has been found after intratracheal, intrapleural, and intraperitoneal administrations [61,64,71], and neoplasms have been observed after the last

two modes of administration. All factors in these studies were not sufficiently similar to allow exact comparisons.

Intratracheal instillation of fibers by Kuschner and Wright [64] resulted in a fibrogenic response in guinea pigs. This study demonstrated a relationship of fiber diameter and length to the degree of cellular change observed in the guinea pigs. Fibers longer than 10 μm consistently produced fibrotic responses whereas shorter fibers did not. The fibers that produced the fibrotic response were generally less than 1 μm in diameter although some fibrosis was observed in the animals that received long fibers with diameters averaging 2 μm [64].

The inhalation experiments [56,58,60] involving fibrous glass have not been as extensive as experiments using other modes of administration. In the most relevant inhalation experiment performed, only slight fibrogenic and no neoplastic responses were reported [58].

The studies by Botham and Holt [59] indicate progressive changes occurring in guinea pigs after a single exposure to "high" concentrations of fibers mostly less than 1 μm in diameter and 20 μm or less in length. Fibers that were retained in the lung were deposited initially in the bronchioles. Some fibers moved inwards to the alveoli where they were engulfed by macrophages. The longest fibers became coated with a ferroprotein Perls-positive substance which attained a beaded form on the fibers. Eventually these structures broke between the beads and most of the fragments were cleared.

The effects of long term inhalation exposure to fibrous glass were presented by Schepers and Delahant [56] and by Gross et al [58]. Schepers and Delahant [56] exposed guinea pigs to fibers 6 μm in diameter at

concentrations of approximately 5 mg/cu m for 20 months and then to fibers with diameters of 3 μm at concentrations of 2 to 2.5 mg/cu m for another 20 months. No controls were used and the significance of pathologic findings is in doubt. No fibrosis was observed but there were manifestations of focal atelectasis. Similar results were found by the investigators [56] after intratracheal administrations of fibers with diameters of 3 μm or less.

The inhalation study by Gross [58] using 100 mg/cu m of dust, of which 70 to 76% was fibrous with average diameters of 0.5 μm and lengths from 5 to 20 μm, revealed no fibrosis except for a few foci of septal collagenous fibrosis in some rats or no atelectasis during 24 months of exposure. By the end of exposure only 20 animals of an initial group of 110 animals of each species, rats and hamsters, were available for evaluation. Since this is a small sample, possible pathologic effects may not have been detected. Microscopic tissue changes that were observed consisted of collections of macrophages with engulfed fibers localized in alveoli. Glass fibers deposited in the lungs of rats and hamsters were not found to be associated with fibrosis or atelectasis. Dust foci in the lungs of animals that survived the longest after exposure were less numerous and smaller than those of animals killed during or shortly after the exposure, suggesting pulmonary clearance of the material [58].

Studies [56,58,61,64] concerning the fibrogenic potential of fibrous glass indicate that length and diameter are important factors. Whether fibrosis is a necessary precursor to neoplasia is speculative [64,77].

The irritant and abrasive effects of fibrous glass on the skin, the upper respiratory tract, and the eye have been reported by a number of

investigators [16-19,27-30,35,36,40].

Erwin [24] observed dermatitis and skin irritation in a group of workers handling fibrous glass fabric and a mixture of copolymer resins in the manufacture of reinforced plastic products. The skin irritation was aggravated because of the necessity of handling the material with bare hands and the frequent washings necessary to remove the plastic fluid from the skin. The small fibers of glass (dimension not stated) seemed to be mechanical irritants and in some cases caused sensitization. The sensitization reaction may have been due to the plastic rather than to the glass fibers particularly if the plastic contained formaldehyde [24]. Heisel and Hunt [28] reported that fabric made from glass fibers with diameters less than 4.6 $\mu$m could be applied directly to the skin without concern for irritation. These findings are supported by those of Possick et al [30] who found that fibers of large diameters were more likely to cause skin irritation. The potential for irritation by glass fibers between 5 and 10 $\mu$m in diameter was considered to be from moderate to high. These observations indicate that concern must be given to all sizes of glass fibers and not to a specific size alone if the total occupational health problem associated with fibrous glass exposure is to be adequately controlled.

A summary of the effects from various exposures to fibrous glass is presented in Table XV-10.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Sincock and Seabright [84] exposed two groups of cultured Chinese hamster cells to glass fibers, glass powder, UICC crocidolite asbestos, and

SFA chrysotile asbestos for 48 hours or 5 days. The dusts were added at a concentration of 0.01 mg/ml. Cells exposed to asbestos showed karyotypic alterations to a greater degree than cells exposed to glass fibers or dust. Exposure for 5 days to the glass fibers produced slightly more, but not statistically significant, alterations than were found in unexposed controls. These findings were not considered by the authors [84] as indicative of a mutagenic potential of fibrous glass.

Stanton et al [72-74,76], Davis [70], Wagner et al [71], and Pott and associates [68,69] have been able to repeatedly produce tumors in animals after either intrapleural or intraperitoneal administration of fibers predominately less than 1 μm in diameter. Stanton et al [76] stated that the probability of tumor formation in rats with fibers less than 0.25 μm in diameter and longer than 8 μm was 85%. The dose in this study was 40 mg per animal.

Davis [70] produced tumors in Balb/C mice and in an unspecified strain of rats after a single injection of long (up to several hundred μm), and thin (average diameter, 0.05 μm) glass fibers. Mice received an intraperitoneal dose of 10 mg and this resulted in a 12% (3/25) tumor response. Rats received an intraperitoneal dose of 25 mg and this resulted in a 16% (3/18) tumor response. Some of the advanced tumors were classified by the investigator [70] as fibrosarcomas.

In similar experiments involving injection of glass fibers into the pleural cavities of mice, Davis [70] found that long fibers (up to several hundred μm) of either 0.05 or 3.5 μm in diameter produced granulomas markedly different in size and structure from short (<20 μm) fibers. The short fibers produced granulomas which never formed adhesions between

lungs, heart, and chest wall. The long fibers produced many large granulomas, which often filled a greater part of the pleural cavity and formed firm adhesions between lungs, heart, and diaphragm. Wagner et al [71] also reported a 12% tumor incidence in rats after intrapleural administration of a 20-mg dose of glass fibers having a median diameter of 0.12 μm. Pott and Friedrichs [68] found a proportional relationship between dose and tumor incidence after intraperitoneal administration. Doses of 2 mg, 10 mg, and 25 mg, each given twice, produced tumors with rates of 27.4, 53.2, and 71.4%, respectively, in rats.

The carcinogenic responses in animals after intrapleural or intraperitoneal administration of fibrous glass are consistent with the responses found after implantation of other foreign body materials such as polyethylene, asbestos, nylon, cellophane, and Teflon. A review of the literature on this subject entitled "Foreign Body Tumorigenesis" has been recently authored by Brand et al [77]. Responses to implanted materials have been described by the relatively synonymous terms "physical carcinogenesis," "solid-state carginogenesis," and "foreign body tumorigenesis." It has been demonstrated that the tumorigenic response depends on physical rather than chemical factors. The most important of these factors is the size and shape of foreign materials which determine the appearance and incidence of foreign body tumors. Most of the tumors found after foreign body implantation have been sarcomatous. The appearance of these tumors is also dependent on the strain and species of the host animal. Rodents are particularly responsive to foreign bodies. The data on the relative responsiveness of humans is equivocal. Another prerequisite of the tumorigenic response is that it is preceded by the

normal reaction of biologic tissues to foreign bodies. Not all foreign body reactions result in tumor formations but all tumorigenic responses begin with foreign body reactions, followed by the appearance of fibrosis and diminished inflammatory reaction. The forces that cause the normal foreign body reaction to develop into a tumorigenic response have not been determined. While these experiments contribute to the elucidation of mechanisms of tumor formation, they do not indicate that fibrous glass will be carcinogenic after inhalation or after exposure in the occupational environment.

The routes of exposure used in many of the intrapleural and intraperitoneal experiments have been considered to be inappropriate to indicate the effects of fibrous glass after inhalation. It is not valid to extrapolate from the results from these intracavitary exposures in animals to humans in the workplace.

Bayliss et al [55] performed one of the few epidemiologic studies designed to detect a risk mortality due to cancer. As a result of a retrospective cohort analysis of mortality patterns in fibrous glass production workers, 49 cases of respiratory disease, malignant and nonmalignant, were found.

Bayliss et al [55] then extended their retrospective cohort mortality study to include a case-control study of a group of workers exposed to fibrous glass of a smaller and potentially more dangerous diameter during the operation of a pilot process. This group was exposed to fibers ranging from 1 $\mu$m to 3 $\mu$m in diameter during 1941-1949. Cases and controls were matched according to birth date, race, sex, and date of employment. The results of the matching indicated that there were four deaths from

malignant respiratory disease in workers who had been in the pilot process compared with no such deaths in the controls. This finding had a probability level between 0.10 and 0.05 which was considered by the authors to be of "borderline" significance [55]. However, this level is not generally considered statistically significant.