Certain Glass Wool Fibers (Inhalable)

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994) as Glass Wool (Respirable Size)

Carcinogenicity

Certain glass wool fibers (inhalable) are *reasonably anticipated to be human carcinogens* based on (1) sufficient evidence of carcinogenicity from studies in experimental animals of inhalable glass wool fibers as a class (defined below) and (2) evidence from studies of fiber properties which indicates that only certain fibers within this class — specifically, fibers that are biopersistent in the lung or tracheobronchial region — are *reasonably anticipated to be human carcinogens.* Because there is considerable variation in the physicochemical and biophysical properties of individual glass wool fibers, carcinogenic potential must be assessed on a case-by-case basis in experimental animals, through either long-term carcinogenicity assays or assays measuring the persistence of fibers in the lung. Regulatory authorities in Germany and the European Union have developed testing protocols and criteria for categorizing fibers with respect to their carcinogenicity that do not require long-term carcinogenicity studies in animals; however, the criteria used by these two groups differ somewhat. Studies on mechanisms of carcinogenesis provide additional support for the findings of studies in experimental animals that certain (inhalable) glass wool fibers are carcinogenic; however, the available studies in humans are inadequate to evaluate the potential carcinogenicity of glass wool fibers.

The class of glass wool fibers consists of fine glass fibers forming a mass resembling wool; individual fibers are defined as being over 5 µm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times as long as its width) (Walton 1982, Breysse *et al.* 1999). There is considerable variation in the physicochemical properties of individual fibers within this class, depending on the manufacturing process and end use. Glass fibers can be classified into two categories based on end use: insulation and special purpose (see Use, below). The physicochemical properties within each category also vary, and there is some overlap of properties between the two use categories. Moreover, a specific glass wool product often contains fibers with a wide range of diameters, as a result of the manufacturing process (see Properties, below, for a discussion of nominal diameter). For cancer hazard identification, it is important that fibers be classified according to their biological activity. For the purpose of this profile, "inhalable" fibers include all fibers that can enter the respiratory tract. Inhalable fibers are of concern because most human lung cancer occurs within the first five generations of the tracheobronchial tree (Quinn *et al.* 1997, Husain 2010).

"Glass Wool (Respirable Size)" was first listed in the *Seventh Annual Report on Carcinogens* as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals. "Respirable" fibers are those that can penetrate into the alveolar region of the lung upon inhalation (EPA 2001) (see Properties for a more detailed description). Since that time, additional studies have been conducted to evaluate the physicochemical properties of glass wool fibers related to carcinogenicity. The listing was changed in the *Twelfth Report on Carcinogens* to "Certain Glass Wool Fibers (Inhalable)," which are listed as *reasonably anticipated to be human carcinogens.*

Cancer Studies in Experimental Animals

Glass wool fibers caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Individual types of glass wool fibers were studied in chronic carcinogenicity bioassays in rats and/or hamsters exposed by a number of routes, including inhalation, intratracheal instillation of fiber suspensions, surgical intrathoracic implantation, and direct exposure to the pleural or peritoneal cavity by injection. The studies employed various glass wool products and treated or sized fractions of the products. Inhalation exposure studies used respirable fibers as defined by World Health Organization criteria (see Properties) unless otherwise specified.

The most biologically relevant studies were of inhalation exposure to respirable or inhalable fibers in rats and hamsters. These studies used the exposure route and fiber dimensions most relevant to human exposure conditions. Although intratracheal instillation (a bolus injection into the trachea) bypasses the upper respiratory airway, exposure by this route also is relevant to human exposure. Both intratracheal and inhalation exposure conditions target the lung and pulmonary clearance mechanisms within that environment. Intrathoracic, intrapleural, and intraperitoneal exposures are less relevant biologically, as they target the mesothelial lining of the pleural and peritoneal cavities; however, studies using these routes do provide information about fiber biodurability (resistance to dissolution or disintegration in the body) and cancer hazard. Studies of the carcinogenicity of glass wool fibers following chronic exposure, described below, are organized by fiber use (special purpose, insulation, unspecified, or experimental) and route of exposure.

Special-Purpose Glass Fibers

The majority of studies that found carcinogenic effects of glass wool fibers tested special-purpose fibers. Most of the studies used type 475 glass fibers; one study tested E-glass fibers; and one tested a series of unspecified special-purpose fibers. Type 475 glass fibers are coded according to mean fiber diameter, with larger numbers indicating larger diameters (e.g., Johns Manville [JM] 110/475 fibers have a greater nominal diameter [1.9 to 3.0 µm] than JM 100/475 fibers [0.28 to 0.38 µm]). Man-made vitreous fiber (MMVF) 33 is a mixture of respirable fibers of type 475 glass codes 104, 108B, and 110.

Inhalation Exposure

Inhalation exposure to E-glass fibers significantly increased the incidences of lung cancer (carcinoma) and total lung tumors (carcinoma and adenoma) in male Wistar rats; mesothelioma was observed in two animals (Cullen *et al.* 2000).

Inhalation exposure to MMVF 33 glass fibers caused a single mesothelioma in a male Syrian golden hamster, but no lung tumors. Although the incidence of mesothelioma was not significantly increased, the mesothelioma was believed to be exposure-related because of (1) the high incidence of fibrosis, mesothelial hypertrophy, and mesothelial hyperplasia of the pleura in exposed hamsters, (2) the rarity of the spontaneous occurrence of this type of tumor, and (3) the presence of glass fibers in the thoracic wall and diaphragm (Hesterberg *et al.* 1997, McConnell *et al.* 1999).

Inhalation exposure of F344 rats to two different glass fibers — (1) Tempstran code 100/475 glass fibers without binder in two sizes (average diameter < 3.5 µm, length either < 10 µm or > 10 µm) and (2) Owens-Corning FM series air-filter media with binder (average diameter 0.5 to 3.5 µm, length > 10 µm) — significantly increased the incidence of mononuclear-cell leukemia in rats (males and females combined) (chi-square test and one-tailed Fisher's exact test). The incidence of mononuclear-cell leukemia also exceeded the range of the historical control values for the testing laboratory. Although F344 rats have a high spontaneous incidence of mononuclear-cell leukemia, these findings were considered to be exposure-related because of the presence of granulomatous pleural and subpleural plaques and glass-

laden macrophages in adjoining lymph nodes. Glass-fiber-related pulmonary and tracheal-bronchial lymph-node lesions were more severe following exposure to the shorter Tempstran 100/475 fibers than to the other fibers tested (Mitchell *et al.* 1986, Moorman *et al.* 1988).

Other Routes of Exposure

Intratracheal instillation of JM 104/475 glass fibers significantly increased the incidences of lung tumors (adenoma, adenocarcinoma, and squamous-cell carcinoma) in female Wistar rats (Pott *et al.* 1987) and thoracic tumors (carcinoma of the lung, mesothelioma, and thoracic sarcoma) in one of two studies in male Syrian hamsters (Pott *et al.* 1984, Feron *et al.* 1985). In female Osborne-Mendel rats administered 11 types of unspecified special-purpose glass fibers by intrathoracic implantation, the incidence of mesothelioma was significantly increased for 7 of the types of glass fiber (compared with the incidence in a control group implanted with autoclaved gelatin-saturated coarse fibrous glass vehicle comparable in weight to the test fibers plus vehicle) (Stanton *et al.* 1977, 1981). Intrapleural or intratracheal injection of type 475 glass fibers (codes 100, 104, or 110) caused mesothelioma in rats (Sprague-Dawley, Wistar, or Osborne-Mendel) (Wagner *et al.* 1976, 1984, Monchaux *et al.* 1981, Pott *et al.* 1987, Smith *et al.* 1987). Sarcoma and unspecified tumors also were observed in rats administered type 475 glass fibers by intraperitoneal injection (Pott *et al.* 1984, Muhle *et al.* 1987, Miller *et al.* 1999).

Insulation Glass Fibers

Types of insulation glass wool fibers tested in experimental animals included Owens-Corning glass wool, MMVF 10 and 10a (both of which represent the respirable fraction of Manville 901 glass fiber), MMVF 11 (the respirable fraction of CertainTeed B glass fiber), and unspecified glass wool fibers. Inhalation exposure of F344 rats to Owens-Corning FG insulation fiberglass with binder (4 to 6 μm in diameter and > 20 μm long) significantly increased the incidence of mononuclear-cell leukemia in rats (males and females combined). Glass-fiber-related pulmonary and tracheal-bronchial lymph-node lesions were observed but were less severe than for exposure to special-purpose fibers. As with the findings for Tempstran 100/475 glass fibers in this strain (discussed above), these findings were considered to be exposure-related (Mitchell *et al.* 1986, Moorman *et al.* 1988). Intraperitoneal injection of MMVF 11 glass fibers caused mesothelioma of the abdominal cavity in male and female Wistar rats (Roller *et al.* 1996, 1997), and intraperitoneal injection of MMVF 10 glass fibers increased tumor rates in male Wistar rats (Miller *et al.* 1999).

Fibers with Unspecified Commercial Applications

For Schleicher and Schuell (S&S 106) glass wool fibers, information on commercial applications is not clear. Intraperitoneal injection of S&S 106 glass fibers in female Wistar rats caused dose-dependent increases in the incidences of mesothelioma and combined tumors (mesothelioma and spindle-cell sarcoma) (Pott 1976).

Experimental Fibers

Male and female Wistar rats injected intraperitoneally with B-1, B-09, or B-20 glass fibers developed mesothelioma of the abdominal cavity (Roller *et al.* 1996, 1997), which was also observed at a low incidence in female Wistar rats injected with the biosoluble glass wool fibers B, P, and V (Grimm *et al*. 2002).

Summary

A range of carcinogenic responses was observed in experimental animal studies; for example, some glass wool fibers were carcinogenic by several routes of exposure, including inhalation; some were carcinogenic only by routes of exposure other than inhalation; and some were not carcinogenic in any studies. Studies in experimental animals demonstrate a greater carcinogenic effect for special-purpose fibers than for insulation wool. In general, special-purpose fibers are more durable than insulation glass wool fibers; these findings thus suggest that durability is an important factor in predicting the potential carcinogenicity of glass wool fibers. The available studies in experimental animals clearly demonstrate that glass wool fibers are carcinogenic; however, their utility for predicting the carcinogenicity of specific fibers or groups of fibers is limited, for several reasons: (1) Only a subset of commercially available fibers have been tested. (2) Commercial applications and specific products may change over time; the specific fibers tested may no longer represent the products to which individuals are exposed. (3) The physicochemical properties of glass wool vary within each category. (4) The sizes of fibers used in various applications overlap, and each specific product contains fibers with a wide range of diameters (see Properties for a discussion of nominal diameter in glass wool products). (5) Testing of some specific fibers was limited. In general, more studies were conducted with special-purpose fibers than insulation fibers. Some fibers, such as 475 glass fibers, were tested under several different sets of experimental conditions by several investigators, whereas other fibers, such as FG insulation fiberglass, were tested in only one study. Advances have been made in the study of fiber properties related to carcinogenicity; as discussed below, mechanistic and biologically based modeling studies of synthetic vitreous fibers (which include glass wool fibers) suggest that fiber shape and biodurability are important determinants of carcinogenicity.

Fiber Properties Related to Carcinogenicity

The potential for exposure to glass wool fibers to cause cancer is influenced by dose, fiber dimensions (length and diameter), and durability. Inhalation exposure studies showed that tumor incidence or lesion severity increased with the concentration of fibers in the lung (Bunn *et al.* 1993, McConnell 1994, Hesterberg *et al.* 1999, McConnell *et al.* 1999). The cumulative lung burden of fibers is related to their deposition and their biopersistence, which is the ability of fibers to remain in the lung. Fiber aerodynamic diameter (see Properties) determines whether a fiber will be deposited in the lungs or the upper airways; thinner fibers will be deposited into the deep lung (Hesterberg and Hart 2001). Because most human lung cancer occurs within the first five generations of the tracheobronchial tree, it is important to consider both inhalable and respirable fibers (Quinn *et al.* 1997). Fiber length can also influence fiber deposition; the deposition fraction for fibers 1 μm in diameter and 20 μm long is fivefold higher in the tracheobronchial region than in the pulmonary region (Muhle and Bellmann 1997). Biopersistence depends on the fiber's biodurability and its physiological clearance by the lung. Fiber size and durability are important determinants of biopersistence (Hesterberg and Hart 2001). Biodurability is determined by fiber dimensions (length and width) and chemical composition (Muhle and Bellmann 1997). Fiber length also affects whether fibers are cleared from the lung; in rats, fibers shorter than 10 μm presumably are phagocytized by alveolar macrophages, but longer fibers cannot be cleared until they dissolve or break into shorter fragments. Macrophage-mediated clearance of insoluble particles is significantly faster in rats than in humans. Long, durable fibers can persist in the lung for extended periods, and the more biopersistent the fiber, the greater its potential to exert biological effects on the lung (Hesterberg and Hart 2001, Bellmann *et al*. 2010).

Bernstein *et al.* (2001a,b) reported that "biopersistence clearance half-time" was a good predictor of both the collagen deposition (fi-

brosis) observed in chronic inhalation and intratracheal instillation studies and the tumor response observed in intraperitoneal injection studies. The inhalation half-times for fibers over 20 μm long were found to correlate with the number of fibers remaining after chronic inhalation exposure. The average collagen score after chronic inhalation exposure correlated with intratracheal instillation half-times for fibers over 20 μm long and for respirable fibers as defined by the World Health Organization ("WHO fibers": diameter < 3 μm, length ≥ 5 μm, and aspect ratio ≥ 3:1). Exposure to fibers with a weighted half-time of less than 40 days by intratracheal instillation or less than 10 days by inhalation exposure resulted in a baseline level of collagen deposits (a precursor of interstitial fibrosis) at the bronchiolar-alveolar junction. Furthermore, the biopersistence half-times of fibers as determined for inhalation (weighted half-time of fibers > 20 μm) and intratracheal instillation (weighted half-time of fibers > 20 μm and half-time of WHO fibers) were predictive of the tumor response in long-term intraperitoneal-injection studies (Bernstein *et al.* 2001b). The short-term biopersistence test is used by both the European Union and Germany to classify the carcinogenicity of synthetic vitreous fibers. Both the European Union and Germany classify synthetic vitreous fibers as possibly or probably carcinogenic, but fibers are exempted from classification if they meet testing criteria for exoneration based on a cancer bioassay or a short-term biopersistence test. The European Union's criteria for exoneration are based on both inhalation and intraperitoneal exposure (in either a cancer bioassay or the short-term biopersistence test), whereas the German criteria are based only on intraperitoneal exposure; the Germans have questioned the sensitivity of the inhalation carcinogenicity assays for fibers in rats (Collier 1995, Wardenbach *et al.* 2005). The German criteria use the half-time of fibers over 5 μm long, whereas the European Union criteria use the weighted half-time of fibers over 20 μm long (Bernstein 2007).

Numerous studies have evaluated the relationship between fiber shape or fiber solubility and tumor incidences, and have attempted to define quantitative values for size and durability that are correlated with tumor incidence or that predict carcinogenicity. Studies investigating synthetic vitreous fiber properties and carcinogenicity demonstrated a relationship between fiber size or shape and tumor incidence or biological activity of fibers related to carcinogenicity (Stanton *et al.* 1977, 1981; Quinn *et al.* 2000). Longer, thinner fibers are carcinogenic; however, the specific fiber dimensions considered to be carcinogenic varied among studies, and the critical length of fibers with respect to carcinogenicity is not clear (Bellmann *et al.* 2010).

As noted above, fiber dissolution is an important determinant of lung clearance. Various investigators have evaluated *in vitro* simulation of fiber dissolution to predict biological durability in the extracellular media. A mathematical model relating the *in vitro* dissolution constant (K_{dis}) to fiber carcinogenicity and fibrosis provided evidence that K_{dis} values at pH 7.4 could be used to predict tumorigenicity for inhalation exposure (Eastes and Hadley 1996). Long fibers (> 20 μm) were considered in this model, as these fibers cannot be rapidly cleared from the lung by macrophages, so their persistence in the lung is related to physical properties of the fiber, such as solubility. The model predicted that a fiber with a dissolution rate of 100 ng/cm^2 per hour or greater has an insignificant chance of producing fibrosis or tumors in rats exposed by inhalation. Although *in vitro* testing is useful for designing soluble fibers, limitations for predicting lung tumorigenicity using K_{dis} have been reported (Bauer *et al.* 1994, Muhle *et al.* 1994, Zoitos *et al.* 1997, Guldberg *et al.* 1998, Bellmann *et al.* 2010). As of 2010, no regulatory agency in the United States or the European Union had adopted the dissolution constant as a predictor of fiber carcinogenicity.

Studies on Mechanisms of Carcinogenesis

Fiber properties such as dimensions, chemical composition, and surface reactivity and the dose of fibers determine whether a fiber can be effectively engulfed by an alveolar macrophage and efficiently cleared from the lungs or remain and cause a chronic inflammatory response (Nguea *et al.* 2008). If fibers are too long for the macrophage to effectively engulf or are too durable to break or dissolve within the lung or macrophage environment, incomplete phagocytosis can result in excessive production of reactive oxygen species (ROS) and inflammatory mediators and their release into the lung, which can lead to chronic inflammation and fibrosis (Hesterberg and Hart 2001). Fibers not cleared by macrophages can also be taken up by lung epithelial cells and translocated to the pleural space, resulting in chronic inflammation, tissue damage, cell proliferation, and fibrosis (Oberdörster 2002). Chronic inflammation, fibrosis, and fibrotic nodules have been found to be associated with mesothelioma formation after intracavity injection of glass wool fibers, suggesting that oxidative stress from inflammation has a role in mesothelioma formation (Grimm *et al.* 2002). An increase in oxidative stress but no increase in mutation frequency was observed in the lungs of rats following intratracheal exposure to glass wool (Topinka *et al.* 2006). Culturing primary rat alveolar cells with glass fibers induced a proinflammatory cytokine, tumor necrosis factor–α, through activation of both mitogen-activated protein (MAP) kinase and nuclear factor–κB (NF-κB) gene transcription pathways (Ye *et al.* 1999, 2001). MAP kinase and NF-κB are important factors in cell-signaling pathways controlling cell proliferation and cell death, and they can be activated by ROS. In these studies, long fibers (16.7 ± 10.6 μm) were more potent than short fibers (6.5 ± 2.7 μm) in activating MAP kinases.

Glass wool fibers have the potential to cause genetic damage (Nguea *et al.* 2008). *In vitro,* they caused production of ROS in cell-free systems and oxidative damage in cell-culture systems. In cultured mammalian cells, they caused DNA damage, micronucleus formation, chromosomal aberrations, and DNA-DNA interstrand crosslinks (NTP 2009). Intratracheal instillation of insulation glass wool caused DNA strand breaks in rat alveolar macrophages and lung epithelial cells. Although fibers of various dimensions caused DNA damage in mammalian cells, longer fibers were more potent in causing these genotoxic effects (Topinka *et al.* 2006).

In cytotoxicity studies, longer fibers were more toxic than shorter fibers to rat alveolar macrophages (Hart *et al.* 1994, Blake *et al.* 1998). Exposure to glass wool fibers in a cell transformation assay caused cytotoxicity and anchorage-independent growth in mouse fibroblasts; amplification of the proto-oncogenes K-*ras*, H-*ras*, c-*fos*, and c-*myc*; and mutations in K-*ras* and *p53* tumor-suppressor genes (Gao *et al.* 1995, Whong *et al.* 1999). Exposure to glass wool fibers also caused cytotoxicity and morphological transformation in Syrian hamster embryo cell cultures (Hesterberg and Barrett 1984). Thick fibers (average diameter = 0.8 μm, average length = 9.5 μm) were 20-fold less potent than thin fibers of the same length (average diameter = 0.13 μm) in causing cell transformation, and shorter fibers (average length = 1.7 μm, average diameter = 0.13 μm) were 10-fold less potent than longer fibers of the same diameter (average length = 9.5 μm). Cytotoxic potencies of the fibers were associated with their transforming potencies. These results provide evidence that fibers can have direct cytotoxic and transforming effects on cells, and that the magnitude of the response is related to fiber dimensions.

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure to glass wool fibers. Although studies of occupational exposure found excess

lung-cancer mortality or incidence, it is unclear that the excess lung cancer was due to exposure specifically to glass wool fibers, because (1) no clear positive exposure-response relationships were observed (however, misclassification of exposure is a concern), and (2) the magnitudes of the risk estimates were small enough to potentially be explained by co-exposure to tobacco smoking.

The data relevant for evaluation of exposure specifically to glass wool fibers are from studies of four major cohorts of glass wool manufacturing workers in the United States (Marsh *et al.* 2001a,b, Youk *et al.* 2001, Stone *et al.* 2001, 2004), Europe (Boffetta *et al.* 1997, 1999), Canada (Shannon *et al.* 2005), and France (Moulin *et al.* 1986) and a hospital-based case-control study of lung cancer among Russian workers exposed to glass wool (Baccarelli *et al.* 2006). The most informative studies are the U.S. multi-plant cohort study and a nested case-control study of lung cancer within that cohort, because they (1) had adequate statistical power to detect an effect, because of the cohort's large size (> 10,000 male and female workers) and long follow-up period, (2) adjusted for tobacco smoking (in the nested case-control study of male workers), (3) used internal analyses to evaluate quantitative exposure to respirable fibers (using non-exposed workers in the cohort as the reference group), and (4) separated the results for women (the only studies to do so). The French study was the least informative, because of its short follow-up period. The U.S. study reported mortality data, the French study reported incidence data, and the European and Canadian studies reported both mortality and incidence data. Respiratory cancer (including upper-respiratory-tract and lung cancer) and mesothelioma were the cancers of interest; the data were inadequate to evaluate cancer at other tissue sites. None of the studies clearly distinguished between exposure to glass wool used for insulation or for special-purpose applications.

Respiratory-System or Lung Cancer

Excesses of respiratory cancer mortality or incidence were found in three of the four cohort studies (not adjusted for smoking) and the case-control study of Russian workers (adjusted for smoking); the fourth (French) cohort had limited statistical power to detect an effect because of the very small number (5) of cases among exposed workers. Findings were statistically significant in the U.S. study (standardized mortality ratio [SMR] = 1.18, 95% confidence interval [CI] = 1.04 to 1.34, 243 exposed deaths, males and females, specific for glass wool plants) and the Canadian study (SMR = 1.63, 95% CI = 1.18 to 2.21, 42 exposed deaths; standardized incidence ratio [SIR] = 1.60, 95% CI = 1.19 to 2.11, 50 exposed cases). A meta-analysis of the four cohorts yielded a summary relative risk (RR) that approached statistical significance (RR = 1.22, 95% CI = 1.00 to 1.49, 920 exposed cases) (Lipworth *et al.* 2009). (The meta-analysis used risk estimates for workers at both filament and glass wool plants in the U.S. study and mortality data for the Canadian and European cohorts.)

The association between cancer and exposure to glass wool fibers among men and women in the U.S. cohort was evaluated by internal analyses, using unexposed workers as the reference group for men and workers exposed to filament fibers for women. The nested case-control study of lung cancer among male workers found no evidence of an association between working in plants manufacturing glass wool fibers and respiratory system cancer (lung, larynx, trachea, or bronchus) after adjusting for tobacco smoking (RR = 1.06, 95% CI = 0.71 to 1.6). In exposure-response analyses, no association was found between cumulative exposure or average intensity or duration of exposure to respirable glass fibers (Marsh *et al.* 2001b, Stone *et al.* 2001, Youk *et al.* 2001). However, exposure misclassification is a concern. Quinn *et al.* (1996, 1997, 2000, 2005) suggested that the indices of exposure (NIOSH Method 7400 B; see Exposure, below) used in these studies may not reflect the fiber characteristics most related to development of cancer, which could result in a considerable loss of power to detect exposure effects.

In contrast to the findings for male workers, there was some evidence for an increased risk of respiratory-system cancer among female workers in glass wool plants (unadjusted RR = 3.24, 95% CI = 1.27 to 8.28), based on 6 cases in exposed workers (Stone *et al.* 2004). Employment duration and time since first employment were significantly related to respiratory-cancer mortality, but no association was found with cumulative exposure to respirable fibers. Estimates were not adjusted for smoking, but a survey of smoking habits among a subset of workers found a slightly lower (24.5%) percentage of current smokers among workers than in the general population (29%). The meaning of the finding of a potential association with lung-cancer mortality among women, but not men, is unclear, because women had lower exposure than men.

The Russian hospital-based case-control study found higher risk estimates for workers exposed at higher levels, but no trends were found for cumulative exposure (Baccarelli *et al.* 2006). Although the Canadian and European studies did not evaluate quantitative exposure to glass wool fibers, they did evaluate risk by employment duration and latency. No clear exposure-response patterns for lung cancer mortality were observed in either study, although an approximately threefold increase in mortality was observed among Canadian workers with over 20 years of employment duration and over 40 years since first exposure (Shannon *et al.* 2005).

Cancer of the Upper Respiratory and Alimentary Tracts

Excesses in the incidence of cancer of the upper respiratory tract and alimentary tract (oral cavity, pharynx, and larynx) were reported for the European cohort (SIR = 1.41, 95% CI = 0.80 to 2.28, 16 exposed cases) and French cohort (SIR = 2.18, 95% CI = 1.31 to 3.41, 19 exposed cases); risks increased with increasing exposure duration in the French cohort (Moulin *et al.* 1986) and time since first employment in the European cohort (P_{trend} = 0.03). Findings for these combined tissue sites were not reported in the Canadian study. Excess mortality from buccal and pharyngeal cancer also was observed in the European study, but was not related to time since first employment or employment duration; no excess of buccal and pharyngeal cancer was observed in the U.S. study. A meta-analysis using mortality data from the U.S. study (not including laryngeal cancer) and incidence data from the European study (not including laryngeal cancer) and the French study found an elevated but statistically nonsignificant risk for head and neck cancer (summary RR = 1.42, 95% CI = 0.91 to 2.1). The interpretation of these findings is unclear, because of limited exposure-response analyses and lack of adjustment for tobacco smoking (Lipworth *et al.* 2009).

Mesothelioma

The available data are inadequate to evaluate the association between glass wool exposure and mesothelioma, a rare cancer strongly linked to asbestos exposure. Mesothelioma was evaluated in detail only for the U.S. cohort; in the other studies, the reporting on mesothelioma either was not specific for exposure to glass wool fibers (Engholm *et al.* 1987, Rodelsperger *et al.* 2001) or did not evaluate co-exposure to asbestos (Boffetta *et al.* 1997). In the U.S. cohort, two cases of mesothelioma were identified among workers with exposure to glass wool but without known exposure to asbestos; in one case, there was uncertainty in the cancer diagnosis, and in the other case, information on asbestos exposure was not complete (Marsh *et al.* 2001a).

Properties

Glass wools fibers are a subcategory of synthetic vitreous fibers, which are manufactured inorganic fibrous materials that contain aluminum or calcium silicates and are made from a variety of materials, including rock, clay, slag, or glass (ATSDR 2004). The chemical composition of glass wool products varies depending on the manufacturing requirement and end use, but almost all contain silicon dioxide as the single largest oxide ingredient for the production of glass (IARC 2002). Silicon dioxide or one of a few other oxides (boron trioxide, phosphorus pentoxide, or germanium dioxide) is required in order to form glass, and these oxides are known as "glass formers." The essential property of a glass former is that it can be melted and quenched into the glassy (amorphous) state. Commercial glasses generally include additional oxides that serve as stabilizers and modifiers or fluxes; they modify the physical and chemical properties of the glass product, including viscosity (NTP 2009). These modifiers include oxides of aluminum, titanium, zinc, magnesium, lithium, barium, calcium, sodium, and potassium.

Glass wool products consist of individual fibers, which have been basically defined since the late 1950s as being over 5 μm long and having an aspect ratio of at least 3:1 (Walton 1982, Breysse *et al.* 1999). Other, more recent, definitions have suggested that an aspect ratio of 5:1 will more readily discriminate fibrous from irregularly shaped particles, and some organizations have adopted this criterion. In addition to differences in the chemical composition of the glass used to make the fibers, the fibers themselves can be modified further by addition of various lubricants, binders, antistatic agents, extenders and stabilizers, and antimicrobial agents.

The primary physical characteristics of glass wool fibers are their diameter and length. The fiber diameter is controlled by the manufacturing process. All glass fibers are manufactured to nominal diameters that vary based on the manufacturing process and the fibers' intended use (ACGIH 2001). The nominal diameter is an estimate of the product's average fiber diameter. Because current glass wool production processes are not capable of producing fibers only at the nominal diameter, the diameters of individual fibers in a glass wool product vary widely around the nominal diameter (IARC 2002). Insulation glass fibers typically have nominal diameters of 1 to 10 μm, and special-purpose fibers have nominal diameters of 0.1 to 3 μm; however, a product with an average diameter of 5 μm can contain fibers with diameters ranging from less than 1 to over 20 μm (ACGIH 2001, IARC 2002).

The manufacturing process also affects fiber length. In glass wool insulation, most fibers are several centimeters long; however, fibers break crosswise, and lengths of less than 250 μm (considered to be the upper limit of respirability) probably are present in all glass wool products (IARC 2002). Respirable fibers are defined as those that can penetrate into the alveolar region of the lung upon inhalation; in humans, a fiber with an aerodynamic diameter of less than 5 μm is respirable (EPA 2001). Aerodynamic diameter, unlike geometric diameter, takes into account fiber density and aspect ratio. The World Health Organization defines respirable fibers as those with an aerodynamic diameter of less than 3 μm, a length of greater than 5 μm, and an aspect ratio of at least 3:1 (WHO 2000). In this profile, "inhalable" fibers include all fibers that can enter the respiratory tract, including respirable fibers; fiber sizes are given as geometric diameter and length except as noted.

Use

Glass fibers can generally be classified into two categories based on usage: (1) low-cost, general-purpose fibers typically used for insulation applications and (2) premium special-purpose fibers used in limited specialized applications. The primary use of glass wool is for thermal and sound insulation. The largest use of glass wool is for home and building insulation in the form of loose wool, blankets or rolls (rather than a loose filling), batts (pre-cut panels), or rigid boards for acoustic insulation. Glass wool is also used for industrial, equipment, and appliance insulation.

Special-purpose glass fibers are used for a variety of applications that require either a specialized glass formulation or a particular diameter. The largest market for special-purpose glass fibers is for battery separator media; the glass wool fibers physically separate the negative and positive plates in a battery while allowing the acid electrolyte to pass through. Another important use is in high-efficiency particulate air filters for settings where high-purity air is required. Special-purpose glass fibers are also used for aircraft, spacecraft, and acoustical insulation.

Production

Manufacture of glass wool consists of three main steps: mixing the raw materials and melting them to form glass; forming fibers (i.e., fiberizing); and finishing the products (Quinn *et al.* 2001, Smith *et al.* 2001, IARC 2002, NTP 2009). Fibers are formed when molten glass at approximately 1,370°C (2,500°F) is either forced through mechanical spinners by centrifugal force (rotary process) and separated with a blast of air or when molten glass filaments are attenuated by steam (steam blowing) or a circular burner flame (flame attenuation) and forced air that breaks the fibers into shorter lengths. The ranges of nominal diameter produced are 5 to 12 μm by steam blowing; less than 2, 2 to 4, or 4 to 8 μm by rotary blowing; and less than 2 or 2 to 4 μm by flame attenuation. If the purpose of the fibers is production of home and building insulation products, the newly formed fibers are usually sprayed with a binder, typically phenol-formaldehyde. The finishing process begins with collection of the fibers within the forming chamber to create a mat on a suction conveyor belt of porous metal in a hood. The fiber mat with binder exits the forming hood via the conveyor carrier through a gas-fired oven, which cures the binder. Final processing consists of cutting the mat into batts, rolls, or other shapes. Uncoated fibers are simply bagged.

In 2000, an estimated 3,388 million pounds (1.7 million tons) of fiberglass were used in building insulation, about 81% in residential construction and 19% in commercial or industrial construction (Maxim *et al.* 2003). The Glass Manufacturing Industry Council reported that in 2002, 10 major manufacturers operated about 40 U.S. plants producing about 3 million tons of all types of glass fiber, including glass wool (ATSDR 2004). Special-purpose glass fibers, produced by at least four U.S. companies, account for only about 1% of total annual U.S. production of synthetic vitreous fiber (Carey 2004).

The U.S. International Trade Commission reports U.S. imports and exports of nonwoven glass fiber insulation products in five product categories (including mats, thin sheets, batts, pipe coverings, and other nonwoven insulation products), some of which are reported only by dollar value, rather than by volume. From 2000 to 2008, the value of U.S. imports in these categories varied from year to year, from a low of $189 million in 2001 to a high of $356 million in 2006 (USITC 2009); for 2017, the value was $337 million (USITC 2018). The value of U.S. exports of glass fiber insulation products increased from $59 million in 2000 (USITC 2009) to $366 million in 2017 (USITC 2018). No specific category was found for imports or exports of special-purpose glass fibers.

Exposure

Occupational exposure to glass fibers by inhalation is the major issue of concern. However, the general population also may be exposed to glass wool fibers in insulation and building materials or in the air near manufacturing facilities or near building fires or implosions. Homeowners engaged in home remodeling projects potentially are exposed to insulation materials through the removal and replacement of existing products; however, no estimates were found of the number of individuals potentially exposed through these activities, or of exposure levels. No information was found on the environmental occurrence of glass fibers or on exposure levels for specific glass-fiber products. The available data suggest that air concentrations of glass fibers in indoor environments do not increase significantly after installation of insulation or from passage of air through ducts lined with glass fibers (NTP 2009).

Occupational exposure may occur during the manufacture of glass wool products, and end users of such products may be exposed during activities such as installation, removal, fabrication, or other work with glass wool outside the manufacturing environment (NTP 2009). Data from the U.S. Economic Census (USCB 2005) indicate that in 2002, 19,318 workers (15,788 in manufacturing) were employed within the North American Industrial Classification System (NAICS) code 327993, which "comprises establishments primarily engaged in manufacturing mineral wool and mineral wool (i.e., fiberglass) insulation products made of such siliceous materials as rock, slag, and glass or combinations thereof." Based on the proportions of glass wool to other mineral wools used in the production of insulation products in North America, it is likely that the majority of the workers were involved in the manufacture of glass fibers. The U.S. Bureau of Labor Statistics reported that about 53,000 workers were employed by insulation contractors in 2000 and that nearly 31,000 workers were employed as "insulation workers" within the NAICS code 238310 (Drywall and Insulation Contractors) in 2007 (BLS 2008). In addition, about 150,000 workers involved in other construction trades, such as drywall installers, carpenters, and heating and cooling specialists, install insulation and are periodically exposed to glass wool insulation materials (Maxim *et al.* 2003). The Occupational Safety and Health Administration estimated that in 1992, 185,000 full-time-equivalent construction workers were employed in the U.S. residential insulation trades (Lees *et al.* 1993).

Workplace airborne fiber exposure levels in the United States generally are measured by a standardized method developed by the National Institute for Occupational Safety and Health and used in its current form for asbestos and other fibers since 1994 (NIOSH 1994). NIOSH Method 7400 (with A or B fiber-counting rules) uses phase-contrast optical microscopy (PCOM) to count fibers deposited on an air-sampling filter (NTP 2009, Quinn *et al.* 2005). For counting purposes, Method A rules define a fiber as having a length of greater than 5 μm and an aspect ratio of at least 3:1 (diameter is not specified), and Method B rules define a fiber as having a length of greater than 5 μm, an aspect ratio of at least 5:1, and a diameter of less than 3 μm. Although these methods do not necessarily specify a minimum fiber diameter, the theoretical limit of resolution for optical microscopy of fibers is 0.25 μm; therefore, fibers less than 0.25 μm in diameter will not be counted. Based on how fibers are defined for counting purposes and on the limitations of PCOM technology, these methods do not count all sizes of fibers collected, but rather a small subset within the very broad range of sizes typically present in any given sample (Quinn *et al.* 1996, 2005).

Other fiber definitions have been proposed. Quinn *et al.* (1996) described three definitions by other research groups based on rationales for biologic activity of fibers and proposed their own exposure index: they defined "hypothetically active fibers" (HAF) (i.e., fibers having carcinogenic potential) as being over 5 μm long and less than 6 μm in diameter, with an aspect ratio of at least 3:1. Quinn *et al.* (2000) examined the potential effect of the use of different counting rules on fiber-exposure data. Fibers in air samples collected in eight U.S. glass-fiber production facilities across a wide range of manufacturing processes and products were counted and sized via electron microscopy, and a total fiber size distribution was obtained for each air sample. The ratio between HAF fibers (as defined above) and NIOSH 7400 B fibers was calculated for five samples with geometric mean diameters ranging from 0.1 to 1.73 μm. The ratios ranged from 7.91 to 0.26. These results demonstrate that the choice of fiber counting rules can have a large impact on estimated levels of exposure to glass fibers, which in some instances could result in considerable underestimation of exposure to biologically important fibers.

Analytical data reported for glass-fiber manufacturing operations generally show higher air fiber concentrations for the production of smaller-diameter fibers than for the production of larger-diameter fibers (NTP 2009). In a U.S. study of insulation glass fibers and special-purpose fibers, fiber concentrations in smaller-diameter-fiber operations were many orders of magnitude higher than concentrations in larger-diameter-fiber (insulation glass) operations; in addition, more of the fibers generated in the smaller-diameter-fiber operations were of respirable size (Dement 1975). Physical characteristics of the production plant, such as the physical layout of the equipment, room size, and local ventilation, can also affect the potential for exposure. Studies of U.S. manufacturing facilities reported maximum concentrations of 1.01 fibers/cm^3 in an individual sample for insulation-wool manufacturing and 21.9 fibers/cm^3 as a mean value for special-purpose-fiber manufacturing (NTP 2009).

For finished products, the potential for exposure depends on the accessibility of individual fibers to the air. Because fibers within a bulk fiber product are trapped by the surrounding material, only the fibers on the surface of the product can become aerosolized. Mechanical handling of products during manufacture, such as stacking, folding, rolling, and chopping, can increase aerosolization of fibers. The geometric mean diameter of airborne fibers increases with the use of oil and binders (Quinn *et al.* 2005), and oil generally is more effective than binders in reducing aerosolization (NTP 2009). The geometric mean diameter of airborne fibers decreases as the nominal diameter of the product being handled decreases (Quinn *et al.* 2005).

Nonmanufacturing occupational exposure levels for end users of glass wool products typically are higher than exposure levels in fiber-manufacturing environments. Exposure levels during installation of insulation vary depending on the product and the task performed. In a comprehensive survey of exposure from residential insulation installation in the early 1990s, workers were monitored during insulation operations in 107 houses in 11 states, and fiber exposure levels were assessed by NIOSH method 7400 B rules. Respirable-fiber concentrations during installation of glass wool batt insulation in homes ranged from 0.02 to 0.41 fibers/cm^3, with a mean of 0.14 fibers/cm^3. The installation of loose fiberglass insulation with a binder resulted in mean exposures of 0.55 fibers/cm^3 for the installer and 0.18 fibers/cm^3 for the feeder. The highest exposures were noted for installation of loose insulation without binder; exposure levels ranged from 1.32 to 18.4 fibers/cm^3 (mean = 7.67 fibers/cm^3) for installers and from 0.06 to 9.36 fibers/cm^3 (mean = 1.74 fibers/cm^3) for feeders (Lees *et al.* 1993).

In another study, average fiber exposure levels for all activities associated with the installation of commercial and residential insulation (except the blowing of thermal insulation into attics) ranged from 0.003 to 0.13 fibers/cm^3 for respirable fibers and from 0.01 to 0.14 fibers/cm^3 for total fibers (only fibers < 1 μm in diameter were

counted). For various tasks during blowing of attic insulation, average respirable-fiber exposure levels ranged from 0.31 to 1.8 fibers/cm^3, and total fiber levels ranged from 0.37 to 2.8 fibers/cm^3. For blowers (the task with the highest exposure levels), individual respirable-fiber exposure levels ranged from 0.67 to 4.8 fibers/cm^3, and total fiber levels ranged from 0.86 to 5.8 fibers/cm^3 (Esmen *et al.* 1982).

Data on exposure to glass fibers during glass wool removal are limited; however, exposure levels appear to be lower than those associated with installation, resembling levels seen in fiber manufacturing operations (Yeung and Rogers 1996).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Fine mineral fiber emissions from facilities manufacturing or processing glass (of average diameter ≤ 1 µm) are listed as a hazardous air pollutant.

New Source Performance Standards: Manufacturers of wool fiberglass are subject to provisions for the control of particulates as prescribed in 40 CFR 60.292 and 293.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

This legally enforceable PEL was adopted from the 1969 United States Department of Labor regulation *Safety and Health Standards for Federal Supply Contracts* shortly after OSHA was established. The PEL may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) = 15 mg/m^3 total fibers; = 5 mg/m^3 respirable fibers (based on the standard for "particles not otherwise regulated").

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) limit = 1 fiber/cm^3 for respirable fibers. (For comparison, the TLV for asbestos = 0.1 fiber/cm^3.)

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) for "fibrous glass dust" = 3 fibers/cm^3 (TWA) for fibers with diameter ≤ 3.5 µm and length ≥ 10 µm; = 5 mg/m^3 (TWA) for total fibers. (For comparison, the REL for asbestos = 0.1 fiber/cm^3 (TWA) for fibers > 5 µm in length.)

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