

FINAL

**Report on Carcinogens
Background Document for
Glass Wool Fibers**

September 9, 2009



U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program
Research Triangle Park, NC 27709

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FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services (DHHS), has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP), which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are reviewed in a multi-step, scientific review process with multiple opportunities for public comment. The scientific peer-review groups evaluate and make independent recommendations for each substance according to specific RoC listing criteria. This Background Document was prepared to assist in the review of glass wool fibers. The scientific information used to prepare Sections 3 through 5 of this document must come from publicly available, peer-reviewed sources. Information in Sections 1 and 2, including chemical and physical properties, analytical methods, production, use, and occurrence may come from published and/or unpublished sources. For each study cited in the background document from the peer-reviewed literature, information on funding sources (if available) and the authors' affiliations are provided in the reference section. The draft background document was peer reviewed in a public forum by an *ad hoc* expert panel of scientists from the public and private sectors with relevant expertise and knowledge selected by the NTP in accordance with the Federal Advisory Committee Act and HHS guidelines and regulations. The document has been finalized based on the peer-review recommendations of the expert panel and public comments received on the draft document. Any interpretive conclusions, comments, or statistical calculations made by the authors or peer reviewers of this document that are not contained in the original citation are identified in brackets [].

A detailed description of the RoC nomination review process and a list of all substances under consideration for listing in or delisting from the RoC can be obtained by accessing the 12th RoC at <http://ntp.niehs.nih.gov/go/9732>. The most recent RoC, the 11th Edition (2004), is available at <http://ntp.niehs.nih.gov/go/19914>.

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PEER-REVIEW

The draft background document on Glass Wool Fibers was peer reviewed by the Report on Carcinogens (RoC) expert panel for Glass Wool Fibers. The panel met in a public forum at the Sheraton Chapel Hill Hotel, Chapel Hill, NC on June 9 – 10, 2009. Members of the expert panel are as follows:

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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

**U.S. Department of Health and Human Services
National Toxicology Program**

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are as follows:

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans^{*}, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans^{*}, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

^{*} This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

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Executive Summary

1 Introduction

2 Glass is an amorphous material produced by solidification from a molten state without
3 crystallization and containing a glass former that can be melted and quenched into a
4 glassy state. Silicon dioxide is the major glass former used for commercial applications.
5 Glass wool refers to fine glass fibers forming a mass resembling wool and most
6 commonly used for insulation and filtration. Glass wool fibers were first introduced into
7 commerce in the 1930s and are now among the world's most extensively used insulating
8 materials. Special-purpose fibers make up a small fraction of the synthetic vitreous fibers
9 (SVFs) market and are used, as the name implies, in specialized applications.

10 Glass wool fiber diameters vary within a product but follow an approximately log-normal
11 distribution. The fiber diameter is controlled by the manufacturing process. Fiber
12 diameters vary based on the manufacturing process and the fibers' intended use. The
13 nominal diameter is an estimate of the average fiber diameter of the product. Insulation
14 wool products typically have nominal diameters of 1 to 10 μm and special-purpose fibers
15 have nominal diameters of 0.1 to 3 μm . The diameters of individual fibers in a glass wool
16 product vary widely around the nominal diameter. Unlike crystalline fibers, such as
17 asbestos, glass fibers do not split lengthwise into fibers with smaller diameters, but only
18 break across the fiber resulting in shorter fibers with the same diameter.

19 SVFs and other mineral fibers have been classified according to origin (natural vs.
20 manufactured), chemistry (organic vs. inorganic), physical form and morphology (e.g.,
21 filaments and wools), or commercial applications (e.g., insulation wools and special-
22 purpose fibers).

23 Fibers, classified by their physical dimensions, have been basically defined since the late
24 1950s as being greater than 5 μm long and having a length-to-width (aspect) ratio of at
25 least 3:1 (i.e., the fiber is at least three times longer than its width). WHO defines fibers
26 as being greater than 5 μm long, thinner than 3 μm , and having an aspect ratio of $> 3:1$.

1 Fibers have also been examined based upon other characteristics, including
2 biopersistence, retention and clearance rates, and biodurability. The European Union
3 (EU) and Germany have established criteria for labeling and classifying SVFs based on
4 their potential to be hazardous to human health.

5 **Human Exposure**

6 The vast majority of SVF produced and used in the United States consists of glass wool
7 used for home and building insulation. Small amounts of glass fibers are produced for
8 special applications such as use in battery separator media, high-efficiency filters, and
9 aircraft insulation. Glass wool is produced by heating the glass to high temperatures,
10 extruding the molten glass to form small streams of glass fibers, and using centrifugal
11 force to attenuate the streams of glass into glass fibers. Finer fibers are formed by flame
12 attenuation. Most general purpose insulation glass wools have nominal diameters ranging
13 from 1 to 10 μm , while special-purpose fibers generally range from 0.1 to 3 μm ;
14 however, product bulk samples may have fibers with diameters that are several times
15 greater or smaller than the nominal diameters. ACGIH noted that because of this
16 variation, all wool fiber products contain respirable fibers. The physical properties of
17 fibers affect their likelihood of becoming airborne, with smaller fibers more likely to
18 become airborne. Because of this, the average diameter and length may be smaller, and
19 the percentage of respirable fibers higher, for airborne fibers compared with the bulk
20 product.

21 Occupational exposure may occur in manufacturing facilities as well as for end-users,
22 such as during installation, removal, fabrication, or otherwise working with glass wool
23 outside the manufacturing environment (end-use). OSHA has estimated that more than
24 225,000 workers in the United States are exposed to synthetic mineral fibers in
25 manufacturing and end-use applications. General population exposure may occur from
26 exposure to SVFs from insulation and building materials or from fibers in the air near
27 manufacturing facilities or areas near building fires or implosions. Exposure may also
28 occur during do-it-yourself home remodeling activities.

1 No traditional biological indices of exposure exist for SVFs, although the measurement
2 of fibers in human lung tissue has been attempted as a means to assess exposure to SVFs.
3 In addition, a recent study investigated the use of nasal lavage as a biomonitoring method
4 for SVFs.

5 Fine mineral fiber emissions are regulated by the EPA, respirable fibers (“particulates not
6 otherwise regulated”) are regulated by OSHA; ACGIH, NIOSH, and OSHA have set
7 guidelines for fibers in the air in the workplace.

8 **Human Cancer Studies**

9 A number of epidemiological studies have evaluated the relationship between glass wool
10 exposure and cancer in humans. The studies fall into three main groups: (1) cohort and
11 case-control studies of workers in SVF manufacture, (2) cohort and case-control studies
12 of workers exposed in glass wool applications (e.g., insulators and construction workers),
13 and (3) population-based, case-control studies.

14 Studies within the SVF manufacturing industry have attempted to distinguish between
15 exposure to different types of SVF, and the large cohort and nested case-control studies
16 of workers exposed in plants predominantly engaged in glass wool manufacture are the
17 most informative. [The principal limitations of the glass wool cohort and case-control
18 studies of manufacturing workers include potential misclassification of exposure,
19 particularly for past exposures for which few monitoring data are available, inadequate
20 length of follow-up in some studies for cancers of longer latency, potential confounding
21 by smoking or co-exposure to other chemicals, and possible misdiagnosis or inadequate
22 ascertainment of some cancer outcomes, such as mesothelioma. Studies of workers in
23 SVF applications (two cohort studies and three case-control studies of respiratory cancer)
24 and the population-based, case-control studies or cancer registry studies (cancers of the
25 respiratory and/or gastrointestinal tract, non-Hodgkin’s lymphoma, breast, colon, ovary
26 and rectum) have generally been unable to distinguish between types of fibers and are
27 consequently less informative, although intermittent exposures might be higher than
28 observed among manufacturing workers (IARC 2002). In addition, these studies
29 generally had small numbers of potentially glass wool-exposed subjects and shorter

1 follow-up times than studies of manufacturing workers, and thus, limited statistical power
2 to detect long-term effects.]

3 Cancer mortality or incidence has been studied in four cohorts of manufacturing workers:
4 (1) a combined cohort of male and female U.S. SVF manufacturing workers including
5 five plants making mostly glass wool and three making glass wool and filament (Marsh *et al.*
6 *et al.* 2001a, Stone *et al.* 2004), (2) a combined cohort of male and female manufacturing
7 workers in five European glass wool plants (Boffetta *et al.* 1997, 1999), (3) a cohort of
8 male manufacturing workers in Canada (Shannon *et al.* 2005), and (4) a cohort of male
9 manufacturing workers in France (Moulin *et al.* 1986). [The cohorts of manufacturing
10 workers in the United States and Europe are the largest studies and have adequate follow-
11 up to detect cancers with longer latencies (220,700 person-years of exposure in the U.S.
12 cohort and approximately 201,000 person-years of exposure in the European cohort).] In
13 both cohorts, several earlier studies of subcohorts have been conducted, together with two
14 nested case-control studies of respiratory cancer in the U.S. cohort (Marsh *et al.* 2001a,
15 Chiazze *et al.* 1992, 1993) and one of lung cancer from part of the European cohort
16 (Gardner *et al.* 1988).

17 Reconstruction of glass wool exposures indicated that measurable exposure to respirable
18 glass wool fibers occurred among production workers, and that exposure was higher in
19 the earlier periods of operations. However, as IARC (2002) noted, the concentrations of
20 fibers to which production workers were exposed were generally low.

21 The potential effect of glass wool exposure on lung and upper respiratory tract cancers
22 has been studied most extensively, due to the structural similarity between glass wool,
23 other SVFs, and asbestos. Findings for respiratory cancers and other tumor sites of
24 interest are discussed below.

25 *Respiratory cancers*

26 Statistically significant increases in respiratory cancer mortality were observed among
27 glass wool-exposed workers in unadjusted analyses in the United States (SMR = 1.18,
28 95% CI = 1.04 to 1.34, $P < 0.05$, lung + larynx, compared with local rates) (Marsh *et al.*

1 2001a), European (SMR = 1.27, 95% CI = 1.07 to 1.50, *P*-value not given, lung only,
2 compared with national rates) (Boffetta *et al.* 1997), and Canadian cohorts (SMR = 1.63,
3 95% CI = 1.18 to 2.21, *P* < 0.05, lung only, compared with regional rates) (Shannon *et al.*
4 2005). Among female workers in the U.S. cohort, no increase in respiratory cancer
5 (trachea, bronchus, and lung) was observed in the whole cohort compared with national
6 or local mortality rates, but in an internal analysis of glass wool-only vs. filament-only-
7 exposed workers, a three-fold increase in these cancers was observed (RR = 3.24, 95% CI
8 = 1.27 to 8.28, Wald *P*-value = 0.014) (Stone *et al.* 2004). Excesses of lung cancer
9 incidence were observed among the European workers (SIR = 1.28, 95% CI = 0.91 to
10 1.74, compared with national rates, *P*-value not given) (Boffetta *et al.* 1999) and
11 Canadian workers (SIR = 1.60, 95% CI = 1.19 to 2.11, *P* < 0.05, compared with regional
12 rates) (Shannon *et al.* 2005), but not among French workers (SIR = 0.74, 95% CI = 0.24
13 to 1.72, compared with regional rates) (Moulin *et al.* 1986).

14 Attempts were made to control for the effects of smoking and other potentially
15 confounding exposures, including asbestos, formaldehyde, and silica, in the nested case-
16 control study of the U.S. cohort. Adjusting for ever/never smoking (using data obtained
17 from a sample of proxies) reduced the risk of lung cancer mortality among U.S. glass
18 wool workers exposed to respirable fibers (mostly from glass wool) from RR = 1.79
19 (95% CI = 0.77 to 4.14, *P* = 0.17) to RR = 1.37 (95% CI = 0.55 to 3.42, *P* = 0.50).
20 (Formaldehyde exposure was also independently associated with lung cancer in this
21 cohort, but models for glass wool and lung cancer adjusting for both formaldehyde and
22 smoking were not presented.) [The European, Canadian, and French studies had few data
23 on potentially confounding exposures.]

24 Several studies evaluated exposure-response relationships for respiratory cancers. In the
25 U.S. cohort and case-control studies, no clear exposure-response relationships with
26 duration of exposure or cumulative exposure were observed. An association between
27 average intensity of exposure was observed in an unadjusted model but not in models
28 adjusted for smoking or other confounders or in weighted-exposure models (Marsh *et al.*
29 2001a, Stone *et al.* 2001, Youk *et al.* 2001). There was a modest trend towards increased
30 risk with longer time since first hire in the U.S. but not the European cohort. Similarly, in

1 the nested case-control studies of lung cancer among the U.K. subgroup of the European
2 cohorts, no clear exposure-response relationships with lung cancer were observed, with
3 the exception of a statistically significant increase among glass wool and/or superfine
4 fiber-exposed workers after 10 to 19 years since first hire in the case-control study of the
5 U.K. subcohort by Gardner *et al.* (1988) (RR = 2.0, confidence intervals not given, 17
6 cases). In the Canadian cohort, there was some evidence of a trend towards increased risk
7 with longer duration of employment, time since first hire, and year of hire (Shannon *et al.*
8 2005).

9 Statistically significant increases in lung cancer risk were found among insulation
10 installers in Germany (OR = 1.48, 95% CI = 1.17 to 1.88, 304 cases) and among
11 combined insulation installers and electrical insulation fitters with either 20 or more years
12 (OR = 1.69, 95% CI = 1.01 to 2.81, 61 cases) or 30 or more years (OR = 2.03, 95% CI =
13 1.04 to 3.95, 47 cases) of potential exposure (Bruske-Hohlfeld *et al.* 2000). However, no
14 increases in lung cancer risk were found in other studies of construction and application
15 workers or in the population-based, case-control studies of lung cancer. [In general, glass
16 wool exposure cannot be distinguished from other SVF exposure in these studies, and
17 few attempts to adjust for smoking and other confounders were conducted.]

18 *Mesothelioma*

19 Only one death from mesothelioma was observed among glass wool-exposed workers in
20 the European cohort (Boffetta *et al.* 1997). Marsh *et al.* (2001b) observed seven possible
21 deaths from malignant mesothelioma among the glass wool- or glass wool + filament-
22 exposed workers, but a review of pathology reports or medical records, which were
23 available for only three of these cases, showed that at least two of them were possible
24 misdiagnoses. An earlier case-control study by Rödelsperger *et al.* (2001) reported a
25 three-fold increase in risk of mesothelioma among mixed SVF-exposed individuals after
26 adjustment for asbestos and other potential confounders (OR = 3.08, 95% CI = 1.17 to
27 8.07, $P < 0.05$, 55 cases), and a two-fold increase in pleural mesothelioma incidence (SIR
28 = 2.13, 95% CI = 1.35 to 3.20, 23 cases) was observed among a cohort of construction
29 workers by Engholm *et al.* (1987), but confounding by asbestos might have occurred in
30 these studies.

1 *Upper respiratory and upper gastrointestinal cancers*

2 Marsh *et al.* (2001a) did not report these cancers separately for the glass wool-exposed
3 workers, but no increases in these cancers were observed in the combined (glass wool-
4 and filament-exposed) cohort (SMR for larynx = 1.01, 95% CI = 0.68 to 1.45, 29 deaths;
5 SMR for buccal cavity and pharynx = 1.11, 95% CI = 0.85 to 1.42, 63 deaths). In the
6 European cohort, a small increase in buccal cavity + pharyngeal mortality and incidence
7 (SMR = 1.47, 95% CI = 0.71 to 2.71, 10 deaths; SIR = 1.31, 95% CI = 0.65 to 2.34, 11
8 cases), and in laryngeal mortality and incidence (SMR = 1.08, 95% CI = 0.29 to 2.75, 4
9 deaths, and SIR = 1.68, 95% CI = 0.55 to 3.93, 5 cases), was observed among glass wool-
10 exposed workers (Boffetta *et al.* 1997, 1999). Moulin *et al.* (1986) reported a statistically
11 significant excess of “upper respiratory and alimentary tract” cancers in the French cohort
12 (SIR = 2.18, 95% CI = 1.31 to 3.41, 19 cases, including one unexposed production
13 worker and one maintenance worker). In a hospital-based, case-control study, Marchand
14 *et al.* (2000) reported small increases in both laryngeal cancers (OR = 1.33, 95% CI =
15 0.91 to 1.95, 133 cases) and hypopharyngeal cancers (OR = 1.55, 95% CI = 0.99 to 2.41,
16 99 cases; each analysis adjusted for smoking, age, and alcohol intake) among men ever
17 exposed to “mineral wools.” When a 15-year latency period was used, the risks of
18 laryngeal and hypopharyngeal cancer increased (OR = 1.5, 95% CI = 1.03 to 2.22, and
19 1.65, 95% CI = 1.05 to 2.58, respectively, cases not specified). No significant interaction
20 with asbestos exposure was observed, but few subjects were exposed to mineral wools
21 and not to asbestos.

22 *Other cancer sites*

23 No statistically significant excesses of other tumors have been reported in the largest
24 cohort mortality or incidence studies of production workers or construction workers.
25 [Note that some studies did not report data for all cancer sites.] A number of elevated
26 risks (SMRs or SIRs above 1.0) have been reported for a number of sites in single
27 studies, but only for the following cancer sites in more than one cohort study (excluding
28 earlier studies of subcohorts or earlier follow-ups): deaths or cases of
29 lymphohematopoietic cancers (Boffetta *et al.* 1997, 1999; Gustavsson *et al.* 1992);
30 cancers of the urinary bladder (Boffetta *et al.* 1997, 1999; Marsh *et al.* 2001a, Stone *et al.*

1 2004); melanoma (Boffetta *et al.* 1999, Gustavsson *et al.* 1992); and stomach cancers
2 (Boffetta *et al.* 1997; Shannon *et al.* 2005; Gustavsson *et al.* 1992).

3 In population-based, case-control or registry studies of subjects with possible exposure to
4 glass wool, statistically nonsignificant increases in pre- and postmenopausal breast cancer
5 and ovarian cancer (Vasama-Neuvonen *et al.* 1999, Weiderpass *et al.* 1999) and in
6 stomach, esophageal, rectal, gallbladder, and pancreatic cancers (Weiderpass *et al.* 2003)
7 were observed among Finnish women. A marginally significant increase in rectal cancer
8 (Dumas *et al.* 2000) and colon cancer (Goldberg *et al.* 2001) was observed among men in
9 Montreal with “substantial” estimated exposure to glass wool. [Note that statistically
10 nonsignificant increases in rectal cancer were also seen in the cohort study of Shannon *et*
11 *al.* (2005), and in pancreatic cancer in the cohort study of Gustavsson *et al.* (1992).]
12 Finally, a marginally significant increase in non-Hodgkin’s lymphoma was observed by
13 Hardell and Ericksson (1999).

14 **Studies in Experimental Animals**

15 Numerous studies of various types of commercial insulation glass wools, special-purpose
16 glass fibers, and some experimental fibers have been conducted for carcinogenicity in
17 experimental animals by inhalation, intraperitoneal (i.p.) injection, intrapleural injection,
18 intratracheal instillation, and intrathoracic injection or implantation.

19 Although all inhalation studies conducted prior to the late 1980s were negative, the
20 results were considered inconclusive because of various study limitations recognized by
21 researchers in the field, including a failure in some studies to produce tumors in positive
22 control groups exposed to asbestos fibers. A series of long-term inhalation studies were
23 conducted in rats and hamsters in the late 1980s and early 1990s to address the
24 limitations of the earlier studies. Two glass wool fibers (MMVF10 and MMVF11) and
25 two special-purpose fibers (JM100/475 and 104E) were tested in separate studies.
26 Significantly increased incidences of lung carcinomas combined with adenomas occurred
27 in male Wistar rats exposed to 104E microfibers but not to JM100/475 fibers; no
28 significant increases in lung tumors or mesotheliomas were reported for male F344 rats
29 exposed to MMVF10, or MMVF11. However, there were apparent positive trends for

1 both adenomas and combined tumors in male F344 rats exposed to MMVF10.
2 Mononuclear-cell leukemia incidence was statistically significant for F344 rats exposed
3 to Owens-Corning or JM100/475 glass fibers for 86 weeks. In the most recent inhalation
4 study in male hamsters, a mesothelioma was observed in 1 of 83 animals exposed to
5 JM100/475 glass fibers for 78 weeks. Although this result was not statistically
6 significant, the authors considered it treatment related.

7 Significantly increased incidences of peritoneal tumors (primarily mesothelioma) were
8 reported in almost all i.p. injection studies in rats using different types of fibers including
9 insulation fibers such as MMVF10 and MMVF11 and special-purpose fibers such as
10 JM475 (various diameters), M753, and E glass. However, no tumors were observed in
11 some studies testing experimental fibers that have low biodurability. In most cases, tumor
12 incidences were similar to those seen in the asbestos treatment groups. In addition,
13 increased incidences of pleural sarcomas occurred in rats following intrathoracic
14 implantation of some glass fibers (depending on the fiber dimensions) but not others.
15 Increased incidences of neoplasms (mesothelioma, pleural sarcoma, and lung carcinoma)
16 were observed in some intrapleural or intratracheal instillation studies in rats exposed to
17 JM100 or JM104 microfibers and in intratracheal instillation studies in hamsters exposed
18 to JM104 microfibers. No tumors were reported following intrapleural or intratracheal
19 instillation of glass wool in mice, guinea-pigs, or rabbits.

20 A number of studies, including both intrathoracic implantation and i.p. injection of fibers,
21 have been conducted with the intent of comparing fibers with different characteristics,
22 such as differing fiber dimensions and biopersistence/durability. The earliest of these
23 studies by Stanton and co-workers using intrathoracic implantation of glass fibers and
24 other natural and synthetic fibers led the authors to conclude that fiber dimensions and
25 durability were important in determining the tumorigenicity of the material. Later studies
26 using i.p. injection reached similar conclusions in many cases, but some data suggest that
27 the relationship might not be completely defined by those fiber characteristics.

28

1 **Deposition, clearance, and retention**

2 Fibers that are carried in the inhaled air to the tracheobronchial region are considered
3 *inhalable* while those that reach the alveolar region are considered *respirable*. Fibers that
4 are inhalable but non-respirable can deposit in the extrathoracic and tracheobronchial
5 regions and can cause adverse effects. Deposition refers to the actual dose deposited in
6 the lung and is influenced by the anatomy and physiology of the airway, respiratory rate,
7 and physical properties of the fiber. Deposition occurs by impaction, sedimentation,
8 interception, and diffusion. Peak deposition occurs in rodents and humans for fibers with
9 aerodynamic diameters of 1 to 2 μm .

10 Clearance and retention of fibers are affected by chemical composition, size distribution,
11 number of fibers deposited, and time since last exposure. Clearance mechanisms also
12 depend on the region of deposition. Short fibers are readily phagocytized by alveolar
13 macrophages and transported from the lower lung to the upper airways and cleared
14 through the mucociliary escalator, or they can be cleared via lymphatics. Long fibers are
15 not effectively cleared by phagocytosis, and can effectively kill the phagocyte, but
16 depending on the fiber type, may be subject to dissolution and transverse breakage.
17 Particle overload (which has been observed in rats) occurs when the deposition rate of
18 poorly-soluble, less toxic particles exceeds the normal clearance rate, and can result in
19 adverse effects.

20 **Dissolution, biodurability, and biopersistence of glass fibers**

21 Dissolution occurs when water molecules attack the surface of the fiber and remove
22 material. Biodurability describes the rate of removal through dissolution or
23 disintegration; biopersistence includes biodurability plus physiological clearance and
24 refers to the capacity of a fiber to persist and to conserve its chemical and physical
25 features over time in the lung. Biodurability is expected to be similar in rats and humans,
26 but biopersistence may be substantially different due to differences in the physiological
27 clearance mechanisms. In general, biodurability of various fibers in the lung has been
28 ranked as follows: glass fibers < refractory ceramic fibers < chrysotile asbestos <
29 amphibole asbestos. Highly durable fibers, such as asbestos, are resistant to dissolution

1 and transverse breakage. Although experimental dissolution rates for glass fibers show
2 variability (up to a 30-fold range), they generally show some correlation with clearance
3 rates of long fibers in short-term biopersistence studies. Certain components of SVFs are
4 subject to leaching resulting in changes in composition over time. The literature indicates
5 that the special-purpose fibers cited in this document tend to have greater biopersistence
6 than the insulation glass wools. The fibers become weaker from fractures, peeling, and
7 pitting and may break.

8 **Toxic effects**

9 Several studies have evaluated mortality from non-malignant respiratory disease or
10 morbidity related to the respiratory system among workers exposed to glass wool. A
11 significantly elevated SMR for non-malignant respiratory disease was found in the earlier
12 updates, but not the most recent update of the large U.S. cohort study. Mixed findings
13 have also been observed for adverse respiratory symptoms, pulmonary function, and lung
14 abnormalities (detected on chest radiographs); workers in some studies were also exposed
15 to asbestos.

16 Various types of glass wool fibers (MMVF10, MMVF11, 104E glass fibers, JM100/475
17 microfibers) caused adverse lung effects (such as inflammation and fibrosis) in rats
18 exposed by inhalation (Bellmann *et al.* 2003, Bermudez *et al.* 2003, Cullen *et al.* 1997,
19 Hesterberg *et al.* 1993, 2002). In hamsters, inhalation of MMVF10 fibers caused
20 inflammatory effects, but not fibrosis (Bermudez *et al.* 2003, Hesterberg *et al.* 1993). In
21 cytotoxicity studies, longer fibers induced greater toxicity in rat alveolar macrophages
22 (Blake *et al.* 1998, Hart *et al.* 1994).

23 **Genetic and related effects**

24 Glass fibers were shown to induce production of reactive oxygen species in cell-free
25 systems and cultured cells, to damage DNA, and to cause chromosomal aberrations,
26 nuclear abnormalities, mutations, gene amplification in proto-oncogenes, and cell
27 transformation in mammalian cells. However, glass wool fibers did not cause mutations
28 in bacteria or cause sister chromatid exchange in mammalian cells, but only two types of
29 fibers were tested in each of these assays. Glass wool fibers also induced DNA strand

1 breaks (measured by the comet assay) in macrophages and lung epithelial cells, and
2 oxidative stress in rats, but did not induce mutations *in vivo*. An increase in mutant
3 frequencies was reported for benzo[*a*]pyrene and rock wool fibers instilled
4 simultaneously in Big Blue rats.

5 Further, fiber persistence may also lead to inflammation-driven (indirect) genotoxicity, as
6 reactive inflammatory cells release reactive oxygen species, growth factors, and
7 cytokines. Fiber characteristics did not appear to be important in the production of
8 reactive oxygen species, and studies assessing oxidative damage by different endpoints
9 were positive for both special-purpose fibers and insulation glass wool fibers. Similarly,
10 fibers of different lengths and diameters were able to cause DNA damage in mammalian
11 cells. However, effects on chromosomes and nuclear abnormalities might be related to
12 fiber characteristics; longer fibers appeared to be more potent in causing these genotoxic
13 effects. Some studies suggested that thinner fibers were also more effective. Results from
14 cell transformation studies also suggested that longer and thinner fibers produced higher
15 transformation efficiency.

16 **Mechanisms of fiber carcinogenicity**

17 Several investigators have evaluated fiber characteristics (dimensions and durability or
18 biopersistence) and tumorigenicity in studies in experimental animals. These studies (by
19 i.p. injection and intrathoracic implantation) show that fiber dimensions and durability
20 were important determinants of tumorigenicity. In intrathoracic implantation studies,
21 pleural sarcomas were correlated with fiber dimensions; long, thin fibers were associated
22 with the highest tumor incidence. Fibers with a high dissolution rate tended to have a low
23 potency in the i.p. assay. A relationship between biopersistence in the lung and pathology
24 was also observed in inhalation studies in rats. Clearance half-times of long fibers (> 20
25 μm) were approximately 400 to 800 days for two types of asbestos, 80 days for E glass,
26 50 days for JM100/475 glass, 15 days for MMVF10, and 9 days for MMVF11.

27 The major proposed mechanisms of fiber-induced carcinogenicity are related to the
28 physical and chemical properties (such as size or dimensions, durability, surface
29 reactivity, and chemical composition) of the fibers and to the inflammatory response that

1 results from the inhalation of fibers. Fiber size affects deposition and clearance, and
2 biodurability and biospersistence are related to biological effects. Fibers can directly
3 interact with target cells (epithelial cells, mesothelial cells, fibroblasts) leading to an
4 inflammatory response and/or genotoxicity. Fibers may induce genotoxic effects by
5 interacting with the spindle apparatus of chromosomes, directly damaging DNA, or
6 indirectly damaging DNA through chronic inflammation. Fibers may also induce
7 epigenetic changes. Alveolar macrophages are activated in response to particulates or
8 fibers deposited in the lung, resulting in increased release of reactive oxygen species,
9 chemical mediators, and cytokines (such as TNF- α) and activation of signalling
10 pathways. A sustained inflammatory reaction may result from incomplete phagocytosis
11 and prolonged interaction of persistent fibers with the cell surface. Chronic imbalance
12 between cytokines and growth factors may contribute to tissue injury, proliferation,
13 and/or apoptosis, which may lead to fibrosis and tumors.

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Abbreviations

ACGIH:	American Conference of Governmental Industrial Hygienists
AES:	alkaline earth silicate wools
AGM:	absorptive glass mat separator
AIE:	average intensity of exposure
AP-1:	transcription factor activator protein-1
BGU:	β -glucuronidase
BLS:	Bureau of Labor Statistics
b.w.:	body weight
CAT:	catalase
CHO:	Chinese hamster ovary
CI:	confidence interval
cm:	centimeter
D:	diameter
d:	day
D _A :	aerodynamic diameter
dG:	deoxyguanosine
DHHS:	Department of Health and Human Services
DNA:	deoxyribonucleic acid
EIPPCB:	European Integrated Pollution Prevention and Control Bureau

EM:	electron microscopy
EPA:	United States Environmental Protection Agency
EU:	European Union
F:	glass filament
F344:	Fischer 344 rats
Fpg:	formamidopyrimidine DNA glycosylase
FPB:	fiber production group
F.R.G.:	Federal Republic of Germany
ft:	feet
GMIC:	Glass Manufacturing Industry Council
GW:	glass wool
HAP:	hazardous air pollutant
HDN:	high alumina containing rock wool
HEPA:	high efficiency particulate air [filter]
h:	hour
HSPP:	Health and Safety Partnership Program
HT:	high-alumina, low-silica wools
i.p.:	intraperitoneal
i.pl.:	intrapleural injection
i.t.:	intratracheal instillation

i.th.:	intrathoracic implantation
IARC:	International Agency for Research on Cancer
ICD:	International Classification of Diseases
IFN:	interferon
IGW:	insulation glass wool
IL:	interleukin
JM:	Johns Manville
K:	kurz, German for short
K_{dis} :	dissolution rate
KI:	carcinogenicity index
KNB:	soluble components index
L:	length (lange, German for long)
LDH:	lactate dehydrogenase
LM:	light microscopy
M:	medium
m:	meter
MFTD:	maximum functionally tolerated dose
mg:	milligram
MMMF:	man-made (or machine-made) mineral fibers
MMVF:	man-made (or machine-made) vitreous fibers

MMWR:	Morbidity and Mortality Weekly Report
MN:	Manville
MTD:	maximum tolerated dose
NA:	not applicable
NAICS:	North American Industrial Classification System
NAIMA:	North American Insulation Manufacturers Association
NF:	nuclear transcription factor
NF- κ B:	nuclear factor kappa B
NHL:	non-Hodgkin's lymphoma
NIOSH:	National Institute for Occupational Safety and Health
NMRD:	non-malignant respiratory disease
NR:	not reported
NS:	not specified
NTP:	National Toxicology Program
8-OHdG:	8-hydroxy-2'-deoxyguanosine
OR:	odds ratio
OSHA:	Occupational Safety and Health Administration
p:	density
PEL:	permissible exposure limit
PVNO:	polyvinyl-pyridine- <i>N</i> -oxide

r:	correlation coefficient
r ² :	coefficient of determination, a statistical measure of goodness of fit of a model
RCF:	refractory ceramic fiber
Rfib:	respirable fibers
Rfib, no FOR:	respirable fibers exposure without concurrent formaldehyde exposure
Rfib + FOR:	concurrent respirable fibers and formaldehyde exposure
RoC:	Report on Carcinogens
ROS:	reactive oxygen species
RR:	relative risk
RSC:	respiratory system cancer
S&S:	Schleicher & Schuell
SEM-EDX:	scanning electron microscopy with energy-dispersive X-ray microanalysis
SES:	socio-economic status
SIR:	standardized incidence ratio
SMR:	standardized mortality ratio
SOD:	superoxide dismutase
SPF:	special-purpose glass fibers
SVFs:	synthetic vitreous fibers
T _{1/2} :	half-time

TIMA:	Thermal Insulation Manufacturers Association
TLV:	threshold limit value
TNF:	tumor necrosis factor
TRGS:	Technical Rules for Hazardous Substances (Germany)
TWA:	time-weighted average
U.K.:	United Kingdom
UICC:	Union Internationale Contre le Cancer (International Union Against Cancer)
USCB:	United States Census Bureau
USDOL:	United States Department of Labor
USITC:	United States International Trade Commission
WHO:	World Health Organization
wk:	week
WT _{1/2} :	weighted lung clearance half-time
WTC:	World Trade Center
χ^2 :	chi-square statistical test
yr:	year
μm :	micron, micrometer, one-millionth of a meter

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1 Introduction

2 Glass wool refers to fine glass fibers forming a mass resembling wool and most
3 commonly used for insulation and filtration. Glass is an amorphous material produced by
4 solidification from a molten state without crystallization and containing a glass former
5 (e.g., silicon dioxide [SiO₂], boron trioxide [B₂O₃], phosphorus pentoxide [P₂O₅], or
6 germanium dioxide [GeO₂]) that can be melted and quenched into a glassy state (IARC
7 2002). Silicon dioxide is the major glass former used for commercial applications
8 because of its availability and low cost, but commercial glasses generally include
9 additional oxides that modify the physical and chemical properties of the glass product,
10 including viscosity, which is an important characteristic for fiberization. These modifiers
11 include oxides of aluminum, titanium, zinc, magnesium, lithium, barium, calcium,
12 sodium, and potassium.

13 There are two categories of glass wool based upon usage in commercial applications:
14 insulation glass wool and special-purpose fibers. Insulation glass wools are used for
15 applications such as thermal, electrical, and acoustical insulation and in weatherproofing,
16 while the term “special-purpose glass fibers” is used to describe a category of fibers
17 distinguished by their use in specialized products that include aircraft and aerospace
18 insulation, battery separators, and high-efficiency filters.

19 Glass wool (respirable size) has been listed in the *Report on Carcinogens* since the
20 Seventh Edition (1994) as *reasonably anticipated to be a human carcinogen*. It was
21 nominated for delisting from the Report on Carcinogens by the North American
22 Insulation Manufacturers Association based on the 2002 IARC reevaluation of glass
23 wool. The 2002 IARC monograph evaluated Man-Made Vitreous Fibers, which included
24 glass wool, as well as continuous glass filament, rock (stone) wool, slag wool, refractory
25 ceramic fibers, and newly developed fibers. Glass wool was further divided into the
26 categories of insulation glass wool and special-purpose fibers (see Sections 1.1.2 and
27 1.2). The 2002 IARC Working Group concluded that there was *inadequate evidence* in
28 humans for the carcinogenicity of glass wool. They further concluded that there was
29 *limited evidence* in experimental animals for the carcinogenicity of insulation glass wool

1 and classified insulation glass wool as Group 3, *not classifiable as to its carcinogenicity*
2 *in humans*. Special-purpose glass fibers such as E-glass and 475 fibers were classified as
3 Group 2B, *possibly carcinogenic to humans*, based on *sufficient evidence* in experimental
4 animals.

5 The following sections provide an overview of the various categories of synthetic
6 vitreous fibers (SVFs) (Section 1.1), the chemical and physical characteristics of glass
7 wools (Section 1.2), and methods for fiber classification (Section 1.3).

8 **1.1 Synthetic vitreous fibers**

9 SVFs are a large category that comprises glass wools, as well as other types of glass
10 fibers not covered by this nomination, e.g., continuous glass filaments, and other types of
11 "wools" such as rock wool, slag wool, and ceramic fibers. The general class of SVFs is
12 defined in Section 1.1.1, and the categories of SVFs as defined by IARC (2002) are
13 discussed in Section 1.1.2.

14 *1.1.1 Definition of SVFs*

15 SVFs are manufactured inorganic fibrous materials that contain aluminum or calcium
16 silicates, and are made from a variety of materials, including rock, clay, slag, or glass
17 (ATSDR 2004). Fibers are distinguished from other irregularly shaped particulate matter
18 based on their tendency to form particles with a large aspect ratio (length to diameter
19 ratio). Fibrous particulate matter can be either naturally occurring, like asbestos, or
20 synthetic. SVFs differ from asbestos and other naturally occurring mineral fibers because
21 they have an amorphous or glass-like rather than a crystalline structure. The absence of a
22 crystalline structure can be used to aid in their identification. Historically SVFs have been
23 referred to as man-made mineral fibers (MMMFs), or man-made vitreous fibers
24 (MMVFs), although the terms used in the United Kingdom have been defined as
25 "machine-made" to preserve the acronyms and maintain gender neutrality. The exact
26 nomenclature and taxonomy used to classify these materials have changed over time and
27 are currently the focus of debate as reviewed by Moore *et al.* (2002).

28 Glass wool fibers were first introduced into commerce in the 1930s and are now among
29 the world's most extensively used insulating materials. IARC (2002) described wool

1 (such as glass wool) as “a mass of tangled, discontinuous fibres of variable lengths and
 2 diameters” and contrasted it with filaments, “which are continuous fibres (of
 3 indeterminate length) with diameters having ranges that are more uniform and typically
 4 thicker than those of wool.”

5 **1.1.2 Categories of SVFs**

6 SVFs and other mineral fibers have been classified according to origin (natural versus
 7 manufactured), chemistry (organic versus inorganic), physical form and morphology
 8 (e.g., filaments and wools), or commercial applications (e.g., insulation wools and
 9 special-purpose fibers). IARC (2002) divided SVFs into the categories shown in Figure
 10 1-1. However, there are a number of commercial and experimental products within each
 11 category that vary in composition, dimensions, durability, and biological activity. The
 12 categories identified by IARC are based on physical form and commercial applications,
 13 but Moore *et al.* (2002) and other authors have proposed methods for grouping fibers
 14 according to potential biological activity (Figure 1-2).

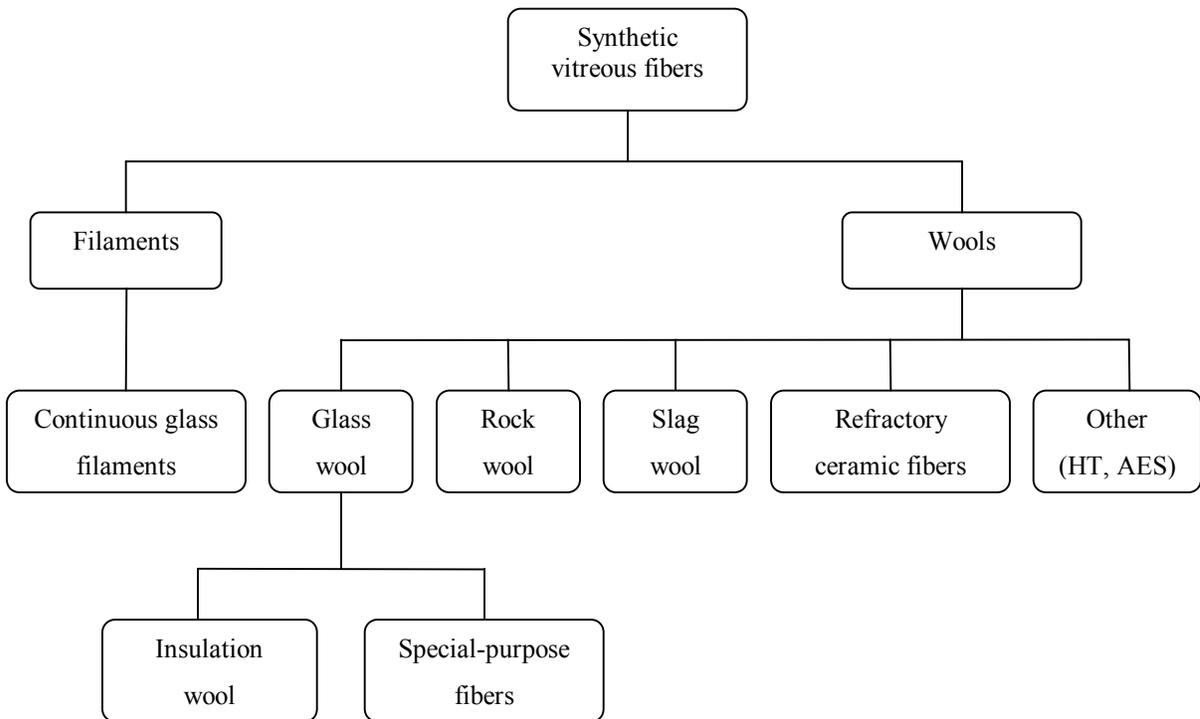


Figure 1-1. Categories of synthetic vitreous fibers

Source: adapted from IARC (2002).

HT = high-alumina, low-silica wools; AES = alkaline earth silicate wools.

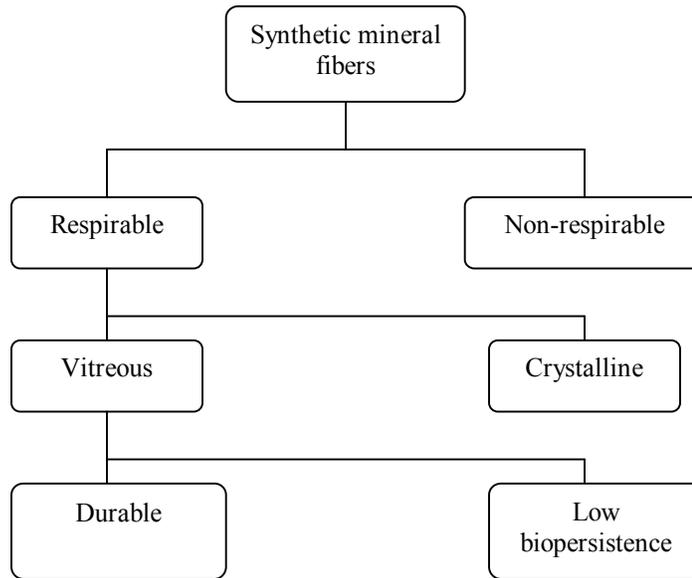


Figure 1-2. Proposed fiber categorization scheme to facilitate hazard identification

Source: adapted from Moore *et al.* (2002).

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As illustrated in Figure 1-1, glass wool can be divided into two sub-categories, insulation wool and special-purpose fibers. Special-purpose fibers make up a small fraction of the glass wool market and are used, as the name implies, in specialized applications (see Section 2.1). Special-purpose fibers are more highly engineered than glass wool and typically contain oxides such as ZnO, ZrO₂, and BaO that improve the ability to fiberize the glass at diameters below 1 μm and increase durability, as reported in a public comment in response to FR 2004 (Carey 2004)¹. Therefore, special-purpose fibers typically are smaller in diameter, more durable, and more biopersistent than the typical insulation glass wool. Biopersistence and toxicity will be discussed later in this review. Although most published information about special-purpose fibers refers to 475 and E-glass, there are many other types. Although each manufacturer has its own product designations, special-purpose fibers share in common certain physical and chemical characteristics described in this section. In addition to 475 and E-glass, examples of other special-purpose fibers include UPF363, Evanite M and B (a version of 475 glass), and

¹ Information provided in a public comment received from Tim Carey of Johns Manville, in response to a Federal Register notice of May 19, 2004 (FR 2004).

- 1 Lauscha A-, B- (also a version of 475 glass), and C-glass. Table 1-1 lists examples of
- 2 insulation glass wools, and Table 1-2 lists examples of special-purpose glass fibers used
- 3 in the studies reviewed in this document.

Table 1-1. Examples of commercial and experimental insulation glass wools

Fiber description	Examples	Comments
Insulation glass wools	French glass fibers (Saint Gobain), Owens-Corning general building insulation, Manville 901 building insulation, CertainTeed B glass, Insulsafe II	Commercial products
Respirable fractions derived from commercial insulation wools	MMVF10, MMVF10a MMVF11	Derived from Manville 901 Derived from CertainTeed B
Experimental fibers	B, M, P, and V fibers B-01-0.9, B-09-0.6, B-09-2.0	European experimental fibers, not commercially produced

Table 1-2. Examples of special-purpose glass fibers

Fiber type	Examples	Comments
475 glass (Tempstran 475)	JM475, JM100/475, JM100, JM102, JM104, JM108, JM110, JM112, Code ^a 100 or Manville Code 100, MMVF33	475 glass is manufactured in different diameters expressed as codes. JM100, JM102, JM104, etc. reflect the relative diameter, with a smaller number representing a finer diameter (see Table 1-3).
E-glass	104E, JM104E, MMVF32	E-glass is a calcium-aluminum borosilicate glass with a much higher calcium and aluminum content and a lower silica component than is typical for insulation wools.
Experimental fibers	Bayer B1, B2, B3	Not commercialized
Other	JM753 Owens-Corning AAA-10 microfiber S&S 106	Discontinued product Special-purpose fiber from a manufacturer other than Johns Manville

^aThe code refers to the diameter of the fiber (see table 1-3).

Table 1-3. Codes for Manville glass fibers

Designation	Range of nominal diameters (μm) ^a	Glass type ^b
JM80	0.24–0.28	475
JM100	0.28–0.38 ^c	475
JM102	0.35–0.42 ^c	475
JM104	0.43–0.53	475, E
JM106	0.54–0.68	475, E
JM110	1.9–3.0	475

Source: WHO 1988.

^aWHO (1988) noted that these specifications were current at the time of that publication; however, specifications have changed over time.

^b475 = general purpose borosilicate; E = electrical grade, alkali-free borosilicate [WHO definitions].

^c[No explanation was reported by WHO for the overlap in range of diameters for codes JM100 and JM102.]

1 1.2 Chemical and physical properties

2 The chemical composition of glass wool products varies depending on the manufacturing
3 requirement and end-use, but almost all contain silicon dioxide as the single largest oxide
4 ingredient (IARC 2002). Silicon dioxide or one of a few other oxides is required in order
5 to form glass, and these oxides are known as “glass formers.” The essential property of a
6 glass former is that it can be melted and quenched into the glassy state. Other oxides are
7 added as stabilizers and modifiers or fluxes. In addition, various lubricants, binders,

1 antistatic agents, extenders and stabilizers, and antimicrobial agents may be added to
2 various products. Lubricants may be added to reduce dust generation. Binders, such as
3 phenol-formaldehyde resins, melamine, or acrylic resins, may serve to hold the fibers
4 together. The binder content for most insulation wool products is low but may reach 25%
5 for some products.

6 Table 1-4 provides chemical composition data that were identified for various glass fibers
7 discussed in this document.

Table 1-4. Reported chemical compositions for various glass fibers (expressed as oxide mass percentages)

Fiber	SiO ₂	Al ₂ O ₃	B ₂ O ₃	CaO	MgO	BaO	ZnO	ZrO ₂	TiO ₂	Na ₂ O +K ₂ O	Na ₂ O	K ₂ O	FeO+ Fe ₂ O ₃	Fe ₂ O ₃	P ₂ O ₅	MnO	SO ₃	F ₂
MMVF10 ^a	57.4	5.17	8.53	7.65	4.16	–	–	–	0.03	–	15.5	1.07	–	0.07	–	–	0.07	–
MMVF10a ^b	57.2	5.1	8.4	7.17	4.48	0.01	–	0.02	< 0.01	–	15.6	1.04	–	0.05	–	–	< 0.03	0.36
MMVF11 ^a	63.5	3.76	4.36	7.27	2.77	–	–	0.02	0.06	–	15.71	1.38	–	0.27	–	–	0.21	–
B ^c	61.4	0.46	3.4	16.3	2.9	–	–	–	0.02	–	14.9	0.32	–	0.06	–	–	–	–
M ^c	57.4	0.5	12	8.3	3.5	–	–	–	–	–	17.9	0.34	–	0.05	–	–	–	–
P ^c	50.93	2.5	–	30.9	10.2	–	–	–	0.09	–	3.55	0.8	–	0.95	0.03	0.05	–	–
V ^c	63.3	2.07	8.2	7.05	3.16	–	–	–	–	–	15	1.15	–	0.12	–	–	–	–
Bayer B-1, B-2 ^d	60.7	–	3.3	16.5	3.2	–	–	–	–	–	15.4	0.7	0.2	–	–	–	–	–
Bayer B3 ^d	58.5	5.8	11	3	–	5	3.9	–	–	–	9.8	2.9	0.1	–	–	–	–	–
Bayer B9 ^e	62	–	5	8.8	–	–	–	–	6	–	15	2.9	–	–	–	–	–	–
E-glass microfiber ^f	54.3	13.9	7.6	19.5	2.4	–	–	–	0.7	–	0.8	0.1	–	0.2	–	–	–	–
JM100/475 ^g	74.5	1.9	–	6.8	–	6.9	–	–	–	–	0.8	8.4	0.6	–	–	–	–	–
JM104E ^g	59.7	11.7	–	28	0.5	–	–	–	–	–	–	–	–	–	–	–	–	–
JM475 ^d	57.9	5.8	10.7	3.0		5	3.9	–	–	–	10.1	2.9	0.1	–	–	–	–	–
JM753 ^d	63.4	–	5.6	6.1	3	–	–	–	–	–	14.6	1.1	2	–	–	–	–	–
MMVF32 ^h	54.3	13.9	7.59	19.5 2	2.43	0.2	–	–	0.66	–	–	–	–	–	–	–	–	–
MMVF33 ^b	58.6	5.9	11.2	1.7	6.0	5.0	4.02	0.03	0.01	12.6	9.6	3.1	–	0.04	0.04	–	–	0.62
UPF 363 ⁱ	58–59	5	7–8	0–0.2	< 0.1	–	–	4	8	16–18	–	–	–	–	–	–	–	< 2
Evanite, M ⁱ	65.8–71.2	3.3–4.4	4.2–5.3	4.8–6.6	2.3–3.3	0–0.2	0–0.4	–	–	–	10.9–12.9	1.6–2	–	–	–	–	–	0.5–1
Evanite B ⁱ	56.4–60.4	5.2–6.4	10–12	1.5–2.3	0.15–0.5	4.5–5.5	3.5–4.5	–	–	–	9–11	2.6–3.4	–	–	–	–	–	0.3–0.7

Fiber	SiO ₂	Al ₂ O ₃	B ₂ O ₃	CaO	MgO	BaO	ZnO	ZrO ₂	TiO ₂	Na ₂ O +K ₂ O	Na ₂ O	K ₂ O	FeO+ Fe ₂ O ₃	Fe ₂ O ₃	P ₂ O ₅	MnO	SO ₃	F ₂
Lauscha glass A ⁱ	69–72	2.5–4	< 0.1	5–7	2–4	–	0–2	–	–	–	10.5–12	4.5–6	–	–	–	–	–	–
Lauscha glass B ⁱ	55–60	4–7	8–11	1.5–5	0.7–2	3.6–6	2–5	–	–	–	9.8–13.5	2.5–4	–	–	–	–	–	< 1
Lauscha glass C ⁱ	63–67	3–5	4–7	4–7	2–4	< 0.1	< 0.1	–	–	–	14–17	0–2	–	–	–	–	–	< 1
JM104/475 ^j	57.9	5.8	10.7	3.0 ⁿ	ⁿ	5.0	3.9	–	–	–	10.1	2.9	–	0.1	–	–	–	–
Glass wool ^l	64.9	3.1	4.7	7.0	2.9	0.1	–	–	0.1	–	15.3	1.5	–	0.3	–	–	–	–
CertainTeed B ^k glass	63.4	3.88	4.45	7.45	2.82	–	–	0.0	0.06	–	15.45	1.32	–	0.25	0.0	0.01	0.33	–
CM 44 ^k	61.7	0.97	9.2	7.15	2.94	–	–	0.0	0.02	–	16.06	0.59	–	0.11	1.05	0.01	0.2	–
B-01/09 ^k	61.5	0.31	3.15	15.6	2.99	–	–	0.04	0.02	–	15.51	0.72	–	0.11	0.0	0.01	0.0	–
B-01 ^l	62.0	–	5.0	8.8	–	–	–	–	6.0	–	15.0	2.9	–	–	–	–	–	–
Fiber A ^m	65.00	1.90	4.70	7.40	2.55	–	–	–	0.02	–	16.10	0.65	–	0.11	1.10	–	0.03	–
Fiber C ^m	61.70	0.97	9.20	7.15	2.94	–	–	–	0.02	–	16.06	0.59	–	0.11	1.05	0.01	0.20	–

^a Hesterberg *et al.* 1993.

^b McConnell *et al.* 1999.

^c Insulation wools developed to be more biosoluble (Grimm *et al.* 2002).

^d Pott *et al.* 1991.

^e Roller *et al.* 1996.

^f Bellmann *et al.* 2003.

^g Cullen *et al.* 2000.

^h Hesterberg *et al.* 1998

ⁱ Carey 2004 (public comment in response to FR 2004).

^j Bellmann *et al.* 1987.

^k Bernstein *et al.* 1996.

^l Roller *et al.* 1996.

^m Experimental fibers (Lambré *et al.* 1998).

ⁿ Bellmann *et al.* 1987 footnote for CaO states “Include [*sic*] MgO.”

1 Important physical properties include fiber dimensions, density, and durability. Glass
2 wool fiber diameters vary within a product but follow an approximately log-normal
3 distribution. However, the fiber diameter is not an inherent property of the type of fiber
4 but is controlled by the manufacturing process. All SVFs are manufactured to nominal
5 diameters that vary based on the manufacturing process and the fibers' intended use
6 (ACGIH 2001). The nominal diameter is an estimate of the average fiber diameter of the
7 product. ACGIH (2001) reported that insulation wool products typically have nominal
8 diameters of 1 to 10 μm , although it was noted that most products have a nominal
9 diameter within the 3 to 10 μm range. Special-purpose fibers have nominal diameters that
10 range typically from 0.1 to 3 μm . Current glass wool production processes are not
11 capable of producing fibers only at the nominal diameter, and as a result, the diameters of
12 individual fibers in a glass wool product vary widely around the nominal diameter. IARC
13 (2002) noted that a product with an average diameter of 5 μm will contain fiber diameters
14 ranging from < 1 to > 20 μm . Unlike crystalline fibers, such as asbestos, glass fibers do
15 not split lengthwise into fibers with smaller diameters. They can only break across the
16 fiber resulting in shorter fibers with the same diameter.

17 The manufacturing process also affects fiber length. In glass wool insulation, most fibers
18 are several centimeters long; however, fibers with lengths of less than 250 μm
19 (considered by IARC as the upper limit of respirability) probably are present in all glass
20 wool products (IARC 2002). Mean fiber lengths for JM475 are 1 to 1.5 mm, and for
21 Evanite filter grade special-purpose fibers they are ≥ 4.5 mm as defined by a public
22 comment in response to FR 2004 (Carey 2004). Fiber densities are not as variable as
23 diameter and length and are typically 2.4 to 2.6 g/cm^3 (IARC 2002).

24 **1.3 Fiber classification**

25 Fibers, classified by their physical dimensions, have been basically defined since the late
26 1950s as being greater than 5 μm long and having a length-to-width aspect ratio of at
27 least 3:1 (i.e., the fiber is at least three times longer than its width) (Breyse *et al.* 1999,
28 Walton 1982). Other more recent definitions have suggested that an aspect ratio of 5:1
29 will more readily discriminate fibrous from irregularly shaped particles. The World
30 Health Organization (WHO) defines fibers as being greater than 5 μm long, thinner than

1 3 μm , and having an aspect ratio of $> 3:1$. The United States National Institute for
 2 Occupational Safety and Health (NIOSH) has two sets of fiber definitions, the so-called
 3 “A” and “B” rules (NIOSH 1994). Table 1-5 compares the NIOSH and WHO fiber
 4 definitions.

Table 1-5. Comparison of WHO and NIOSH fiber counting definitions

Source	Aspect ratio	Length, (μm)	Diameter, (μm)
NIOSH 7400 Method “A” Rules (7400A)	$\geq 3:1$	> 5	NS
NIOSH 7400 Method “B” Rules (7400B)	$\geq 5:1$	> 5	< 3
WHO European Reference Method	$\geq 3:1$	≥ 5	< 3

NS = not specified.

5 Depending on the production process, fibers can have relatively large or small diameters.
 6 The diameter of a fiber is an important property because very thin fibers can enter the
 7 respiratory tract and deposit deep in the lungs (see Section 2). Fibers with diameters less
 8 than 3 μm are usually considered able to penetrate into the lower respiratory tract of
 9 humans. These fibers are usually called “respirable,” although the term thoracic is more
 10 accurate. Baron has shown that the fraction with diameters less than 3 μm agrees well
 11 with the thoracic deposition fraction (Baron 1996). Since possible bronchogenic effects
 12 (i.e., lung cancer) are under consideration, a thoracic fraction is appropriate. This review
 13 will focus on the so-called “respirable” glass wool fibers since these are the fiber sizes
 14 that present the greatest inhalation risk.

15 Dose, dimension, and durability have been termed the three Ds, all of which are
 16 important in determining the carcinogenicity of fibers (see Section 5.3). See the Glossary
 17 and Section 5 for definitions of durability and the related terms biodurability,
 18 biopersistence, dissolution rate (k_{dis}), and Z-score. Several classification systems exist
 19 based on these characteristics; the following is a discussion of the European and German
 20 classification systems for labeling SVFs.

21 1.3.1 European classification system

22 In 1997, the European Union (EU) established criteria for labeling and classifying SVFs
 23 based on their potential human health hazard under the Dangerous Substances Directive

1 [67/548/EEC] (Hesterberg and Hart 2001). Under this system, all SVFs are considered
 2 irritants and are classified for carcinogenicity according to the criteria in Table 1-6.

Table 1-6. European carcinogenicity classification

Classification	Definition & criteria
(1) Carcinogen	Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to the substance and the development of cancer.
(2) Probable carcinogen	A substance that should be regarded as if it is carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of cancer, generally on the basis of appropriate long-term animal studies or other relevant information. SVF Criteria ^a : Diameter $\leq 6 \mu\text{m}^b$; Solubility Index (KNB) $\leq 18\%$
(3) Possible carcinogen	A substance that is of concern as a possible human carcinogen, but available information is not adequate for a valid assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2. SVF Criteria ^a : Diameter $\leq 6 \mu\text{m}^b$; Solubility Index $> 18\%$.
(0) Not classified as a carcinogen	Exempt from carcinogenicity classification (but still considered an irritant). SVF Criteria ^a : Diameter $> 6 \mu\text{m}^b$

Source: Hesterberg and Hart 2001.

^a Criteria used to classify insulation wools composed of fiber glass or rock/stone/slag wools that have not been evaluated in a carcinogenicity or biopersistence test.

^b Nota R of Commission Directive 97/548/EEC, 12/5/97, states: “length-weighted geometric mean diameter less 2 standard errors greater than $6 \mu\text{m}$.” This is roughly equivalent to a geometric mean diameter of $6 \mu\text{m}$.

3 Based on this classification system, SVFs with diameters greater than $6 \mu\text{m}$ are not
 4 considered carcinogenic (because they are nonrespirable), but they are considered
 5 irritants (Hesterberg and Hart 2001). Untested SVFs with diameters $\leq 6 \mu\text{m}$ are
 6 categorized in Category 2 or 3 depending on the results of the Soluble Components Index
 7 (KNB). The KNB is equal to the sum of the percent composition of the more rapidly
 8 dissolving components ($\text{Na}_2\text{O} + \text{K}_2\text{O} + \text{CaO} + \text{MgO} + \text{BaO}$). This sum of alkali and
 9 alkaline earth oxides is also described by the term “Z-score,” and fibers with a Z-score
 10 less than or equal to 18% are considered to represent a greater potential hazard than those
 11 with a Z-score greater than 18% (Moore *et al.* 2002). However, Moore *et al.* (2002) noted
 12 that fibers are not customarily defined by their total alkali and alkaline earth oxides, and
 13 that it is not clear that such a “bright line” can divide the continuum of glass fibers into
 14 categories of risk or hazard. Nevertheless, Moore noted that the EC Directive would
 15 place glass microfibers (i.e., special-purpose fibers) in Category 2 (probable), and

1 standard insulation glass wools in Category 3 (possible). [However, many of the special-
 2 purpose fibers have Z-scores > 18%, e.g., JM104E = 28.5 and M753 = 24.8, and thus
 3 would be included in Category 3 along with insulation glass wools.] A Category 3 fiber
 4 can be exempted from carcinogenicity classification (but still be considered an irritant) if
 5 it passes one of the four tests described in Table 1-7. All of these tests are conducted in
 6 rats. In their final conclusions, Moore *et al.* reported that they did “not believe that there
 7 is scientific justification for the use of Z-scores as a basis for classifying substances as
 8 carcinogens.”

Table 1-7. European tests for upgrading the classification of an SVF

Test	Criteria for passing test
Intraperitoneal injection test	noncarcinogenic
Chronic inhalation test	noncarcinogenic
Inhalation biopersistence test	fibers longer than 20 μm : $\text{WT}_{1/2}^{\text{a}} < 10$ days
Intratracheal instillation biopersistence test	fibers longer than 20 μm : $\text{WT}_{1/2} < 40$ days

Source: Hesterberg and Hart 2001.

^a $\text{WT}_{1/2}$ = weighted lung clearance half-time.

9 The weighted lung clearance half-time ($\text{WT}_{1/2}$) is calculated by weighting each clearance
 10 half-time ($T_{1/2}$) by multiplying it by the proportion of fibers in that pool ($a_1/[a_1 + a_2]$ or
 11 $a_2/[a_1 + a_2]$) and then summing the two weighted $T_{1/2}$ values and dividing by 2
 12 (Hesterberg and Hart 2001).

13 1.3.2 German classification system

14 Soon after the European classification system was enacted, Germany enacted its own
 15 criteria for classifying SVFs according to carcinogenicity (Hesterberg and Hart 2001).
 16 Germany considers every SVF to be carcinogenic, and very strict worker protection
 17 requirements are required unless the fibers pass one of the three tests outlined in Table 1-
 18 8. These include the carcinogenicity index (KI), biopersistence test, and intraperitoneal
 19 (i.p.) injection test. The KI is another solubility index that tries to predict fiber dissolution
 20 rate based on fiber composition. In the biopersistence test (intratracheal instillation), rats
 21 are instilled with 0.5 mg of fibers per day for 4 days, with a total dose of 2 mg. Lung
 22 burdens are evaluated for up to 3 months. The lung clearance half-time ($T_{1/2}$) for the
 23 fibers must be less than 40 days to pass this test. The intraperitoneal injection test is

1 conducted using the same protocol as that used by the European carcinogenicity
 2 classification (see Section 1.3.1) (Bernstein and Sintes 1999). In order to pass this test,
 3 the tumor incidence must not be significantly elevated above the level seen in controls
 4 (Hesterberg and Hart 2001).

Table 1-8. German tests for noncarcinogenic classification

Test	Criterion for Passing Test
KI (carcinogenicity index)	KI > 40 $KI = [Na_2O + K_2O + CaO + MgO + BaO + B_2O_3]^a - 2 \times (Al_2O_3)^a$
Biopersistence test: intratracheal instillation	$T_{1/2}$ of WHO fibers < 40 days
Intraperitoneal injection test	noncarcinogenic

Source: Hesterberg and Hart 2001.

^a Concentrations of oxides as per cent of total mass.

5 **1.4 Summary**

6 Glass is an amorphous material produced by solidification from a molten state without
 7 crystallization and containing a glass former that can be melted and quenched into a
 8 glassy state. Silicon dioxide is the major glass former used for commercial applications.
 9 Glass wool refers to fine glass fibers forming a mass resembling wool and most
 10 commonly used for insulation and filtration. Glass wool fibers were first introduced into
 11 commerce in the 1930s and are now among the world's most extensively used insulating
 12 materials. Special-purpose fibers make up a small fraction of the SVF market and are
 13 used, as the name implies, in specialized applications.

14 Glass wool fiber diameters vary within a product but follow an approximately log-normal
 15 distribution. The fiber diameter is controlled by the manufacturing process. Fiber
 16 diameters vary based on the manufacturing process and the fibers' intended use. The
 17 nominal diameter is an estimate of the average fiber diameter of the product. Insulation
 18 wool products typically have nominal diameters of 1 to 10 μ m and special-purpose fibers
 19 have nominal diameters of 0.1 to 3 μ m. The diameters of individual fibers in a glass wool
 20 product vary widely around the nominal diameter. Unlike crystalline fibers, such as
 21 asbestos, glass fibers do not split lengthwise into fibers with smaller diameters, but only
 22 break across the fiber resulting in shorter fibers with the same diameter.

1 SVFs and other mineral fibers have been classified according to origin (natural vs.
2 manufactured), chemistry (organic vs. inorganic), physical form and morphology (e.g.,
3 filaments and wools), or commercial applications (e.g., insulation wools and special-
4 purpose fibers).

5 Fibers, classified by their physical dimensions, have been basically defined since the late
6 1950s as being greater than 5 μm long and having a length-to-width (aspect) ratio of at
7 least 3:1 (i.e., the fiber is at least three times longer than its width). WHO defines fibers
8 as being greater than 5 μm long, thinner than 3 μm , and having an aspect ratio of $> 3:1$.

9 Fibers have also been examined based upon other characteristics, including
10 biopersistence, retention and clearance rates, and biodurability. The European Union
11 (EU) and Germany have established criteria for labeling and classifying SVFs based on
12 their potential to be hazardous to human health.

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1 **2 Human Exposure**

2 The vast majority of glass wool manufactured in the United States is used in home and
3 building insulation products. A small percentage is used for a number of special
4 applications; such as for aircraft and aerospace insulation, as battery separators, and in
5 filtration products. Occupational exposure can occur in glass wool production facilities
6 and other facilities, such as fiberglass insulating operations and pipe insulation
7 installation. Limited information is available on environmental exposure and occurrence
8 of glass fibers, but general population exposure can occur where they are used, e.g., as
9 insulation materials, or from fibers in the air near manufacturing facilities.

10 This section provides information on the uses of glass fibers and glass-fiber products
11 (Section 2.1); on the manufacturing process, production levels, and levels of imports and
12 exports (Section 2.2); on occupational exposures (Section 2.3); on environmental
13 occurrence and general population exposure (Section 2.4); on biological indices of
14 exposure (Section 2.5); and on regulations and guidelines for glass fibers that are
15 intended to reduce exposure (Section 2.6).

16 **2.1 Uses for glass fibers**

17 Glass fibers can generally be classified into two categories: low cost general-purpose
18 fibers typically used for insulation applications and premium special-purpose fibers used
19 in limited specialized applications (Wallenberger *et al.* 2001). Another class of glass
20 fibers is the continuous glass filaments, also referred to as glass textile fiber (IARC
21 2002); however, these filaments are produced in nominal diameters ranging from 5 to 25
22 µm with very narrow variation around this mean value. Due to the larger diameter of
23 these glass fibers, they are not considered respirable and therefore are not reviewed in
24 this background document.

25 **2.1.1 Glass wool for insulation**

26 Glass wool has many commercially valuable physical properties, including low thermal
27 conductivity and volumetric heat capacity, that enable glass wool materials to be
28 effectively used for insulation purposes. As a result, the primary uses of glass wool are
29 for thermal and sound insulation. The largest glass wool use is for home and building

1 insulation purposes in the form of loose wool, batts (insulation in the form of a blanket,
 2 rather than a loose filling), blankets or rolls, or in the form of rigid boards for acoustic
 3 insulation. Glass wool is also used for industrial, equipment, and appliance insulation. A
 4 summary of the main insulation wool uses as defined by IARC is presented in Table 2-1.

Table 2-1. Insulation wool uses

Sectors	Subsectors	Location	Function
Buildings	Residential	Roof, wall, floor	Thermal, acoustic, fire protection
	Offices and shops	Roof, wall, floor	Thermal, acoustic, fire protection
	Schools	Partition Ceiling	Thermal, acoustic, fire protection Acoustic
Transportation	Railway	Partition	Thermal, acoustic, fire protection
	Automotive	Headliner and hood pad	Thermal, acoustic
		Silencer	Acoustic
	Maritime	Partition Fire protection door	Thermal, acoustic, fire protection Fire
Airplanes	NR	NR	
Industry	Buildings	Roof, wall, floor	Thermal, acoustic, fire protection
	Air conditioning	Duct	Thermal
	Fluid transportation	Pipe	Thermal
	Ovens, furnaces	Lining or wall	Thermal
Agriculture	Buildings	Breeding shed	Thermal, fire
Health	Hospitals/medical centers	Roof, floor Partition, wall, door Ceiling	Thermal, acoustic, fire protection Thermal, acoustic, fire protection Acoustic
	Medical equipment	Absorbent pad	NR
Domestic equipment	NA	Oven	Thermal

Source: IARC 2002.

NA = not applicable; NR = not reported.

5 **2.1.2 Non-insulation uses (special-purpose fibers)**

6 Special-purpose glass fibers are limited-production materials compared with insulation
 7 glass wool, but they are used for a variety of applications that either require a specialized
 8 glass formulation or particular diameter requirements. Typical products have nominal
 9 fiber diameters of less than 3 µm and frequently less than 1 µm with an average diameter
 10 ranging from 0.1 to 3 µm compared with the average of 1 to 10 µm for insulation glass
 11 wool fibers (ACGIH 2001). These specialty fibers are used in aircraft and aerospace
 12 insulation, as battery separators, and in filtration products. The largest market for special-

1 purpose glass fibers is for battery separator media, with the primary component of such
 2 media being an acid-resistant borosilicate glass fiber. The purpose of the glass fiber
 3 media is to physically separate the positive and negative plates of the battery, while
 4 allowing the acid electrolyte to pass through the media (IARC 2002).

5 Another use of special-purpose glass fibers is in high-efficiency particulate air (HEPA)
 6 filters that are used in settings where high-efficiency filtration of air is required.

7 Examples include use in hospitals, clean rooms of pharmaceutical laboratories, nano-
 8 technology industries, microbiological laboratories, and nuclear power plants. These
 9 filters are used to increase the quality of indoor air, as these filters can remove sub-
 10 micron particulate matter as described by a public comment in response to FR 2004
 11 (Carey 2004). See Table 2-2 for some examples of special-purpose glass fibers and their
 12 commercial uses.

Table 2-2. Some examples of special-purpose glass fibers and their commercial uses

Special-purpose glass fiber use category	Glass type or trade name	Nominal fiber diameter	Composition	End-use applications
Battery separator media	LFI C-glass Evanite M-glass JM253 and JM475	0.6–3 µm	acid-resistant borosilicate glass	AGM—absorptive glass mat separator for use in flooded and sealed lead acid batteries automotive, electric vehicle, flashlight, hearing aid, and computer batteries
Filtration: air and liquid	Micro-Strand ^a glass fibers (100 and 200 series)—Johns Manville JM475 Evanite B-glass LFI A- and B-glass	0.2–5.5 µm	varies with product use, but generally high purity fibrous silica	Fiber media containing glass microfibers can be converted into a wide variety of products: batts, blankets, webs, flat or pleated ‘papers,’ and cylindrical filter cartridges. They can be wrapped, molded, sewn, or laminated to other substrates. Final products are used in the nuclear, electronic, automotive, pharmaceutical, aerospace, and chemical industries Corrosion-resistant glass microfibers can be used in clean-room filters for electronics industry applications

Special-purpose glass fiber use category	Glass type or trade name	Nominal fiber diameter	Composition	End-use applications
Insulation	Micro-fiber felt ^a (Johns Manville) JM475	0.6–4 μm	borosilicate glass	Aircraft and spacecraft: thermal, and acoustical insulation, gas and air filtration in a medium temperature range (up to 900°F)
	Q-fibers ^a (Johns Manville)	0.75–1.59 μm	High-purity silica (or quartz)	Aerospace, automotive and chemical industry applications (originally developed for manufacturing tile sheathing on space shuttles). Can withstand temperatures up to 2,300°F (1,260°C). Insulation products for nuclear power industry

Source: Zguris *et al.* 2005.

^aJohns Manville trade names.

LFI–Lauscha Fiber International (A-glass is low boron alkali silicate, B-glass is borosilicate, C-glass is acid-resistant borosilicate, and E-glass is calcium aluminoborosilicate).

1 2.2 Production, import, and export information

2 2.2.1 Production methods

3 The major methods for fiber manufacture historically have been steam attenuation, the
4 rotary or centrifugal process, and flame attenuation (Dement 1975). Only the latter two
5 methods remain in use today. Glass for fiber manufacture is almost always based on
6 silicon dioxide with varying amounts of other inorganic oxides, including oxides of
7 alkaline earths, alkalis, aluminum, boron, iron, and zirconium (IARC 2002) (see also
8 Table 1-4). In some cases, the additional oxides occur in the raw materials used to make
9 the glass, while in others specific oxides are added in order to enhance the manufacturing
10 process or the performance of the final product. The raw materials commonly used in the
11 manufacture of insulation glass wool and special-purpose fibers are listed in Table 2-3.

Table 2-3. Raw materials commonly used in the manufacture of insulation glass wool and special-purpose fibers

Raw material	Desired element	Source	Insulation glass wool	Special-purpose fibers
Colemanite	B	Mined		x
Dolomite	Ca, Mg	Mined	x	x
Fluorspar	F	Mined		x
Kaolin clay	Al	Mined	x	x
Limestone	Ca	Mined	x	x
Nepheline syenite	Al	Mined	x	
Silica sand	Si	Mined	x	x
Ulexite	B	Mined	x	
Wollastonite	Ca, Si	Mined		x
Zircon sand	Zr, Si	Mined		x
Burned dolomite	Ca, Mg	Processed	x	x
Cullet	Si, Ca, Mg, Na, B	Recycled	x	
Alumina	Al	Manufactured	x	x
Borax (5 H ₂ O)	B	Manufactured	x	
Magnesite	Mg	Manufactured		x
Manganese dioxide	Oxidizing power	Manufactured	x	
Sodium nitrate	Oxidizing power	Manufactured	x	
Sodium carbonate	Na	Manufactured	x	
Sodium sulfate	Oxidizing power	Manufactured	x	
Zirconia	Zr	Manufactured		x

Source: IARC 2002.

1 Raw materials for a specific batch of glass fibers are first weighed and blended using
2 automated processes before being added to the fiberglass furnace, where the materials are
3 melted and homogenized at approximately 1,370°C (2,500°F) using either electricity or
4 gas as the heat source (Wallenberger *et al.* 2001).

5 *Rotary or centrifugal method*

6 Steam blowing was initially used in the 1940s but was quickly replaced by the flame-
7 attenuation process. Spinning processes were the next innovation to be introduced in the
8 mid-1950s and were further enhanced with the addition of the rotary process, which
9 remains the predominant method of manufacturing today (IARC 2002).

1 In the rotary process, fibers are produced as centrifugal force extrudes the molten
2 material through small holes in the side of the spinning device (Burgess 1995). In the
3 refiner section of the furnace, the temperature of the glass melt is lowered to about
4 1,260°C (2,300°F) (IARC 2002). A stream of molten glass from the fiberglass furnace
5 flows along a heated forehearth lined with refractory material to a point directly above
6 the fiber-forming station where it pours through single-orifice bushings into rotary
7 centrifugal spinners (EIPPCB 2001). The molten glass is then extruded from the sidewall
8 holes as small streams of glass to form the primary glass fibers through centrifugal action
9 and aerodynamic drag forces. The primary fibers pass through a circular burner flame,
10 whose hot gases attenuate the fibers to their final diameter and break the fibers into
11 shorter lengths (IARC 2002). The resulting fibers, which have a range of lengths and
12 diameters, form a veil of randomly interlaced fibers, which are sprayed with a phenolic
13 (usually phenol-formaldehyde) resin binder and lubricant (usually mineral oil or paraffin
14 oil) to improve the integrity, resilience, durability, and handling quality of the finished
15 product. The lubricating oils are added to reduce dust and lint formation of the final
16 product and reduce the amount of airborne fibers during their use. A gas-fired oven dries
17 the product and cures the binder. The resin-coated fibers are formed into a mat of fibers.
18 The resultant fibers typically range from 0.5 to 6 μm in diameter; however, the
19 distribution of lengths is extremely broad (Moore *et al.* 2002).

20 As noted in Section 1, the nominal diameter is an estimate of the average fiber diameter
21 of the wool product; however, within that product, the diameters of individual fibers vary
22 widely around the nominal diameter, and all wool products will contain some percentage
23 of respirable fibers (ACGIH 2001). Because smaller fibers become airborne more easily
24 than larger fibers and because larger diameter fibers fall out of suspension in air faster
25 than small diameter fibers, the distribution of airborne fiber diameters will differ from
26 that of the product (ACGIH 2001, Krantz 1988); [i.e., the average diameter of airborne
27 fibers will be smaller than the nominal diameter of the product]. In an assessment of
28 occupational exposures to MMMF in Sweden, Krantz (1988) reported that median
29 diameters of airborne fibers were in all cases much smaller, by almost one order of
30 magnitude, than the nominal diameters of the products. ACGIH (2001) noted that in
31 general, as nominal diameters decrease, exposure levels increase.

1 IARC (2002) reported that most fibers in insulation glass wool products have been found
2 to be several centimeters in length, although fibers with lengths of less than 250 μm
3 (which IARC reported as the upper limit for respirability) probably are present in all wool
4 products. Fiber length contributes significantly to the ease with which a fiber becomes
5 airborne, with shorter fibers of the same diameter becoming airborne more easily than
6 longer fibers. As noted in Section 1, glass fibers do not break lengthwise, but rather break
7 across the fiber resulting in shorter fibers with the same diameter.

8 *Flame-attenuation method*

9 A flame-attenuation process is used to produce very small diameter fibers, and this
10 method is generally used to produce special-purpose fibers. The glass used to produce the
11 fibers can be produced earlier and cooled into preforms, often as glass marbles (EIPPCB
12 2001). The marbles are added to a heated pot for the production of fibers in a process
13 described as pot and marble.

14 The flame-attenuation method of producing fibers is a two-step procedure (IARC 2002).
15 In the first step, the melt is drawn through the bushings of the furnace to produce strands
16 of coarse fibers. The fibers are then remelted with a high-temperature gas flame, which is
17 usually mounted at right angles to the primary fibers. The flame attenuates the coarse
18 fibers into finer fibers, which are propelled by high-velocity gases through a forming
19 tube. There, the fibers are sprayed with a binder and formed into mats, which can be
20 further processed into a variety of special-purpose applications (IARC 2002). Special-
21 purpose glass fibers are more highly engineered than glass wool products, and thus are
22 significantly more expensive, according to a public comment from Johns Manville (Carey
23 2004).

24 *2.2.2 U.S. production*

25 Insulation products comprise the vast majority of synthetic vitreous fibers (SVFs)
26 produced in the United States, and glass wool is the predominant SVF used for insulation
27 products. IARC reported that in 1999, North American demand for glass wool insulation
28 made up 54.8% of world demand in that category, while North American demand for
29 rock or slag wool insulation made up only 7.6% of world demand for that category. In the
30 year 2000, an estimated 3,388 million pounds (1.7 million tons) of fiberglass were used

1 in building insulation (commercial and residential), with approximately 79.1% being
2 produced as batts, blankets, or board, and the remaining 20.9% produced as blown or
3 loose-fill insulation (Maxim *et al.* 2003). Furthermore, Maxim *et al.* presented an
4 estimate that 80.9% of the fiberglass insulation sold was used for residential construction
5 and 19.1% for commercial or industrial construction.

6 ATSDR (2004) reported 2002 Glass Manufacturing Industry Council (GMIC) data that
7 indicated that 10 major manufacturers were operating about 40 plants within the United
8 States, and the production volume of all glass fiber types, including glass wool, was
9 estimated at about 3 million tons annually.

10 Special-purpose glass fibers make up a very small amount of the total SVFs produced in
11 the United States, accounting for only about 1% of the total annual production (Carey
12 2004)². In the United States, there are at least four companies that produce special-
13 purpose glass fibers, with imports occurring in increasing amounts from China and other
14 Asian countries. Special-purpose glass fibers products are not generally available to the
15 general public. They usually are sold by the fiber manufacturer to commercial users in
16 final products or alternatively to other manufacturers, where they are made into final
17 products (Carey 2004).

18 Hesterberg and Hart (2001) reported that E glass was no longer produced as a microfiber
19 in the United States and Europe but only as continuous filaments (most of which are too
20 thick to be respirable). JM753 also is a discontinued product (Angus Crane, personal
21 communication to Sanford Garner, SRA, International, February 11, 2005).

22 *2.2.3 Import and export of glass fibers*

23 The United States International Trade Commission (USITC) reports information on
24 imports and exports only by cost. The combined value of imports of insulation products
25 consisting of the five product categories labeled (1) *mats, nonwoven, of glass fibers*; (2)
26 *thin sheets (voiles), nonwoven, of glass fibers*; (3) *batts of nonwoven glass fibers*; (4) *pipe*
27 *coverings of nonwoven glass fibers*; and (5) *other insulation products of nonwoven glass*

² Information herein attributed to Carey 2004 was provided in a public comment received in response to FR 2004.

1 *fibers* varied considerably from 2000 to 2008 with a maximum value of \$356 million in
2 2006 and a minimum value of \$189 million in 2001; the value for 2008 was \$196 million
3 (USITC 2009a). The value of exports for the product category *insulation products of*
4 *glass fibers* increased steadily from \$59 million in 2000 to \$121 million in 2008 [note
5 that the product categories differ for imports and exports] (USITC 2009b). No category
6 for special-purpose fibers was identified for imports or exports.

7 **2.3 Occupational exposures**

8 Data from the latest U.S. Economic Census (USCB 2005) indicate that in 2002, there
9 were 19,318 total workers (15,788 in manufacturing) employed within the North
10 American Industrial Classification System (NAICS) code 327993, which “comprises
11 establishments primarily engaged in manufacturing mineral wool and mineral wool (i.e.,
12 fiberglass) (*sic*) insulation products made of such siliceous materials as rock, slag, and
13 glass or combinations thereof.” [Based on the proportions of glass wool to other mineral
14 wools used in the production of insulation products in North America (see Section 2.2.2),
15 it is likely that the majority of the workers are involved in the manufacture of glass
16 fibers.] The number listed for 2002 was slightly lower than in 1997 (21,610 total
17 employees with 17,791 in manufacturing). OSHA estimated that there were more that
18 225,000 workers in the United States exposed to synthetic mineral fibers in
19 manufacturing and end-use applications. Synthetic mineral fibers were defined as
20 “fibrous inorganic substances made primarily from rock, clay, slag, or glass” (Maxim *et*
21 *al.* 2003). No other national level data were found to estimate the total number of people
22 exposed occupationally; [however, significant U.S. occupational exposure can be inferred
23 through review of a combined cohort of production workers (Marsh *et al.* 2001a) (see
24 Section 3.2.1.1)]. This cohort consisted of workers employed during the period from
25 1945 to 1978 in 8 plants that produced glass wool or glass wool and filament. In a 1992
26 follow-up evaluation, the cohort had a total of 26,679 workers.

27 The remainder of this section provides information on occupational exposure to glass
28 fibers during their manufacture (Section 2.3.1), and from non-manufacturing activities
29 (i.e., during installation or removal) (Section 2.3.2). The data on occupational exposures
30 are reported for specific product types as presented in the source documents, and fiber

1 manufacturing methods and diameters are reported when available. Because of the
2 importance of the non-U.S. occupational epidemiology studies that are presented in
3 Section 3, non-U.S. exposure data are presented in this section following the U.S. data.

4 *2.3.1 Exposure during manufacturing*

5 Initial studies of airborne exposure to glass fibers were conducted in the late 1960s.
6 These studies included gravimetric analysis and reported exposures in terms of mg/m³.
7 These early exposure studies (Corn *et al.* 1976, Corn and Sansone 1974, Esmen *et al.*
8 1978) demonstrated that similar mass-based exposures can result in highly variable fiber
9 counts. This variability is determined by the fiber diameter distribution of the material.
10 As a result, subsequent exposure assessments relied on fiber counts (fibers/cm³) using
11 optical (phase-contrast) or electron microscopic methods of analysis. For the purposes of
12 this report, only fiber count exposure estimates will be reported. Fiber counts may vary
13 between different studies depending on how a countable fiber was defined and based on
14 the sampling and analytical techniques employed.

15 [The development and evolution of sampling and analytical techniques combined with
16 the adoption of different fiber definitions that have been used historically makes
17 comparison of airborne fiber concentrations across time somewhat problematic. In
18 addition, U.S. and European conventions are not exactly comparable. Because of widely
19 varying fiber size distributions, there is no universally appropriate conversion factor
20 between the various methods. This means that the reader should not draw fine
21 distinctions in interpreting reported exposures. Differences in averaging times (often
22 unspecified) also make comparison of fiber concentration estimates of exposure between
23 studies difficult. In general, reported exposure concentrations in manufacturing
24 environments generally represent 8-hour time-weighted averages (TWA) while reported
25 exposure concentrations in non-manufacturing environments generally represent task-
26 length averages (or TLA). During manufacturing operations, TWA levels that are based
27 on sampling times of less than 8 hours are still representative of 8-hour TWA levels.
28 Unless noted otherwise, levels presented for manufacturing operations are 8-hour
29 TWAs.]

1 *Production processes: glass fiber exposures and co-exposures*
 2 The air contaminants produced by the major production processes in glass fiber
 3 production facilities include the fibers themselves and other emissions associated with
 4 various processes (Smith *et al.* 2001). The exposure assessment by Smith *et al.* was
 5 conducted as part of the epidemiologic studies of Marsh *et al.* (2001a,b,c). Smith *et al.*
 6 also described the presence in the work areas of exposures other than the fibers
 7 themselves (Table 2-4) and identified co-exposures to substances that met the following
 8 criteria: (1) they are widely used, (2) there is a reasonable likelihood of exposure, (3) they
 9 have been used for more than 10 years, and (4) there must be a possible cancer risk,
 10 particularly lung cancer. Based on these criteria, the authors identified the following co-
 11 exposures in the SVF industry (listed in alphabetical order): aromatic hydrocarbons,
 12 arsenic, asbestos, asphalt, crystalline silica, epoxide compounds, formaldehyde, phenol
 13 (as a possible promoter), polycyclic aromatic hydrocarbons, radioactivity, styrene, and
 14 urea (as a possible promoter).

Table 2-4. Emissions from different production operations

Production operation ^a	Emissions ^a
Furnace: glass making	furnace fume, trace metals, crystalline silica dust
Fiberizer: wool forming (nominal diameter) ^b staple forming (> 12 μm) steam blowing (5–12 μm) rotary blowing (< 2; 2–4; 4–8 μm) flame attenuation (< 2; 2–4 μm)	airborne fibers ^c (concentration and size depend on nominal diameter), formaldehyde, aerosol of uncured phenol-formaldehyde binder
Curing oven/curing press	formaldehyde, condensation oil aerosol, pyrolysis products, polycyclic aromatic hydrocarbons
Trimming and packaging	fibers, resin particles, amorphous glass particles
Off-line fabrication	fibers, resin particles, paint and amorphous glass particles
Material handling	fibers, amorphous particles

Source: Smith *et al.* 2001.

^aThe authors noted that the list of operations and emissions was not exhaustive.

^bThe nominal diameter of the bulk fiber is determined by measuring the length-weighted size distribution; the common sizes produced by each type are also listed, but other sizes might be made.

^cAn airborne glass fiber was defined by the authors as < 5 μm in diameter with a length to width ratio > 3:1.

15 *Glass fiber exposures in manufacturing facilities*

16 One of the earliest studies of glass wool exposures was conducted in five manufacturing
 17 facilities (Johnson *et al.* 1969). Four of the five plants in this survey manufactured glass

1 wool insulation. The fifth plant produced continuous glass filaments for textile fabrics.
2 Samples were collected for periods ranging from two to seven hours. A portion of the
3 sampling medium was rendered transparent, and fibers with an aspect ratio of 3 or greater
4 and a length greater than 5 μm were counted using 430x magnification. Fiber
5 concentrations within fiber operations collected in the glass wool insulation plants
6 without any size-selective inlet ranged from 0.0 to 1.01 fibers/cm³.

7 Dement (1975) surveyed fiber exposures in four glass wool production facilities
8 manufacturing large-diameter ($> 1.0 \mu\text{m}$) insulation products and six plants
9 manufacturing small-diameter ($< 1.0 \mu\text{m}$) [special-purpose] glass fibers for use as filter
10 paper and aircraft insulation. Analysis of the 167 samples collected across different
11 products and fiber-forming methods as well as for scrap reclamation and the category “all
12 other operations” from the four facilities manufacturing large-diameter insulation
13 products showed mean fiber concentrations ranging from 0.04 to 0.2 fibers/cm³
14 (sampling times not reported). Based on 123 samples from the six plants manufacturing
15 small-diameter [special-purpose] glass fibers, the mean airborne fiber concentrations
16 ranged from 1.0 to 21.9 fibers/cm³ across bulk fiber handling and fabrication/finishing
17 operations for three products (bulk fiber production, filter paper manufacturing, and
18 aircraft insulation fabrication) (sampling time not provided).

19 Median airborne fiber diameters ranged from 1.1 to 4.3 μm and lengths ranged from 19 to
20 70 μm . Dement (1975) classified respirable fibers as being less than 3.5 μm in diameter
21 and less than 50 μm in length. The percentage of fibers in the four large-diameter
22 insulation glass wool manufacturing plants with diameter less than 3.5 μm ranged from
23 35% to 98% of the total fibers, while the percentage of fibers less than 50 μm in length
24 ranged from approximately 40% to 91%. For the small-diameter [special-purpose] fiber
25 production facilities, the percentage of fibers less than 3.5 μm and the percentage of
26 fibers less than 50 μm were not presented; however, across bulk-fiber-handling and
27 fabrication/finishing operations for the six plants the percentage of fibers with diameters
28 of less than or equal to 3.8 μm ranged from 89% to 100%, while the percentage of fibers
29 less than or equal to 48 μm in length ranged from 70% to 97%. Dement concluded that
30 based on the sampling data from this study, fiber concentrations in small-diameter

1 [special-purpose] fiber operations are many orders of magnitude higher than
2 concentrations seen in larger diameter [insulation-wool] fiber operations, and in addition,
3 the smaller diameters and shorter lengths make the fibers more respirable.

4 The largest collection of U.S. glass wool manufacturing exposure data was gathered by
5 Corn and Sansone (1974) and Esmen *et al.* (1979) in a series of studies in support of a
6 large epidemiologic investigation (Enterline and Henderson 1975). Corn and Sansone
7 reported the results of 115 air samples collected in three glass wool manufacturing
8 facilities; however, one of the plants produced only fiberglass-reinforced plastics, and the
9 data for this plant are not reported in Table 2-5. To avoid overload with particles,
10 sampling filters were changed every 2 hours and, therefore, reported levels do not
11 represent full-shift TWA concentrations. Phase-contrast optical microscopy was used, and
12 fibers greater than 5 μm in length were reported (this is similar to NIOSH method 7400A
13 counting rules). The percentage of respirable fibers less than 3.5 μm in diameter and
14 greater than 5 μm in length was also reported. Across both plants, mean fiber
15 concentrations (greater than 5 μm in length) ranged from 0.02 to 1.41 fibers/cm³. The
16 range includes means for both personal and stationary sampling across different fiber
17 manufacturing, fabrication, and non-manufacturing tasks. The highest fiber concentration
18 was 3.16 fibers/cm³ measured in a filter-tube finishing operation. The percentage of
19 fibers in the respirable size range was highly variable but generally ranged from 20% to
20 60%.

21 Esmen *et al.* (1979) reported on the exposures of U.S. production workers in 16 facilities
22 that produced glass wool, glass filament, rock wool, and slag wool products. Seven of the
23 plants studied produced glass wool (two of the seven facilities also produced continuous
24 glass filament); for the plants that produced only loose glass fibers, the nominal diameters
25 ranged from 3 to 10 μm . One facility produced glass fibers with nominal diameters
26 ranging from 0.05 to 1.6 μm [fiber diameters that are generally associated with special-
27 purpose glass fibers], and one facility received fibers with nominal diameters ranging
28 from 7 to 10 μm from another facility and prepared the fibers for manufacturing
29 [fabrication]. Samples were collected during 7- to 8-hour collection periods and fiber
30 counting and sizing methods adhered to guidelines established by OSHA for asbestos [no

1 additional counting and sizing information was provided]. Across several plant
2 operations (i.e., forming, production, manufacturing, maintenance, quality control, and
3 shipping), the overall plant mean concentrations across the eight facilities manufacturing
4 or fabricating the larger diameter fibers ranged from 0.0094 to 0.042 fibers/cm³ for fibers
5 greater than 5 µm in length. Mean exposure levels in the plant producing small-diameter
6 [special-purpose] fibers ranged from 0.0097 to 1.56 fibers/cm³ with an overall mean of
7 0.78 fibers/cm³.

8 In another study, Esmen *et al.* (1982) evaluated airborne exposure levels of fine-diameter
9 [special-purpose] fibers in two facilities that fabricated aircraft insulation products.
10 Counting and sizing of fibers was performed by phase-contrast optical microscopy and
11 electron microscopy, and sampling times were based on task-length rather than 8-hour
12 work shifts. Mean airborne respirable fiber (i.e., diameters < 3 µm) concentrations ranged
13 from 0.05 to 1.7 fibers/cm³ across different jobs/tasks (e.g., sewer, cutter, cementer) for
14 two production facilities. The highest single concentration observed was 3.8 fibers/cm³.

15 A follow-up study of five of the nine glass fiber plants surveyed by Esmen *et al.* (1979)
16 was reported in 1984 (Hammad and Esmen 1984). Roughly 200 samples were obtained
17 and analyzed using the same methods described by Esmen *et al.* (1979). Four of the
18 facilities produced large-diameter glass fibers (nominal diameters ranging from 1 to 15
19 µm), and one facility produced small-diameter [special-purpose] glass fibers (nominal
20 diameters ranging from 0.05 to 1.6 µm). For the large-diameter fiber production facilities,
21 across various areas of the production facilities, mean fiber concentrations ranged from
22 0.0047 to 2.22 fibers/cm³. (The value of 2.22 fibers/cm³ was from the quality control area
23 of one of the facilities; the next highest mean value at this facility was 0.46 fibers/cm³.)
24 For the facility producing small-diameter [special-purpose] fibers, mean fiber
25 concentrations ranged from 0.048 to 6.77 fibers/cm³ across production areas.

26 Using historical exposure data from glass fiber production facilities, Smith *et al.* (2001)
27 estimated airborne glass fiber exposure levels from the production of insulation glass
28 wool and small-diameter [special-purpose] fibers for two time periods: before 1980 and
29 from 1980 to 1990. Different methods had been used to collect and analyze the exposure

1 data. Plant-level mean concentrations for insulation glass wool production ranged from
2 0.045 to 0.262 fibers/cm³ and the simple [unweighted] mean of the plants combined was
3 0.15 fibers/cm³ for the period before 1980. For the period after 1980, plant means ranged
4 from 0.026 to 0.278 fibers/cm³ with a simple [unweighted] mean for the plants combined
5 of 0.091 fibers/cm³. For small-diameter [special-purpose] fibers, plant-level mean
6 concentrations for the period before 1980 ranged from 0.027 to 1.94 fibers/cm³ with a
7 simple [unweighted] mean for the plants combined of 0.662 fibers/cm³. Exposure levels
8 measured after 1980 ranged from 0.025 to 1.86 fibers/cm³ with a simple [unweighted]
9 mean of 0.745 fibers/cm³ for the plants combined.

10 In collaboration with the North American Insulation Manufacturers Association
11 (NAIMA), Marchant *et al.* (2009) summarized exposure data collected or commissioned
12 by NAIMA. As part of the Health and Safety Partnership Program (HSPP) (see Section
13 2.6.2), NAIMA developed an occupational exposure database for SVF. To populate the
14 database, existing exposure data were collected from various sources, and NAIMA or its
15 member companies also commissioned new exposure monitoring studies. Various
16 sampling and analytical methods were used for the data that were collected; however,
17 only fibers meeting the NIOSH 7400B rule were included in the results presented by
18 Marchant *et al.* In addition, only personal sampling results for periods of at least 240
19 minutes were included in the results. Means of samples collected in glass wool
20 manufacturing and fabrication environments (N = 2,304), ranged from 0.03 to 0.16
21 fibers/cm³. Although not specifically denoted as special-purpose glass fibers, data were
22 also provided for several product categories generally associated with special-purpose
23 fiber applications. For example, for aircraft insulation manufacturing, the mean respirable
24 fiber concentration was 0.06 fibers/cm³ for primary manufacturing, 0.03 fibers/cm³ for
25 secondary manufacturing, and 0.13 fibers/cm³ for fabrication. Filtration products had a
26 mean concentration of 0.22 fibers/cm³ for primary manufacturing, 0.02 fibers/cm³ for
27 secondary manufacturing, and 1.15 fibers/cm³ for fabrication.

28 Exposure levels similar to those reported in the U.S. studies have been reported in non-
29 U.S. studies. In a large survey of occupational exposures to MMVF, Head and Wagg
30 (1980) assessed respirable fiber levels in 25 plants and construction sites in the United

1 Kingdom, including 3 insulation glass wool manufacturing facilities and 4 facilities that
2 manufactured glass fiber paper and filtration products using special-purpose fibers.
3 Parallel sampling was used to estimate total airborne dust and fibers. Single gravimetric
4 samples were taken for dust analyses, and, over the same time-period, multiple samples
5 were taken for fiber-count analyses in order to avoid overload with particles. The authors
6 noted that the results did not represent full-shift averages. Samples were analyzed using
7 phase-contrast optical microscopy, and respirable fibers were defined as those with a
8 diameter of less than 3 μm and length greater than 5 μm . Overall mean respirable fiber
9 concentrations across the three insulation glass wool plants ranged from 0.12 to 0.31
10 fibers/cm³, while individual samples ranged from 0.003 to 1.1 fibers/cm³. For special-
11 purpose fibers, overall mean concentrations ranged from 0.08 to 3.70 fibers/cm³, while
12 individual samples ranged from 0.02 to 18.83 fibers/cm³. The maximum fiber count was
13 found at a paper-slitting machine. The authors noted that higher dust levels were found at
14 conversion processes (where fibers are converted to finished products) due to the greater
15 degree of manipulation of the materials.

16 In support of a large European occupational epidemiologic study of MMVF, the Institute
17 of Occupational Medicine, in Edinburgh, U.K., measured the concentrations of airborne
18 MMVF fibers in 13 European production plants, including 4 glass wool plants. Fiber
19 counts were made using phase-contrast optical microscopy, and fiber size was assessed
20 using scanning electron microscopy. Respirable fibers were considered those with length
21 $\geq 5 \mu\text{m}$, diameter $< 3 \mu\text{m}$, and aspect ratio ≥ 3 . Sampling periods were generally 7 to 8
22 hours, but filters were changed more frequently if the researchers considered that high
23 dust levels would result in a filter density that would make optical fiber counting
24 difficult. The results of this analysis were initially reported by Ottery *et al.* (1984).
25 However, around the time of that publication, it became apparent to the European
26 scientific community that the phase-contrast optical microscope methods that were used
27 to measure fiber levels did not always produce the same results when applied by different
28 laboratories. This culminated in an effort in Europe to standardize the sampling and
29 evaluation of man-made mineral fibers and to harmonize the performance of various
30 national laboratories that were using those methods. Because of this effort, the sampling
31 data from Ottery *et al.* were reanalyzed using a different counting method (WHO/EURO

1 phase-contrast optical microscope reference method) and determined to be too low by a
2 factor of about 2.2. The results of the reanalysis were reported by Cherrie *et al.* (1986)
3 and these results are presented in Table 2-5. The authors noted that the maximum mean
4 concentration was associated with the manufacture of special fine fiber earplugs. [It is
5 likely that these levels were associated with special-purpose fibers; however, Cherrie *et*
6 *al.* did not specify categories for glass wool fibers, and the facility for which these levels
7 were associated produced both insulation wools and “special fine fiber earplugs.”]

8 Krantz (1988) reported the results of an analysis of occupational exposure to SVF in nine
9 Swedish factories that produced insulation wools (rock or glass wools) or special-purpose
10 fiber products. Personal sampling was performed usually over two full shifts with
11 sampling time varying between 2 and 8 hours depending on operation and fiber level.
12 Fiber counting was performed using phase-contrast optical microscopy at a magnification
13 of 500x. Respirable fibers were defined as having an aspect ratio ≥ 3 and a diameter ≤ 3
14 μm ; fibers with lengths $< 5 \mu\text{m}$ were not counted. The results for the two categories of
15 fibers are presented in Table 2-5. The authors noted that for both insulation wools and
16 special-purpose fibers the maximum median diameter for airborne glass fibers was below
17 $1 \mu\text{m}$, and that when this value was compared with the nominal fiber diameter of the
18 product, it was obvious that it was the fine (thin) fibers in the product that became
19 airborne. It was also noted that, for the whole study, between 73% and 94% of the
20 airborne fibrous dust was respirable.

21 Yeung and Rogers (1996) reported the results of a large study reviewing the national
22 profile of occupational exposure to SVF, including glass wool, in Australia. SVF data
23 consisting of 1,572 samples from 252 sampling activities was collected by standardized
24 questionnaire from a number of different sources throughout Australia, including
25 government agencies, occupational health and safety consultants, SVF manufacturers and
26 end-users, and academia. All data were validated for technical integrity and it was also
27 noted that 87% of the sampling results were analyzed in accredited laboratories. The
28 authors reported that the nominal diameter of bulk glass wool typically ranged between 5
29 and $8 \mu\text{m}$ and that between 10% and 20% of fibers in the product were less than $3 \mu\text{m}$ in
30 diameter. Based on 94 samples, the geometric mean fiber concentration was 0.03

1 fibers/cm³, and the range across all samples was from less than 0.01 fibers/cm³ to 0.2
2 fibers/cm³.

3 In 1990, an Australian standard of 0.5 fibers/cm³ was established for all forms of MMVF.
4 Yeung and Rogers compared sampling data from before the establishment of the
5 regulatory limit with data collected after its establishment and noted that no quantitative
6 trend or difference in airborne exposure levels between the two time periods was
7 apparent.

Table 2-5. Occupational exposure to glass fibers in production facilities

Reference	Sample description	Fiber definition	Exposure levels (fibers/cm ³) ^a
U.S. data			
Johnson <i>et al.</i> 1969	Personal samples from workers in 4 plants manufacturing glass wool insulation products.	aspect ratio ≥ 3 total fibers $> 5 \mu\text{m}$ in length	0.0–1.01 (range of individual samples)
Dement 1975	Glass fiber exposures of workers in 4 glass wool production facilities manufacturing large-diameter ($> 1 \mu\text{m}$) insulation products (A, B, C, D) and 6 facilities manufacturing small-diameter ($< 1 \mu\text{m}$) [special-purpose] glass fiber products (C, E, F, G, H, I) [Plant C produced both large and small diameter fibers]	aspect ratio not specified ^b total fibers $> 5 \mu\text{m}$ in length	<i>Large-diameter ($> 1 \mu\text{m}$) fiber plants</i> 0.04–0.2 (range of means collected across four different products and fiber forming methods as well as for scrap reclamation and the category “all other operations”) <i>Small-diameter ($< 1 \mu\text{m}$) fiber plants</i> 1.0–21.9 (range of means across bulk fiber handling and fabrication/finishing operations for 3 products)
Corn and Sansone 1974	Personal samples from workers in 3 glass wool manufacturing facilities, conducted in support of large epidemiologic study of SVF Plants A and B manufactured various glass fiber products, including different types of insulation. It is uncertain if special-purpose fibers were produced at either plant. Plant C produced only fiberglass-reinforced plastics, so results are presented for plants A and B only.	aspect ratio not specified ^b total fibers $> 5 \mu\text{m}$ in length	Plant A 0.03–0.08 Plant B 0.02–1.41 (range of means for both personal and stationary sampling across different fiber manufacturing, fabrication, and non-manufacturing tasks)
Esmen <i>et al.</i> 1979	Personal sampling of airborne exposure levels in 5 large-diameter (1–12 μm) glass fiber production facilities, 2 large-diameter glass fiber and continuous filament production facilities, 1 large-diameter glass fiber fabrication facility, and 1 small-diameter [special-purpose] glass fiber production facility from 1975–78	aspect ratio not specified ^b total fibers $> 5 \mu\text{m}$ in length	0.0094–0.042 (range of overall means of 8 large-diameter manufacturing/fabricating facilities)

Reference	Sample description	Fiber definition	Exposure levels (fibers/cm ³) ^a
Esmen <i>et al.</i> 1982	Airborne glass fiber exposure to fine-diameter [special-purpose] fibers during manufacture and fabrication of aircraft insulation products in 2 facilities (A & B) Average nominal fiber diameter in plant A = 1 µm; not reported for plant B	aspect ratio not specified ^b length > 5 µm diameter < 3 µm	0.05–1.7 (range of means for different jobs/tasks across two plants)
Hammad and Esmen 1984	Follow-up study of 5 of the 9 glass wool production facilities sampled in Esmen <i>et al.</i> (1979) Plant 1: wool insulation and continuous filament (nominal diameters 5–15 µm) Plant 2: insulation products (nominal diameters 6–10 µm) Plant 3: insulation and flotation wool, filtration media (nominal diameters 1–6 µm) [insulation glass wool and special-purpose fibers] Plant 4: wool insulation and continuous filament (nominal diameters 1–12 µm) [insulation glass wool and special-purpose fibers] Plant 5: very fine fibrous glass for filtration media, thermal insulation, and aerospace applications [i.e., special-purpose fibers] (nominal diameters 0.05–1.6 µm)	aspect ratio not specified ^c	Plant 1 0.0047–0.028 Plant 2 0.015–0.062 Plant 3 0.012–2.22 (next highest 0.46) Plant 4 0.010–0.28 Plant 5 0.048–6.77 (range of means across work areas; includes results from two sampling periods)
Marsh <i>et al.</i> 2001a	Exposures of U.S. man-made vitreous fiber cohort workers from 1970 to 1987 in 5 plants producing mostly glass wool	aspect ratio > 3:1 length > 5 µm diameter < 3 µm	0.049–0.211 (range of plant-level mean concentrations across plants producing mostly glass wool)
Smith <i>et al.</i> 2001	Airborne glass fiber exposures in 4 plants manufacturing insulation wool and small-diameter fibers	aspect ratio > 3:1 length > 5 µm diameter < 3 µm	<i>Insulation glass wool</i> 0.045–0.262 (range of means across plants before 1980) 0.026–0.278 (range of means across plants after 1980) <i>Small-diameter fibers</i> 0.027–1.94 (range of means across plants before 1980) 0.025–1.86 (range of means across plants after 1980)

Reference	Sample description	Fiber definition	Exposure levels (fibers/cm ³) ^a
			after 1980)
Marchant <i>et al.</i> 2009 [data collected or commissioned by NAIMA]	Exposure levels for primary and secondary manufacturing and fabrication of insulation glass wool and for specific product categories (i.e., aircraft insulation [assumed special-purpose fibers], filtration products [assumed special-purpose fibers], and a combined category of “all other products” which consisted of appliance insulation, duct insulation, and pipe insulation). Note that product categories were not distinguished as glass wool or rock/slag wool.	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	Range of means for exposure data aggregated by primary manufacturing, secondary manufacturing, and fabricating <i>Insulation glass wool</i> 0.03–0.16 <i>Filtration products</i> 0.02–1.15 <i>Aircraft insulation</i> 0.03–0.13 <i>All other products</i> 0.02–0.14
Non-U.S. data			
Head and Wagg 1980 U.K.	Occupational exposures across 3 insulation glass wool manufacturing plants Exposure levels across 4 production facilities using glass micro-fibers [i.e., special-purpose fibers] in the manufacture of high-efficiency filters	Respirable fibers: aspect ratio ≥ 3 length > 5 μm diameter < 3 μm	<i>Insulation glass wool manufacturing</i> 0.12–0.31 (range of means across plants) 0.003–1.10 (range of individual samples) <i>Glass microfiber manufacturing</i> 0.08–3.70 (range of means across plant/product combinations) 0.02–18.83 (range of individual samples)
Cherrie <i>et al.</i> 1986 (update of Ottery <i>et al.</i> 1984) Europe	Surveys of 4 glass wool plants. Mean values range across 7 job categories	Respirable fibers: ^d aspect ratio ≥ 3 length ≥ 5 μm diameter < 3 μm	0.01–1.6 (range of means across job groups and manufacturing facilities) 0.01–4.02 (range of individual samples across all job groups and manufacturing facilities)
Krantz 1988 Sweden	Personal sampling in 9 factories that produced insulation wools (rock and glass) and/or special-purpose glass fiber products (earplugs): number of facilities not specified by type of product	Respirable fibers: aspect ratio ≥ 3 length ≥ 5 μm diameter ≤ 3 μm	<i>Insulation wools</i> 0.18 (mean across all jobs/facilities) 0.01–1.8 (range of individual samples across all jobs/facilities) <i>Special-purpose glass fibers products</i>

Reference	Sample description	Fiber definition	Exposure levels (fibers/cm ³) ^a
			0.47 (mean across all jobs/facilities) 0.08–2.4 (range of individual samples across all jobs/facilities)
Yeung and Rogers 1996 Australia	Levels for fiberglass manufacturing across all jobs/processes. Data collected by standardized questionnaire and includes both personal and stationary sampling; type of fiber (special-purpose or insulation wool) not specified	Respirable fiber Aspect ratio: ≥ 3 Length > 5 μm Diameter < 3 μm	0.03 ^c (geometric mean of all samples) < 0.01–0.2 (range of all individual samples)

^aExposure measured using using phase-contrast microscopy unless indicated otherwise.

^bAssumed to be 3:1.

^cAssumed to be the same as Esmen *et al.* 1979.

^dStudy is an update of Ottery *et al.*, and the fiber definition came from that paper.

^ePhase-contrast microscopy not specified for these data.

1 2.3.2 *Non-manufacturing occupational exposures*

2 Exposures can occur while installing, removing, fabricating, or otherwise working with
3 glass wool outside the manufacturing environment. These applications are sometimes
4 referred to as end-use, and workers engaged in these applications, therefore, can be
5 referred to as end-users. Since glass wool is primarily used for insulation purposes, most
6 of the end-use exposure data focuses on insulation activities. Exposures in these end-user
7 applications are typically higher than in the fiber manufacturing environments.

8 Eight-hour TWA exposure estimates are not well suited to describe exposures for
9 insulation installation and other end-use tasks because of the nature of these trades
10 (Fowler *et al.* 1971). Typically, these workers are exposed during a working day to a
11 series of peak exposures while they are handling the material. Fowler *et al.* described the
12 scenario for end-users where one worker ordinarily cuts, applies, and finishes a single
13 piece of insulation material and noted that this differs from exposures in a production
14 plant where a worker likely performs a single task throughout the workday with less
15 exposure fluctuation. Because of this, end-use exposures are typically measured for the
16 period of active work (i.e., as task-length average concentrations) rather than for the full
17 work shift (i.e., 8-hour TWA). As such, exposure levels between end-use operations and
18 manufacturing operations often are not directly comparable.

19 As cited by Maxim *et al.* (2003), the United States Department of Labor (USDOL),
20 Bureau of Labor Statistics (BLS) (2009), reported that approximately 53,000 workers
21 were employed by insulation contractors in the year 2000. This number was projected to
22 grow to 60,000 by 2010. In May 2007 the U.S. Bureau of Labor Statistics reported that
23 nearly 31,000 workers were employed as “insulation workers” within the NAICS Code
24 238310 (Drywall and Insulation Contractors). Additionally, workers involved in other
25 construction trades such as drywall installers, carpenters, and heating and cooling
26 specialists also install insulation. Approximately 150,000 of these workers have periodic
27 exposure to glass wool insulation materials (Maxim *et al.* 2003). Lees *et al.* (1993) cited
28 OSHA estimates that in 1992, there were 185,000 full-time–equivalent construction
29 workers employed in the U.S. residential insulation trades.

1 Residential homeowners engaged in home remodeling projects are potentially exposed to
2 insulation materials through the removal and replacement of existing products. No data
3 were identified regarding the number of individuals involved in these activities, although
4 the majority of these projects involve the installation of batt and/or blanket insulation,
5 rather than loose fill insulation (Maxim *et al.* 2002).

6 Fowler *et al.* (1971) sampled a variety of fiberglass insulating operations, including duct
7 wrapping, wall and plenum insulation, pipe insulation and fan housing insulation. Task-
8 length average (20 to 60 minutes) total breathing zone fiber concentrations ranged from
9 0.48 to 8.08 fibers/cm³ with a median of 1.26 fibers/cm³ and a mean of 1.8 fibers/cm³
10 based on phase-contrast optical microscopy. Fowler *et al.* estimated that about half of the
11 airborne fibers generated during installation were less than 3.5 µm in diameter. Mean
12 exposure levels to workers of other trades working close to the insulation operations were
13 0.1 fibers/cm³.

14 Worker breathing-zone exposure levels for insulation glass wool during the installation of
15 commercial and residential insulation in buildings was evaluated by Esmen *et al.* (1982).
16 Counting and sizing of fibers was performed by phase-contrast optical microscopy and
17 electron microscopy, and sampling times were based on task-length rather than 8-hour
18 work shifts. The average respirable fiber exposure of workers for all applications, except
19 the blowing of thermal insulation into attics, ranged from 0.003 to 0.13 fibers/cm³.
20 Average respirable glass wool exposure levels for various tasks during blowing attic
21 insulation ranged from 0.31 to 1.8 fibers/cm³. The range of individual exposure levels for
22 the blower (the task with the highest exposure levels) was 0.67 to 4.8 fibers/cm³.

23 Jacob *et al.* (1992) characterized the task-length (typically 1 to 2 hours) fiber
24 concentrations during the installation of residential glass wool insulation in 13 cities
25 throughout the United States. Sample collection and fiber counting methods followed
26 NIOSH Method 7400 with some modifications that allowed for identification of fiber
27 type (7400A method for total fibers and 7400B for respirable fibers). Jacob *et al.* reported
28 results as a combination of counting fibers deposited on the filter and rinsed from the
29 cowl. A cowl-rinsing procedure reported by Breysse *et al.* (1990) was used to evaluate

1 the deposition of fibers on the inside of the collection cowl. The average fraction of fibers
2 on the cowl was reported to be 25% of the total fiber counts. Based on differential
3 counting, Jacob *et al.* reported total respirable fibers as well as respirable glass wool
4 fibers (fiber identity based on morphology and polarized light). Glass fibers were found
5 to account for between 40% and 70% of the respirable fibers. Mean respirable fiber
6 exposure to installers during the installation of batt insulation was 0.059 fibers/cm³ with a
7 95% confidence interval of 0.049 to 0.073 fibers/cm³. Mean respirable-fiber exposures
8 during blowing wool insulation ranged from 0.12 to 0.91 fibers/cm³ across products and
9 tasks, with the installers having the highest mean exposures.

10 Lees *et al.* (1993) conducted a comprehensive residential insulation installation exposure
11 survey in the early 1990s. Workers were monitored during insulation operations in 107
12 houses in 11 different states, and results were presented as task-length averages. Similar
13 to Jacob *et al.* (1992), fiber counts included fibers deposited on the inside of the
14 conducting cowl. Lees *et al.* (1993) reported respirable fiber (NIOSH 7400B rules)
15 concentrations during installation of glass wool batt insulation in homes ranging from
16 0.02 to 0.42 fibers/cm³, with a mean of 0.14 fibers/cm³. The installation of loose
17 fiberglass insulation that had a binder resulted in mean exposures of 0.55 fibers/cm³ for
18 the installer and 0.18 fibers/cm³ for the feeder. The highest exposures were noted for
19 installation of loose insulation without binder. For installers, exposure levels ranged from
20 1.32 to 18.4 fibers/cm³, with a mean of 7.67 fibers/cm³, while for feeders, levels ranged
21 from 0.06 to 9.36 fibers/cm³, with a mean of 1.74 fibers/cm³.

22 More recently, Marchant *et al.* (2009) reported an overall mean SVF exposure level
23 during glass wool installation operations of 0.39 fibers/cm³ and a mean level of 0.26 for
24 retrofit/removal operations based on data from the NAIMA database on occupational
25 exposures to SVF (see previous section on manufacturing exposures). In a task-exposure
26 analysis, the mean batt insulation installation exposure level was 0.11 fibers/cm³, while
27 the mean loose-fill insulation installation exposure level was 0.51 fibers/cm³. Fiber
28 sampling and counting were conducted using NIOSH 7400B rules, and a minimum
29 sampling time of 240 minutes was required for inclusion in the database.

1 In addition to residential and building insulation, insulation glass wool is fabricated for
2 and used in a variety of other commercial products. Using NIOSH 7400A and B
3 techniques, Jacob *et al.* (1993) evaluated glass wool exposures in 11 different end-user
4 manufacturing environments, including the fabrication and assembly of metal building
5 and manufactured housing insulation, pipe insulation, small appliance manufacturing, air
6 handling ducts, and water heaters. The mean concentration of respirable fibers (NIOSH
7 7400B fibers) ranged from 0.006 to 0.087 fibers/cm³. These counts included fibers rinsed
8 from the cowl.

9 Data on exposures during glass wool removal are limited. Jacob *et al.* (1993) assessed
10 exposures during pipe and ceiling board removal. The arithmetic mean total fiber
11 exposure was 0.29 fibers/cm³ with a 95% confidence interval of 0.2 to 0.41 fibers/cm³.

12 Breysse *et al.* (2001) reported end-user glass wool exposures in a variety of commercial
13 applications. Applications sampled included duct board, duct liner, duct wrap fabrication
14 and installation, and pipe insulation installation. Samples were collected using NIOSH
15 Method 7400 (both A and B methods were applied but only the 7400B results were
16 reported). A task-based sampling strategy was employed; therefore, exposure levels
17 reflect task-length average concentrations. Fiber samples were analyzed using phase-
18 contrast microscopy, and concentrations were reported according to NIOSH 7400B
19 counting rules and included cowl fibers. The addition of cowl fibers increased
20 concentrations by 35% to 47%. Mean end-user fiber concentrations ranged from 0.03 to
21 0.68 fibers/cm³ across products and tasks. The highest fiber concentrations, from 0.17 to
22 2.13 fibers/cm³, were found during duct wrap insulation installation.

23 Exposure levels similar to those reported in the U.S. studies have been reported in non-
24 U.S. studies (Head and Wagg 1980, Perrault *et al.* 1992, Yeung and Rogers 1996).

25 Head and Wagg (1980) studied airborne concentrations of respirable insulation glass
26 wool fibers in three manufacturing plants and two construction sites in the United
27 Kingdom, and reported slightly higher levels among workers installing domestic glass
28 wool insulation than for production workers. The maximum mean level for installation of

1 fiberglass insulation blankets in a domestic loft was 1.02 fibers/cm³ with a maximum
2 individual level of 1.76 fiber/cm³.

3 In the early 1990s an occupational exposure survey of MMVF insulation products was
4 conducted at several industrial construction sites in Montreal, Canada where workers
5 were installing or removing insulation (Perrault *et al.* 1992). Area sampling was
6 performed with sampling times ranging from 0.5 to 4 hours for the whole study (which
7 included analyses of other fibers and locations). Respirable fibers (defined by the authors
8 as having a diameter of < 3 µm, a length of > 5 µm and an aspect ratio > 3:1) were
9 counted using phase-contrast optical microscopy based on WHO methodology. For glass
10 wool, two sites were investigated: one site where refractory fibers and glass wool
11 products were being installed and another site where only glass wool insulation was
12 being installed. A geometric mean of 0.01 fibers/cm³ was reported for the site where only
13 glass wool insulation was being installed.

14 As discussed earlier, Yeung and Rogers (1996) reported the results of a large study to
15 review the national profile of occupational exposure to MMVF in Australia. MMVF
16 exposure data, including data from installation and removal activities, were collected by
17 standardized questionnaire from a number of different sources throughout Australia. For
18 non-manufacturing exposures, slightly higher levels were reported for glass wool
19 installation compared with removal (maximum geometric means of 0.12 fibers/cm³
20 versus 0.04 fibers/cm³ and maximum individual samples of 0.8 fibers/cm³ versus 0.2
21 fibers/cm³). Levels associated with glass wool removal were similar to levels associated
22 with production, which had a geometric mean concentration of 0.03 fibers/cm³ and a
23 range of less than 0.01 to 0.2 fibers/cm³.

Table 2-6. Non-manufacturing occupational exposure to glass wool

Reference	Sample description	Fiber definition	Exposure levels (fibers/cm ³) ^a
U.S data			
Fowler <i>et al.</i> 1971	Fiberglass insulating operations including duct wrapping, wall and plenum insulation, pipe insulation, and fan housing insulation	total fibers	1.8 (mean of breathing zone samples across operations) 0.48–8.08 (range of individual breathing zone samples across operations)
Esmen <i>et al.</i> 1982	Worker exposure to glass wool during the installation of blown glass wool insulation, building insulation, ducts, and acoustical ceilings	aspect ratio not specified length > 5 µm diameter < 3 µm	0.003–1.8 (range of means across tasks during blowing insulation into attics) 0.0028–0.13 (range of means across all other tasks)
Jacob <i>et al.</i> 1992	Fiber concentrations during the installation of batt and blown residential glass wool insulation in 13 cities throughout the U.S. (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 µm diameter < 3 µm	0.059 (mean for batt insulation installation) 0.12–0.91 (range of means across blown glass wool products and tasks)
Lees <i>et al.</i> 1993	Worker exposure during residential glass wool insulation installation operations (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 µm diameter < 3 µm	0.14 (mean for installation of batts) 0.18, 0.55 (means for feeder and installer, respectively, for blown insulation that contained a binder) 1.74, 7.67 (means for feeder and installer, respectively, for blown insulation that contained no binder)
Jacob <i>et al.</i> 1993	Glass wool exposures in 11 different end-user manufacturing environments (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 µm diameter < 3 µm	0.006–0.087 (range of means for various fabrication and assembling operations) 0.13 (mean for pipe and ceiling insulation removal)
Breyse <i>et al.</i> 2001	End-user (fabrication and installation) glass wool exposures for a variety of commercial applications (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 µm diameter < 3 µm	0.03–0.68 (range of means across products and tasks)
Marchant <i>et al.</i> 2009	Exposure levels from glass wool insulation installation operations collected or commissioned by NAIMA	aspect ratio ≥ 5:1 length > 5 µm diameter < 3 µm	0.39 (overall mean, installation) 0.26 (overall mean, retrofit/removal) 0.11 (mean, batt installation)

Reference	Sample description	Fiber definition	Exposure levels (fibers/cm ³) ^a
			0.51 (mean, loose fill installation)
Non-U.S data			
Head and Wagg 1980 U.K.	Occupational exposure sampling during installation of fiberglass blanket insulation at two domestic sites	respirable fibers: length > 5 µm diameter < 3 µm	0.38, 1.02 (mean levels for the two sites) 0.24–1.76 (range of individual samples across both sites)
Perrault <i>et al.</i> 1992 Canada	Sampling performed at a major industrial construction site during installation of fiberglass insulation around ventilation ducts	respirable fiber aspect ratio: > 3:1 length > 5 µm diameter < 3 µm	0.01 (geometric mean)
Yeung and Rogers 1996 ^b Australia	Levels for installation and removal of fiberglass insulation products: data collected by standardized questionnaire and includes both personal and stationary sampling	respirable fiber aspect ratio: ≥ 3:1 length > 5 µm diameter < 3 µm	<i>Installation</i> 0.06 (< 0.01–0.8) (geometric mean and range) <i>Removal</i> 0.03 (< 0.01–0.2) (geometric mean and range)

^aExposure measured using using phase-contrast microscopy unless indicated otherwise.

^bPhase-contrast microscopy not specified for these data.

2.4 Environmental occurrence and general population exposure in the United States

No information was identified on environmental occurrence and exposure to specific glass fiber products; therefore, most of the data presented in this section are from occurrence and exposure to SVFs as a group.

SVFs do not occur naturally in the environment, but they may be released into the environment during production, installation, use, removal, and disposal. Additionally, SVFs and glass fibers were found in air and dust samples following the terrorist attacks on the World Trade Center in September, 2001. [It also is likely that elevated levels could result from building implosions or structure fires.] Like other inorganic substances, SVFs do not undergo typical transformations in the environment, such as photolysis and biodegradation. As described in Section 1, SVFs are reasonably soluble under acidic or alkaline conditions, dissolving about 2 to 4 times quicker than crystalline fibers such as asbestos. The transport and partitioning of SVFs are largely governed by fiber size, with large fibers removed from air and water by gravitational settling at a rate dependent upon their size. Small fibers may remain suspended for long periods of time.

The primary route of SVF release into the environment is through the air. No published data were identified on quantities of SVFs released into the environment in the United States, or on contamination of soil, water, or food by SVFs. There are limited data on general population non-occupational exposures to SVFs. [Non-occupational exposures might occur during do-it-yourself home remodeling activities due to release of glass wool fibers from insulation and building materials.]

Jacob *et al.* (1992) measured airborne glass wool concentrations before and after insulation installation. Post-installation mean respirable fiber concentrations were low, ranging from 0.002 fibers/cm³ for batt installation to 0.001 fibers/cm³ for blowing wool operations. Post-installation concentrations were not significantly different from pre-installation concentrations.

2.4.1 Indoor and ambient levels

In order to assess the fiber release from air ducts lined with fiberglass, Balzer *et al.* (1971) measured fiber levels in 13 buildings. Results suggested that there was no increase

1 in fiber concentration due to air passing through ducts lined with fiberglass. Additionally,
2 Balzer *et al.* found that the glass fiber concentration outside of the buildings averaged
3 0.0002 fibers/cm³.

4 Miller *et al.* (1995) analyzed the fiber concentrations in living spaces of 14 homes both
5 prior to installation of insulation and again the evening following installation. Total fibers
6 were measured at levels ranging from < 0.001 to 0.009 fibers/cm³ before installation, and
7 from 0.03 to 0.012 fibers/cm³ one day post-installation using phase-contrast microscopy
8 and NIOSH 7400B counting rules. The mean living-space fiber concentrations were not
9 significantly elevated after installation. Similar results were obtained when using
10 scanning electron microscopy to count only SVFs. These results suggest airborne fiber
11 concentrations diminish rapidly following installation.

12 In order to evaluate concern that the erosion of SVFs from insulation materials may
13 contribute to fiber levels in the indoor environment, Carter *et al.* (1999) collected 205
14 area samples in 51 residential and commercial buildings. Twenty-one air samples were
15 collected simultaneously outdoors at 19 buildings. All samples were analyzed by phase-
16 contrast microscopy following the NIOSH 7400B counting rules. The mean value for all
17 respirable indoor fibers was 0.008 fibers/cm³ with a median value of 0.007 fibers/cm³ and
18 a maximum value of 0.029 fibers/cm³. Ninety-seven percent (97%) of the respirable
19 fibers identified by scanning electron microscopy with energy-dispersive X-ray
20 microanalysis (SEM-EDX) were determined to be organic. MMVF were detected in only
21 two samples. The median of the outdoor samples collected at 19 different locations was <
22 0.001 fibers/cm³, and individual samples ranged from < 0.001 to 0.009 fibers/cm³.

23 Switala *et al.* (1994) assessed the concentration of respirable glass fibers near a large
24 fiberglass wool manufacturing facility in an urban area, and also in a rural area, both in
25 Ohio. Airborne glass fiber concentrations based on phase-contrast microscopy and
26 NIOSH 7400B rules ranged from < 1.0×10^{-5} to 1.4×10^{-4} fibers/cm³. These levels were
27 similar to the measured levels in ambient air from a rural site located 10 miles away from
28 the plant. The concentration of glass fiber concentrations at the rural location ranged from

1 1.0×10^{-5} to 1.5×10^{-4} fibers/cm³, during the same sampling period. Glass fibers
2 accounted for <math>< 1\%</math> of the total respirable fibers measured at these sites.

3 2.4.2 Other possible sources of exposure

4 The general public could be exposed to glass fibers from building implosions, structure
5 fires, natural disasters, or terrorist attacks. Although no data were identified for airborne
6 glass concentrations for such events, Lioy *et al.* (2002) suggested that high levels of
7 airborne glass fibers resulted from the collapse of the World Trade Center based on
8 samples of settled dust following the terrorist attacks on the World Trade Center in New
9 York City on September 11, 2001. Lioy *et al.* reported the results of dust samples that
10 were taken on September 16 and 17 from three undisturbed locations within a mile of the
11 World Trade Center site. All three samples consisted of 40% glass fibers (mass
12 percentage), with the remaining mass consisting of varying amounts of nonfiber material
13 (cement/carbon), cellulose, and chrysotile asbestos. Landrigan *et al.* (2004) suggested
14 that compounds and materials present in the plume from the World Trade Center event
15 would be similar to those found in plumes from building fires or building implosions.
16 Exposure from the World Trade Center event was primarily from inhalation or ingestion
17 of dust directly after the event or due to resuspension of dust during clean-up activities
18 following the event (Landrigan *et al.* 2004, Lioy *et al.* 2002). Additional indoor exposure
19 to residents may have also occurred from resuspended residual dust remaining in the
20 residence or from ventilation systems not properly cleaned.

21 Studies reporting general population exposures to airborne glass fibers in ambient air are
22 summarized in Table 2-7.

Table 2-7. General U.S. population exposure to glass wool in ambient air

Reference	Sample description	Fiber description	Exposure levels (fibers/cm ³) ^a
Balzer <i>et al.</i> 1971	Airborne fiber concentrations both inside and outside 13 buildings with fiberglass-lined duct work	Fiber counting technique pre-dates any of the current specifications	No increase in glass fiber concentration due to air passing through ducts lined with fiberglass. The average glass fiber concentration outside the buildings was 0.0002
Jacob <i>et al.</i> 1992	Airborne glass wool concentrations before and several hours after insulation installation	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	Batt insulation: Mean fiber concentration before installation: 0.002 after installation: 0.001 Blowing wool operations: Mean fiber concentration before installation: 0.001 after installation: 0.001
Switala <i>et al.</i> 1994	Airborne respirable glass fiber concentrations near a large glass wool production facility, and in a rural location	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	Outside plant: < 1.0 × 10 ⁻⁵ –1.4 × 10 ⁻⁴ Rural: < 1.0 × 10 ⁻⁵ –1.5 × 10 ⁻⁴
Miller <i>et al.</i> 1995	Airborne fiber concentrations in the living areas of 14 homes both before and approximately 24 hr after glass wool insulation installation	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	Before installation: < 0.001–0.009 24 hr after installation: 0.03–0.012
Carter <i>et al.</i> 1999	Airborne fiber concentrations in 51 residential and commercial buildings with fiberglass insulation materials and simultaneous outdoor sampling at 19 sites	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	Inside buildings: Mean: 0.008 Median: 0.007 Maximum: 0.029 Outside buildings: < 0.001–0.009

^aExposure measured using using phase-contrast microscopy unless indicated otherwise.

1 **2.5 Biological indices of exposure**

2 There are no traditional biological indices of exposure for SVFs, as these are not
3 compounds that metabolize or break down in the body in the usual sense. Assessment of
4 biological exposure to SVFs has been attempted through the measurement of fiber
5 retention in human lung tissue (IARC 2002). In a study of autopsies of glass, rock, and
6 slag wool workers in the United States, analytical transmission electron microscopy was
7 used to determine retention of fibers in the lung 12 years after the end of exposure. No
8 significant difference was observed between SVFs in the lungs of 112 production
9 workers (101 glass wool and 11 rock or slag wool workers) or controls (112 consecutive
10 autopsies from the same hospital) in the study. The authors concluded that either the
11 SVFs disappeared from the lungs in less than 12 years, the workers did not inhale enough
12 SVFs to result in a difference when compared with the controls 12 years after the end of
13 the exposure, or the fixative fluids used for the lungs could have altered some retained
14 fibers (IARC 2002).

15 In a study investigating a possible biomonitoring method for SVF exposure, Paananen *et*
16 *al.* (2004) performed nasal lavage on workers from 2 factories and measured
17 concentrations of MMVF by electron microscopy. Cytokines (IL-6, IL-8, TNF-alpha, and
18 IFN-gamma) were also assayed, and inflammatory cells (lymphocytes, eosinophils,
19 neutrophils, and macrophages) were counted microscopically. In nasal lavage samples,
20 the mean concentration of MMVF (length > 1.5 μm) was 3,260 fibers/cm³ in factory 1,
21 11,680 fibers/ cm³ in factory 2, and below 55 fibers/ cm³ in the control group. The group-
22 specific mean concentration of MMVF in nasal lavage samples correlated with
23 production rates and airborne fiber levels in both plants. No significant differences in the
24 biological response (inflammatory cells, cytokines) were found between the exposed
25 groups and the control group. The authors concluded that nasal lavage could be used as a
26 biomonitoring method in the assessment of MMVF exposure.

27 **2.6 Regulations and guidelines**

28 *2.6.1 Regulations*

29 **U.S. Environmental Protection Agency (EPA)**

1 *Clean Air Act*

2 National Emission Standards for Hazardous Air Pollutants (NESHAP): Fine mineral fiber
3 emissions from facilities manufacturing or processing glass (of average diameter 1
4 micrometer (μm) or less) is listed as a Hazardous Air Pollutant (HAP)

5 New Source Performance Standards (NSPS): Manufacturers of wool fiberglass are
6 subject to provisions of NSPS for the control of particulates as prescribed in 40 CFR
7 60.292 and 293.

8 **Occupational Safety and Health Administration (OSHA)**

9 Permissible Exposure Limit (PEL) = 15 mg/m^3 (total); 5 mg/m^3 (respirable) (based on
10 regulation for "particulates not otherwise regulated")

11 *2.6.2 Guidelines*

12 **American Conference of Governmental Industrial Hygienists (ACGIH)**

13 Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 1 fiber/cm^3
14 (respirable fibers)

15 **National Institute for Occupational Safety and Health (NIOSH)**

16 Recommended Exposure Limit (REL) = 3 fibers/cm^3 (TWA) (fibers with diameter ≤ 3.5
17 μm & length $\geq 10 \mu\text{m}$); 5 mg/m^3 (TWA) (total) (listing is for "fibrous glass dust")

18 **Occupational Safety and Health Administration (OSHA)**

19 Health and Safety Partnership Program (HSPP) for manufacturers:

20 Maximum concentration of 1 WHO fiber/cc (cm^3), 8-hour TWA for respirable SVF
21 (WHO fiber is a fiber with diameter $< 3 \mu\text{m}$, length $\geq 5 \mu\text{m}$ and length to diameter
22 ratio $\geq 3:1$)

23 **2.7 Summary**

24 The vast majority of SVF produced and used in the United States consists of glass wool
25 used for home and building insulation. Small amounts of glass fibers are produced for
26 special applications such as use in battery separator media, high-efficiency filters, and
27 aircraft insulation. Glass wool is produced by heating the glass to high temperatures,

1 extruding the molten glass to form small streams of glass fibers, and using centrifugal
2 force to attenuate the streams of glass into glass fibers. Finer fibers are formed by flame
3 attenuation. Most general purpose insulation glass wools have nominal diameters ranging
4 from 1 to 10 μm , while special-purpose fibers generally range from 0.1 to 3 μm ;
5 however, product bulk samples may have fibers with diameters that are several times
6 greater or smaller than the nominal diameters. ACGIH noted that because of this
7 variation, all wool fiber products contain respirable fibers. The physical properties of
8 fibers affect their likelihood of becoming airborne, with smaller fibers more likely to
9 become airborne. Because of this, the average diameter and length may be smaller, and
10 the percentage of respirable fibers higher, for airborne fibers compared with the bulk
11 product.

12 Occupational exposure may occur in manufacturing facilities as well as for end-users,
13 such as during installation, removal, fabrication, or otherwise working with glass wool
14 outside the manufacturing environment (end-use). OSHA has estimated that more than
15 225,000 workers in the United States are exposed to synthetic mineral fibers in
16 manufacturing and end-use applications. General population exposure may occur from
17 exposure to SVFs from insulation and building materials or from fibers in the air near
18 manufacturing facilities or areas near building fires or implosions. Exposure may also
19 occur during do-it-yourself home remodeling activities.

20 No traditional biological indices of exposure exist for SVFs, although the measurement
21 of fibers in human lung tissue has been attempted as a means to assess exposure to SVFs.
22 In addition, a recent study investigated the use of nasal lavage as a biomonitoring method
23 for SVFs.

24 Fine mineral fiber emissions are regulated by the EPA, respirable fibers (“particulates not
25 otherwise regulated”) are regulated by OSHA; ACGIH, NIOSH, and OSHA have set
26 guidelines for fibers in the air in the workplace.

3 Human Cancer Studies

This section reviews cohort and case-control studies that evaluated exposure to glass wool and cancer risk. Most of the cohort studies have been mortality studies; few incidence studies have been conducted. The largest studies were conducted with workers involved in the manufacture of synthetic vitreous fibers (SVF). These include (1) combined cohort mortality studies of U.S. workers conducted by the University of Pittsburgh, which included a total of nearly 26,700 workers potentially exposed to glass wool at the last follow-up (Marsh *et al.* 2001a,b,c, Stone *et al.* 2004), together with nested case-control studies of this cohort (Chiazze *et al.* 1992, 1993, Enterline *et al.* 1987, Marsh *et al.* 2001a, Stone *et al.* 2001, Youk *et al.* 2001), (2) a European cohort mortality study comprising a total of 6,936 glass wool-exposed workers with at least one year of employment at the last follow-up (Boffetta *et al.* 1997), an incidence study of 2,611 workers from this cohort (Boffetta *et al.* 1999), and a nested case-control study of part of this cohort (Gardner *et al.* 1988), (3) a smaller Canadian cohort studied by Shannon *et al.* (2005, 1984, 1987), and (4) a smaller hospital-based French cohort studied by Moulin *et al.* (1986). Other cohort studies have been conducted with workers exposed to glass wool during use, mainly through employment in insulation work in the construction industry.

Section 3.1 describes cohort and case-control studies of manufacturing workers who were exposed mostly to glass wool, rather than to mixed fibers including rock or slag wool, glass filament, or special fibers. Section 3.2 describes findings for workers exposed mostly to mixed glass wool and glass filament. Section 3.3 briefly reviews cohort studies and a series of mainly population-based, case-control studies of potential mixed SVF exposure.

3.1 Glass wool exposure: cohort and case-control studies

Data from the groups in these studies that were exposed mostly to glass wool are reported in Table 3-4 and discussed below.

1 3.1.1 U.S. cohort

2 A number of U.S. plants (Table 3-1) manufacturing one or more SVFs have been studied
3 by various investigators from the 1980s onwards, both as separate cohorts and, under the
4 direction of the University of Pittsburgh, as a combined cohort. Parts of this cohort were
5 previously studied and followed up by Enterline and colleagues (Bayliss *et al.* 1976,
6 Enterline and Henderson 1975, Enterline and Marsh 1980, 1984, Enterline *et al.* 1983,
7 Enterline *et al.* 1987, Marsh *et al.* 1990, Morgan *et al.* 1981), including nested case-
8 control studies of respiratory cancers by Enterline *et al.* (1987), and Chiazze *et al.* (1992,
9 1993, see below).

10 The cohort (Table 3-4), including production and maintenance workers from eight plants
11 in seven states that produced glass wool or glass wool and filament, comprising white
12 male workers only, was followed up initially until 1977 and then 1982 (Enterline and
13 Marsh 1984, Enterline *et al.* 1983, Enterline *et al.* 1987), and subsequently to 1985
14 (Marsh *et al.* 1990). The cohort was then expanded to include nonwhite and women
15 workers and followed until 1992 (Marsh *et al.* 2001a,b,c, Stone *et al.* 2004). The most
16 recent follow-up also included a second nested case-control study, a more detailed
17 characterization of work histories and exposures, and an examination of the effect of
18 smoking and other co-exposures. No statistically significant increase in respiratory cancer
19 mortality was observed among glass wool-exposed workers either in the cohort SMR
20 analysis or in the nested case-control study before or after controlling for smoking in the
21 1982 follow-up (Enterline *et al.* 1987). In the 1985 follow-up (Marsh *et al.* 1990), 340
22 deaths from respiratory cancer were observed among a total of 11,380 workers (SMR =
23 1.12 [95% CI = 1.00 to 1.24, according to IARC (2002)]); a trend towards an increase in
24 risk with increasing time since first employment but not with duration of employment
25 was observed.

26 U.S. cohort study: 1992 update (Marsh *et al.* 2001a)

27 In the 1992 follow-up, five of the plants produced mostly glass wool with a small amount
28 of continuous glass filament production, and four plants (two of which were combined as
29 Plant 15) produced a mixture of glass wool and continuous filament. Four of the eight

- 1 plants also made small diameter (< 1.5 μm) glass or quartz microfibers for special
- 2 applications as well as larger glass wool fibers and/or filament (Table 3-4).

Table 3-1. Plants making glass wool or glass wool + filament in the United States (University of Pittsburgh study)

Plant No.	Location	Principal type of SVF	Total person-years of job-location-weighted exposure to respirable fibers (1992 update)	Total number of workers exposed to respirable fibers (1992 update)
1	Parkersburg, WV	mostly wool ^a	11,276	1,032
4	Kansas City, KS	mostly wool	31,337	3,692
6	Santa Clara, CA	mostly wool ^a	17,868	2,680
11	Defiance, OH	mostly wool	21,927	2,281
14	Shelbyville, IN	mostly wool	9,532	1,276
9	Newark, OH	wool + filament ^a	85,379	9,856
10	Waterville, OH	wool + filament ^a	11,433	1,892
15	Kansas City, KS	wool + filament	31,942	3,970

Source of data: Marsh *et al.* 2001a.

^aSpecial-application glass or quartz microfibers (< 1.5 μm) were also made at this plant.

1 In this follow-up, female workers and male workers employed between 1963 and 1978
2 were included to make a total of 32,110 workers, of whom 26,679 were exposed to glass
3 wool or glass wool and filament. Female workers made up 12.5% of the entire cohort
4 (including glass wool, wool and filament, and filament workers) and represented 9.5% of
5 the person-years of employment. In this follow-up, approximately half the cohort had > 5
6 years of employment. Most of the male workers were engaged in production. Short-term
7 workers (< 1 year or, in two plants, < 6 months) were excluded. Approximately half of
8 the cohort had > 30 years from first employment to the last ascertainment of vital status,
9 80% of the cohort > 20 years, and nearly all workers had > 10 years. Death certificates
10 were obtained for 98.2% of deaths in the first follow-up and 98.8% in the second.
11 Standardized mortality ratios (SMRs) were calculated for white males and females from
12 both local (county) rates and U.S. population rates. The cohort study had 80% statistical
13 power to detect a 10% or greater excess risk of respiratory cancer, although the power
14 was less for the female workers when analyzed separately.

15 Detailed exposure matrices were constructed from a combination of historical
16 technological data and industrial hygiene data, collected from 1970 to 1990, to estimate
17 plant-, job title-, and department-specific exposures and individual worker job histories.
18 The air contaminants produced by the major production processes in glass fiber
19 production facilities include the fibers themselves and other emissions associated with
20 various processes (Quinn *et al.* 2001, Smith *et al.* 2001) (see Table 2-5). Smith and
21 coworkers used airborne fiber data contained in manufacturer databases to assign
22 respirable fiber exposures to workers in the cohort study. Estimated fiberglass exposures
23 to small-diameter fibers measured before 1980 ranged from 0.027 to 1.94 fibers/cm³ with
24 a mean of 0.662 fibers/cm³. Estimated exposure levels measured after 1980 were very
25 similar, ranging from 0.025 to 1.86 fibers/cm³ with a mean of 0.745 fibers/cm³.

26 For the nested case-control study and internal analyses of female workers (discussed
27 below), mean, median, and cumulative exposures to respirable fibers (Rfib) (defined as
28 fibers with diameter $\leq 3 \mu\text{m}$, length $> 5 \mu\text{m}$, aspect ratio $> 3:1$) and a range of other
29 compounds were estimated from plant start-up to the end of 1987 (or closure if before
30 this date) (Quinn *et al.* 2001, Smith *et al.* 2001, Stone *et al.* 1996). The median average

1 exposure to Rfib in the five glass wool plants ranged from 0.039 to 0.167 fibers/cm³, and
2 the median cumulative exposure ranged from 1.839 to 6.382 fibers/cm³-months. In the
3 three glass wool + filament plants, the median average exposure ranged from 0.018 to
4 0.040 fibers/cm³ and the median cumulative exposure from 0.892 to 1.833 fibers/cm³-
5 months. No distinction was made between respirable fibers from glass wool and from
6 filament. It is important to note, however, that respirable fiber concentrations in filament
7 operations were often up to three orders of magnitude lower than glass wool fibers and
8 frequently below or at the limit of detection. Thus the estimated Rfib levels essentially
9 reflect glass wool exposure. Smith *et al.* (2001) also identified co-exposures to substances
10 that met the following criteria: (1) they were widely used, (2) there was a reasonable
11 likelihood of exposure, (3) they had been used for more than 10 years, and (4) there must
12 have been a possible cancer risk, particularly lung cancer. Based on these criteria, the
13 authors identified the following co-exposures in the SVF industry: aromatic
14 hydrocarbons, arsenic, asbestos, asphalt, crystalline silica, epoxide compounds,
15 formaldehyde, phenol (as a possible promoter), polycyclic aromatic hydrocarbons,
16 radioactivity, styrene, and urea (as a possible promoter).

17 With respect to respiratory cancers, Marsh *et al.* reported statistical results for combined
18 respiratory system cancers (larynx, trachea, bronchus, and lung; ICD 160–163), and for
19 other cancers. A total of 838 deaths from lung cancer was reported for the entire cohort,
20 together with 29 deaths from cancer of the larynx and 7 other respiratory system cancers.
21 Among the combined (male and female) cohort, a slight excess of respiratory cancer was
22 observed among combined short- and long-term workers in mostly glass wool (SMR =
23 1.18, 95% CI = 1.04 to 1.34, $P < 0.05$, 243 deaths) but not in glass wool + filament (SMR =
24 1.02, 95% CI = 0.94 to 1.12, n.s., 490 deaths) or filament-only plants (SMR = 1.04,
25 95% CI = 0.87 to 1.22, n.s., 141 deaths). A small, but statistically significant excess of
26 respiratory cancers was observed among all workers (exposed to glass wool and/or
27 filament) with 1 to 5 years employment (SMR = 1.12, 95% CI = 1.01 to 1.24, $P < 0.05$,
28 378 deaths). No excess of respiratory cancers was observed among long-term (> 5 years
29 employment) workers for either mostly glass wool (SMR = 1.06, 95% CI = 0.90 to 1.26,
30 n.s., 138 deaths), glass wool + filament (SMR = 1.03, 95% CI = 0.91 to 1.16, n.s., 277
31 deaths), or filament-only plants (SMR = 0.96, 95% CI = 0.76 to 1.19, n.s., 81 deaths)

1 (Table 3-2). According to calculations made by IARC (2002), the SMR for respiratory
 2 cancer for all eight plants was 1.06, 95% CI = 0.99 to 1.14, 733 deaths) using county
 3 rates for comparison (U.S. rates were slightly lower). For the four plants making special
 4 fibers, the SMR calculated by IARC (2002) was 1.06, 95% CI = 0.97 to 1.15, 490
 5 deaths). Among all workers in the 10 fiberglass plants in this study (including those
 6 making filament only, which comprised approximately 17% of the total cohort), a slight
 7 trend towards increasing respiratory cancer mortality with time since first employment
 8 and calendar time was observed but not with duration of employment. Workers in the
 9 entire cohort hired between 1950 and 1959 had slightly higher rates for respiratory
 10 cancers than those hired before or after that period [data not shown]. No consistent
 11 relationship with age at hire was observed among the whole cohort [data not shown].

Table 3-2. Respiratory (larynx and lung) cancers in the United States (University of Pittsburgh cohort–1992 follow-up; males and females combined)

Plants	Principal fiber type	Respiratory cancer cases/all exposed workers, 1992 update	SMR (95% CI) ^c (all workers) ^d	SMR (95% CI) ^c (workers with ≥ 5 years employment) ^d
1 ^a ,4,6 ^a ,11,14	mostly glass wool ^b	243/10,961	1.18 (1.04–1.34)	1.06 (0.90–1.26)
9 ^{a,e} ,10 ^{a,e} ,15 ^e	glass wool and filament	490/15,718	1.02 (0.94–1.12)	1.03 (0.91–1.16)
2,5	filament	141/5431	1.04 (0.87–1.22)	0.96 (0.76–1.19)
1	glass wool and special application	35/1,032	1.04 (0.72–1.45)	0.97 (0.63–1.43)
6	glass wool and special application	54/2,680	1.28 (0.96–1.67)	1.12 (0.73–1.65)
9	glass wool and special application	374/9,856	1.05 (0.94–1.16)	1.03 (0.89–1.18)
10	glass wool and special application	27/1,892	0.85 (0.56–1.24)	1.16 (0.71–1.80)

Source: adapted from data in Marsh *et al.* 2001a. 32,110 male and female workers with > 1 year employment (except for one glass wool and one glass wool + filament plant where workers with > 6 months employment were included) (1945 to 1978) followed up to 1992 with 98.8% ascertainment of cause of death.

^a Special application fibers (< 1.5 µm diameter) also made.

^b Includes some filament operations.

^c Compared with local county rates. The use of local county mortality rates to calculate SMRs resulted in slightly lower estimated risks compared with national rates.

^d In the whole cohort, including filament workers, there were 15,404 short-term workers (< 5 years employment) and 16,706 long-term workers (≥ 5 years employment).

^e Separate facilities or buildings used for making either wool or filament.

1 With respect to other cancers, an analysis of mortality due to mesothelioma among the
2 entire 10-plant cohort was conducted (Marsh *et al.* 2001b), but it was complicated by the
3 lack of consistent diagnostic identification by the International Classification of Diseases
4 (ICD) codes, particularly in older versions, according to the authors. Using different
5 classification schemes to identify “possible” malignant mesothelioma deaths, 10 such
6 cases were initially identified via death certificates in the entire cohort (16 plants,
7 including 6 other plants with rock/slag wool production). Eight of ten possible deaths had
8 potential asbestos exposure, according to the authors. Pathology reports for five of these
9 deaths revealed that two were not mesothelioma and three were doubtful. No excess of
10 mesothelioma was found in the glass wool cohort using a broad definition of
11 mesothelioma spanning several ICD revisions or a more strict definition that focused on
12 pleural mesothelioma. [However, SMR analyses may not be appropriate for evaluating
13 mesotheliomas (see Section 3.5.2).]

14 No other cancers were found in statistically significant excess; nonsignificant excesses of
15 buccal cavity and pharynx cancers (SMR = 1.11, 95% CI = 0.85 to 1.42, 63 deaths) and
16 bladder and other urinary organs cancers (SMR = 1.07, 95% CI = 0.82 to 1.37, 64 deaths,
17 county comparisons) were observed among the entire glass wool and filament cohort (10
18 plants) (Marsh *et al.* 2001a). The SMR for all 2,243 cancer deaths combined was 0.94
19 (95% CI = 0.90 to 0.98; county comparison) in the total fiber-exposed cohort, [which
20 suggests the possibility of a healthy-worker effect].

21 Smoking is the major potential confounder for respiratory system cancers. An early
22 attempt to adjust for the effect of smoking on respiratory cancer mortality for the male
23 Newark, Ohio workers in the U.S. cohort was conducted by Chiazzo *et al.* (1995) based
24 on smoking data obtained from interviews with proxies or survivors with a 13% sample
25 of the original Newark cohort (used in a subsequent case-control analysis; see below).
26 The estimated smoking prevalence thus obtained was compared with expected smoking
27 rates for white males obtained from several National Health Interview Surveys.
28 According to this method, some 82% of the cohort were estimated to have ever smoked
29 compared with an expected 73%; when SMRs were adjusted for smoking, they decreased
30 (in the Newark cohort followed to 1982) from 119.6 to 107.8 (range 105.4 to 110.2 for

1 minimum and maximum smoking estimates). A somewhat higher prevalence of ever
2 smokers was observed among male fiberglass workers compared with the 1980 U.S.
3 population. (Some 76% had ever smoked and most had started before the age of 20.)
4 Rates were also higher than among local populations. A slightly lower than expected rate
5 of ever smoking was observed among the sample of female smokers (41.8% vs. 44.5% in
6 the U.S. population). No relationship between smoking and level of glass wool exposure
7 was observed. Adjustment for estimated smoking reduced all respiratory cancer SMRs to
8 non-significance (Marsh *et al.* 2001c), and the authors estimated that approximately 7%
9 of the observed excess of respiratory cancers in males could be attributable to smoking.
10 (Note that the effect of smoking on respiratory cancer risk was also examined in a nested
11 case-control study of this cohort, described below, together with the effects of other
12 potential exposures, such as formaldehyde. No attempt to adjust for formaldehyde or
13 other exposures was made in the external analysis of mortality in this cohort, however.)

14 *U.S. cohort study: detailed mortality study of female workers (Stone et al. 2004)*
15 Stone *et al.* (2004) conducted a more detailed mortality study of the 266 cancer deaths,
16 including 53 deaths from respiratory cancers, observed among the 4,008 women in the
17 1992 follow-up. The women were employed from 1945 to 1978 (the period of 1940 to
18 1978 was used for one plant) with at least one year of employment (6 months was used as
19 the minimum for two plants). Less than 2% were lost to follow-up. Only 633 (15.8%) of
20 the women worked in the five glass wool plants, and the majority of these worked in
21 packing, transport, or inspection rather than production. Of the remaining women, 1,765
22 (44.0%) worked in the wool and filament plants and 1,610 (40.2%) in filament plants.
23 The median average level and median cumulative level of exposure to respirable fibers in
24 glass wool plants was 0.059 fibers/cm³ and 2.951 fibers/cm³-months, respectively, and
25 0.008 fibers/cm³ and 0.318 fibers/cm³-months, respectively, in the plants making a
26 combination of glass wool and filament. Filament exposures were very low, with an
27 average median of 0.001 fibers/cm³ and cumulative exposure of 0.079 fibers/cm³-month.
28 These are somewhat lower exposures than those experienced by the male cohort. A large
29 number of the female workers had minimal exposure (close to the limits of detection) and
30 less than five years of employment. SMRs were presented for the whole SVF cohort only
31 (including filament-only workers).

1 With respect to respiratory cancers, excluding the larynx, the observed SMR was 0.99
2 (95% CI = 0.74 to 1.29, 52 deaths) compared with national rates and 1.02 (95% CI = 0.76
3 to 1.34) compared with county rates (Stone *et al.* 2004). One death from cancer of the
4 larynx was observed (SMR = 0.98, 95% CI = 0.02 to 5.48, county comparison). No other
5 excess cancer deaths were observed. In an internal analysis, respiratory cancers among
6 women who were potentially exposed to mostly glass wool were compared with women
7 potentially exposed to filament only. Only the 3,563 women who were alive and at risk at
8 44 years of age (the age at death of the youngest respiratory cancer case) were included.
9 All respiratory cancer mortality (ICD 160–163) was significantly elevated among mostly
10 glass wool-exposed workers in a univariate analysis (relative risk [RR] = 3.24, 95% CI =
11 1.27 to 8.28, 6 deaths). In a multivariate model including average and cumulative
12 exposure and time since first employment, the estimated RR increased to 3.69 (95% CI =
13 1.38 to 9.87) when glass wool-exposed women were compared with filament only-
14 exposed women. The risk of respiratory cancer was significantly associated with duration
15 of employment (Wald *P* value = 0.020): women with between five and nine years
16 employment had a statistically significant elevated relative risk of 2.30 (95% CI = 1.24 to
17 4.27, 16 deaths) on univariate analysis compared with workers with less than 5 years
18 employment, but not with 10 to 19 years (RR = 0.82, 95% CI = 0.34 to 1.98, 6 deaths),
19 or 20 or more years of employment (RR = 0.67, 95% CI = 0.23 to 1.92, 4 deaths). [Note
20 that the numbers of cases in the latter group were small.] Time since first employment
21 was associated with an increased risk of respiratory cancers (Wald *P* value = 0.037),
22 particularly for workers with > 30 years since first employment relative to those with <
23 20 years since first employment. Women hired between 1950 and 1970 had higher rates
24 of respiratory cancer than those hired before 1950 or after 1970 (Wald *P* value = 0.042).
25 Neither the average level nor cumulative level of Rfib exposure was related to respiratory
26 cancer mortality in the entire cohort. Multivariate analyses confirmed the patterns seen in
27 the univariate analysis. No statistically significant effects of other exposures were
28 observed in this cohort; cumulative exposure to formaldehyde was examined in both
29 univariate and multivariate analyses but was not significantly associated with glass wool
30 exposure or respiratory cancers.

1 With respect to other cancers among the entire female cohort (Stone *et al.* 2004), a
2 nonsignificantly elevated risk of cancer of the bladder and other urinary organs was
3 observed in the entire cohort (SMR = 1.62, 95% CI = 0.70 to 3.20, 8 deaths, local
4 comparison) , but no excess mortality for other cancer sites was observed. Deaths from
5 several specific cancers (breast, and lymphatic and hematopoietic cancers) occurred
6 significantly less often than in the comparison populations. The SMR for all causes of
7 death was 0.77 (95% CI = 0.72 to 0.82, 930 deaths, county comparison) in this cohort,
8 [which suggests the possibility of a healthy-worker effect as in the male cohort].

9 *Case-control studies*

10 Enterline *et al.* (1987) conducted a nested case-control study of workers who had died
11 from respiratory cancers between 1950 and 1982 from the first follow-up of the U.S.
12 cohort from 1977 to 1982. The case-control study included all 333 cases or deaths from
13 respiratory cancers occurring from 1950 to 1982 among workers exposed to glass wool
14 and continuous filament. A random sample of 529 workers without malignant respiratory
15 cancer or nonmalignant respiratory disease, 43 or more years of age and stratified by age,
16 year of birth, and plant were selected as controls, representing about 4% of the cohort.
17 Smoking data were obtained from interviews with surviving cases and controls or
18 proxies. All cases and controls used in the analyses had data either on ever-smoking
19 status (242 cases and 387 controls) and/or duration and time since starting smoking (211
20 cases and 374 controls). In maximum likelihood backward stepwise logistic regression
21 models, smoking was, as expected, significantly related to respiratory cancers (estimate
22 of log odds ratio = 2.59 in step 1 of a model with year of birth, age, smoking and
23 cumulative glass wool exposure plus an interaction term, using 242 cases and 387
24 referents). Time-weighted cumulative exposure to glass wool was not significantly
25 associated with respiratory cancer risk before (log odds ratio estimate = -0.0224 in step 1
26 of the above model) or after controlling for different measures of smoking, nor was there
27 evidence of an interaction effect between smoking and cumulative exposure to glass wool
28 among these cases (the interaction term in the above model for ever smoking was 0.0146,
29 $P = 0.7024$; in addition, there was no interaction effect between years of smoking and
30 exposure to glass wool). [Note that only 27% of the cases and controls were ever
31 smokers, which may decrease the power to detect an interaction effect.] Among 34- to

1 44-year-old referents (representing 5% of the referents) and 65+ year olds (representing
2 24% of the referents) a somewhat greater percentage was estimated to have ever smoked
3 than in the U.S. white male population (34 to 44 year olds: 75% for referents vs. 71.2%
4 for U.S. white male population; 65+ year olds: 73.4% for referents vs. 66.7% for U.S.
5 white male population). Among the 45 to 64 year olds, representing 71% of the referents,
6 the proportion of ever smokers was similar to that of the U.S. population (79.2% vs.
7 78.4%, respectively).

8 Chiazze *et al.* (1992, 1993) conducted a nested case-control study of the Newark, Ohio
9 cohort (Plant 9), employed for one year or more from 1940 to 1962 and followed until
10 1982. Exposure and work histories were reconstructed from employment, plant process,
11 and industrial hygiene records. In addition to glass wool and filament, exposures were
12 estimated for asbestos, talc, formaldehyde, respirable silica, and asphalt. In an initial
13 analysis of 162 cases of lung cancer and 363 controls, unadjusted odds ratios (ORs) for
14 cumulative respirable glass wool exposure (using workers with < 100 fibers/cm³-days
15 exposure as a reference) were 1.43 (95% CI = 0.90 to 2.72, 37 cases) for 100 to 299.9
16 fibers/cm³-days and 0.95 (95% CI = 0.56 to 1.61, 27 cases) for ≥ 300 fibers/cm³-days
17 (Chiazze *et al.* 1993). Only year of hire before 1945 and employment duration of less
18 than five years were significantly associated with an increase in lung cancer in the
19 unadjusted analysis. [The authors did not conduct an analysis by time since first
20 exposure, and did not indicate a possible reason for the increase in lung cancer among
21 workers hired prior to 1945. In a separate analysis of lung cancer among workers exposed
22 to fine fibers, made in the 1940s until 1950, no association with lung cancer was
23 observed, although the number of exposed workers was small (10 cases and 24 controls).
24 Demographic and smoking data were obtained by interview, mainly with proxy
25 respondents, for approximately 87% of cases and 79% of controls. Among subjects for
26 whom interview data were available were 152 deaths from respiratory cancers, including
27 144 lung cancer deaths, which were matched with 276 respiratory cancer and 260 lung
28 cancer controls, all from within the plant. In a conditional logistic regression model,
29 which also simultaneously adjusted for smoking, education, age at first hire, year of hire,
30 asbestos, formaldehyde, silica, talc, and asphalt, odds ratios for lung cancer were
31 significantly associated only with smoking (6+ months vs. less than 6 months) and age at

1 first hire, and nonsignificantly elevated with year of hire before 1945 (Chiazze *et al.*
2 1993). In this model, nonsignificant odds ratios of 1.72 (95% CI = 0.77 to 3.87) for
3 cumulative exposure of 100 to 299.99 fibers/cm³-days and 0.58 (95% CI = 0.20 to 1.71)
4 for cumulative exposure of ≥ 300 fibers/cm³-days were observed in comparison with lung
5 cancers among workers with exposure of < 100 fibers/cm³-days. Ever smoking (6 months
6 or more) yielded an adjusted odds ratio of 26.17 (95% CI = 3.32 to 206.5) for lung
7 cancer. [No actual industrial hygiene records existed for the period of employment of the
8 cohort, and a number of changes in industrial process took place over the years,
9 according to the authors, who relied on a historical reconstruction of exposures to
10 characterize workers' exposure profiles (Chiazze *et al.* 1993). Smoking and other
11 demographic data were obtained from proxies, and 14% of respiratory cancer cases and
12 22% of their controls who did not have interview data were excluded. A large majority of
13 the cohort smoked (57% to 96%, depending on the decade of birth, for occasional +
14 regular smokers), and nearly all the lung cancer cases occurred among smokers.]

15 A nested case-control study was also conducted with male workers who had died of
16 respiratory cancers between 1970 and 1992, from the later (1992) follow-up of the entire
17 cohort (Marsh *et al.* 2001a, Stone *et al.* 2001, Youk *et al.* 2001). Approximately 40% of
18 the workers had < 5 years employment. Adjustment for smoking was possible for 631
19 cases and 570 randomly selected age-matched controls at risk during the 1970 to 1992
20 time period and who were alive at the time the age-matched case died. Data on smoking
21 was obtained by interviews with proxies of the cases and either proxies of the
22 respondents or the respondents themselves. Subjects were classified as ever or never
23 smokers: 609 cases were ever smokers and 22 cases were never smokers. In the
24 unadjusted analysis, Rfib exposure was associated with a nonsignificantly elevated risk of
25 respiratory cancers (RR = 1.79, 95% CI = 0.77 to 4.14, $P = 0.17$, 622 exposed, 9
26 unexposed cases). After adjustment for ever smoking, the relative risk was slightly
27 decreased (RR = 1.37, 95% CI = 0.55 to 3.42, $P = 0.50$). For respiratory cancers among
28 workers in the five mostly glass wool plants, the unadjusted relative risk of respiratory
29 cancers (compared with 92 cases among workers in filament-only plants) was 1.12 (95%
30 CI = 0.77 to 1.62, 183 cases); this risk decreased slightly after adjustment for ever
31 smoking (RR = 1.06, 95% CI = 0.71 to 1.60). For workers exposed to both glass wool

1 and filament, the adjusted relative risk was 1.01 (95% CI = 0.69 to 1.47, 356 cases). No
2 association with duration of employment or time since first employment was observed in
3 either unadjusted or adjusted analyses. [Note that race was a significant risk factor for
4 respiratory cancers but was not included in further analyses because most of the excess
5 risk was associated with unknown race.]

6 Marsh *et al.* (2001a) also evaluated several measures of exposure to respirable fibers
7 (average, cumulative, and duration) and respiratory cancer risk. Relative risks were
8 calculated for deciles of each exposure measure. Non-baseline levels of average intensity
9 of exposure to respirable fibers (Rfib-AIE) were associated with relative risks ranging
10 from 1.23 to 2.47 for individual deciles of exposure in the unadjusted model; several of
11 the exposure decile-specific RRs for average intensity of exposure were statistically
12 significant in the models after controlling for smoking or for smoking and plant.
13 Statistically significant heterogeneity was observed in the unadjusted RRs ($P = 0.02$), but
14 the heterogeneity was not statistically significant after controlling for ever smoking ($P =$
15 0.07) or plant and ever smoking ($P = 0.19$). A test for exposure-response trend was not
16 statistically significant, however. No association was observed between respiratory
17 cancer risk and cumulative exposure to respirable fibers ($P > 0.30$) or duration of
18 exposure ($P > 0.21$). Neither of the trend tests for cumulative exposure or duration of
19 exposure was statistically significant.

20 The association between average intensity of exposure to respirable fibers and respiratory
21 cancers was reanalyzed by different models in two later publications (Stone *et al.* 2001,
22 Youk *et al.* 2001). Youk *et al.* performed analyses using weighted exposure estimates.
23 These included time lags (where exposure is discounted for a specified period before the
24 start of the observation time) and unlagged or lagged time windows (so that only
25 exposures occurring within certain time frames are counted). Adjusting for smoking, risk
26 estimates for deciles of exposure measures for both average intensity and cumulative
27 exposure to respirable fibers were lower in the weighted models compared with the
28 unweighted models; no relationship between increasing average or cumulative exposure
29 to respirable fibers and respiratory cancer was observed.

1 Stone *et al.* (2001) performed analyses that allowed the modeling of collinearity, effect
2 modification, and potential confounding by co-exposures, including quantitative
3 estimates of formaldehyde and silica exposure and qualitative estimates of other
4 exposures, as well as the effects of smoking and demographic variables. No association
5 was observed between average intensity, cumulative exposure, or duration of exposure to
6 respirable fibers and respiratory cancers in numerous polynomial models that included
7 quantitative measures of exposure to respirable fibers, formaldehyde, and silica as
8 continuous variables in the same model.

9 Ever smoking accounted for some of the heterogeneity in risk among the different plants
10 according to the authors, suggesting a possible correlation between smoking and
11 exposure to fiber type. Stone *et al.* (2001) reported that nonsmokers had somewhat lower
12 average intensity of exposure and cumulative exposure to respirable fibers than smokers.
13 However, there was no evidence of an interaction effect between smoking and average
14 respirable fiber exposure ($P = 0.60$) (Stone *et al.* 2001).

15 As noted, a number of other potential exposures (arsenic, asbestos, asphalt, epoxy,
16 formaldehyde, polycyclic aromatic hydrocarbons, phenolics, silica, styrene, and urea)
17 were examined in association with respiratory cancer risk in the case-control study,
18 although with the exception of formaldehyde and silica, only qualitative (exposed or non-
19 exposed) estimates of exposure were available. Using dichotomous variables for each of
20 the co-exposures and adjusting for ever smoking, Marsh *et al.* (2001a) reported a
21 statistically significant positive association for formaldehyde and a significant inverse
22 association for epoxy exposure. In a further analysis using estimates of glass fiber,
23 formaldehyde, and crystalline silica exposure as continuous rather than dichotomous
24 variables (Stone *et al.* 2001), higher levels of formaldehyde exposure were significantly
25 associated with respiratory cancer risk before and after adjustment for smoking. A trend
26 towards increasing risk with the higher silica-exposed group was also observed.
27 Misclassification of exposure to at least some of the co-exposures was considered likely,
28 in part due to the short duration of employment of approximately 40% of the workers in
29 the case-control study (Stone *et al.* 2001).

1 *Strengths and limitations*

2 [Strengths of the study include (1) the representation of close to one million person-years
3 at risk in the combined male and female U.S. cohort (Marsh *et al.* 2001a), which had 80%
4 statistical power to detect a 10% or greater excess risk of respiratory cancer, although the
5 female cohort study of Stone *et al.* (2004) had considerably less power, (2) almost
6 complete ascertainment of vital status, and (3) adequate length of follow-up for most
7 expected latency periods. Most of the male workers were engaged in production, and
8 reconstruction of exposures was detailed and based in part on industrial hygiene samples.
9 The major limitations include qualitative rather than quantitative assessments of levels of
10 several potentially confounding co-exposures and limited smoking data, which were
11 obtained mainly from proxies and which did not permit detailed analyses by level or
12 duration of smoking. In addition, approximately 40% of the cohort was short-term
13 workers (less than five-years employment) and had higher rates of respiratory cancers,
14 but analyses of cancers among these workers by demographics, smoking, and
15 occupational co-exposures were not analyzed separately.]

16 3.1.2 *European cohort*

17 IARC has conducted cancer mortality and incidence studies of SVF-exposed male and
18 female production workers in 13 SVF plants across 7 European countries since 1976
19 (Boffetta *et al.* 1992, 1997, 1999 Gardner *et al.* 1986, 1988, Saracci *et al.* 1984, Simonato
20 *et al.* 1986). The 8,335 workers, representing 201,105 person-years at risk, were exposed
21 to glass wool from five factories, one in each of five countries, and were included in a
22 cohort mortality follow-up by Boffetta *et al.* (1997) (Table 3-3). The U.K. plant, which
23 constituted the largest subcohort and 70% of expected deaths, also produced some
24 continuous filament and other specialty fibers of varying diameters (Gardner *et al.* 1988,
25 Gardner *et al.* 1986). In addition, a cancer incidence study was conducted with workers in
26 three of the five countries (excluding the United Kingdom and Italy, which did not have
27 national cancer registries) by Simonato *et al.* (1986). The latter cohort was also followed
28 up in an incidence study by Boffetta *et al.* (1999).

Table 3-3. Plants and workers exposed to glass wool in the European cohort study (Boffetta *et al.* 1997)

Country	No. of workers	Average exposure (fibers/cm ³)
United Kingdom	4,145	0.01–0.16
Sweden	2,022	0.01–1.00
Finland	924	0.01–0.05
Norway	644	0.01–0.07
Italy	600	no information
TOTAL	8,335	

1 Cherrie *et al.* (1986) conducted exposure measurements for four of the glass fiber plants
2 included in the European cohort and reported a range for respirable concentrations of
3 fibers from 0.01 to 1.00 fibers/cm³, with the highest concentrations being associated with
4 the manufacture of special fine fiber earplugs. The mean concentrations in main
5 production ranged from 0.01 to 0.05 fibers/cm³ and in secondary production from 0.02 to
6 1.00 fibers/cm³, and are closely comparable with the ranges seen in main and secondary
7 production in the U.S. manufacturing plants. With respect to individual plants, the ranges
8 for average concentrations of respirable fibers across all job categories were 0.01 to 1.00
9 fibers/cm³ (Sweden), 0.01 to 0.05 fibers/cm³ (Finland), 0.01 to 0.07 fibers/cm³ (Norway),
10 and 0.01 to 0.16 fibers/cm³ (United Kingdom). The plant in Italy produced glass wool
11 from 1946 to 1960 only, and no contemporary measurements of glass wool were
12 available.

13 *Individual cohorts*

14 Parts of the European cohort have been studied by individual investigators in the
15 component countries. In an early study of part of the Norwegian cohort (Andersen and
16 Langmark 1986), one plant producing glass wool was included, but constituted only 23%
17 (N = 546) of their total cohort, the remainder being exposed to rock wool. Cancer
18 mortality and incidence were reported mainly for both exposed groups combined. A
19 slight excess of all cancer deaths was observed. A statistically significant excess cancer
20 incidence of the buccal cavity and pharynx (SIR = 1.68, 7 cases), and nonsignificantly
21 elevated risks of cancers of the intestine (SIR = 1.24, 17 cases), trachea, bronchus, or
22 lung (SIR = 1.39, 20 cases), and bladder (SIR = 1.20, 8 cases) were reported in the whole

1 cohort [CIs were not specified]. Workers with > 1 year of employment and > 20 years
2 since first exposure had a two-fold increase in the risk of lung cancer (SIR = 2.06, 9 cases
3). Among the glass wool workers, lung cancer incidence was reported separately and was
4 lower than expected (2 cases among those with > 1 year of employment, SIR = 0.69; SIR
5 = 0.63 for the 2 cases among all glass wool workers).

6 Bertazzi *et al.* (1986) conducted an early study of cancer mortality in a manufacturing
7 plant in Italy, which became part of the European cohort. This plant produced mostly
8 glass wool for about 15 years, until 1960, and then only continuous filament. No asbestos
9 use was reported. Male workers (N = 1,098) with greater than one year of employment
10 hired up to 10 years prior to the end of follow-up were included, and 98.9% were
11 successfully followed up for the period from 1944 to 1983. A slight excess of total cancer
12 deaths was observed compared with national referents; a statistically nonsignificant
13 increase in laryngeal cancer was observed (SMR = 1.88, 95% CI = 0.52 to 4.88, 4 deaths,
14 compared with regional comparison rates). This increase occurred mainly among workers
15 hired prior to 1960 before age 25 and who had at least 15 years since first employment
16 and the greatest cumulative exposure. No significant increases in lung or other cancers
17 were observed (SMR = 0.96, 95% CI = 0.50 to 1.68, 12 lung cancer deaths, compared
18 with regional rates).

19 In an earlier mortality and incidence study of the Swedish cohort (Plato *et al.* 1995b),
20 male and female glass wool manufacturing workers were included (N = 1970). Mortality
21 was followed from 1952 to 1990 and cancer incidence from 1958 to 1989. No smoking
22 data were available in this study. No excess of mortality from all cancers combined was
23 observed when compared with either regional or national rates (SMR = 1.00, 95% CI =
24 0.82 to 1.22, 102 deaths, regional comparison). No excess of lung cancers was observed
25 (SMR = 0.97, 95% CI = 0.57 to 1.69, 14 deaths, regional comparison), except for a
26 nonsignificant excess among workers with 30 or more years since first employment
27 (SMR = 1.43, 95% CI = 0.74 to 3.05, 8 deaths, regional comparison). No significant
28 excesses of other cancers occurred. A similar pattern was observed with lung cancer
29 incidence (SIR = 0.93, 95% CI = 0.54 to 1.48, 17 cases, regional comparison).

1 In an earlier mortality study of the U.K. glass wool and filament manufacturing workers
2 (Gardner *et al.* 1986), 4,766 male and female workers at a glass wool manufacturing
3 plant were followed from 1946 until 1984. Some asbestos exposure also occurred in this
4 cohort. A slight but nonsignificant excess of lung cancers was observed among males
5 (SMR = 1.24, 95% CI = 0.98 to 1.59, 69 deaths) but not females (SMR = 0.96, 95% CI =
6 0.60 to 3.09, 7 deaths) when local comparison rates were used. A significant excess of
7 stomach cancer occurred among women workers (SMR = 1.53, 95% CI = 1.02 to 6.04, 6
8 deaths, local rates).

9 The Finnish cohort of glass wool manufacturing workers was studied by Teppo and
10 Kojonen (1986). Some asbestos exposure in addition to glass wool exposure occurred in
11 the plant. Among 616 male and 325 female workers, employed from 1953 to 1977 and
12 followed for an average of 12.1 years to 1981, a slight but nonsignificant excess of all
13 cancers combined was observed among female workers (SMR = 1.16, CI not specified,
14 12 deaths), and a deficit among male workers (SMR = 0.74, CI not specified, 11 deaths).
15 A slight decrease in lung cancer deaths was observed. A similar pattern was observed for
16 cancer incidence among both sexes combined, with no observed excess of lung cancer
17 (SIR = 0.61, 95% CI = 0.17 to 1.56, 4 cases). Only bone cancer was significantly
18 increased (SIR = 10.26, 95% CI = 1.24 to 37.05, 2 cases). [The study was limited by
19 small numbers of exposed subjects and short follow-up time.]

20 *Combined cohort studies*

21 The combined cohort, consisting of the glass wool cohorts from five countries described
22 above, was followed up for mortality until 1990 or 1992, depending on the subcohort
23 (Boffetta *et al.* 1997), and for incidence until 1995 (Boffetta *et al.* 1999). A nested case-
24 control study was also conducted. Loss to follow-up was between approximately 2% and
25 10%. Exposure was considered in three technological phases (early, intermediate, and
26 late) representing the highest to lowest relative exposure periods (Boffetta *et al.* 1997).

27 *Mortality study.* With respect to respiratory cancers, an excess of lung cancer deaths
28 (SMR = 1.27, 95% CI = 1.07 to 1.50, 140 deaths) was observed among 6,936 glass wool
29 workers with at least one year of employment and representing 167,675 person-years at
30 risk (Boffetta *et al.* 1997). [It should also be noted that in the total cohort, including

1 workers exposed to glass wool, rock and slag wool, or filament, the SMR for lung cancer
2 was slightly higher among short-term workers with less than one year of employment
3 (SMR = 1.48, 95% CI = 1.18 to 1.83, 83 deaths) than longer term workers; analyses for
4 short-term workers exposed only to glass wool were not presented, however.] Adjustment
5 of SMRs for local factors reduced the SMR to 1.12 (95% CI = 0.95 to 1.31). Seventy-
6 eight percent (78%) of the observed lung cancer deaths occurred in the U.K. cohort, in
7 which the SMR was significantly elevated (SMR [national rates] = 1.37, 95% CI = 1.13
8 to 1.65, 109 deaths). None of the other four glass wool plants had statistically significant
9 excess of lung cancers, [although the number of deaths was low and confidence intervals
10 were wide]. Analysis by technological phase did not suggest a consistent trend in lung
11 cancer mortality; SMRs for workers with greater than one year of employment were 1.07
12 (95% CI = 0.64 to 1.67, 19 deaths) for the early phase, 1.40 (95% CI = 1.14 to 1.70, 100
13 deaths) for the intermediate phase, and 1.02 (95% CI = 0.63 to 1.56, 21 deaths) for the
14 late phase (see Table 3-4). No trend with duration of employment was observed: SMRs
15 were 1.11 (95% CI = 0.82 to 1.46, 50 deaths) for 1 to 4 years; 1.18 (95% CI = 0.80 to
16 1.68, 301 deaths) for 5 to 9 years; 1.68 (95% CI = 1.23 to 2.25, 451 deaths) for 10 to 19
17 years; and 1.17 (95% CI = 0.66 to 1.93: 15 deaths) for 20+ years. No increase in lung
18 cancer risk with time since first employment was observed: SMRs were 1.6 (18 deaths)
19 for 0 to 9 years, 0.89 (5 deaths) for 10 to 19 years, 1.30 (9 deaths) for 20 to 29 years, and
20 1.65 (13 deaths) for 30 or more years [95% CIs not specified]. With respect to other
21 cancers, a significant increase in all cancer deaths combined was observed among glass
22 wool workers (SMR = 1.11, 95% CI = 1.01 to 1.22, 460 deaths). Some, mostly
23 statistically nonsignificant, increases in specific cancers were observed. Buccal cavity
24 and pharyngeal cancer (SMR = 1.47, 95% CI = 0.71 to 2.71, 10 deaths) showed a slight
25 excess in glass wool workers, as did bone cancer (SMR = 2.66. 95% CI = 0.86 to 6.21, 5
26 deaths), bladder cancer (SMR = 1.13, 95% CI = 0.62 to 1.89, 14 deaths), lymphatic and
27 hematopoietic cancers (SMR = 1.42, 95% CI = 0.94 to 2.07, 27 deaths) and cancers of ill-
28 defined and unspecified sites (SMR = 1.69, 95% CI = 1.13 to 2.42, 29 deaths). One death
29 from mesothelioma among the glass wool cohort was reported.

30 *Incidence study.* In the cancer incidence study, 2,611 glass wool workers with greater
31 than one year of employment, representing 68,523 person-years at risk, were studied

1 (Boffetta *et al.* 1999). Loss to follow-up was approximately 6% for the whole cohort. A
2 nonsignificant excess risk of lung cancer was observed (SIR = 1.28, 95% CI = 0.91 to
3 1.74, 40 cases). A slight trend towards an increase in the relative risk for lung cancer was
4 observed with increasing time since first employment (RR = 2.3, 95% CI = 0.6 to 9.2, 15
5 deaths, for > 30 years vs. RR = 1.9, 95% CI = 0.8 to 4.8, 15 deaths, for 20 to 29 years,
6 compared with a referent of 1 to 19 years since first employment), in contrast to the
7 combined mortality study and findings for the U.K. and Italian cohorts. No relationship
8 between relative risk and duration of employment was observed, using a 15-year lag and
9 adjusting for age, gender, country, time since first employment, and technological phase:
10 RRs were 0.8 (95% CI = 0.3 to 2.0, 8 cases) for 5 to 9 years, 0.8 (95% CI = 0.3 to 2.4, 4
11 cases) for 10 to 19 years, and 0.7 (95% CI = 0.08 to 5.3, 1 case) for 20 or more years,
12 compared with a referent of 1 to 4 years of employment. Similarly, no relationship
13 between lung cancer risk and technological phase was observed, adjusting for age,
14 gender, country, and time since first employment: the RR for early vs. late phase
15 (referent) was 0.6 (95% CI = 0.2 to 1.5, 20 cases); no cases were observed in the
16 intermediate phase (Table 3-4). As in the mortality study, a statistically nonsignificant
17 increase in the SIR for combined oral cavity, pharynx, and larynx cancers was observed
18 (SIR = 1.41, 95% CI = 0.80 to 2.28, 16 cases). SIRs in excess of 1.00 were also observed
19 for stomach cancer (SIR = 1.05, 95% CI = 0.67 to 1.57, 24 cases), breast cancer (SIR =
20 1.08, 95% CI = 0.72 to 1.55, 29 cases), bladder cancer (SIR = 1.39, 95% CI = 0.88 to
21 2.08, 23 cases), skin melanoma (SIR = 1.13, 95% CI = 0.54 to 2.08, 10 cases), leukemia
22 (SIR = 1.25, 95% CI = 0.54 to 2.46, 8 cases), and other, not otherwise defined sites (SIR
23 = 1.01, 95% CI = 0.78 to 1.29, 65 cases), but none was statistically significant. The
24 observed incidence of all cancers combined was slightly lower than the expected rate
25 (SIR = 0.99, 95% CI = 0.89 to 1.11, 324 cases).

26 *Strengths and limitations.* [Strengths of the study include the large size of the cohort,
27 almost complete ascertainment of vital status, and adequate length of follow-up to
28 observe long latency cancers such as lung cancer. The major limitations were the
29 imprecision of exposure classification within the plants, the absence of work history
30 information for the early years of the study (pre-1977), and the confinement of the
31 exposure assessment to the assignment of technological phases within plants. No direct

1 exposure measurements were used in either the SMR or SIR analyses. In addition, no
2 information on potentially confounding exposures, including smoking or other co-
3 exposures, was available.]

4 *Case-control study*

5 A nested case-control study of lung cancers was conducted on 3,548 male and 1,186
6 female workers at the U.K. glass wool plant, which also produced superfine fibers (1 to 3
7 μm and 2 to 5 μm diameter) for part of the time (Gardner *et al.* 1988). Up to eight sex-
8 and age-matched controls from the workforce with greater than one year of employment
9 who were alive at the time of death of the case were randomly selected. Based on
10 information about manufacturing processes and job title or category, potential exposure
11 to different types of SVF and asbestos was assigned to cases and controls. No direct
12 measurements of glass fiber levels were available, except for those taken during a survey
13 conducted in 1977 (as part of the cohort study). No data on smoking and other exposures
14 were available. Seventy-three (73) deaths from lung cancer (66 males and 7 females) and
15 506 controls were included in the final analysis. The relative risk for lung cancer for all
16 respirable superfine and other glass wool fibers (defined as diameter $\leq 3 \mu\text{m}$, length > 5
17 μm , and aspect ratio $> 3:1$) was 1.2 (95% CI = 0.7 to 2.0, 33 exposed deaths). (For glass
18 wool separately, the relative risk for lung cancer was 1.1 (95% CI = 0.7 to 1.9, 31 deaths)
19 and for superfine fibers separately it was 1.3 (95% CI = 0.3 to 5.8, 2 deaths.) Within
20 individual categories of glass wool fiber types, no statistically significant increases in
21 lung cancer risk were observed. No relationship between duration of exposure, time since
22 first exposure or job category and lung cancer was observed, except for a statistically
23 significant relative risk (RR = 2.0) for 17 lung cancer deaths observed among workers
24 exposed to glass wool and/or superfine fibers with 10 to 19 years since first exposure (CI
25 not stated). No significant association between lung cancer and asbestos was observed,
26 and addition of asbestos exposure to the regression models did not alter the relative risk
27 estimates for glass wool. [The power of the study was not stated, but the numbers of
28 deaths among the different categories of fibers were small; too few workers were exposed
29 to superfine fibers, in particular, for conclusions to be drawn, according to the authors. In
30 addition, only 48% of the original cohort had five or more years of employment. It is not

1 clear whether the length of time since first exposure (not stated) was adequate to detect
2 long-latency cancers for a number of the workers.]

3 3.1.3 Canadian cohort

4 This cohort mortality study included 2,557 male workers employed in glass wool
5 manufacture for at least 90 days from 1955 to 1977. The first follow-up study was
6 conducted in 1984 (Shannon *et al.* 1984, 1987) and the second study extended the follow-
7 up from 1984 to the end of 1997 and included data on cancer incidence from 1969 to
8 1997 (Shannon *et al.* 2005). Findings from the latest follow-up are discussed below.

9 The cohort consisted of 2,576 men employed for at least 90 days from 1955 to 1977 in
10 three groups followed to 1997: those who worked only in the manufacturing plant, those
11 who worked only in the office, and those who worked in both (“mixed exposure”)
12 (Shannon *et al.* 1984, 1987, 2005). No direct measurements of exposure were available
13 prior to 1978; samples taken subsequently suggested average levels below 0.1 fibers/cm³
14 and peaks generally less than 0.2 fibers/cm³. Average concentrations between 1977 and
15 1990 were approximately 0.03 fibers/cm³ (Shannon *et al.* 2005). [It is not clear what
16 proportion of these fibers was in the respirable range.] Ascertainment of vital status was
17 complete for 97% of the cohort, but only 502 workers were followed beyond 20 years
18 after first exposure, 13 of whom were office workers [with little opportunity for
19 exposure]. No smoking data were available.

20 A total of 94 deaths from all cancers combined was observed among the manufacturing
21 plant workers (SMR = 1.15, 95% CI = 0.93 to 1.40); 12 among office workers (SMR =
22 1.13, 95% CI = 0.59 to 1.98) and 6 among workers with mixed (plant and office)
23 exposure (SMR = 0.47, 95% CI = 0.17 to 1.03) (Shannon *et al.* 2005). All subsequent
24 analyses were of plant-only workers.

25 With respect to respiratory cancers, a significant excess of lung cancer was observed
26 among plant-only workers (SMR = 1.63, 95% CI = 1.18 to 2.21, $P < 0.05$, 42 deaths).
27 Among plant-only workers with > 20 years of employment, the SMR for lung cancer was
28 1.89 (95% CI = 1.10 to 3.03, $P < 0.05$, 17 deaths) and for plant-only workers with > 20
29 years of employment and > 40 years since date of first exposure, the SMR for lung cancer

1 was 2.82 (95% CI = 1.13 to 5.82, $P < 0.05$, 7 deaths). For plant-only workers employed
2 prior to 1960, lung cancer mortality was also significantly elevated (SMR = 1.72, [CI not
3 stated], $P < 0.05$, 31 deaths). No other trends with duration of employment or date since
4 first exposure were statistically significant. When only lung cancer deaths since the end
5 of the first follow-up among plant-only workers were considered, the SMR was 1.42,
6 95% CI = 0.90 to 2.13; 23 deaths).

7 In the cancer incidence part of the study, comparing rates with cancer registry data for
8 Ontario (available only from 1969), 50 cases of lung cancer were observed among plant-
9 only workers from 1969 to 1996, yielding a significant SIR of 1.60 (95% CI = 1.19 to
10 2.11, $P < 0.05$). Fifty-four (54) cases of lung cancer were observed among all workers
11 combined (SIR = 1.34, 95% CI = 1.01 to 1.75, $P < 0.05$). SIRs in excess of 1.00 were
12 also observed for kidney, rectal, and stomach cancer, but none was significant. No
13 significant trends with duration of employment or date since first exposure were
14 observed, although, as in the case of lung cancer mortality, the highest SIR occurred
15 among the group with the longest duration of employment according to the authors [SIRs
16 not reported]. While comparison with province-based cancer mortality and incidence data
17 were considered less than ideal, the authors noted that local (county) rates were too
18 unstable to permit comparison.

19 The authors concluded that, notwithstanding the lack of direct exposure data and lack of
20 smoking data, there was a suggestion of a modest effect of glass wool on lung cancer
21 rates in both the mortality and morbidity data. The authors also considered that the lack
22 of an increase in mortality or morbidity from known non-cancer, smoking-related
23 diseases such as cardiovascular and respiratory disease suggested that smoking among
24 exposed workers was not excessive.

25 With respect to other cancers in the extended mortality study, no significantly elevated
26 cancers were observed among plant workers, although kidney cancer rates were
27 somewhat higher than expected (SMR = 1.46, 95% CI = 0.30 to 4.27, 3 deaths). In the
28 cancer incidence study, a statistically significant excess of kidney cancer was observed in
29 the whole cohort (SIR = 1.92, 95% CI = 1.05 to 3.21, $P < 0.05$, 14 cases) but did not

1 reach significance among the plant-only workers (SIR = 1.92, 95% CI = 0.96 to 3.43, 11
2 cases). The authors concluded that glass wool is unlikely to be a causal factor in kidney
3 cancer, in part because no other cohort study has observed such an effect. They suggested
4 that silica might be a factor, since it is associated with renal disease, although as noted,
5 no direct measurements of silica or other agents were available for this cohort. [It should
6 also be noted that the overall all-cause SMR in this cohort was low (0.88), suggesting a
7 healthy-worker effect.]

8 3.1.4 French cohort

9 A small cohort incidence study, initiated as a result of an observed “excess” of cancers of
10 the pharynx, larynx, and buccal cavity by an industrial physician, was conducted on male
11 workers in a single glass wool plant in France (Moulin *et al.* 1986). All 1,374 male
12 workers employed between 1975 and 1984 with a minimum of one year of employment
13 were studied. Follow-up was conducted up to the time of study (1984), so that the
14 maximum length of follow-up was approximately 10 years. Approximately 12,800
15 person-years at risk were available for analysis, of which slightly more than half were
16 among potentially exposed production workers. Men lost to follow-up (N = 101) were
17 considered to be still living and contributed 465 person-years to exposure. Twenty-five
18 percent (25%) of the entire cohort was followed for more than 20 years since first hire,
19 and the average duration of employment was 16 years. Cancers were identified from
20 company insurance records, and regional cancer rates were used for comparison. The
21 mean diameter of fibers in the plant was 6.4 μm , with 30% < 3 μm and 10% < 1 μm . The
22 average concentration of respirable fibers was < 0.2 fibers/cm³. Smoking data were
23 collected for 966 men still working at the factory in 1983 and estimated for the remainder
24 of the cohort. Forty-one cases of cancer were reported over the total of 10 years of
25 follow-up. Five cases of lung cancer were observed in the whole cohort (SIR = 0.74, 95%
26 CI = 0.24 to 1.72). Referent cancer rates used for the estimation of standardized incidence
27 ratios were calculated based on the average of three regional cancer registries in France,
28 weighted by population size. (Although none of the referent population rates included the
29 region in which the plant was located, mortality rates for the plant region were similar to
30 those for the regions in which incidence data were available, according to the authors.)

1 Among potentially exposed production workers, there were four cases of lung cancer, too
2 few to permit an adequate examination of a trend by duration of employment (Table 3-4).
3 An increase in cancers of the upper respiratory tract or upper gastrointestinal tract
4 combined (ICD 8th Revision codes 141–149 and 161) was observed, which included
5 cancer of the larynx, buccal cavity, and pharynx (SIR = 2.18, 95% CI = 1.31 to 3.41, 19
6 cases in the entire cohort) and 17 among potentially exposed production workers).
7 Among the production workers with > 10 years duration of employment, a significant
8 increase in the risk of these latter cancers was observed (Table 3-4). No other SIRs for
9 specific cancers were reported by the authors, but the SIR for all other cancers combined
10 (excluding lung, upper respiratory and digestive tract cancers) was lower than expected
11 (SIR = 0.77, 95% CI = 0.45 to 1.24, 17 cases), [suggesting the possibility of a healthy-
12 worker effect]. Smoking was not taken into account in the statistical analyses, but the
13 authors noted that the smoking prevalence among the current employees was similar to
14 population values, with approximately 75% ever-smokers; slightly fewer heavy current
15 smokers than expected were observed.

16 [The principal limitations of the study include the small numbers of potentially exposed
17 production workers and short follow-up time (10 years), yielding only 12,800 person-
18 years of risk, only approximately half of which occurred among production workers. In
19 addition, it is not clear whether the reliance on company insurance records to identify
20 cancer incidence cases might have resulted in the misclassification or omission of certain
21 cases.]

Table 3-4. Retrospective cohort and nested case-control studies for mostly glass wool exposures

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
Marsh <i>et al.</i> 2001a Marsh <i>et al.</i> 2001b Marsh <i>et al.</i> 2001c United States	<p><i>Retrospective cohort mortality study</i></p> <p>32,110 male and female (12.5%), mainly white workers at 10 plants: 5 glass wool (GW) 3 GW and continuous filament (GW + F) 2 glass filament (F)</p> <p>Employed > 1 year (6 mo 2 plants); 48% of workers had < 5 years employment</p> <p>Employed: 1945–78 Follow-up: 1946–92</p> <p><i>Person-years</i> (exposed to respirable fibers): GW: 91,931 GW+F: 220,694 F: 45,796 10 plants: 266,490</p> <p>~98.8% death certificates obtained</p> <p>SMRs based on local rates (SMRs based on national rates were slightly higher)</p>	<p><i>Exposure assessment</i></p> <p>Exposure matrices based on industrial hygiene measurements and knowledge of past processes, and workers’ job histories</p> <p><i>Median plant-level exposures (respirable fibers)</i></p> <p><u>5 GW plants</u> avg. intensity: 0.039–0.167 f/cm³ cumulative: 1.839–6.382 f/cm³-mo</p> <p><u>3 GW + F plants</u> avg. intensity: 0.018–0.040 f/cm³ cumulative: 0.892–1.833 f/cm³-mo</p> <p>4 plants also made < 1.5 μm diameter specialty fibers</p>	<p>SMR (95% CI); no. of deaths (local comparison)</p> <p><i>Total cohort (10 plants)</i> all causes 0.90 (0.88–0.92); 8,436 all cancers 0.94 (0.90–0.98); 2,243</p> <p><i>Cancers with non-significant increased SMRs</i> buccal cavity and pharynx 1.11 (0.85–1.42); 63 urinary bladder and other urinary tumor 1.07 (0.82–1.37); 64 mesothelioma 10 possible deaths (7 GW or GW + F)</p> <p><i>Respiratory cancer (lung + larynx)</i></p> <p><u>Fiber production group</u> GW: 1.18 (1.04–1.34); 243 GW + F: 1.02 (0.94–1.12); 490 F: 1.04 (0.87–1.22); 141</p> <p><u>Total cohort</u> all 1.06 (1.00–1.14); 874 duration (yr) < 5 1.12 (1.01–1.24); 378 ≥ 5 1.03 (0.94–1.12); 496</p> <p><u>Exposure-response relationships</u> SMRs increased slightly with time since first employment and calendar period of follow-up but not with duration of employment</p>	<p><i>Confounding</i></p> <p>Adjusting for estimated smoking reduced SMRs to nonsignificance</p> <p>Estimated smoking prevalence from sample of workers suggested slightly higher rates of ever-smokers in males and slightly lower rates in females compared with 1980 U.S. population</p> <p>Exposure to 15 other agents monitored, including formaldehyde (FOR), asbestos, silica</p>

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
Stone <i>et al.</i> 2004 United States	<p><i>Retrospective cohort mortality study</i></p> <p>4,008 females (mainly white) employed > 1 year (6 mo 2 plants) from the 10 plant cohort established by Marsh (see above for details)</p> <p><u>No. workers for product</u> GW: 633 (15.8%) GW+F: 1,765 F: 1,610</p> <p>98.5% death certificates obtained (10 plants)</p> <p><u>Analyses:</u></p> <p><u>External:</u> SMRs based on local rates</p> <p><u>Internal:</u> respiratory system cancer (N = 53) 3,563 women – alive at or beyond > 44 yrs</p> <p><u>Multivariate regression:</u> Rfib-cum and FOR-cum evaluated in 4 models that also adjusted for fiber production group (FPG) and the following variables identified in univariate analyses: Model 1: FPG only</p>	<p><i>Exposure assessment</i></p> <p>Same as in Marsh <i>et al.</i> above, with the addition of quantitative exposure assessment for respirable fibers (diameter ≤ 3 μm, length > 5 μm, aspect ratio > 3:1) and formaldehyde (FOR); qualitative assessment for other exposures</p> <p><u>Median exposure levels (respirable fibers)</u></p> <p><u>GW plants:</u> avg. intensity: 0.059 f/cm³ cumulative: 2.951 f/cm³-mo</p> <p><u>GW+F plants:</u> avg. intensity: 0.008 f/cm³ cumulative: 0.318 f/cm³-mo</p> <p><u>F plants:</u> avg. intensity: 0.001 f/cm³ cumulative: 0.079 f/cm³-mo</p> <p>Majority of the women had Rfib-cum exposure less than 20 f/cm³-mo</p> <p>90% person-years associated with Rfib</p> <p><u>5 exposure patterns examined:</u> (1) no Rfib (small numbers) (2) Rfib, no FOR (3) Rfib + FOR, no phenolics, no urea (4) Rfib + FOR + phenolics, no urea</p>	<p>SMR (95% CI); no. of deaths (local comparison)</p> <p><i>Total cohort (10 plants)</i></p> <p>all causes 0.77 (0.72–0.82); 914 all cancers 0.77 (0.68–0.87); 266</p> <p><i>Cancers with increased SMRs and respiratory cancers</i></p> <p>urinary bladder and other urinary tumors 1.62 (0.70–3.20); 8 respiratory cancer (trachea, bronchus, lung) 1.02 (0.76–1.34); 52 laryngeal cancer 0.98 (0.02–5.48); 1</p> <p><i>Internal analyses for respiratory cancer: RR (95% CI); cases or P_{trend}</i></p> <p><u>Univariate analyses</u></p> <p><i>Fiber production group</i></p> <p>F: 1.0 (ref); 18 GW+F: 1.36 (0.76–2.45); 29 GW: 3.24 (1.27–8.28); 6 P_{trend} 0.014</p> <p><i>Exposure-response P_{trend}</i></p> <p>Employment duration 0.020 Year of hire 0.042 Time since first exposure 0.037</p> <p>P > 0.05 for age at hire, exposure pattern and plant</p> <p>Rfib-cum (f/cm³) 1.00 (0.96–1.06); 49</p> <p><u>Multivariate regression</u></p> <p>No association with Rfib-cum or FOR in</p>	<p><i>Confounding</i></p> <p>Two-thirds of the workers exposed to formaldehyde; correlation between glass fibers; r = 0.71 for GW, and 0.74 for F & GW + F Smoking information not ascertained</p> <p><i>Limitations</i></p> <p>Few exposed cases Most women worked < 5 years. Women had lower exposures than male workers</p>

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments																		
	<p>Model 2: FPG + yr of hire Model 3: FPG + employment duration Model 4: FPG + time since first employment</p> <p>Test for interaction between Rfib and FOR was performed.</p>	<p>no urea (5) all</p>	<p>any of the four models</p> <p>Similar findings as univariate: $P < 0.05$ for duration of employment (model 3), time since first exposure and FPG (model 4), but $P > 0.05$ for year of hire.</p> <p>Test for interaction (Rfib and FOR) $P > 0.66$</p>																			
<p>Chiazze <i>et al.</i> 1992 Chiazze <i>et al.</i> 1993 United States</p>	<p><i>Nested case-control study of respiratory cancer</i></p> <p>Cohort: glass wool production and maintenance workers at plant 9 from Marsh <i>et al.</i> cohort, employed > 1 year, and followed 1940–82</p> <p><u>Cases:</u> 144 confirmed deaths from lung cancer available for matched analyses</p> <p><u>Controls:</u> 260 workers matched for age and survival</p> <p>Unadjusted matched analysis (162 cases and 363 controls); conditional logistic regression analysis examined other exposures, smoking, employment, and demographic</p>	<p><i>Exposure assessment</i></p> <p>Cumulative exposure to GW or GW+F based on employee work history and historical exposure reconstruction</p>	<p>OR (95% CI) for lung cancer</p> <p><i>Unadjusted model</i></p> <p><u>Cumulative exposure: (Rfib (f/cm³))</u></p> <table> <tr> <td>< 100</td> <td>1.0 (ref); 98</td> </tr> <tr> <td>100–299.9 f/cm³</td> <td>1.43 (0.90–2.27); 37</td> </tr> <tr> <td>≥ 300 f/cm³</td> <td>0.95 (0.56–1.61); 27</td> </tr> </table> <p><u>Year of hire</u></p> <table> <tr> <td>1945 or later</td> <td>1.0 (ref)</td> </tr> <tr> <td>before 1945</td> <td>2.18 (1.39–3.42)</td> </tr> </table> <p><u>Employment duration</u></p> <table> <tr> <td>5 years or more</td> <td>1.0 (ref)</td> </tr> <tr> <td>< 5 years</td> <td>1.11 (0.76–1.61)</td> </tr> </table> <p><i>Adjusted model (smoking and demographic variables)</i></p> <table> <tr> <td>Never smokers</td> <td>1.0 (ref)</td> </tr> <tr> <td>≥ 6 mo smokers</td> <td>26.1 (3.32–206.5)</td> </tr> </table>	< 100	1.0 (ref); 98	100–299.9 f/cm ³	1.43 (0.90–2.27); 37	≥ 300 f/cm ³	0.95 (0.56–1.61); 27	1945 or later	1.0 (ref)	before 1945	2.18 (1.39–3.42)	5 years or more	1.0 (ref)	< 5 years	1.11 (0.76–1.61)	Never smokers	1.0 (ref)	≥ 6 mo smokers	26.1 (3.32–206.5)	<p><i>Confounding</i></p> <p>Lung cancer was significantly associated with smoking but not with exposure to talc, asbestos, silica, asphalt fumes, or total particulates</p>
< 100	1.0 (ref); 98																					
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Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments												
	variables; final model included all significant variables from first step															
Marsh <i>et al.</i> 2001a Stone <i>et al.</i> 2001 Youk <i>et al.</i> 2001 United States	<p><i>Nested case-control study of respiratory cancer (lung and larynx)</i></p> <p><u>Cohort:</u> U.S. cohort established by Marsh <i>et al.</i> 2001a</p> <p><u>Cases:</u> 631 males with smoking information who died from respiratory cancer 1970–92</p> <p><u>Controls:</u> 570 males, age matched with smoking information, selected randomly from all males at risk 1970–92</p> <p>Relative risks calculated by conditional logistic regression in univariate and multivariate models adjusted for ever-smoking prevalence</p> <p><u>Summary exposure measures:</u> RRs estimated for deciles of each exposure measure, <i>P</i>-values calculated for global test and for trend Marsh <i>et al.</i> 2001 –</p>	<p><i>Exposure Assessment</i></p> <p>Same as Marsh <i>et al.</i> above</p> <p>Job location-weighted exposures were determined for a given time period, plant, department, and job title, and were used to determine quantitative exposure to respirable fibers (Rfib)</p> <p>Other agents – quantitative exposure estimated for formaldehyde (FOR); qualitative estimation for other agents</p> <p><u>Summary exposure measures:</u> Rfib duration (Rfib-dur) Rfib cumulative (Rfib-cum) Rfib average intensity exposure (Rfib-AIE)</p>	<p>Adjusted RR (95% CI); no. of deaths for respiratory cancers</p> <p>Rfib 1.37 (0.55–3.42); 622</p> <p><u>Fiber production group</u></p> <p>F: 1.0 (Ref); 92 GW: 1.06 (0.71–1.60); 183 GW+F: 1.01 (0.69–1.47); 356</p> <p><i>P_{trend}</i></p> <p>Duration of employment <i>P</i> > 0.05 Time since first employment <i>P</i> > 0.05</p> <p><u>Rfib summary exposure measures (Marsh <i>et al.</i> 2001a) <i>P</i> for Global Test for heterogeneity</u></p> <table border="0"> <tr> <td>Smoking:</td> <td>Unadjusted</td> <td>Adjusted</td> </tr> <tr> <td>Rfib-dur</td> <td><i>P</i> > 0.21</td> <td><i>P</i> > 0.21</td> </tr> <tr> <td>Rfib-cum</td> <td><i>P</i> > 0.30</td> <td><i>P</i> > 0.30</td> </tr> <tr> <td>Rfib-AIE</td> <td><i>P</i> = 0.02</td> <td><i>P</i> = 0.07</td> </tr> </table> <p>(Rfib-AIE, <i>P</i> = 0.19 when adjusted for smoking and plant). Some statistically significant RR for specific deciles of AIE exposure found in the two adjusted models, none of the test for trends were significant</p> <p><u>Rfib summary exposure measures: time weighted (Youk <i>et al.</i> 2001) or polynomial models (Stone <i>et al.</i> 2001)</u></p> <p>No association with Rfib-AIE</p>	Smoking:	Unadjusted	Adjusted	Rfib-dur	<i>P</i> > 0.21	<i>P</i> > 0.21	Rfib-cum	<i>P</i> > 0.30	<i>P</i> > 0.30	Rfib-AIE	<i>P</i> = 0.02	<i>P</i> = 0.07	<p><i>Confounding</i></p> <p>Smoking and race were significantly associated with respiratory cancer risk</p> <p>Smoking information obtained from interviews with proxies and survivors</p> <p>98% of workers exposed to Rfib, 91% to FOR, and 77% to phenolics; other exposures included urea, silica, and asbestos</p> <p>Formaldehyde exposure significantly related to respiratory cancer before and after adjustment for smoking, no association with exposure to other substances</p> <p>Small numbers prevented evaluation of effect modification by smoking</p>
Smoking:	Unadjusted	Adjusted														
Rfib-dur	<i>P</i> > 0.21	<i>P</i> > 0.21														
Rfib-cum	<i>P</i> > 0.30	<i>P</i> > 0.30														
Rfib-AIE	<i>P</i> = 0.02	<i>P</i> = 0.07														

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
	adjusted for smoking and smoking and plant Youk <i>et al.</i> 2001 – exposure-weighted models (time lags or lagged time windows) Stone <i>et al.</i> 2004 – orthogonal polynomial models adjusted for co-exposure to other agents		or Rfib-cum	
Boffetta <i>et al.</i> 1997 U.K., Norway, Finland, Italy, and Sweden	<i>Retrospective cohort mortality study</i> Employed: > 1 year Employed: 1933–77 Follow-up: 1933–90 or 92 6,936 male and female glass wool manufacturing workers in 5 countries (part of larger cohort of SVF workers) Person-years: 167,675 96% follow-up SMRs calculated using national rates	<i>Exposure assessment</i> Based on work histories Historical exposure investigation. Workers were assigned to three technological phases of production process based on date of first employment: early (assumed highest exposures) intermediate late (assumed lowest exposures)	SMR (95% CI); no. of deaths (national comparison) all causes 1.05 (1.00–1.10); 1,679 all cancers 1.11 (1.01–1.22); 460 <i>Cancers with increased SMRs</i> buccal cavity and pharynx 1.47 (0.71–2.71); 10 urinary bladder 1.13 (0.62–1.89); 14 stomach 1.01 (0.73–1.37); 41 bone 2.66 (0.86–6.21); 5 LH (not leukemia) 1.42 (0.94–2.07); 27 ill-defined sites 1.69 (1.13–2.42); 29 respiratory cancers (trachea, bronchus, and lung) 1.27 (1.07–1.50); 140 laryngeal cancer 1.08 (0.29–2.75); 4 “other” cancers 1.04 (0.84–1.28); 91 mesothelioma 1 death <i>Lung cancer</i> <i>Plants with significant SMRs</i> 10 (U.K.) 1.37 (1.13–1.65); 109	<i>Confounding</i> The U.K. plant also produced asbestos and superfine fibers; potential exposure to bitumen at another plant. <i>Other comments</i> Among rock/slag workers (part of the large SVF cohort), lung and oral cancer were significantly related to time since first employment in internal analyses, but no internal analyses were reported for glass wool workers

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
			<p><u>Technological phase</u></p> <p>early 1.07 (0.64–1.67); 19 intermediate 1.40 (1.14–1.70); 100 late 1.02 (0.63–1.56); 21</p> <p><u>Duration of employment</u></p> <p>1–4 years 1.11 (0.82–1.46); 50 5–9 years 1.18 (0.80–1.68); 30 10–19 years 1.68 (1.23–2.25); 45 20+ years 1.17 (0.66–1.93); 15</p> <p><u>Time since first employment</u></p> <p>0–9 years 1.60; 18 10–19 years 0.89; 5 20–29 years 1.30; 9 30+ years 1.65; 13</p>	
<p>Boffetta <i>et al.</i> 1999</p> <p>Norway, Finland, and Sweden</p>	<p><i>Retrospective incidence study</i></p> <p>2,611 male and female workers glass wool production workers at 3 plants</p> <p>Employed: > 1 yr Employed: 1933–77 Follow-up: 1933–95 Person-years: 68,523 Follow-up rate: 94.2%</p> <p>SIRs calculated using national rates</p> <p>RR for lung cancer and cancers of the oral cavity,</p>	<p><i>Exposure Assessment</i></p> <p>Work histories</p> <p>Workers assigned to 3 technological phases (early, intermediate, and late) as reported above</p>	<p>SIR (95% CI); no. of cases (national comparison)</p> <p>all cancers 0.99 (0.89–1.11); 324</p> <p><i>Cancers with elevated SIR</i></p> <p>lung cancer 1.28 (0.91–1.74); 40 buccal cavity, pharynx 1.31 (0.65–2.34); 11 larynx 1.68 (0.55–3.93); 5 bladder 1.39 (0.88–2.08); 23 breast 1.08 (0.72–1.55); 29 skin melanoma 1.13 (0.54–2.08); 10 leukemia 1.25 (0.54–2.46); 8 “other” cancers 1.01 (0.78–1.29); 78 mesothelioma no cases</p>	<p>Subset (3 of 5 factories) of Boffetta <i>et al.</i> 1997 cohort</p> <p>Work histories available until 1977</p> <p>Slight trend towards increase in lung cancer for those with > 30 yr since first employment vs. < 30 yr</p>

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
	<p>pharynx, and larynx were calculated using models that included age, gender, age, country, technological phase, time since first employment and employment duration</p>		<p>Regression analyses: RR (95% CI) no. of cases</p> <p>P_{trend}</p> <p><i>Lung cancer</i></p> <p><u>Time since first employment</u> ($P_{trend} = 0.2$)</p> <p>≤ 19 yr 1.0 (ref), 10 cases</p> <p>20–29 yr 1.9 (0.8–4.8); 15</p> <p>≥ 30 yr 2.3 (0.6–9.2); 15</p> <p><u>Employment duration (with 15-yr lag)</u></p> <p>1–4 years 1.0 (ref)</p> <p>5–9 years 0.8 (0.3–2.0); 8</p> <p>10–19 years 0.8 (0.3–2.4); 4</p> <p>20+ years 0.7 (0.08–5.3); 1</p> <p>$P_{trend} > 0.05$</p> <p><u>Technological phase</u></p> <p>late 1.0 (ref); 20</p> <p>intermediate NA</p> <p>early 0.6 (0.2–1.5); 20</p> <p>$P_{trend} > 0.05$</p> <p><i>Oral cavity, pharynx and larynx</i></p> <p><u>Time since first employment</u> ($P_{trend} = 0.03$)</p> <p>≤ 19 yr 1 (ref); 2</p> <p>20–29 yr 9.1 (1.6–52.7); 7</p> <p>≥ 30 yr 12.2 (1.1–132); 7</p> <p><u>Employment duration (with 15-yr lag) and technological phase</u></p> <p>$P_{trend} > 0.05$, no consistent patterns; no cases in intermediate phase</p>	

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
Gardner <i>et al.</i> 1988 UK	<i>Nested case-control study of lung cancer mortality</i> <u>Cohort:</u> U.K. plant was part of the Boffetta cohort 3,548 men, 1,186 women Employed > 1 year Employed: 1946–78 Follow-up: 1948–84 <u>Cases:</u> 73 (66 men, 7 women) non-office workers who died from lung cancer <u>Controls:</u> 506 workers randomly chosen and matched by age, gender, and alive at the death of corresponding case (up to 8 controls for each case) RR calculated by conditional logistic regression for matched case-control sets	<i>Exposure Assessment</i> Factory records (job titles, dates, and clock numbers, type of fiber produced) used to code job descriptions. Workers categorized by fiber type and occupational groups Superfine (specialty) fibers (1–3 or 2–5 µm diameter) and glass wool fibers produced by flame attenuation process (superfine only), Owens blowing process and rotary TEL (derived from Laboratoire Experimental Thermique) process, both of which resulted in respirable fibers (diameter < 3 µm, length > 5 µm and aspect ratio > 3:1)	RR (95% CI): cases/controls for lung cancer <i>Fiber type</i> all respirable fibers 1.2 (0.7–2.0); 33 all glasswool 1.1 (0.7–1.9); 31 all superfine fibers 1.3 (0.3–5.8); 2 Higher RR for glass wool produced by Owens (1.4) than TEL process (0.9) <i>Occupational category</i> No significant associations observed for most general categories, but lung cancer significantly elevated for granulating/blowing wool workers, maintenance engineer workers, boilermen, and warehouse workers <i>Employment duration and time since first exposure</i> No significant associations	<i>Confounding</i> Workers also exposed to asbestos OR = 1.5 (0.8–2.5, 24 deaths); controlling for asbestos did not alter results for glass wool or superfine fibers No data on smoking available <i>Other limitations</i> Small number of exposed cases in the subgroup analyses
Shannon <i>et al.</i> 2005 Ontario, Canada	<i>Retrospective mortality and incidence study</i> 2,557 male glass wool manufacturing workers; extended follow-up of Shannon <i>et al.</i> cohort <u>Mortality</u> Employed: > 90 days	<i>Exposure Assessment</i> Work histories and information on production Historical exposures estimated to be < 1 f/cm ³ <i>Workers divided into 3 groups:</i> production plant only (~50%) office-only	<u>Mortality study among plant workers</u> SMR (95% CI); no. of deaths (Ontario comparison) all causes 0.93 (0.83–1.05); 299 all cancers 1.15 (0.93–1.40); 94 <i>Cancers with elevated SMRs</i> kidney cancer 1.46 (0.30–4.27); 3	<i>Confounding</i> Potential exposure to formaldehyde, phenol, carbon monoxide, solvents, asphalt fumes, total dust, crystalline silica; most exposures were less than current threshold levels

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
	<p>Employed: 1955–77 Follow-up: 1955–97 Person-years: 73,761 96.6% of the cohort was traced <u>Incidence</u> Follow-up: 1969–96</p> <p>SIRs and SMRs calculated using local (Ontario) rates and adjusted for age and calendar year</p>	<p>mixed plant and office Analyses refer to plant workers only Due to the uncertainty of historical exposures, cumulative exposure was not calculated Exposure measurements taken 1977–90: Range: 0.01 to 0.32 f/cm³ Average: 0.03 f/cm³</p>	<p>lung cancer 1.63 (1.18–2.21); 42 Lung cancer (95% CI not reported) Date of first employment pre-1960 1.72; 31, <i>P</i> < 0.05 1960–1970 1.55, 9, <i>P</i> > 0.05 post-1970 1.01; 2, <i>P</i> > 0.05 Employment duration (yr) > 20 1.89 (1.10–3.03); 17 > 20 + > 40 yr time since first exposure 2.82 (1.13–5.82) Incidence study among plant workers SIR (95% CI); no. of cases Cancers with elevated SIRs lung cancer 1.60 (1.19–2.11); 50 kidney cancer 1.92 (0.96–3.14); 11 rectal cancer 1.01 (0.44–2.0); 8 stomach cancer 1.05 (0.39–2.29); 6 Significantly elevated SIRs observed for lung and kidney cancer among all plant and office workers combined</p>	<p>threshold levels No information on smoking Other comments Not all cancer rates reported</p>
<p>Moulin <i>et al.</i> 1986 France</p>	<p>Retrospective cohort incidence study 1,374 male glass wool manufacturing workers employed > 1 yr Person-years: 12,793 Employed: 1975–84 Follow-up: < 2–10 yr SIRs calculated using</p>	<p>Exposure assessment Workers divided into: production workforce (~ ½) administrative staff maintenance staff Production workforce further divided according to work duration in workplaces contaminated by fibers</p>	<p>SIR (95% CI); no. of cases (regional comparison) Upper respiratory & alimentary tract cancers (buccal cavity, larynx, pharynx) all workers 2.18 (1.31–3.41); 19 Production workers: exposure duration^a 1–9 yr 2.02 (0.41–5.84); 3 10–19 yr 3.04 (1.22–6.27); 7 ≥ 20 yr 3.33 (1.34–6.87); 7</p>	<p>Confounding Smoking data obtained for 966 men still present at the factory, estimated smoking in cohort similar to national population rates Other limitations Short follow-up period Small numbers of exposed</p>

Reference geographical location	Population, follow-up, and methods	Exposure assessment and exposure levels	Effects	Comments
	regional rates	<i>Environmental surveys 1981</i> Average fiber concentrations < 0.2 f/cm ³	<p><i>Lung cancer</i></p> <p>all workers 0.74 (0.24–1.72); 5</p> <p><u>Production workers: exposure duration</u></p> <p>1–9 yr 1.82 (0.22–6.57); 2</p> <p>10–19 yr 0.63 (0.02–3.48); 1</p> <p>≥ 20 yr 0.56 (0.01–3.10); 1</p> <p><i>Other cancers</i></p> <p><i>All other cancers combined (excluding lung, upper respiratory, and GI cancers)</i></p> <p>all workers 0.77 (0.45–1.24); 17</p> <p><u>Production workers: employment duration</u></p> <p>1–9 yr 1.08 (0.29–2.77); 4</p> <p>10–19 yr 0.94 (0.31–2.20); 5</p> <p>≥ 20 yr 0.73 (0.20–1.86); 4</p>	cases Cases identified from social insurance records

LH – lymphohematopoietic.

^aAnalyses are for exposed production workers.

1 **3.2 Mixed glass wool and continuous filament**

2 *3.2.1 U.S. cohort*

3 Taking the data for those workers who had estimated exposure to both glass wool and
4 continuous filament (N = 15,718) (Marsh *et al.* 2001a), similar SMRs were observed for
5 respiratory cancer mortality among workers with mixed (glass wool + filament) exposure
6 (SMR = 1.02, 95% CI = 0.94 to 1.12, 490 deaths, all workers, and SMR = 1.03, 95% CI =
7 0.91 to 1.16, 277 deaths, workers with 5 or more years of employment) and among
8 workers in the three plants that produced only continuous filament (SMRs = 1.04, 95%
9 CI = 0.87 to 1.22, 141 deaths, all workers, and SMR = 0.96, 95% CI = 0.76 to 1.19, 81
10 deaths, workers with 5 or more years of employment). Similarly, in the nested case-
11 control study, the relative risk of respiratory cancer among workers with mixed glass
12 wool and filament exposure is 1.01 (95% CI = 0.69 to 1.47, 356 cases, adjusted for
13 smoking) when filament-exposed workers are used as the referent. (Note that the RR for
14 glass wool-exposed workers is 1.06, 95% CI = 0.71 to 1.60, adjusted for smoking). [Note
15 that filament exposure in the three plants producing both types of fiber appears to be very
16 low, suggesting that, as IARC (2002) pointed out, “mixed exposure” workers can be
17 considered to be exposed mainly to glass wool.]

18 In the case-control study conducted by Chiazzè *et al.* (1992, 1993) of 166 lung cancer
19 deaths among workers from one of the plants in the U.S. cohort (described above), that
20 produced both glass wool and continuous glass filament, a decrease in lung cancer risk
21 with cumulative exposure to respirable fibers of both types combined was observed.

22 *3.2.2 European cohort*

23 It appears that the five glass wool plants included in the European cohort produced
24 mostly glass wool. In the case of the plant in the United Kingdom, continuous filament
25 and other special superfine fibers were also produced (Gardner *et al.* 1986), and it is also
26 possible that some workers from the other plants in the combined cohort also had
27 exposure to filament (or other SVF). Among the U.K. workers, no analyses by fiber type
28 were conducted in the mortality study; as noted above, an overall excess of lung cancer
29 deaths was observed when national but not regional comparison rates were used. [In the
30 subsequent nested case-control study of lung cancer among the U.K. workers (Gardner *et*

1 *al.* 1988) only one case was observed in association with exposure to continuous filament
2 only, and it is not possible to evaluate the risk of lung cancer associated with mixed glass
3 wool and filament exposure. The relative risk for lung cancer among workers exposed to
4 superfine fibers (2 cases) is higher than for glass wool but not significant (Table 3-4).]

5 **3.3 Mixed SVF exposure (not otherwise specified)**

6 There are several other studies of workers and/or populations that might have been
7 exposed to SVF including glass wool, but, with the exception of the case-control studies
8 by Siemiatycki (1991), Dumas *et al.* (2000), and Baccarelli *et al.* (2006), in which the
9 authors attempted to distinguish cases with estimated glass wool exposure from those
10 with other SVF exposure, exposure was mixed and/or no data were available to
11 categorize exposure by fiber type. The principal studies are reviewed briefly here. These
12 studies are described in Tables 3-5 and 3-6.

13 **3.3.1 Cohort studies**

14 In a cohort mortality and incidence study of 135,035 male construction workers exposed
15 to SVF in Sweden (Engholm *et al.* 1987), all but 11 of whom were followed up until
16 1982, no excesses of all cancer mortality (SMR = 0.84, 95% CI = 0.81 to 0.88, 2,153
17 deaths) or incidence (SIR = 0.94, 95% CI = 0.91 to 0.97, 3,810 cases) or lung cancer
18 mortality (SMR = 0.86, 95% CI = 0.79 to 0.95, 444 deaths) or incidence (SIR = 0.91,
19 95% CI = 0.83 to 1.00, 440 cases) were observed. An excess of pleural cancer cases (SIR
20 = 2.13, 95% CI = 1.35 to 3.20, 23 cases) was observed, however. The authors concluded
21 that considerable exposure to asbestos might also have occurred among these cases,
22 based on the observed incidence of pleural mesothliomas, which they considered to be
23 closely correlated with asbestos exposure, even though in 21 of these cases, the workers
24 answered “no” to asbestos exposure on an exposure questionnaire. In a nested case-
25 control study of this cohort, in which industrial hygienists estimated average exposures,
26 the relative risk for lung cancer was not statistically significantly elevated among workers
27 estimated to have low-medium or high SVF exposure but no asbestos exposure, after
28 adjustment for smoking and population density (RR = 2.12, 95% CI = 0.99 to 4.54), nor
29 among those with both medium to high SVF and asbestos exposure (RR = 1.21, 95% CI

1 = 0.60 to 2.47, adjusting for asbestos exposure), but the RR was significantly elevated
2 among those with substantial exposure only to asbestos (Table 3-5).

3 Cancer mortality and incidence were investigated in a cohort of 2,807 male workers,
4 1,068 of whom were classified as potentially exposed to SVF and 397 with unknown
5 exposure, who were employed in 11 plants in the Swedish prefabricated wooden house
6 industry (Gustavsson *et al.* 1992, Plato *et al.* 1995a, 1997). Men employed for a
7 minimum of one year from the start of SVF use [year not identified in papers] to 1971
8 were followed from 1968 to 1985. It was not possible to distinguish glass wool from rock
9 wool exposure since both sources of insulation material were used at different periods.
10 The other principal exposure was wood dust. The numbers of deaths from both combined
11 cancers and specific cancers, including lung cancer (SMR = 0.68, 95% CI = 0.37 to 1.13,
12 14 deaths), were lower than expected rates. Stomach cancer was statistically significantly
13 increased (SMR = 1.59, 95% CI = 1.00 to 2.41, 22 deaths), and several cancer sites
14 showed elevated but not statistically significant increases in SMRs (pancreas, liver,
15 lymphomas, and all lymphohematopoietic cancers). No relationship between the
16 estimated level of exposure, duration of employment or time since first employment was
17 observed. The incidence study yielded similar results, with a statistically significant
18 excess for stomach cancer (SIR = 1.78, 95% CI = 1.15 to 2.63, 25 cases) (Table 3-6), and
19 elevated but not statistically significant increases in SIRs for pancreas, liver, all
20 lymphohematopoietic cancers, nasal, melanoma, and other skin cancers.

Table 3-5. Retrospective cohort and nested case-control studies for unspecified SVFs

Reference geographical location	Population, follow-up, and methods	Exposure	Effects	Comments
Engholm <i>et al.</i> 1987 Sweden	<i>Retrospective mortality and incidence study</i> 135,026 male construction workers Follow-up: 1971–83 Person-years: 1,403,067 Only 11 workers lost to follow-up Average follow-up: 9.4 years Incidence determined by linkage to cancer registries and mortality obtained from national files SIRs and SMRs calculated from national rates	Exposure assessment Mixed SVF + asbestos exposure based on self-reports (based on interview at one or more occupational health service check-ups between 1971 and 1974) for SVF and asbestos Smoking assessed (never, former, current moderate, and current heavy) based on self-reports	<i>SMR (95% CI); no. of cases</i> all causes 0.68 (0.66–0.69); 7,356 all cancers 0.84 (0.81–0.88); 2,153 respiratory cancer 0.86 (0.79–0.95); 444 <i>SIR (95% CI); no. of cases</i> all cancers 0.94 (0.91–0.97); 3,810 lung cancer 0.91 (0.83–1.00); 440 pleural cancer 2.13 (1.35–3.20); 23 larynx cancer 0.81 (0.60–1.07); 48	<i>Confounding</i> Probable confounding by asbestos: 18,025 workers exposed to asbestos and SVF <i>Limitations</i> Short follow-up period Some inconsistencies in self-reported exposures and smoking data among workers with more than one questionnaire
Engholm <i>et al.</i> 1987 Sweden	<i>Nested case-control study: lung cancer and pleural mesothelioma</i> <u>Cohort:</u> Swedish cohort established by Engholm <i>et al.</i> 1987 (above) <u>Cases:</u> 424 lung cancer cases and 24 pleural mesothelioma	Industrial hygienists estimated average intensity of exposure based on job tasks: Category 1: no exposure Categories 2–5: lowest to highest intensity Category 6: not assigned	<i>RR for lung cancer (95% CI)</i> SVF 1.12 (0.88–1.41) asbestos 0.93 (0.66–1.31) Similar RRs for SVF and asbestos found in models with both SVF and asbestos <u>Exposure categories</u> 4–5 SVF only 2.12 (0.99–4.54) 4–5 asbestos only 2.55 (0.77–8.28) 3 SVF only 0.96 (0.41–2.21)	Most of the cases and controls were only exposed to SVF (as determined by questionnaire) Poor correlation with self-reported exposure to asbestos and intensity of exposure; correlation was better for SVF

Reference geographical location	Population, follow-up, and methods	Exposure	Effects	Comments
	<p>diagnosed after first health check</p> <p><u>Controls:</u> 5 controls matched per case, matched for date of health check-up and age, and alive at diagnosis of case</p> <p>RR calculated by conditional logistic regression and adjusted for smoking and population density</p>		<p>3 asbestos only 4.64 (0.46–46.8)</p> <p>3–5 SVF only 1.45 (0.80–2.62)</p> <p>3–5 asbestos only 2.89 (1.02–8.14)</p> <p>3–5 SVF (adjusted for asbestos) 1.21 (0.60–2.47)</p> <p>RR slightly lower in models with both SVF and asbestos; for exposure category 3, RR for asbestos higher in models not adjusting for smoking</p> <p>RR for pleural mesothelioma highest in asbestos intensity level 2</p> <p>No association with exposure category level for SVF or asbestos</p>	<p>Strong association between exposure to asbestos and SVF</p> <p>Some evidence to suggest that subjects were unaware of their exposures to asbestos (no association was found between self-reported exposure to asbestos and pleural mesothelioma)</p>
<p>Gustavsson <i>et al.</i> 1992</p> <p>Plato <i>et al.</i> 1995a</p> <p>Plato <i>et al.</i> 1997</p> <p>Sweden</p>	<p>2,807 male workers at 11 factories making prefabricated wooden houses (1,068 exposed to SVF, 1,342 workers unexposed to SVF)</p> <p>Employed > 1 year by 12/31/1971</p> <p>Mortality follow-up: 1969–88</p> <p>Person-years: 49,527</p> <p>Incidence follow-up: 1969–85</p> <p>Person years: 43,778</p> <p>SMR calculated using regional rates and SIR</p>	<p><i>Exposure assessment</i></p> <p>Current levels available, past exposure estimated by occupational hygienists</p> <p>SVF (glass wool + rock wool) exposure levels were classified for every work period in the work history for all individuals.</p> <p>Respirable fibers (personal sampling): 0.09–1.9 mg/m³ (mean 0.5 mg/m³), 8-hour TWA</p> <p>Exposures divided into 5 categories:</p>	<p>SMR (95% CI); no. of deaths</p> <p><i>Total cohort</i></p> <p>all causes 0.89 (0.82–0.97); 554</p> <p>all cancer 1.02 (0.85–1.20); 137</p> <p>lung cancer 0.68 (0.37–1.13); 14</p> <p><i>Cancers with increased SMR</i></p> <p>stomach 1.59 (1.00–2.41); 22</p> <p>liver 1.67 (0.45–4.28); 4</p> <p>pancreas 1.34 (0.71–2.29); 13</p> <p>prostate 1.01 (0.63–1.55); 21</p> <p>genitourinary tract 1.01 (0.48–1.86); 10</p> <p>lymphomas 1.63 (0.70–3.22); 8</p> <p>all lymphohematopoietic 1.05 (0.58–1.72); 15</p>	<p><i>Confounding</i></p> <p>Smoking data on 73% of cohort; cohort workers may have smoked less than average, and the regionally based rates for mortality do not account for lower smoking rates. May be a small amount of residual negative confounding</p> <p>Workers also exposed to wood dust</p> <p><i>Other limitations</i></p> <p>Small number of deaths and cases</p>

Reference geographical location	Population, follow-up, and methods	Exposure	Effects	Comments																																				
	using national rates	<table border="1"> <thead> <tr> <th>Category</th> <th>Mean f/cm³</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>no exposure</td> <td>1,342</td> </tr> <tr> <td>1</td> <td>0.06</td> <td>215</td> </tr> <tr> <td>2</td> <td>0.09</td> <td>375</td> </tr> <tr> <td>3</td> <td>0.11</td> <td>478</td> </tr> <tr> <td>9</td> <td>unknown</td> <td>397</td> </tr> </tbody> </table>	Category	Mean f/cm ³	N	0	no exposure	1,342	1	0.06	215	2	0.09	375	3	0.11	478	9	unknown	397	<p><u>Exposure response</u></p> <p>no increased risk of stomach or lung cancer with increasing latency, employment duration, or exposure category (stomach cancer also elevated in category 1, workers not exposed to SVF)</p> <p>SIR (95% CI); no. of cases</p> <table border="1"> <tbody> <tr> <td>all cancers</td> <td>0.94 (0.82–1.09); 194</td> </tr> <tr> <td>lung</td> <td>0.47 (0.24–0.85); 11</td> </tr> </tbody> </table> <p><i>Cancers with increased SIR</i></p> <table border="1"> <tbody> <tr> <td>stomach</td> <td>1.78 (1.15–2.63); 25</td> </tr> <tr> <td>liver</td> <td>1.45 (0.62–2.86); 8</td> </tr> <tr> <td>pancreas</td> <td>1.43 (0.71–2.56); 11</td> </tr> <tr> <td>nasal</td> <td>2.00 (0.03–1,113); 1</td> </tr> <tr> <td>melanoma</td> <td>1.28 (0.51–2.64); 7</td> </tr> <tr> <td>other skin</td> <td>1.23 (0.53–2.43); 8</td> </tr> <tr> <td>lymphohematopoietic</td> <td>1.35 (0.85–2.02); 23</td> </tr> </tbody> </table>	all cancers	0.94 (0.82–1.09); 194	lung	0.47 (0.24–0.85); 11	stomach	1.78 (1.15–2.63); 25	liver	1.45 (0.62–2.86); 8	pancreas	1.43 (0.71–2.56); 11	nasal	2.00 (0.03–1,113); 1	melanoma	1.28 (0.51–2.64); 7	other skin	1.23 (0.53–2.43); 8	lymphohematopoietic	1.35 (0.85–2.02); 23	
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LH = lymphohematopoietic cancer.

1 3.3.2 Other case-control and cancer registry studies

2 Several population-based or hospital-based, case-control studies have examined SVF and
3 cancer outcomes. With the exception of the studies by Siemiatycki (1991), Dumas *et al.*
4 (2000), and Baccarelli *et al.* (2006), none of these studies attempted to distinguish glass
5 wool exposure from other SVF exposure. Most of the studies were on respiratory cancer,
6 and are described in Table 3-6.

7 *Respiratory cancer*

8 Among 176 cases of lung cancer studied in a population-based, case-control study by
9 Kjuus *et al.* (1986), no association between SVF and lung cancer was observed after
10 adjustment for smoking (OR = 1.0, 95% CI = 0.4 to 2.5, 13 exposed cases).

11 Siemiatycki (1991) conducted a population-based, case-control study from 1979 to 1986
12 in which the associations between 11 cancer sites and occupational exposures were
13 examined among men in Montreal. Cases were compared with both other cancer controls
14 and population controls. The OR for potential exposure to “glass wool” (based on
15 converting job histories to probable exposure by industrial hygienists and chemists) and
16 lung cancer was 1.2, 95% CI = 0.5 to 2.5, 11 exposed cases, compared with population
17 controls), after controlling for age, smoking, demographic variables, and other exposures.
18 [Note that odds ratios based on population controls were very similar to those based on
19 other cancer controls.] A subsequent report of this study was described by Pintos *et al.*
20 (2008), together with a second case-control study of lung cancer among males and
21 females 35 to 75 years of age exposed to either SVF (not otherwise classified) or
22 asbestos. This study was conducted between 1996 and 2001 among the same population
23 of Montreal as the earlier study. Data on smoking and demographic variables were
24 obtained by interviews with survivors or, in some cases, proxies. Pintos *et al.* (2008)
25 designated exposures as SVF (not otherwise classified). In their report of the first study,
26 “nonsubstantial” exposure to SVF among men was associated with an odds ratio for lung
27 cancer of 1.03 (95% CI = 0.67 to 1.58, 62 cases), but a decrease in risk for “substantial”
28 exposure was also observed (OR = 0.63, 95% CI = 0.23 to 1.43, 13 cases). In the second
29 study, again reporting for males only, the OR for nonsubstantial exposure was 1.16 (95%
30 CI = 0.74 to 1.81, 67 cases), and for substantial exposure, the OR = 1.48, (95% CI = 0.52

1 to 4.21, 11 cases). In the pooled analysis, the ORs for nonsubstantial and substantial
2 exposure were 1.10 (95% CI = 0.81 to 1.49, 129 cases) and 0.86 (95% CI = 0.45 to 1.63,
3 24 cases), respectively. All odds ratios were adjusted for smoking, asbestos, and
4 demographic variables. According to the authors, no interaction between smoking and
5 potential SVF exposure was observed, but the number of never smokers in this
6 population was small.

7 Martin *et al.* (2000) also conducted a small nested case-control study of lung cancer
8 among a cohort of French male utility workers and reported a decrease in risk among 33
9 cases (as determined from a company-specific, job-exposure matrix) who were
10 potentially exposed to SVF compared with 8 controls (OR = 0.73, 95% CI = 0.32 to 1.7,
11 adjusted for socioeconomic status and asbestos exposure).

12 Bruske-Hohlfeld *et al.* (2000) and Pohlabein *et al.* (2000) analyzed pooled data from two
13 case-control studies of lung cancer incidence among male workers in a variety of
14 occupations in Germany. Exposure to SVF occurred mainly outside the production
15 industry and among construction workers in this cohort, and was estimated on the basis
16 of job descriptions obtained from a questionnaire administered to participants. Potential
17 exposure to SVF had occurred for 304 cases and 170 controls as insulation mat installers
18 and for 55 cases and 52 controls as electrical insulation fitters. For SVF exposure (not
19 otherwise classified) among insulation installers, a statistically significant increase in
20 lung cancer risk was observed; the odds ratio for all workers after adjustment for smoking
21 and asbestos exposure was 1.48 (95% CI = 1.17 to 1.88, 304 cases). Among electrical
22 fitters, the OR was 1.00 (95% CI = 0.63 to 1.58, 55 cases). Among all workers with > 20
23 years of SVF exposure, a risk of 1.69 (95% CI = 1.01 to 2.81, 61 cases, adjusted for
24 asbestos and smoking) was observed; those with > 30 years of exposure had a risk of 2.03
25 (95% CI = 1.04 to 3.95, 47 cases, both adjusted for asbestos and smoking). Among
26 insulation installers who reported using glass or mineral wool only and who did not
27 report asbestos exposure, the odds ratio was not statistically significant (1.56, 95% CI =
28 0.92 to 2.65, 51 cases, adjusted for smoking).

1 A hospital-based, case-control mortality study of lung cancer among Russian workers
2 exposed to glass wool and/or other SVF was conducted by Baccarelli *et al.* (2006) using
3 autopsy data. Job-specific exposure data were obtained from monitoring data collected by
4 industrial hygiene centers. The 474 male and 66 female lung cancer deaths were matched
5 with 582 controls on age, gender, region, and year of death. Controls with smoking-
6 related diseases were excluded. After adjusting for age, smoking, and location, the OR
7 for 10 male cases of glass wool exposure was 1.77 (95% CI = 0.57 to 5.51). For 14 male
8 cases exposed to other SVF (excluding glass wool but including slag wool and ceramic
9 fibers) the OR was 3.34 (95% CI = 1.18 to 9.45). After additional adjustment for asbestos
10 exposure (found among four subjects with lung cancer), the OR among male workers
11 exposed only to glass wool was 1.56 (95% CI = 0.49 to 5.02, number of deaths not
12 specified); for other SVF, excluding glass wool, the OR was 3.25 (95% CI = 1.16 to 9.11,
13 number of deaths not specified). There were only two cases of SVF exposure among
14 women, and no excess risk was observed. Analysis of the data by exposure duration and
15 level and cumulative exposure for workers exposed either to glass wool alone or to all
16 SVF did not reveal any significant trends, although the OR for average intensity of
17 exposure among workers exposed to more than 75% of the maximum allowable
18 concentration (MAC) of glass wool (reported by the authors as 2 mg/cm³) was higher
19 (OR = 3.61, 95% CI = 0.64 to 20.4) than for workers exposed to less than 75% of the
20 MAC (OR = 0.83, 95% CI = 0.16 to 4.18; both ORs adjusted for smoking, age, and
21 region).

22 A multi-center case-control incidence study of lung cancer among workers exposed for at
23 least one year to asbestos and/or mixed SVF was conducted by Carel *et al.* (2007) among
24 newly diagnosed workers in Central and Eastern Europe and the United Kingdom. The
25 2,205 male cases were frequency matched with 2,305 controls. Exposure and potential
26 confounders were determined by in-person interviews with the subjects. Forty-nine
27 percent (49%) of the 115 SVF-exposed cases were exposed to glass wool alone, and a
28 further 27% to glass wool and mineral fibers. Data were presented only for mixed SVF
29 exposure, however. After adjustment for age, smoking, regional center, asbestos, and
30 other exposures, the OR for SVF exposure was not significant (OR = 1.23, 95% CI =

1 0.88 to 1.7, 115 cases). No significant trends with exposure duration, level, or cumulative
2 exposure were observed, and no differences were noted by country of residence.

3 Marchand *et al.* (2000) conducted a hospital-based, case-control study of cancer
4 incidence of the larynx and hypopharynx in association with SVF and/or asbestos
5 exposure. The analysis included 296 cases of laryngeal cancer and 201 cases of
6 hypopharyngeal cancer that were matched with 295 hospital-based controls who had
7 other types of cancer. For those ever exposed to “mineral wool” (which could include
8 both glass wool and rock/slag wool), nonsignificant excesses of laryngeal cancer (OR =
9 1.33, 95% CI = 0.91 to 1.95, 130 cases) and hypopharyngeal cancer (OR = 1.55, 95% CI
10 = 0.99 to 2.41, 99 cases) were observed after adjustment for age, smoking, and alcohol
11 consumption. (Statistically significant increases in laryngeal cancer [OR = 1.51, 95% CI
12 = 1.03 to 2.22, number of cases not specified] and hypopharyngeal cancer [OR = 1.65,
13 95% CI = 1.05 to 2.58, number of cases not specified] were observed among the mineral
14 wool group [adjusted for smoking, age and alcohol consumption] if a 15-year latency
15 period was used in the exposure calculation.) After adjustment for the effect of asbestos,
16 to which most of the subjects were also exposed, the odds ratios for ever exposure to
17 mineral wool were slightly reduced (OR for laryngeal cancer = 1.23, 95% CI = 0.79 to
18 1.91, 130 cases; OR for epilarynx = 1.61, 95% CI = 0.85 to 3.04, 51 cases; OR for
19 hypopharynx = 1.51, 95% CI = 0.90 to 2.52, 99 cases). No other types of fibers were
20 associated with ORs exceeding 1.00, with the exception of laryngeal cancer in association
21 with microfiber exposure [OR adjusted for smoking, age, and alcohol = 1.28, 95% CI =
22 0.51 to 3.22, 16 cases].

23 *Other cancers*

24 In a case-control incidence study, Rodelsperger *et al.* (2001) investigated mesotheliomas
25 among 137 German men recruited from clinics in Hamburg and compared their
26 occupations, 125 of which were determined by interview, with those of 125 age-, sex-,
27 year of birth- and residence-matched controls randomly selected from population
28 registries and also interviewed using a structured questionnaire. [Note that the response
29 rate among controls was only 63%.] Cases of mesothelioma were confirmed by a panel
30 of pathologists. Detailed self-reported job histories were used to categorize workers

1 according to exposure to SVF (not otherwise classified) and asbestos, and to
2 quantitatively estimate average levels of fiber exposure, according to three levels of
3 exposure, and cumulative exposure. Conditional logistic regression was used to calculate
4 odds ratios separately for job categories and industries. The risk of mesothelioma among
5 ever SVF-exposed cases was OR = 6.12 (95% CI = 2.90 to 12.93, $P < 0.05$, 55 cases),
6 adjusted for age and region of residence, and 3.08 (95% CI = 1.17 to 8.07, $P < 0.05$),
7 after additional adjustment for asbestos exposure. Two cases of mesothelioma were not
8 exposed to asbestos.

9 A case-control study of the Montreal population (see Siemiatycki 1991), using controls
10 with cancers other than lung, rectal, or other digestive system cancers, examined the
11 association between rectal cancer and a range of occupational exposures (Dumas *et al.*
12 2000). Exposures were assigned for cases and controls by industrial hygienists based on
13 interview data for lifetime occupations. Fourteen cases with “any” estimated exposure to
14 glass wool had an OR (adjusted for age, education, respondent status, alcohol, and
15 smoking) of 0.9 (95% CI = 0.5 to 1.6); eight cases with “substantial” estimated exposure
16 to glass wool had an unadjusted OR of 4.3 (95% CI = 1.7 to 11.3) compared with
17 controls with other cancers (except lung and other intestinal cancers). None of the
18 analyses adjusted for other exposures, however.

19 Goldberg *et al.* (2001) also examined the association between 497 cases of colon cancer
20 and a range of occupational exposures in the same male population, using a combined
21 referent group consisting of 1,514 age-matched controls with other cancers plus a second
22 group of 533 population-based controls; ORs of 1.9 (95% CI = 0.4 to 1.6, 15 cases) and
23 2.0 (95% CI = 0.8 to 5.4, 6 cases), adjusted for age, smoking, and exposure to “selected
24 noncollinear” occupational agents and to nonoccupational risk factors) were observed in
25 association with “nonsubstantial” and “substantial” glass wool exposure, respectively.
26 [Note that it is not clear whether the analysis included adjustment for asbestos and other
27 specific exposures, however.]

28 Vasama-Neuvonen *et al.* (1999) and Weiderpass *et al.* (1999, 2003) conducted cancer
29 registry-based studies of 5,072 cases of ovarian cancer (Vasama-Neuvonen *et al.* 1999),

1 23,638 cases of breast cancer (Weiderpass *et al.* 1999), and 7,935 cases of
2 gastrointestinal cancer (Weiderpass *et al.* 2003) (diagnosed between 1971 and 1995) in
3 association with occupational exposures among the entire female Finnish working
4 population. A statistically nonsignificant association with SVF (not otherwise classified)
5 (SIR = 1.3, 95% CI = 0.9 to 1.8, number of cases not specified) was observed for ovarian
6 cancer, after controlling for various demographic and childbirth variables, when
7 occupations with 20% or more people with estimated exposure were compared with those
8 with less than 20% exposed. Among the breast cancer cases, a significant trend towards
9 increasing incidence with higher estimated exposure levels to SVF was observed;
10 medium to high exposure was associated with a significant increase in incidence (SIR =
11 1.32, 95% CI = 1.05 to 1.66, number of cases not specified), and low exposure with an
12 SIR of 1.01 (95% CI = 0.90 to 1.12). However, the excess cancers occurred among
13 building workers who were estimated by the authors to have also had asbestos exposure,
14 which was independently associated with a similar level of risk in this cohort. Relative
15 risks were calculated for women with gastrointestinal cancer designated as having either
16 no, low, or medium/high exposure to occupational agents, including SVF. A statistically
17 significant elevation in risk of stomach cancer was observed among women designated as
18 having low exposure to SVF (RR = 1.23, 95% CI = 1.01 to 1.49, number of cases not
19 specified) (Weiderpass *et al.* 2003). The same relative risk was observed in women with
20 medium to high potential exposure but was not significant. Compared with nonexposed
21 women, the trend was significant ($P = 0.03$).

22 In a small population-based, case-control study in Sweden of 404 cases of non-Hodgkin's
23 lymphoma (NHL) conducted by Hardell and Eriksson (1999), a significantly increased
24 risk of NHL was associated with potential exposure to glass wool as ascertained by
25 questionnaire in a univariate analysis (OR = 1.5, 95% CI = 1.0 to 2.3, 63 cases and 76
26 controls). [Note that some cases and controls were deceased, and proxies were used for
27 questionnaires.] No trend with increasing exposure was noted. [No other variables were
28 considered, however.]

Table 3-6. Studies (case-control and cancer registry studies) of mixed exposure to SVF

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
Lung Cancer				
Kjuus <i>et al.</i> 1986 Southeast Norway	<i>Hospital-based, 1979–83</i> <u>Cases:</u> 176 males (< 80 yrs), incident lung cancer, identified at 2 hospitals <u>Controls:</u> 176 hospital patients, age-matched OR calculated by unconditional logistic regression; adjusted for smoking	<i>Exposure assessment</i> > 3 years exposure to glass fibers (GF) and rock wool (RW) assessed on occupational titles and questionnaires	RR GF/RW 1.0 (0.4–2.5); 13	Controls excluded patients with COPD but included those with heart, lung and other diseases or other malignant neoplasms.
Siemiatycki 1991 Montreal, Canada	<i>Population-based, 1979–85</i> <u>Cases:</u> 857 males, incident lung cancer <u>Controls:</u> 1,360 other cancers and 533 population controls (matched by age and area of residence of all cancer cases) OR adjusted for age, smoking, demographic factors and occupational exposures	<i>Exposure assessment</i> > 5 years of exposure to glass wool, rock (stone) wool, or slag wool	OR (90% CI), using population controls Glass wool 1.2 (0.5–2.5); 11	ORs compared with cancer controls similar to those for population controls; cancer controls excluded lung and digestive system cancers
Pintos <i>et al.</i> 2008 Montreal, Canada	<i>Population-based</i> Study I (1979–86) (substantially the same population as Siemiatycki, 1991) <u>Cases:</u> 857 male (35–70 yr), lung <u>Controls:</u> 1,349 other cancers and 533 population controls (matched by age and area of residence of all cancer cases) Study II (1996–2001)	<i>Exposure assessment</i> Exposure to SVF (glass fibers and slag wool fibers combined) assessed by questionnaire	OR using population controls “nonsubstantial” exposure Study I 1.03 (0.67–1.58); 62 Study II 1.16 (0.74–1.81); 67 Pooled I & II 1.10 (0.81–1.49); 129 “substantial” exposure Study I 0.63 (0.23–1.43); 13 Study II 1.48 (0.52–4.21); 11 Pooled I & II 0.86 (0.45–1.63); 24	Adjusted for smoking, asbestos, and demographic variables In Study II, lung cancer data were collected for males and females but reported for males only

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
	<p><u>Cases</u>: 741 males (35–75 yr) <u>Controls</u>: 899, matched by age and area of residence of lung cancer cases</p> <p>OR calculated by unconditional logistic regression; adjusted for age, ethnicity, SES, smoking, study # and other variables</p>			
<p>Martin <i>et al.</i> 2000 France</p>	<p><i>Nested case control</i>, 1978–89 Utility workers <u>Cases</u>: 310 males, incident lung cancer <u>Controls</u>: 1,225, cancer-free and matched by age</p> <p>OR calculated by conditional logistic regression; adjusted for socioeconomic status and asbestos exposure</p>	<p><i>Exposure assessment</i> Exposure to SVF based on job-exposure matrix (JEM)</p>	<p>OR SVF 0.73 (0.32–1.70); 33</p>	
<p>Brüske-Hohlfeld <i>et al.</i> 2000 Pohlabeln <i>et al.</i> 2000 Germany</p>	<p><i>Population-based</i>, 1988–96 Construction/insulation installation workers and electrical fitters (≤ 75 yr) <u>Cases</u>: 3,498 males, incident lung cancer <u>Controls</u>: 3,541, age and region matched</p> <p>OR calculated by conditional logistic regression; all analyses adjusted for smoking; some analyses adjusted for asbestos</p>		<p><u>OR adjusted for asbestos</u> Installers 1.48 (1.17–1.88); 304 Fitters 1.00 (0.63–1.58); 55</p> <p>SVF all workers (years of exposure)- > 20 1.69 (1.01–2.81); 61 > 30 2.03 (1.04–3.95); 47</p> <p><u>OR exposed to SVF only, no asbestos</u> Installers 1.56 (0.92–2.65); 51</p>	<p>Data pooled from 2 studies Exposure did not distinguish between glass, or rock/slag wool</p>
<p>Baccarelli <i>et al.</i> 2006 Leningrad Province, Russia</p>	<p><i>Lung cancer deaths</i>, 1993–98 <u>Cases</u>: 474 males, 66 females <u>Controls</u>: 453 males, 129 females, matched by gender, age, region and year of death</p> <p>OR calculated by unconditional multiple logistic regression; adjusted for age,</p>	<p><i>Exposure assessment</i> Exposure to glass wool and other SVFs (including cumulative exposure scores) based on monitoring data obtained by local</p>	<p>OR (95% CI) no. of male cases <u>Glass wool exposure</u> All 1.77 (0.57–5.51); 10 <i>Average intensity of exposure</i> <u>MAC</u> <u>OR (95% CI)</u> < 75% 0.83 (0.16–4.18)</p>	<p>Cases and controls identified from autopsy records Controls who died from smoking-related diseases were excluded</p>

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
	smoking, region of residence	obtained by local hygiene centers	<p>≥ 75% 3.61 (0.64–20.4)</p> <p><i>Cumulative exposure Score*</i> <u>OR (95% CI)</u></p> <p>< 5 1.79 (0.16–20.2)</p> <p>> 5 1.77 (0.49–6.36)</p> <p>(*calculated as average intensity of exposure × total duration of exposure)</p> <p><i>Additional adjustment for asbestos</i></p> <p>Glass wool 1.56 (0.49–5.02)</p> <p>Other SVF 3.24 (1.16–9.11); 14</p>	Only 2 females exposed to SVF
Carel <i>et al.</i> 2007 Central and Eastern Europe and the UK (7 countries)	<p><i>Population-based</i>, 1998–2002</p> <p><u>Cases</u>: 2,205 males (< 25 yr)</p> <p><u>Controls</u>: 2,305 males, age matched</p> <p>OR calculated by unconditional logistic regression; adjusted for age, smoking, occupational exposure, and asbestos</p>	<p><i>Exposure assessment</i></p> <p>> 1 year exposure to SVF (glass wool, mineral wool fibers) determined by questionnaire</p>	<p>OR</p> <p>SVF 1.23 (0.88–1.71); 115</p>	Approximately half of SVF workers estimated to be exposed to glass wool alone
Laryngeal and Hypopharyngeal Cancer				
Marchand <i>et al.</i> 2000 France	<p><i>Hospital-based</i>, 1989–91</p> <p>Included in analyses (males):</p> <p><u>Cases</u>: 296 laryngeal cancer and 201 hypopharyngeal cancer</p> <p><u>Controls</u>: 295 hospital patients with other (nonrespiratory) cancers</p> <p>OR calculated by unconditional logistic regression; adjusted for age, smoking,</p>	<p><i>Exposure assessment</i></p> <p>Exposure to SVF (microfibers, mineral wools, ceramic fibers, glass filaments) determined using a French-population JEM</p>	<p><i>OR for larynx</i></p> <p>mineral wools 1.33 (0.91–1.95); 130</p> <p>> 15-yr lag 1.51 (1.03–2.22)</p> <p>microfiber 1.28 (0.51–3.22); 16</p> <p><i>OR for hypopharynx</i></p> <p>mineral wools 1.55 (0.99–2.41); 99</p> <p>> 15-yr lag 1.65 (1.05–2.58)</p>	<p>ORs adjusted for age, smoking, and alcohol</p> <p>Most SVF-exposed workers considered to be exposed to asbestos; adjusting for asbestos reduced ORs slightly</p>

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
	alcohol consumption		microfibers: 0.78 (0.26–2.38); 7	Mineral wools = rock/slag/and glasswool
Mesothelioma				
Rödelsperger <i>et al.</i> 2001 Hamburg, Germany	<i>Population-based</i> , 1988–91 <u>Cases</u> : 125 males <u>Controls</u> : 125 males, matched by age, gender and region of residence OR calculated by conditional logistic regression; adjusted for asbestos	<i>Exposure assessment</i> Exposure based on questionnaire information on job history and occupational exposures to SVF (and asbestos and other mineral fibers)	OR (95% CI) no. of cases Ever exposed 3.08 (1.17–8.07); 55 <i>Cumulative exposure (geometric mean × 5)</i> <u>f-yr</u> <u>OR</u> > 0–0.015 0.78 (0.16–3.77); 10 > 0.015–0.15 3.11 (0.56–17.2); 11 > 0.15–1.5 7.95 (0.88–72.3); 20 > 1.5 5.43 (0.72–41.0); 14	Residual confounding with asbestos possible
Gastrointestinal cancers				
Dumas <i>et al.</i> 2000 Montreal, Canada	<i>Population-based</i> , 1979–85 Males (same population as Siemiatycki 1991 above) <u>Cases</u> : 257 rectal cancer <u>Controls</u> : 1,295 other cancers and 533 population controls OR calculated by unconditional logistic regression, any exposure adjusted for lifestyle and demographic factors, substantial exposure unadjusted	Glass wool exposure based on occupational questionnaire	OR (95% CI); no. of cases <i>Exposure to glass wool (cancer controls)</i> “any” 0.9 (0.5–1.6); 14 “substantial” 4.3 (1.7–11.3); 8 (unadjusted)	Controls with other cancers were drawn from Montreal hospitals and excluded lung and digestive system cancers Population controls were age-stratified and randomly selected

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
<p>Goldberg <i>et al.</i> 2001 Montreal, Canada</p>	<p><i>Population-based, 1979–85</i> (same population as Siemiatycki 1991) <u>Cases</u>: 497 colon cancer (males 35–70 yr) <u>Controls</u>: 1,514 other cancer and 533 age-matched OR calculated by unconditional logistic regression, using control subjects with other cancers as referent group; adjusted for age, smoking, occupational and non-occupational exposures</p>	<p>> 5 years exposure to glass fibers and mineral wool fibers, estimated from job histories Concentration scale: Low (near background) Medium (intermediate) High (handled product in concentrated form) Non-substantial – low Substantial – medium high Workweek frequency < 5%, 5–30%, > 30%</p>	<p>OR (95% CI); no. of cases <i>Exposure to glasswool</i> “nonsubstantial” 0.9 (0.4–1.6); 15 “substantial” 2.0 (0.8–5.4); 6</p>	<p>OR for mineral fibers same as for glass fibers [Possible mixed exposures] Other cancer control group excluded lung, peritoneum and other digestive cancers</p>

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
<p>Weiderpass <i>et al.</i> 2003 Finland</p>	<p><i>Population-based</i>, all women born 1907–1945 Finnish cancer registry cases 1971–1995 <u>Cases:</u> 7,935 gastrointestinal cancers (ICD7 codes 150–157) Internal comparisons of low to high exposure, adjusted for job turnover rate</p>	<p>Exposure assessed by national occupational survey and construction of national job-exposure matrix</p>	<p>Exposure level <i>RR for stomach cancer</i> no 1.0 (ref) low 1.23 (1.01–1.49) medium/high 1.23 (0.85–1.77) <i>P</i> for trend = 0.03 <i>RR for esophageal cancer</i> no 1.0 (ref) low 1.29 (0.83–2.00) medium/high 1.61 (0.80–3.25) <i>P</i> for trend = 0.09 <i>RR for rectal cancer</i> no 1.0 (ref) low 1.06 (0.83–1.35) medium/high 0.82 (0.47–1.42) <i>P</i> for trend = 0.85 <i>RR for gallbladder cancer</i> no 1.0 (ref) low 0.88 (0.60–1.31) medium/high 1.03 (0.55–1.95) <i>P</i> for trend = 0.76 <i>RR for pancreatic cancer</i> no 1.0 (ref) low 0.97 (0.74–1.27) medium/high 1.34 (0.89–2.03) <i>P</i> for trend = 0.38</p>	

Reference geographical location	Population, study period, methods	Exposure	Effects: OR, RR or SIR ^a 95% CI; no. of cases	Comments
Non-Hodgkin's Lymphoma				
Hardell and Eriksson 1999 Northern and middle Sweden	<i>Population-based</i> , 1987–90 <u>Cases</u> : 404 males (≥ 25 yrs) <u>Controls</u> : 741 males, age-matched OR calculated by conditional logistic regression	Glass wool Exposure to pesticides and other agents assessed by questionnaires and telephone interviews	OR (95% CI); no. of cases 1.5 (1.0–2.3); 63 No trend with increasing estimated exposure	Case and controls include deceased males
Breast and Ovarian Cancer				
Weiderpass <i>et al.</i> 1999 Finland	<i>Registry-based</i> , 1971–95 <u>Cases</u> : 23,638 incident breast cancer SIR adjusted for demographics, childbirth, and other variables	Exposure to SVF assessed using job titles and Finnish JEM <i>Three categories of exposure based on median exposure with exposure probability > 0</i> zero low medium/high	SIR (95% CI) Occupations with < 20% vs. > 20% women potentially exposed to SVF <i>Premenopausal breast cancer</i> < 20% 1.0 (ref) 20+% 1.15 (0.74–1.79) <i>Postmenopausal breast cancer</i> < 20% 1.0 (ref) 20+% 1.30 (1.02–1.64)	Possible asbestos exposure
Vasama-Neuvonen <i>et al.</i> 1999 Finland	<i>Registry-based</i> , 1971–95 <u>Cases</u> : 5,072 incident ovarian cancer SIR adjusted for demographics, childbirth, and other variables	Exposure to SVF assessed using job titles and Finnish JEM Mean level among exposed = 0.2 f/cm ³	SIR (95% CI) Occupations with < 20% vs. 20+% potentially exposed to SVF < 20% 1.0 (ref) 20+% 1.3 (0.9–1.8)	Possible asbestos exposure

^aOR = odds ratio; RR = risk ratio; SIR = standardized incidence ratio.

1 **3.4 Other reviews**

2 Epidemiological studies of glass wool and other SVF exposure were reviewed by IARC
3 (1988, 2002). IARC (1988) classified glass wool, rock wool, and slag wool as possibly
4 carcinogenic to humans (Group 2B). The 2001 IARC working group (IARC 2002)
5 evaluated the cohort and case-control studies of glass wool manufacturing workers and
6 studies of mixed SVF exposure among construction workers and other users that are
7 included in the present background document (with the exception of the more recent
8 update of the U.S. cohort by Stone *et al.* (2004), the most recent update of the Canadian
9 cohort by Shannon *et al.* (2005) and the case-control studies of mixed SVF exposure by
10 Baccarelli *et al.* (2006), Carel *et al.* (2007) and Pintos *et al.* (2008). Based primarily on
11 evidence from the U.S. and European cohort and nested case-control studies, IARC
12 (2002) concluded that the epidemiological evidence for the carcinogenicity of glass wool
13 was “inadequate” and thus did not permit a conclusion regarding the presence or absence
14 of a causal association.

15 In addition, WHO reviewed the data for glass wool and other SVFs in 2000 (WHO
16 2000). They pointed to the difficulty of distinguishing the effects of SVFs from smoking
17 and other co-exposures on lung cancer rates, and concluded that the epidemiological data
18 available to that date suggested no excesses of lung cancers among production workers
19 exposed to glass wool or glass microfibers and no increases in incidence of mesothelioma
20 among production workers. (WHO did conclude, however, that at least part of the excess
21 cancers observed among rock/slag wool-exposed workers was attributable to exposure to
22 those fibers.) WHO did not evaluate upper respiratory tract cancers or other cancer sites.
23 Several other reviews of the carcinogenicity of glass wool in humans have been published,
24 including those by Infante *et al.* (1994), Lee *et al.* (1995), Wilson *et al.* (1999), and
25 Hesterberg and Hart (2001). In addition, de Vuyst *et al.* (1995) and Steenland and
26 Stayner (1997) have reviewed earlier studies of lung cancer among a number of cohort
27 and case-control studies of glass wool-exposed populations.

28 **3.5 Summary by tumor site**

29 This section summarizes the findings by cancer sites. [Note that, in a number of the
30 cohort studies, the principal cancer sites of interest have been lung cancer and upper

1 respiratory tract cancers, due mainly to the structural similarity between glass wool, other
2 mineral fibers, and asbestos; because less emphasis has been placed on other cancer sites,
3 not all sites are reported on in individual studies, and detailed analyses such as exposure-
4 response relationships were not evaluated.]

5 3.5.1 Lung cancer

6 The two largest combined cohort mortality studies in the United States and Europe
7 (Boffetta *et al.* 1997, Marsh *et al.* 2001a), at their latest follow-ups, reported SMRs for
8 respiratory cancer of 1.18 (95% CI = 1.04 to 1.34; lung + larynx) (Boffetta *et al.*) and
9 1.27 (95% CI = 1.07 to 1.50, lung only) (Marsh *et al.*) (males and females combined).
10 Separate subcohort mortality studies of the U.S. and European cohorts and the incidence
11 studies generally reported small elevations of respiratory cancer risk similar to those
12 observed in the later combined follow-up studies. Shannon *et al.* (2005) reported an SMR
13 of 1.63 (95% CI = 1.18 to 2.21) and an SIR of 1.60 (95% CI = 1.19 to 2.11) for lung
14 cancer in their second follow-up of a Canadian cohort of glass wool manufacturing
15 workers, but no smoking data were available. Moulin *et al.* (1986) reported a decreased
16 incidence of respiratory cancer among glass wool manufacturing workers in France (SIR
17 = 0.74, 95% CI = 0.24 to 1.72) based on 5 cases and a short follow-up period.

18 A modest trend of increasing risk of lung cancer among workers with longer time since
19 first employment (> 30 years) was noted in the U.S. cohort by Marsh *et al.* (2001a) and
20 among workers with > 30 years since first hire in the European cohort (Boffetta *et al.*
21 1997). With respect to duration of exposure, the U.S. workers with < 5 years of
22 employment had higher SMRs for respiratory cancer than longer-term workers, although
23 there was no consistent trend towards an increase in respiratory cancer with increasing
24 duration of employment (Marsh *et al.* 2001a). A statistically significant increase in lung
25 cancers was seen among relatively short-term workers (5 to 9 years of employment)
26 using workers with < 5 years of employment as the referent group, but not among longer-
27 term workers, [although the smaller numbers of long-term workers limited the power to
28 detect an effect if present]. In the European mortality cohort, workers with < 1 year of
29 employment had slightly higher rates of lung cancer than those with > 1 year of
30 employment (these workers were excluded from further analysis). There was an increase

1 in lung cancer risk with duration of employment among workers with 10 to 19 years of
2 employment in the mortality study (Boffetta *et al.* 1997), but no trend with duration of
3 employment was observed in the incidence study (Boffetta *et al.* 1999).

4 In the nested case-control studies of U.S. glass wool manufacturing workers (Chiazze *et*
5 *al.* 1992, Chiazze *et al.* 1993, Marsh *et al.* 2001a, Stone *et al.* 2001, Youk *et al.* 2001) no
6 significant associations between duration of employment, time since first hire, average
7 intensity of exposure and cumulative exposure to glass wool and lung cancer were
8 observed using various measures of estimated exposure to respirable fibers and
9 controlling for smoking and some co-exposures. However, in the unadjusted analysis,
10 significant heterogeneity was observed with average intensity of exposure and respiratory
11 cancer (Marsh *et al.* 2001a). Similarly, an earlier nested case-control study of U.K.
12 workers (Gardner *et al.* 1988) found no increase in lung cancer risk in association with
13 glass wool exposure, with the exception of a 2-fold increase in risk among workers with
14 10 to 19 years since first hire, who might also have had exposure to superfine fibers.
15 Lung cancers were significantly elevated in certain specific job categories, however,
16 including those employed in granulating wool, warehouse workers with unspecified jobs,
17 electrical maintenance workers, and boilermen maintenance workers, although the
18 numbers of cases in these categories were small.

19 There are comparatively few women workers in SVF manufacturing, and few have been
20 studied. It is noteworthy that, in the detailed follow-up study of women workers in the
21 U.S. cohort (Stone *et al.* 2004), women workers were estimated to have lower average
22 exposures to glass wool than male workers, and no overall increase in respiratory cancers
23 was observed in comparison with national or local rates. However, a statistically
24 significant three-fold increase in respiratory cancer was observed when an internal
25 comparison of glass wool vs. filament-exposed workers was conducted (although only six
26 deaths were observed).

27 Two cohort studies (Engholm *et al.* 1987, Gustavsson *et al.* 1992) and several case-
28 control studies (Baccarelli *et al.* 2006, Brüske-Hohlfeld *et al.* 2000, Carel *et al.* 2007,
29 Kjuus *et al.* 1986, Martin *et al.* 2000, Pintos *et al.* 2008, Pohlabein *et al.* 2000,

1 Siemiatycki 1991) have investigated lung cancer, mainly in association with unclassified
2 or mixed SVF. Statistically nonsignificant excesses of lung cancer were observed by
3 Siemiatycki (1991) in association with glass wool (OR = 1.20, 95% CI = 0.5 to 2.5, 11
4 cases), and by Baccarelli *et al.* (2006) in association with glass wool (OR = 1.77, 95% CI
5 = 0.57 to 5.51, 10 cases). In the case of mixed SVF exposure, Kjuus *et al.* (1986) found
6 no association with lung cancer in an early study (OR = 1.0, 95% CI = 0.4 to 2.5, 13
7 cases). Carel *et al.* (2007) observed a small increase in lung cancer in association with
8 mixed SVF exposure (OR = 1.23, 95% CI = 0.88 to 1.71, 115 cases), and Pintos *et al.*
9 (2008) observed a marginal increase in lung cancer among a population estimated to have
10 “nonsubstantial” exposure to mixed SVF (OR = 1.10, 95% CI = 0.81 to 1.49, 129 cases)
11 but not among a smaller group with “substantial” exposure (OR = 0.86, 95% CI = 0.45 to
12 1.63, 24 cases). However, (Brüske-Hohlfeld *et al.* 2000, Pohlabein *et al.* 2000) observed
13 a statistically significant increase in lung cancer among all workers ever potentially
14 exposed to SVF vs. never exposed (OR = 1.48, 95% CI = 1.17 to 1.88, 304 cases,
15 adjusted for smoking and asbestos) and which was mainly confined to workers with 20 to
16 30 years and 30 or more years of employment.

17 Berrigan (2002) conducted a meta-analysis of SMRs for respiratory cancers in 10 case-
18 control and 10 cohort mortality studies of SVF exposure, including a combined analysis
19 of five cohorts exposed to glass wool (Boffetta *et al.* 1997, 140 deaths; Enterline and
20 Henderson 1975, 5 deaths; Marsh *et al.* 2001a, 243 deaths; Morgan *et al.* 1981, 39 deaths;
21 Shannon *et al.* 1987, 19 deaths), representing a total of 446 observed deaths from
22 respiratory cancers (vs. 370.1 expected). Aggregate estimates of risk were calculated
23 using standard methods for fixed effects; individual SMRs were weighted by the inverse
24 of the variance estimate. National rates were used to calculate SMRs with the exception
25 of the data from Marsh *et al.* (2001a). The author noted that the use of local rates tended
26 to yield lower SMR estimates than national rates in seven of the cohort studies included
27 in the meta-analysis. The case-control studies of glass wool-exposed workers included
28 Enterline *et al.* (1987), Engholm *et al.* (1987), Gardner *et al.* (1988), Chiazzie *et al.* (1992,
29 1993), Bruske-Hohlfeld *et al.* (2000), and Marsh *et al.* (2001a). Aggregate estimates of
30 risk for case-control studies were not calculated due to heterogeneity of results and the
31 use of different exposure levels. The combined SMR for all five cohorts was 1.23 (95%

1 CI = 1.10 to 1.38), compared with SMRs of 1.08 (0.93 to 1.26) for glass filament and
2 1.32 (1.15 to 1.52) for rock wool. [Note: some laryngeal cancers were included in this
3 analysis].

4 3.5.2 *Mesothelioma*

5 Data for mesotheliomas reported among glass wool-exposed populations are summarized
6 in Table 3-7.

7 Marsh *et al.* (2001b) observed 10 possible deaths (7 among glass wool or glass wool +
8 filament workers) from mesothelioma based on death certificates, at least three of which
9 were found to be doubtful based on pathology reports. A deficit of mesothelioma was
10 observed among glass wool-exposed workers relative to expected rates, using different
11 coding schemes, according to the authors. Boffetta *et al.* (1997) observed only one death
12 from mesothelioma among glass wool-exposed workers, but the authors did not calculate
13 expected rates for this cancer. In a smaller cohort study, Engholm *et al.* (1987) reported a
14 significant excess of pleural mesothelioma among male construction workers (SIR =
15 2.13, 95% CI = 1.35 to 3.20, 23 cases). A number of these cases were associated with
16 occupations with potential exposure to asbestos (e.g., plumbers), according to the authors,
17 although self-reported asbestos exposure was considered to be unreliable in this cohort. It
18 also is not clear to what extent exposure to SVF might have occurred among these cases.
19 An earlier case-control study by Rodelsperger *et al.* (2001) reported a three-fold increase
20 in risk of mesothelioma after adjustment for asbestos and other potential confounders, but
21 the authors acknowledged the possibility of residual confounding by asbestos in this
22 analysis.

23 [Mesothelioma is strongly linked to asbestos, and extremely rare without asbestos
24 exposure. Unlike lung cancer, there is just one major established cause. The largest study
25 in the United States showed that 88% of pleural mesothelioma in adult men was
26 attributable to asbestos (Spirtas *et al.* 1994). The consequence of this is that the
27 “expected” numbers from the general population are largely due to asbestos exposure and
28 cannot be used as a comparison with observed mesotheliomas among glass wool workers
29 not exposed to asbestos. Therefore the SMR for glass wool workers not known to be
30 exposed to asbestos is underestimated.

1 A second concern with evaluating mesothelioma is that while there is a need to assess the
2 medical evidence that deaths labeled on death certificates as being due to mesothelioma
3 actually had mesothelioma, there is also a parallel need to review deaths from other
4 causes as well. Selikoff *et al.* (1992) reviewed medical records for all deaths in the U.S.
5 insulator cohort, and the overall effect was to increase the numbers of mesothelioma
6 identified in the study. In the Marsh *et al.* cohort study, medical evidence was obtained
7 only for deaths classified on death certificates as due to mesothelioma, with a reduction
8 in the number of known cases.]

Table 3-7. Mesothelioma among glass wool-exposed populations.

Reference geographical location	Study design, Population,	Exposure	Effects	Comments
<p>Marsh <i>et al.</i> 2001a Marsh <i>et al.</i> 2001b U.S.</p>	<p>Retrospective cohort mortality study of manufacturing workers in 8 glass wool (GW) or glass wool + filament (GW+F) plants</p> <p>32,100 male + female workers GW: 91,931 person-years of follow-up GW + F: 220,694 person-years of follow-up</p>	<p>Respirable fibers: Average: 0.018–0.167 f/cm³ Cumulative: 0.892–6.382 f/cm³-mo</p> <p>4 plants also made specialty (< 1.5 µm) fibers</p>	<p>10 “possible” deaths from malignant mesothelioma</p> <p>7 in GW or GW + F plants 3 exposed mostly to GW; all male; no pathology reports 4 exposed to GW + F; pathology or medical reports available on 3 cases found that these cases were ≤ “50%” likely to be mesothelioma</p> <p>1 case in filament-only plant; pathology available for 1 case, unlikely to be a mesothelioma 2 cases in rock wool plants; pathology report available for 1 case found it was unlikely to be a mesothelioma</p>	<p>Asbestos exposure was considered probable for 2 GW+F workers (0.38 years and 2.46 years of exposure; otherwise not quantified) and for 1 rock wool-exposed worker (2.18 fibers/cm³-mo)</p> <p>Using a broad definition of possible malignant mesothelioma deaths (164 GW or GW + F deaths) SMR = 0.89 (95% CI = 0.76–1.04, county comparison); using malignant + benign codes for later period yielded similar results.</p> <p>Note: Only 1 possible case of pleural mesothelioma observed (rock wool worker); ruled out on pathology report</p>
<p>Boffetta <i>et al.</i> 1997 U.K., Norway, Finland, Sweden, Italy</p>	<p>Retrospective cohort mortality study</p> <p>6,936 male and female GW workers > 1 year of employment</p> <p>167,675 person-years of follow-up</p>	<p>Previous study of exposures in these plants conducted (Cherrie <i>et al.</i> 1986)</p> <p>Range of mean respirable fiber concentrations: 0.01–1.00 fibers/cm³ (similar to U.S. plants)</p> <p>Highest concentrations in superfine fiber processes</p>	<p>1 death from mesothelioma in GW cohort (U.K. factory) (plus 4 cases observed among rock wool-exposed workers)</p>	<p>Possible small-scale asbestos exposure due to use of asbestos yarn or cloth noted in 2 of the GW plants (Finland and U.K), but not otherwise noted</p>

Reference geographical location	Study design, Population,	Exposure	Effects	Comments
Boffetta <i>et al.</i> 1999 Norway, Sweden, Finland	Retrospective cohort incidence study 2,611 male and female manufacturing workers 68,523 person-years of follow-up	See Boffetta <i>et al.</i> 1997	No cases of mesothelioma observed	
Engholm <i>et al.</i> 1987 Sweden	Registry-based incidence cohort; nested case-control study Male construction workers (inc. wood workers, insulators, metal workers, plumbers, etc.) 23 cases of pleural mesothelioma diagnosed after 1 st health check; 5 controls per case	Job histories obtained by self-reported questionnaire; SVF and asbestos potential for exposure assigned by industrial hygienists to one of 6 levels (0 = 0; 1-5 low to high; 6 = unknown)	Unadjusted RRs for pleural mesothelioma and asbestos exposure: <u>Level: RR (cases)</u> 0: 1.0 (12) 1: 0.82 (5) 2: 16.3 (3) 3: 2.2 (2) 5: no cases Unknown: 0.49 (1) Analysis by SVF exposure not performed	21 cases of pleural mesothelioma were among subjects self-reporting no asbestos exposure but were considered to have potential for asbestos exposure by job type.
Rödelsperger <i>et al.</i> 2001 Hamburg, Germany	Hospital-based, case-control study 125 male cases 125 male controls	Job histories obtained by questionnaire; SVF and asbestos cumulative exposure assigned by industrial hygienists Range 0→ 1.5 fiber-years (geometric mean × 5) for SVF; Range 0→ 15.0 fiber-years for asbestos	OR (95% CI); no. of cases <i>SVF/Asbestos combined analyses</i> +/- 15.1 (1.05–218.0); 2 +/+ 61.3 (12.9–292.0); 53 -/+ 19.8 (4.7–83.0); 61 <i>OR for SVF adjusted for asbestos (ever vs. never):</i> Ever vs. never: 3.08 (1.17–8.07; 55 <i>P</i> < 0.05 two-sided)	Considerable overlap of periods when estimated exposure to both SVF and asbestos occurred. Cumulative exposure to SVF approx. one-tenth levels for asbestos. Residual confounding by asbestos possible for observed association between SVF and mesothelioma.

Reference geographical location	Study design, Population,	Exposure	Effects	Comments
			<p><i>Cum. exp. to SVF vs. non-exposed range 0.78–5.43, all n.s.</i></p> <p><i>ORs for asbestos (unadj.) cum. exp. range 7.9–45.4</i></p>	

1 3.5.3 Upper gastrointestinal and upper respiratory cancers (other than lung)

2 Marsh *et al.* (2001a) reported that the SMRs for laryngeal cancer among all the workers
3 in the entire glass fiber cohort (including filament-exposed workers) was 1.04 (95% CI =
4 0.70 to 1.5, 29 deaths). A nonsignificant decrease in SMR observed for “other”
5 respiratory cancer was 0.80 (95% CI = 0.32 to 1.66, 7 deaths). Adjusting for smoking
6 reduced the risk for laryngeal cancer as well as for lung cancer. Boffetta *et al.* (1999,
7 1997) reported statistically nonsignificant excesses of cancer of the larynx among glass
8 wool-exposed workers, and nonsignificant excesses of cancers of the upper
9 gastrointestinal tract (esophagus, buccal cavity, oral cavity, and/or pharynx) also have
10 been reported in both of these cohorts. Moulin *et al.* (1986) also reported a significant
11 excess of “upper respiratory and alimentary tract” cancers (SMR = 2.18, 95% CI = 1.31
12 to 3.41), but specific cancer sites were not reported. Marchand *et al.* (2000) reported
13 excesses of laryngeal (OR = 1.33, 95% CI = 0.91 to 1.95, 130 cases) and hypopharyngeal
14 cancer (OR = 1.55, 95% CI = 0.99 to 2.41, 99 cases; all adjusted for age, smoking, and
15 alcohol) associated with exposure to “mineral wools” (consisting of rock/slag wool and
16 glass wool) in a case-control study. Increases in risk also were reported for buccal cavity
17 and pharynx (SMR = 1.11, 95% CI = 0.85 to 1.42, 63 deaths, among combined glass
18 wool and filament-exposed workers) by Marsh *et al.* (2001a), and among glass wool-
19 exposed workers by Boffetta *et al.* (1997) (SMR = 1.47, 95% CI = 0.71 to 2.71, 10
20 deaths), and Boffetta *et al.* (1999) (SIR = 1.31, 95% CI = 0.65 to 2.34, 11 cases). [Given
21 the low expected rates for these cancers, the power to detect significant increases in
22 mortality or incidence of these cancer sites and to adjust for potential confounders is
23 limited even in large cohort studies.]

24 3.5.4 Other cancer sites

25 [Note that not all cohort studies reported data for each cancer site. In this summary,
26 findings for subcohorts or earlier follow-ups of the multi-site U.S. and European, and
27 Canadian cohorts have not been included separately.]

28 Among glass wool-manufacturing workers, a number of elevated risks (SMRs or SIRs
29 above 1.0) for deaths or cases in other cancer sites have been reported; these sites
30 included: bladder (SIR = 1.39, 95% CI = 0.88 to 2.08, 23 cases, Boffetta *et al.* 1999;

1 SMR = 1.13, 95% CI = 0.62 to 1.89, 14 deaths, Boffetta *et al.* 1997; SMR = 1.07, 95% CI
2 = 0.82 to 1.37, 64 deaths, Marsh *et al.* 2001a; 1.62, 95% CI = 0.70 to 3.20, 8 deaths,
3 Stone *et al.* 2004); stomach (SMR = 1.01, 95% CI = 0.73 to 1.37, 41 deaths, Boffetta *et*
4 *al.* 1997; SIR = 1.05, 95% CI = 0.39 to 2.29, 6 cases, Shannon *et al.* 2005); kidney (SMR
5 = 1.46 (95% CI = 0.30 to 4.27, 3 deaths, and SIR = 1.92, 95% CI = 0.96 to 3.43, 11 cases,
6 Shannon *et al.* 2005); rectum (SIR = 1.01, 95% CI = 0.44 to 2.00, 8 cases, Shannon *et al.*
7 2005); bone (SMR = 2.66, 95% CI = 0.86 to 6.21, 5 deaths, Boffetta *et al.* 1997);
8 leukemia (SIR = 1.25, 95% CI = 0.54 to 2.46, 8 cases, Boffetta *et al.* 1999, and non-
9 leukemia lymphohematopoietic cancers (SMR = 1.42, 95% CI = 1.42, 95% CI = 0.94 to
10 2.07, 27 deaths, Boffetta *et al.* 1997); skin melanoma (SIR = 1.13, 95% CI = 0.54 to 2.08,
11 10 cases, Boffetta *et al.* 1999); breast (SIR = 1.08, 95% CI = 0.72 to 1.55, 29 cases,
12 Boffetta *et al.* 1999); ill-defined sites (SMR = 1.69, 95% CI = 1.13 to 2.42, 29 deaths)
13 and “other” malignancies (SMR = 1.04, 95% CI = 0.84 to 1.28, 91 deaths, Boffetta *et al.*
14 1997), SIR = 1.01, 95% CI = 0.78 to 1.29, 65 cases, Boffetta *et al.* 1999).

15 Among other SVF-exposed workers, statistically significantly increased risks in stomach
16 cancer mortality and incidence (SMR = 1.59, 95% CI = 1.00 to 2.41, 22 deaths; SIR =
17 1.78, 1.15 to 2.63, 25 cases) were observed among male workers in the Swedish
18 prefabricated wooden house industry (Gustavsson *et al.* 1992). In addition, statistically
19 nonsignificant increases were observed in this study for cancers of the liver (SMR = 1.67,
20 95% CI = 0.45 to 4.28, 4 deaths, and SIR = 1.45, 95% CI = 0.62 to 2.86, 8 cases);
21 pancreas (SMR = 1.34, 95% CI = 0.71 to 2.29, 13 deaths, and SIR = 1.43, 95% CI = 0.71
22 to 2.56, 11 cases); prostate (SMR = 1.01, 95% CI = 0.63 to 1.55, 21 deaths);
23 genitourinary system (SMR = 1.01, 95% CI = 0.48 to 1.86, 10 deaths); lymphoma (SMR
24 = 1.63, 95% CI = 0.70 to 3.22, 8 deaths); and all lymphohematopoietic cancers (SMR =
25 1.05, 95% CI = 0.58 to 1.72, 15 deaths, and SIR = 1.35, 95% CI = 0.85 to 2.02, 23 cases);
26 nasal cancer (SIR = 2.00, 95% CI = 0.03 to 11.13, 1 case); melanoma (SIR = 1.28, 95%
27 CI = 2.64, 7 cases); and other skin (SIR = 1.23, 95% CI = 0.85 to 2.02, 8 cases).

28 In addition, in population-based, case-control or registry-based studies of subjects with
29 possible exposure to glass wool or mixed SVF, increases in premenopausal and
30 postmenopausal breast cancer risk were observed (SIR = 1.15, 95% CI = 0.74 to 1.79 and

1 SIR = 1.30, 95% CI = 1.02 to 1.64, respectively, for occupations in which at least 20% of
2 women were potentially exposed to SVF) were observed by Weiderpass *et al.* (1999). A
3 marginal increase in ovarian cancer (SIR = 1.3, 95% CI = 0.9 to 1.8) also was observed in
4 association with occupations in which at least 20% of women were potentially exposed to
5 SVF (Vasama-Neuvonen *et al.* 1999). Several studies have reported some increases in
6 cancers of the gastrointestinal tract in association with potential SVF exposure. In a study
7 of gastrointestinal cancers and occupation among Finnish women by Weiderpass *et al.*
8 (2003), increases in cancers of the stomach (RR = 1.23, 95% CI = 1.01 to 1.49, low
9 exposure, and RR = 1.23, 95% CI = 0.85 to 1.77, medium/high exposure), esophagus (RR
10 = 1.29, 95% CI = 0.83 to 2.00, low exposure, and RR = 1.61, 95% CI = 0.80 to 3.25,
11 medium/high exposure); rectum (RR = 1.06, 95% CI = 0.83 to 1.35, low exposure only);
12 gallbladder (RR = 1.03, 95% CI = 0.55 to 1.95, medium/high exposure); and pancreas
13 (RR = 1.34, 95% CI = 0.89 to 2.03, medium/high exposure) were observed. A
14 statistically significant increase in rectal cancer also was observed among 8 male cases
15 with “substantial” estimated exposure to glass wool (OR = 4.3, 95% CI = 1.7 to 11.3) in a
16 hypothesis-generating study by Dumas *et al.* (2000), and an increase in colon cancer (OR
17 = 2.0, 95% CI = 0.8 to 5.4, 6 cases with “substantial” estimated exposure) was observed
18 by Goldberg *et al.* (2001). Finally, a marginally significant increase in non-Hodgkin’s
19 lymphoma (OR = 1.5, 95% CI = 1.0 to 2.3, 63 cases) was observed in a case-control
20 study, primarily focused on pesticide exposures, by Hardell and Ericksson (1999).

21 **3.6 [Methodological issues]³**

22 Several methodological considerations are important in interpreting the epidemiology
23 studies.

24 **3.6.1 Statistical power of the studies**

25 The most informative studies are the U.S. and European cohort and nested case-control
26 studies of glass wool production workers. The principal methodological strengths of these
27 cohort and case-control studies are, first, that adequate numbers of workers have been
28 followed over a sufficient period of time to detect cancers with both shorter and longer

³ The title of this section is bracketed to indicate the presence of opinion throughout this section rather than bracketing specific statements.

1 latencies, and they yield a large number of person-years at risk and thus sufficient power
2 to detect modest increases in cancer mortality for all but very rare cancers. Second,
3 ascertainment of vital status was close to complete, with little evidence of systematic bias
4 in follow-up. There also were sufficient cancer outcomes to permit some exposure-
5 response relationships to be examined and some confounding variables to be taken into
6 account in internal comparisons and/or case-control analyses. In addition, the U.S. cohort
7 was expanded to include women and non-white subjects. Other cohort and case-control
8 studies are smaller and have relatively low statistical power to detect effects. It should
9 also be noted that average glass wool exposures are one-tenth or less of the exposure
10 levels for asbestos in the cohorts studied for asbestos (see, for example, Armstrong *et al.*
11 1988, Levin *et al.* 1998, Newhouse and Berry 1979).

12 3.6.2 *Ascertainment of vital status and diagnoses*

13 Mortality and incidence studies rely on complete and accurate ascertainment of vital
14 status or cancer incidence and accurate diagnoses. Follow-up for the larger cohort studies
15 was almost complete and unlikely to be biased in terms of exposure status within the
16 cohorts. Reliance on reported underlying cause of death from death certificates is known
17 to result in some misdiagnoses and incomplete information, but is likely to be
18 nondifferential and thus would bias findings towards the null. Cancer diagnoses obtained
19 in incidence studies from medical records or cancer registries may be more accurate and
20 complete than death certificate data, although some misdiagnoses and information errors
21 occur. The potential impact of misdiagnosis or misclassification of cancer endpoints is
22 clearly more pronounced for rarer cancers where only a few cases are expected, such as
23 cancer of the larynx or pharynx, than for more common cancers such as lung cancer, or
24 where the possibility of misdiagnosis without additional (e.g., histopathological)
25 confirmation is greater, such as with mesotheliomas.

26 3.6.3 *Appropriateness of comparison populations and control groups*

27 In the standardized mortality studies of Marsh *et al.* (2001a) and Boffetta *et al.* (1997),
28 both national and regional or local comparison expected rates of lung cancer were used to
29 calculate SMRs. In both studies, slightly higher SMRs were obtained when national
30 rather than local (county) comparison rates were used or adjusted for. (Depending on the

1 mobility and other characteristics of the exposed population, local populations are likely
2 to be more representative of the exposed population, assuming that expected cancer rates
3 are calculated from large enough populations to be robust.)

4 In the U.S. and French cohorts, SMRs for all cancers combined were slightly lower than
5 expected (in Marsh *et al.* 2001a, for example, all-cause cancer mortality was 0.94 (95%
6 CI = 0.90 to 0.98, county comparison) and in the French cohort of Moulin *et al.* (1986)
7 the cancer incidence rate for cancers other than respiratory and upper gastrointestinal
8 tract was 0.77 (95% CI = 0.45 to 1.24), suggesting the possibility of a healthy-worker
9 effect. However, in the European combined cohort (Boffetta *et al.* 1997) the SMR for all
10 cancers among the glass wool workers was slightly elevated (1.11, 95% CI = 1.01 to
11 1.22), although the SIR was not (0.99, 95% CI = 0.89 to 1.11). In the second follow-up of
12 the Canadian cohort (Shannon *et al.* 1987) the SMR for all cancers was also elevated
13 among plant workers (SMR = 1.15, 95% CI = 0.93 to 1.40), although all-cause SMR
14 among plant workers was slightly decreased compared with expected rates (SMR = 0.93).

15 3.6.4 *Determination of exposure-response relationships*

16 Due to a lack of actual exposure measurements across time and in each job category in
17 most of the cohort studies, the construction of job-exposure matrices was based primarily
18 on limited monitoring data and/or knowledge of industrial processes and industrial
19 hygiene practices, changes in these practices over several decades in some cohorts, and
20 job descriptions. In addition, the biopersistence of glass wool fibers (see Section 5) might
21 obscure delineation of meaningful relationships between, on one hand, duration of
22 exposure, or changes in levels of exposure over time, and cancer risk. In addition, the
23 exclusion of short-term workers with either < 1 year or < 6 months of employment, as
24 was done in a number of cohort studies, means that the effect of very short-term
25 exposures was not examined.

26 Adequate follow-up time, especially for cancers of longer latency, such as lung cancer
27 (which might have an average latency of 20 or more years) is also necessary in order to
28 be able to adequately examine exposure-response relationships for such cancers. In the
29 most recent follow-ups of both the U.S. and European cohorts, relatively large numbers
30 of workers had more than 15 to 30 or more years since first exposure. In several other

1 cohort studies, however, the time since first exposure, at least for parts of the cohorts,
2 might have been insufficient to detect an effect if present.

3 It is possible that referent occupational groups or populations might also have been
4 exposed to glass wool. The possibility of misclassification of exposure among “exposed”
5 and “unexposed” groups, or cases and controls, can significantly impact the ability to
6 detect modest effects of exposure if present, and would generally tend to bias findings
7 towards the null. In the case of the Stone *et al.* (2004) cohort study, for example, internal
8 controls that were exposed to glass filament were used in one comparison, and might
9 possibly have been also exposed to glass wool. In the nested case-control studies,
10 potentially exposed reference groups might have been used for some comparisons (e.g.,
11 in Marsh *et al.* 2001a). In plants where workers could have had several jobs or where
12 their jobs did not involve fixed processes or locations within the plant (e.g., maintenance
13 workers, truck drivers, packers, cleaners, etc.) it might be more difficult to characterize
14 exposure than for fixed process jobs. Exposure might also depend on the extent to which
15 airborne exposure to fibers was controlled and contained. According to exposure
16 reconstruction studies carried out by Marsh, Boffetta, and others, the use of resin binders,
17 improved ventilation, and other control measures from, in most cases, the mid 60s to 70s
18 resulted in lower estimated exposures to production workers in later years, and
19 presumably less ambient contamination in the vicinity of the production areas. However,
20 characterization of early exposures was limited by a lack of documented exposure-
21 monitoring data in these and other cohort and case-control studies.

22 3.6.5 Potentially confounding exposures

23 For lung cancer, the most significant confounding exposure is smoking. Boffetta *et al.*
24 (1997), citing a model of lung cancer and smoking proposed by Axelson (1978),
25 estimated that a 20% difference in the proportion of smokers could result in a 30%
26 increase in lung cancer among SVF-exposed workers compared with unexposed
27 referents. Smoking data for workers in the European, French, and Canadian cohorts were
28 not available. In the case of the French cohort, an estimate of smoking prevalence was
29 based on information obtained from 966 workers still employed at the factory; the
30 authors concluded that smoking was similar to that in the general population and reported

1 no association with the SIR for lung cancer. Attempts to estimate the extent of smoking
2 and its relationship to observed lung cancer rates in the U.S. case-control studies were
3 based on interviews with samples of survivors or proxy respondents. The estimated
4 proportion of smokers in this study (Buchanich *et al.* 2001, Marsh *et al.* 2001a,c, Stone *et*
5 *al.* 2001) was somewhat higher than that of the general population, although the
6 proportion of smokers in the female cohort appears to be slightly lower. Marsh *et al.*
7 (2001c) estimated that approximately 7% of the observed increase in respiratory cancers
8 in the entire cohort could be attributable to smoking, and adjusting for this reduced the
9 SMRs for respiratory cancers to nonsignificance. In the case-control study of this cohort
10 (Marsh *et al.* 2001a, Stone *et al.* 2001), ever smoking accounted for a 13-fold increase in
11 risk of lung cancer compared with never smoking; adjustment for ever smoking slightly
12 lowered the risk for lung cancer attributable to glass wool from RR = 1.12 (95% CI =
13 0.77 to 1.62) to 1.06 (95% CI = 0.71 to 1.60). Residual confounding could obscure a
14 relationship between glass wool and lung cancer, however. Note, however, that in an
15 earlier case-control study of part of the U.S. cohort (Chiazze *et al.* 1992, 1993), adjusting
16 for smoking and other variables did not appear to decrease the risk of lung cancer
17 associated with moderate levels of respirable fiber exposure, although the risk for higher
18 levels was slightly attenuated.

19 In a number of cohort and case-control studies, including the U.S. cohort, some workers
20 were exposed not only to glass wool but also to glass (continuous) filament, rock wool or
21 other SVF. In the case of continuous filament, the external (SMR) analysis of the U.S.
22 cohort (Marsh *et al.* 2001a) indicated that filament-only workers had a lower risk than
23 glass wool-only workers, but a slightly higher risk than that observed among mixed glass
24 wool + filament workers. In the nested case-control study of this cohort, a lower risk was
25 observed among workers exposed to filament than to either glass wool alone or glass
26 wool + filament (see Table 3-2). IARC considered the workers in the wool and filament
27 plants in the U.S. cohort to be largely exposed to glass wool (IARC 2002). Exposure to
28 glass filament in other studies also appears to yield a nonsignificant risk of respiratory
29 cancers; the meta-analysis by Berrigan *et al.* (2002) estimated that the overall respiratory
30 cancer risk from filament exposure is low (RR = 1.08, 95% CI = 0.93 to 1.26), whereas
31 for rock wool, the estimated risk is higher than for glass wool (RR = 1.32, 95% CI = 1.15

1 to 1.52), although smoking or other confounding exposures might account for some or all
2 of the increase in risk. Exposure to superfine fibers might also be associated with an
3 increase in the risk of respiratory cancer, as suggested, for example, by data from
4 Gardner *et al.* (1988). For mixed glass wool and other SVF exposures, especially if they
5 included rock or slag wool, or superfine fibers, it is not possible to distinguish the
6 contribution of one or other type of fiber to the risk of lung cancer.

7 Other potentially confounding exposures in the glass wool manufacturing industries
8 include asbestos, asphalt, resins, formaldehyde (used in glass wool binders), polyaromatic
9 hydrocarbons, phenolics, silica, styrene, and urea, according to Marsh *et al.* (2001a). Of
10 these, formaldehyde was the most prevalent exposure in the U.S. study and was
11 independently associated with a significant increase in risk of lung cancer (RR = 1.61,
12 95% CI = 1.02 to 2.57, adjusted for smoking), although formaldehyde has not clearly
13 been associated with lung cancer in other studies. Asbestos is a potential concern both in
14 manufacturing and in construction and other industries that use glass wool, particularly
15 where asbestos might have been used in the past. As noted above, mesothelioma has
16 rarely been observed in the absence of asbestos exposure. Construction workers and fiber
17 installation workers could also be exposed to asbestos during, for example, remediation
18 work on older buildings. In the U.S. cohort, however, no evidence of a confounding
19 effect of asbestos was observed in the nested case-control study (Marsh *et al.* 2001a). Of
20 the 10 possible cases of mesothelioma observed in the whole cohort, most appeared to be
21 associated with asbestos, according to the authors (Marsh *et al.* 2001b). In the Boffetta *et*
22 *al.* study (1997), 4 deaths from mesothelioma occurred in the last follow-up of the entire
23 cohort, but only one among glass wool workers, and at least three were related to
24 asbestos exposure, according to the authors. Silica exposure is also a possible concern for
25 respiratory cancers, but in the U.S. cohort, no relationship was observed, nor were any
26 other potentially confounding exposures significantly associated with respiratory cancers.

27 **3.7 Summary**

28 A number of epidemiological studies have evaluated the relationship between glass wool
29 exposure and cancer in humans. The studies fall into three main groups: (1) cohort and
30 case-control studies of workers in SVF manufacture, (2) cohort and case-control studies

1 of workers exposed in glass wool applications (e.g., insulators and construction workers),
2 and (3) population-based, case-control studies.

3 Studies within the SVF manufacturing industry have attempted to distinguish between
4 exposure to different types of SVF, and the large cohort and nested case-control studies
5 of workers exposed in plants predominantly engaged in glass wool manufacture are the
6 most informative. [The principal limitations of the glass wool cohort and case-control
7 studies of manufacturing workers include potential misclassification of exposure,
8 particularly for past exposures for which few monitoring data are available, inadequate
9 length of follow-up in some studies for cancers of longer latency, potential confounding
10 by smoking or co-exposure to other chemicals, and possible misdiagnosis or inadequate
11 ascertainment of some cancer outcomes, such as mesothelioma. Studies of workers in
12 SVF applications (two cohort studies and three case-control studies of respiratory cancer)
13 and the population-based, case-control studies or cancer registry studies (cancers of the
14 respiratory and/or gastrointestinal tract, non-Hodgkin's lymphoma, breast, colon, ovary
15 and rectum) have generally been unable to distinguish between types of fibers and are
16 consequently less informative, although intermittent exposures might be higher than
17 observed among manufacturing workers (IARC 2002). In addition, these studies
18 generally had small numbers of potentially glass wool-exposed subjects and shorter
19 follow-up times than studies of manufacturing workers, and thus, limited statistical power
20 to detect long-term effects.]

21 Cancer mortality or incidence has been studied in four cohorts of manufacturing workers:
22 (1) a combined cohort of male and female U.S. SVF manufacturing workers including
23 five plants making mostly glass wool and three making glass wool and filament (Marsh *et*
24 *al.* 2001a, Stone *et al.* 2004), (2) a combined cohort of male and female manufacturing
25 workers in five European glass wool plants (Boffetta *et al.* 1997, 1999), (3) a cohort of
26 male manufacturing workers in Canada (Shannon *et al.* 2005), and (4) a cohort of male
27 manufacturing workers in France (Moulin *et al.* 1986). [The cohorts of manufacturing
28 workers in the United States and Europe are the largest studies and have adequate follow-
29 up to detect cancers with longer latencies (220,700 person-years of exposure in the U.S.
30 cohort and approximately 201,000 person-years of exposure in the European cohort).] In

1 both cohorts, several earlier studies of subcohorts have been conducted, together with two
2 nested case-control studies of respiratory cancer in the U.S. cohort (Marsh *et al.* 2001a,
3 Chiazze *et al.* 1992, 1993) and one of lung cancer from part of the European cohort
4 (Gardner *et al.* 1988).

5 Reconstruction of glass wool exposures indicated that measurable exposure to respirable
6 glass wool fibers occurred among production workers, and that exposure was higher in
7 the earlier periods of operations. However, as IARC (2002) noted, the concentrations of
8 fibers to which production workers were exposed were generally low.

9 The potential effect of glass wool exposure on lung and upper respiratory tract cancers
10 has been studied most extensively, due to the structural similarity between glass wool,
11 other SVFs, and asbestos. Findings for respiratory cancers and other tumor sites of
12 interest are discussed below.

13 *Respiratory cancers*

14 Statistically significant increases in respiratory cancer mortality were observed among
15 glass wool-exposed workers in unadjusted analyses in the United States (SMR = 1.18,
16 95% CI = 1.04 to 1.34, $P < 0.05$, lung + larynx, compared with local rates) (Marsh *et al.*
17 2001a), European (SMR = 1.27, 95% CI = 1.07 to 1.50, P -value not given, lung only,
18 compared with national rates) (Boffetta *et al.* 1997), and Canadian cohorts (SMR = 1.63,
19 95% CI = 1.18 to 2.21, $P < 0.05$, lung only, compared with regional rates) (Shannon *et al.*
20 2005). Among female workers in the U.S. cohort, no increase in respiratory cancer
21 (trachea, bronchus, and lung) was observed in the whole cohort compared with national
22 or local mortality rates, but in an internal analysis of glass wool-only vs. filament-only-
23 exposed workers, a three-fold increase in these cancers was observed (RR = 3.24, 95% CI
24 = 1.27 to 8.28, Wald P -value = 0.014) (Stone *et al.* 2004). Excesses of lung cancer
25 incidence were observed among the European workers (SIR = 1.28, 95% CI = 0.91 to
26 1.74, compared with national rates, P -value not given) (Boffetta *et al.* 1999) and
27 Canadian workers (SIR = 1.60, 95% CI = 1.19 to 2.11, $P < 0.05$, compared with regional
28 rates) (Shannon *et al.* 2005), but not among French workers (SIR = 0.74, 95% CI = 0.24
29 to 1.72, compared with regional rates) (Moulin *et al.* 1986).

1 Attempts were made to control for the effects of smoking and other potentially
2 confounding exposures, including asbestos, formaldehyde, and silica, in the nested case-
3 control study of the U.S. cohort. Adjusting for ever/never smoking (using data obtained
4 from a sample of proxies) reduced the risk of lung cancer mortality among U.S. glass
5 wool workers exposed to respirable fibers (mostly from glass wool) from RR = 1.79
6 (95% CI = 0.77 to 4.14, $P = 0.17$) to RR = 1.37 (95% CI = 0.55 to 3.42, $P = 0.50$).
7 (Formaldehyde exposure was also independently associated with lung cancer in this
8 cohort, but models for glass wool and lung cancer adjusting for both formaldehyde and
9 smoking were not presented.) [The European, Canadian, and French studies had few data
10 on potentially confounding exposures.]

11 Several studies evaluated exposure-response relationships for respiratory cancers. In the
12 U.S. cohort and case-control studies, no clear exposure-response relationships with
13 duration of exposure or cumulative exposure were observed. An association between
14 average intensity of exposure was observed in an unadjusted model but not in models
15 adjusted for smoking or other confounders or in weighted-exposure models (Marsh *et al.*
16 2001a, Stone *et al.* 2001, Youk *et al.* 2001). There was a modest trend towards increased
17 risk with longer time since first hire in the U.S. but not the European cohort. Similarly, in
18 the nested case-control studies of lung cancer among the U.K. subgroup of the European
19 cohorts, no clear exposure-response relationships with lung cancer were observed, with
20 the exception of a statistically significant increase among glass wool and/or superfine
21 fiber-exposed workers after 10 to 19 years since first hire in the case-control study of the
22 U.K. subcohort by Gardner *et al.* (1988) (RR = 2.0, confidence intervals not given, 17
23 cases). In the Canadian cohort, there was some evidence of a trend towards increased risk
24 with longer duration of employment, time since first hire, and year of hire (Shannon *et al.*
25 2005).

26 Statistically significant increases in lung cancer risk were found among insulation
27 installers in Germany (OR = 1.48, 95% CI = 1.17 to 1.88, 304 cases) and among
28 combined insulation installers and electrical insulation fitters with either 20 or more years
29 (OR = 1.69, 95% CI = 1.01 to 2.81, 61 cases) or 30 or more years (OR = 2.03, 95% CI =
30 1.04 to 3.95, 47 cases) of potential exposure (Bruske-Hohlfeld *et al.* 2000). However, no

1 increases in lung cancer risk were found in other studies of construction and application
2 workers or in the population-based, case-control studies of lung cancer. [In general, glass
3 wool exposure cannot be distinguished from other SVF exposure in these studies, and
4 few attempts to adjust for smoking and other confounders were conducted.]

5 *Mesothelioma*

6 Only one death from mesothelioma was observed among glass wool-exposed workers in
7 the European cohort (Boffetta *et al.* 1997). Marsh *et al.* (2001b) observed seven possible
8 deaths from malignant mesothelioma among the glass wool- or glass wool + filament-
9 exposed workers, but a review of pathology reports or medical records, which were
10 available for only three of these cases, showed that at least two of them were possible
11 misdiagnoses. An earlier case-control study by Rödelsperger *et al.* (2001) reported a
12 three-fold increase in risk of mesothelioma among mixed SVF-exposed individuals after
13 adjustment for asbestos and other potential confounders (OR = 3.08, 95% CI = 1.17 to
14 8.07, $P < 0.05$, 55 cases), and a two-fold increase in pleural mesothelioma incidence (SIR
15 = 2.13, 95% CI = 1.35 to 3.20, 23 cases) was observed among a cohort of construction
16 workers by Engholm *et al.* (1987), but confounding by asbestos might have occurred in
17 these studies.

18 *Upper respiratory and upper gastrointestinal cancers*

19 Marsh *et al.* (2001a) did not report these cancers separately for the glass wool-exposed
20 workers, but no increases in these cancers were observed in the combined (glass wool-
21 and filament-exposed) cohort (SMR for larynx = 1.01, 95% CI = 0.68 to 1.45, 29 deaths;
22 SMR for buccal cavity and pharynx = 1.11, 95% CI = 0.85 to 1.42, 63 deaths). In the
23 European cohort, a small increase in buccal cavity + pharyngeal mortality and incidence
24 (SMR = 1.47, 95% CI = 0.71 to 2.71, 10 deaths; SIR = 1.31, 95% CI = 0.65 to 2.34, 11
25 cases), and in laryngeal mortality and incidence (SMR = 1.08, 95% CI = 0.29 to 2.75, 4
26 deaths, and SIR = 1.68, 95% CI = 0.55 to 3.93, 5 cases), was observed among glass wool-
27 exposed workers (Boffetta *et al.* 1997, 1999). Moulin *et al.* (1986) reported a statistically
28 significant excess of “upper respiratory and alimentary tract” cancers in the French cohort
29 (SIR = 2.18, 95% CI = 1.31 to 3.41, 19 cases, including one unexposed production
30 worker and one maintenance worker). In a hospital-based, case-control study, Marchand

1 *et al.* (2000) reported small increases in both laryngeal cancers (OR = 1.33, 95% CI =
2 0.91 to 1.95, 133 cases) and hypopharyngeal cancers (OR = 1.55, 95% CI = 0.99 to 2.41,
3 99 cases; each analysis adjusted for smoking, age, and alcohol intake) among men ever
4 exposed to “mineral wools.” When a 15-year latency period was used, the risks of
5 laryngeal and hypopharyngeal cancer increased (OR = 1.5, 95% CI = 1.03 to 2.22, and
6 1.65, 95% CI = 1.05 to 2.58, respectively, cases not specified). No significant interaction
7 with asbestos exposure was observed, but few subjects were exposed to mineral wools
8 and not to asbestos.

9 *Other cancer sites*

10 No statistically significant excesses of other tumors have been reported in the largest
11 cohort mortality or incidence studies of production workers or construction workers.
12 [Note that some studies did not report data for all cancer sites.] A number of elevated
13 risks (SMRs or SIRs above 1.0) have been reported for a number of sites in single
14 studies, but only for the following cancer sites in more than one cohort study (excluding
15 earlier studies of subcohorts or earlier follow-ups): deaths or cases of
16 lymphohematopoietic cancers (Boffetta *et al.* 1997, 1999; Gustavsson *et al.* 1992);
17 cancers of the urinary bladder (Boffetta *et al.* 1997, 1999; Marsh *et al.* 2001a, Stone *et al.*
18 2004); melanoma (Boffetta *et al.* 1999, Gustavsson *et al.* 1992); and stomach cancers
19 (Boffetta *et al.* 1997; Shannon *et al.* 2005; Gustavsson *et al.* 1992).

20 In population-based, case-control or registry studies of subjects with possible exposure to
21 glass wool, statistically nonsignificant increases in pre- and postmenopausal breast cancer
22 and ovarian cancer (Vasama-Neuvonen *et al.* 1999, Weiderpass *et al.* 1999) and in
23 stomach, esophageal, rectal, gallbladder, and pancreatic cancers (Weiderpass *et al.* 2003)
24 were observed among Finnish women. A marginally significant increase in rectal cancer
25 (Dumas *et al.* 2000) and colon cancer (Goldberg *et al.* 2001) was observed among men in
26 Montreal with “substantial” estimated exposure to glass wool. [Note that statistically
27 nonsignificant increases in rectal cancer were also seen in the cohort study of Shannon *et*
28 *al.* (2005), and in pancreatic cancer in the cohort study of Gustavsson *et al.* (1992).]
29 Finally, a marginally significant increase in non-Hodgkin’s lymphoma was observed by
30 Hardell and Ericksson (1999).

1 **4 Studies of Cancer in Experimental Animals**

2 The carcinogenicity of glass wool fibers has been investigated in experimental animals
3 (primarily rats and hamsters) by several routes of administration. Furthermore, published
4 reviews covering several decades of research are available (Bunn *et al.* 1993, Davis 1986,
5 Ellouk and Jaurand 1994, Enterline 1991, Gross 1986, Hesterberg and Chase 1996,
6 Hesterberg and Hart 2001, IARC 1988, 2002, Miller *et al.* 1999a, Pott *et al.* 1989, Roller
7 and Pott 1998, Rossiter and Chase 1995, WHO 1988, 2000). The data and findings from
8 these reviews and other publicly available, peer-reviewed carcinogenicity studies in
9 experimental animals are summarized in this section. Inhalation studies are discussed in
10 Section 4.1, intraperitoneal (i.p.) injection studies are discussed in Section 4.2, and
11 studies that used other routes of administration (i.e., intrathoracic, intratracheal, or
12 intrapleural injection or implantation) are discussed in Section 4.3. Section 4.4 describes
13 studies that evaluated fiber characteristics and tumorigenicity, Section 4.5 provides a
14 brief summary of the IARC evaluations (IARC 1988, 2002), and Section 4.6 summarizes
15 the information in this section.

16 This document discusses carcinogenicity data for a wide variety of glass fibers. Some of
17 the studies used fibers derived from commercial products made in the United States or
18 Europe, while some used experimental fibers. Even when commercial products were
19 used, fibers were often size-separated, ball-milled, coated, uncoated, or chemically
20 treated to increase the number of respirable fibers or to examine effects of other fiber
21 properties. In a number of cases, test fibers were identified with generic terms such as
22 fiberglass, glass fibers, borosilicate glass fibers, or glass microfibers. A few studies
23 investigated many different types of synthetic vitreous fibers (SVFs) covering a broad
24 range of fiber dimensions and other properties. The general categories and descriptions of
25 glass fibers discussed in this section are provided in Table 4-1. More information on the
26 properties and uses of these glass fibers was provided in Sections 1 and 2.

Table 4-1. Insulation glass wools, including special-purpose and experimental fibers^a

Category	Fiber description	Comments
Consumer products	CertainTeed B glass Insulsafe II MMVF11 German glass wool Manville 901 MMVF10 MMVF10a Owens Corning	Most all of these products are used in building insulation. MMVF11 represents the respirable fraction derived from CertainTeed B glass and MMVF10 represents the respirable fraction derived from Manville 901. MMVF10a fiberglass has a lower fluorine content than MMVF10 (McConnell <i>et al.</i> 1999).
Special-purpose commercial products	Tempstran Code 100/475 JM475 Manville Code 100 JM100 JM104 JM108B JM104/475 JM110 JM112 JMC102 JMC104 MMVF33 JM753 JME-glass microfibers 104E	Many special-purpose fibers are made in a variety of diameters (expressed as codes). Thus JM100, 104, 112, etc. reflect the relative diameter of the fiber with a smaller number representing a finer diameter. All of the listed products through MMVF33 represent JM475 glass. MMVF33 was derived from a mixture of codes 104, 108B, and 110.
Experimental fibers	A and C fibers B, M, P, and V glass B-01-0.9 B-09-0.6 B-09-2.0 Bayer B1, B2, and B3	In most cases, these designations represent fibers that were engineered to be more soluble and less biodurable than the typical commercial fibers

^a This table is not intended to be exhaustive but provides a list of the types of fibers used in the experimental animals studies reviewed in this section.

1 **4.1 Inhalation studies**

2 Doses in inhalation studies are expressed as the concentration (usually in mg/m³) and/or
3 fiber number (fibers/cm³). It is generally accepted that fiber number rather than mass is
4 the better measure of dose because equal masses of fibers with different dimensions will
5 have large differences in the number of fibers. Fiber numbers are frequently expressed as
6 the number of WHO fibers (the number of fibers ≥ 5 μm in length, < 3 μm in diameter,
7 and having an aspect ratio of at least 3:1) or the number of fibers > 20 μm in length. The
8 number of WHO fibers is believed to represent the number of respirable fibers while the
9 number of fibers longer than 20 μm represents fibers that are the most biopersistent

1 (Hesterberg and Hart 2001). Nevertheless, as long fibers can be broken into short fibers,
2 biopersistence of short fibers may be greater than that of longer fibers.

3 Inhalation studies of fibers present specific challenges. Ideally the system should be
4 capable of generating a consistent cloud of respirable fibers without breaking, grinding,
5 or contaminating the fibers. Exposures may be whole body or nose only. The advantage
6 of nose-only systems is that they allow greater control of exposure levels and provide
7 more uniform dosing. Exposures in most of the earlier studies were whole body while
8 most of the later studies used nose-only systems.

9 *4.1.1 Early studies in rodents*

10 Schepers and Delahant (1955) conducted the first chronic inhalation study of insulation
11 glass wool. Fifty (50) white rats and 100 guinea-pigs were exposed in inhalation
12 chambers to medium-caliber (~6 μm diameter) glass wool (0.14 mg/ft^3 [4.9 mg/m^3]) for
13 up to 20 months. At 20 months, the glass wool was replaced with glass cotton (maximum
14 diameter 3 μm) at 0.03 to 0.07 mg/ft^3 [1.1 to 2.5 mg/m^3] for another 20 months (guinea-
15 pigs) or 4 months (rats). [No controls were mentioned.] The animals were sacrificed in
16 groups of three to five at various intervals throughout the study. Seventeen (17) guinea-
17 pigs and 20 rats died before the end of the study. Early deaths in guinea-pigs were due to
18 pneumonia and, in rats, were due to lung inflammation. Bronchitis was observed after 12
19 months, and bronchial epithelial hyperplasia was reported at 18 months. No tumors were
20 reported, and the authors concluded that, unlike asbestos, glass wool was not fibrogenic
21 (i.e., did not cause fibrosis). In a subsequent study, Schepers (1974) exposed 100 guinea-
22 pigs for 44 months and 50 rats for 28 months to aerosols of glass wool (0.15 mg/m^3) and
23 cotton dust (0.03 mg/m^3). Fiber diameters in the aerosol were mostly in the range of
24 about 2 to ≥ 10 μm with 20% ≤ 2 μm . Fiber lengths were mostly in the range of about 5
25 μm to more than 50 μm with 30% ≤ 5 μm . Non-neoplastic lesions of the bronchial
26 epithelium, peribronchiolar structures, and pulmonary parenchyma were observed in 57
27 guinea-pigs. No pulmonary lesions were reported in 300 controls. Pulmonary lesions
28 (macrophage accumulation in subpleural alveolar spaces) occurred in 16 rats compared
29 with 2 out of 310 controls. No neoplastic lesions occurred in either species.

1 Gross *et al.* (1970) studied the pulmonary reactions in rats [strain not provided] and
2 hamsters exposed to high concentrations of specially prepared fibrous glass dust obtained
3 from the three largest producers of fibrous glass. One batch was coated with a phenol-
4 formaldehyde resin, another batch was coated with a starch binder, and a third batch was
5 left uncoated. Groups of 30 rats or hamsters were exposed in inhalation chambers for 6
6 hours per day, 5 days per week for 24 months to concentrations of 106 to 135 mg/m³
7 [fiber numbers not provided]. Control groups included 20 rats and 20 hamsters. [No
8 hamsters or rats were exposed to asbestos (positive controls).] Samples collected during
9 the experiment indicated that 70% to 76% of the dust was fibrous. The average diameter
10 was 0.5 µm and the average length was about 10 µm (range 5 to 20 µm). Interim
11 sacrifices of 5 animals each were conducted at 6 months and 12 months. The remaining
12 animals were held until their deaths. There were no differences in tissue reactions for the
13 three types of fibrous dusts. Pulmonary response to the three types of fibrous dusts was
14 similar in both species and was characterized by relatively small accumulations of
15 macrophages without significant stromal change. At 6- and 12-months exposure in rats,
16 phagocytic cells filled with glass dust were noted in moderately enlarged satellite lymph
17 nodes and by 24 months, there was some evidence of collagen formation in the stroma. In
18 contrast, hamster lymph nodes containing glass-dust-filled phagocytic cells were not
19 enlarged, and there was no apparent change in the stroma at 24 months. Pneumonia and
20 the endemic presence of chronic bronchitis and its sequelae were observed in rats. Some
21 hamsters died from pneumonia [number not provided]. [No tumors were reported.]

22 Mitchell *et al.* (1986) and Moorman *et al.* (1988) (reporting on the same data) conducted
23 a chronic inhalation study using commercial grade Owens-Corning insulation fiberglass
24 with binder or Tempstran Code 100/475 special-purpose glass fibers without binder.
25 Groups of 50 male and 50 female F344 rats were exposed (whole body) for 7 hours/day,
26 5 days/week for 86 weeks and held until 80% mortality. The target concentrations were
27 15 mg/m³ for the Owens-Corning insulation and 5 mg/m³ for the 475 glass. There were
28 two exposure groups for each type of glass fiber. One group was exposed to Owens-
29 Corning fibers 4 to 6 µm in diameter and > 20 µm in length, and another group was
30 exposed to shorter and thinner fibers (> 10 µm in length and 0.5 to 3.5 µm in diameter).
31 For the 475 glass, the average fiber diameter was < 3.5 µm, but average fiber lengths

1 were > 10 µm in one group and < 10 µm in the other. A control group included 50 male
2 and 50 female rats exposed to filtered and conditioned air.

3 Pulmonary macrophage aggregates and granulomas that contained glass fibers were
4 observed in treatment groups. A moderate to severe inflammatory response in the region
5 of fibrous glass-laden macrophage aggregates was present in lung and pleural tissue.
6 Glass-laden macrophages were also evident in thymic and tracheobronchial lymph nodes.
7 Pleural and subpleural plaques resulted from accumulations of granulomatous foci but
8 there was no evidence of treatment-related neoplastic lesions in the respiratory tract.
9 Mononuclear-cell leukemia incidence in the treatment groups ranged from about 35% to
10 42% compared with 21% in the controls and was statistically significant (Table 4-2). The
11 authors speculated that the presence of the glass fibers in the lung and lymphoid tissue
12 might have stimulated cells with a high spontaneous incidence of neoplasia or might have
13 a direct genotoxic effect on stem leukocytes in the pulmonary and/or lymphoid tissue
14 resulting in an increased incidence or probability of cancer (Moorman *et al.* 1988).

Table 4-2. Mononuclear-cell leukemia in rats exposed to glass wool fibers

Group (mg/m ³)	Fiber dimensions (µm)		Incidence (%)		
	diameter	length	males	females	combined
Control	–	–	10/50 (20)	11/49 (22.4)	21/99 (21.2)
Owens-Corning (15)	4–6	> 20	17/50 (34)	20/50 (40)	37/100 (37)*
	0.5–3.5	> 10	18/50 (36)	19/50 (38)	37/100 (37)*
Tempstran 100/475 (5)	< 3.5	> 10	20/50 (40)	15/49 (30.6)	35/99 (35.4)*
	< 3.5	< 10	25/50 (50)	17/49 (34.7)	42/99 (42.4)**

Source: Mitchell *et al.* 1986, Moorman *et al.* 1988.

* $P < 0.05$; ** $P < 0.01$ (compared with controls, Chi square test).

15 Several inhalation studies of glass fibers in rodents were conducted in the 1980s and
16 reviewed by IARC (1988, 2002). None of these studies showed significantly increased
17 incidences of neoplastic lesions in the respiratory tract. However, all of these studies
18 were considered inconclusive by IARC (2002) because of several technical limitations. In
19 many cases the test fibers were too short, too thick, or were inadequately characterized.
20 Other study limitations included small numbers of animals, inadequate survival data, lung
21 burdens of fibers that were too small or were not reported, whole body instead of nose-
22 only exposure, or the absence of a strong tumorigenic response in positive control groups
23 exposed to asbestos fibers. These studies are not reviewed in detail but are summarized in

1 Table 4-3. Subsequently, a series of inhalation studies in rodents specifically designed to
2 address the limitations of these earlier studies was conducted, and those studies are
3 reviewed in Section 4.1.2. Inhalation studies in primates are reviewed in Section 4.1.3.

Table 4-3. Inhalation carcinogenicity studies of glass wool in rodents published prior to 1988^a

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol ^b	Pulmonary tumor incidence	Comments/limitations	Reference
Rats							
Sprague-Dawley	M (46)	Fiberglass (0.2–6.5 µm)	7.3×10^5 fibers/L, ~168 WHO fibers/cm ³ (> 5 µm)	6 h/d, 5 d/wk, 3 mo (observed at 24 mo)	2/11 (adenoma) 0/13 (controls)	Dust was not fibrogenic, only 7% had an aspect ratio $\geq 3:1$, short exposure period, no lung dose, small number of animals at risk due to interim sacrifices, 3/13 tumors in positive controls (amosite)	Lee <i>et al.</i> 1981
Wistar	M/F (24/24)	Ground glass wool, resin free (69% < 1 µm)	5 mg/m ³ , 48 WHO fibers/cm ³ (42% > 10 µm)	12–24 mo (observed at 12, 19, 24 or 28 mo)	1/45 (epidermoid carcinoma)	Type of glass fiber not specified, no lung dose, 9/47 tumors in positive controls (chrysotile)	Le Bouffant <i>et al.</i> 1984
	M/F (24/24)	JM100 (95% < 1 µm)	5 mg/m ³ , 332 WHO fibers/cm ³ (25% > 20 µm)	5 h/d, 5 d/wk, 24 mo (observed at 28 mo)	0/48	Fibers were relatively short, 9/47 tumors in positive controls (chrysotile)	
F344	M/F (24/24)	JM100 (0.3 µm)	10 mg/m ³ (71% < 10 µm)	7 h/d, 5 d/wk, 12 mo (life)	1/48 (adenoma)	Results from concurrent studies at two laboratories. Fibers were relatively short, 12/48 and 11/56 tumors in positive control groups (chrysotile)	McConnell <i>et al.</i> 1984
	M/F (28/27)	JM100 (0.3 µm)	10 mg/m ³ (71% < 10 µm)	7 h/d, 5 d/wk, 12 mo (life)	0/55		
F344	NR (56)	Glass wool, resin and non-resin coated (47%–52% < 1 µm)	10 mg/m ³ , 240–320 WHO fibers/cm ³ (58%–72% 5–20 µm)	7 h/d, 5d/wk, 3–12 mo (observed at 3, 12, and 24 mo)	1/48, resin coated (adenocarcinoma) 1/47, non-coated (adenoma)	Type of glass fiber not specified, mass of fibers in lung declined rapidly after exposure stopped, 12/48 tumors in positive controls (chrysotile)	Wagner <i>et al.</i> 1984a

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol ^b	Pulmonary tumor incidence	Comments/limitations	Reference
	NR (56)	JM100 (97% < 1 µm)	10 mg/m ³ , 1,400 WHO fibers/cm ³ (93% < 20 µm)	7 h/d, 5 d/wk, 12 mo (life)	1/48 (adenocarcinoma)	Fibers were relatively short, inadequate survival data, 12/48 tumors in positive controls (chrysotile)	
F344	M/F (50/50)	Owens-Corning (4–6 µm)	15 mg/m ³ (> 20 µm)	7 h/d, 5 d/wk, 86 wks (observed until 80% mortality)	0/50	Mononuclear-cell leukemia was increased (37% in both treatment groups vs. 21% in controls, see Table 4-2)	Mitchell <i>et al.</i> 1986 Moorman <i>et al.</i> 1988
		Owens-Corning (0.5–3.5 µm)	15 mg/m ³ (> 10 µm)		0/50		
	M/F (50/49)	100/475 (< 3.5 µm)	5 mg/m ³ (> 10 µm)		0/50	Mononuclear-cell leukemia was increased (35% vs. 21% in controls, see Table 4-2)	
			5 mg/m ³ (< 10 µm)		0/50	Mononuclear-cell leukemia was increased (42% vs. 21% in controls, see Table 4-2)	
Osborne-Mendel	F (52)	Insulsafe II with silicon lubricant (1.4 µm)	10 mg/m ³ , 100 fibers/cm ³ (37 µm)	6 h/day, 5 d/wk, 24 mo (observed at death)	0/52	Nose-only exposure, non-fiber/fiber ratio 6:1, fibers were short, 3/57 tumors in positive controls (crocidolite)	Smith <i>et al.</i> 1987
	F (57–61)	Manville building insulation (1.4 µm) ^c	1.2–12 mg/m ³ , 10–100 fibers/cm ³ (31 µm)	6 h/day, 5 d/wk, 24 mo (observed at death)	0/57 (high level) 0/61 (low level)	Nose-only exposure, non-fiber/fiber ratio 38:1, low fiber concentration, 3/57 tumors in positive controls (crocidolite)	
	F (58)	Owens-Corning building insulation (3 µm) ^c	9 mg/m ³ , 25 fibers/cm ³ (114 µm)	6 h/day, 5 d/wk, 24 mo (observed at death)	0/58	Nose-only exposure, non-fiber/fiber ratio 31:1, low fiber concentration, fibers were coarse and thick, 3/57 tumors in positive controls (crocidolite)	

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol ^b	Pulmonary tumor incidence	Comments/limitations	Reference
	F (57)	Manville Code 100 (0.4 µm)	0.3–3 mg/m ³ , 300–3,000 fibers/cm ³ (7.5 µm)	6 h/d, 5 d/wk, 24 mo, nose only (life)	0/57	Low survival in all groups including controls, 3/47 tumors in positive controls (crocidolite)	
Wistar	F (108)	JM104/475 (0.4 µm)	3.0 mg/m ³ , 252 WHO fibers/cm ³ (4.8 µm)	5 h/d, 4 d/wk, 12 mo, nose only (life)	1/107 (squamous-cell carcinoma)	Fibers were short, 1/100 tumors in positive controls (chrysotile and crocidolite)	Muhle <i>et al.</i> 1987
Guinea-pigs							
Guinea-pigs	M (32)	Fiberglass (0.2–6.5 µm)	7.3 × 10 ⁵ fibers/L (> 5 µm)	6 h/d, 5 d/wk, 3 mo (observed at 24 mo)	2/7 (adenoma) 0/5 (controls)	Fiberglass dust was not fibrogenic but only 7% had an aspect ratio ≥ 3:1, short exposure period, no lung dose, small number of animals at risk due to interim sacrifices, no tumors in positive controls (amosite)	Lee <i>et al.</i> 1981
Hamsters							
Hamsters	NR (34)	Fiberglass (0.2–6.5 µm)	7.3 × 10 ⁵ fibers/L (> 5 µm)	6 h/d, 5 d/wk, 3 mo (observed at 24 mo)	0/9	Fiberglass dust was not fibrogenic but only 7% had an aspect ratio ≥ 3:1, short exposure period, no lung dose, small number of animals at risk due to interim sacrifices, no tumors in positive controls (amosite)	Lee <i>et al.</i> 1981
Syrian golden hamsters	M (60)	Insulsafe II with silicon lubricant (1.4 µm)	10 mg/m ³ , 100 fibers/cm ³ (37 µm)	6 h/day, 5 d/wk, 24 mo (observed at death)	0/60	Nose-only exposure, non-fiber/fiber ratio 6:1, fibers were short, no tumors in positive controls (crocidolite)	Smith <i>et al.</i> 1987
	M (65–66)	Manville building insulation (1.4 µm) ^c	1.2–12 mg/m ³ , 10–100 fibers/cm ³ (31 µm)	6 h/day, 5 d/wk, 24 mo (observed at death)	0/66 (high level) 0/65 (low level)	Nose-only exposure, non-fiber/fiber ratio 38:1, low fiber concentration, no tumors in positive controls (crocidolite)	

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol ^b	Pulmonary tumor incidence	Comments/limitations	Reference
	M (61)	Owens-Corning building insulation (3 µm) ^c	9 mg/m ³ , 25 fibers/cm ³ (114 µm)	6 h/day, 5 d/wk, 24 mo (observed at death)	0/61	Nose-only exposure, non-fiber/fiber ratio 31:1, low fiber concentration, fibers were coarse and thick, no tumors in positive controls (crocidolite)	
	M (70)	Manville Code 100 (0.4 µm)	0.3–3 mg/m ³ , 300–3,000 fibers/cm ³ (7.5 µm)	6 h/d, 5 d/wk, 24 mo, nose only (life)	0/69	Low survival (< 25% to 24 mo) including controls, no tumors in positive controls (crocidolite)	

F = females; M = males; NR = not reported.

^a The IARC Working Group (IARC 2002) considered these studies inconclusive because of several technical limitations, including inadequate characterization of test fibers, test fibers that were too short or too thick, small numbers of animals tested, inadequate survival data, short exposure periods, lung burdens of fibers that were too small or were not reported, whole body instead of nose-only exposure, or the absence of a strong tumorigenic response in positive control groups exposed to asbestos fibers.

^b Whole-body exposures in inhalation chambers unless otherwise noted.

^c With phenol-formaldehyde binder.

1 4.1.2 Later studies in rodents

2 Beginning in 1988, a series of subchronic and chronic inhalation studies was initiated at
3 the Research and Consulting Company in Geneva, Switzerland to address the limitations
4 of the earlier studies (Bunn *et al.* 1993, Hesterberg *et al.* 1999, Hesterberg *et al.* 1997,
5 Hesterberg *et al.* 1993, Hesterberg *et al.* 1995, McConnell 1994, McConnell *et al.* 1999).
6 The subchronic studies supported a maximum tolerated dose (MTD) of 30 mg/m³ (250 to
7 300 WHO fibers/cm³) for chronic studies in rats and hamsters (Hesterberg *et al.* 1999,
8 Hesterberg *et al.* 1996a). These studies used nose-only exposure, examined several
9 different types of synthetic fibers in male F344 rats and Syrian golden hamsters, used
10 preparations that contained a large proportion of long fibers (mean length of about 20
11 µm) and respirable fibers (mean diameters of 1 µm or less), used an exposure protocol (6
12 hours/day, 5 days/week for 18 months to 2 years) designed to mimic occupational
13 exposure, included at least three exposure concentrations, and included sham-exposed
14 negative controls and asbestos-exposed positive controls (Hesterberg and Hart 2001).
15 Rats were 8 weeks old at the beginning of these studies and hamsters were 9 to 15 weeks
16 old. Fibers used in these studies were size separated from commercial glass wools to
17 achieve the desired properties. Approximately 2,000 pounds of bulk insulation product
18 were needed to obtain 20 pounds of size-separated fibers used in the inhalation studies
19 (Hesterberg *et al.* 1993). Hesterberg and Hart (1994) also compared human occupational
20 exposures to glass fibers with exposures used in one of the chronic rat studies and
21 reported that the aerosol used in the rat study was 30-fold more concentrated than the
22 highest human occupational exposures (blowing insulation of unbound fiber glass).

23 Two other inhalation studies with glass microfibers (100/475 and 104E) and amosite
24 asbestos were conducted at the Institute of Occupational Medicine, Edinburgh, Scotland
25 (Cullen *et al.* 2000, Davis *et al.* 1996). The primary focus of these studies was to compare
26 methods for determining and predicting fiber pathogenicity. The pathogenicity and
27 durability of the different fibers were examined by conducting long-term inhalation and
28 injection studies, *in vitro* tests, and several short-term tests.

1 *Rat*

2 Groups of 112 to 120 male F344 rats were exposed to the respirable fraction of Manville
3 901 glass wool (MMVF10) or CertainTeed B glass wool (MMVF11) at 3, 16, or 30
4 mg/m³ (~30, 150, 240 WHO fibers/cm³) for 2 years (Bunn *et al.* 1993, Hesterberg *et al.*
5 1993, Hesterberg *et al.* 1995, McConnell *et al.* 1994). In addition, a recovery group was
6 exposed for 1 year and then held for 1 year without further exposure. The fibers were
7 processed from commercial insulation wools to meet the length and diameter criteria
8 mentioned above. Six animals per group were sacrificed at 3- to 6-month intervals to
9 assess gross and microscopic changes in the lung. Chrysotile and crocidolite asbestos
10 were used as positive controls in studies conducted by the same researchers with partially
11 overlapping study times beginning in 1988 and ending in 1993 (Rossiter and Chase
12 1995). The authors stated that fiber-to-fiber comparisons between chrysotile or
13 crocidolite and SVFs are not appropriate because of major differences in fiber dimensions
14 and aerosol concentrations (Hesterberg and Hart 2001). The lungs of groups exposed to
15 MMVF10 or MMVF11 showed minimal progression of reversible cellular changes, and
16 the recovery group showed that alveolar bronchiolization (change from the normal flat to
17 cuboidal epithelium) and granular formation were partially or totally reversed.
18 Bronchoalveolar adenomas occurred in the non-exposed control group and in all but one
19 treatment group. Exposure to insulation glass wools did not cause a significant increase in
20 lung tumors or mesotheliomas in this study. [However, NTP calculated an apparent
21 positive trend for both adenomas and combined tumors in male F344 rats exposed to
22 MMVF10 ($P = 0.041$ and $P = 0.047$, respectively, for one-tailed Cochran-Armitage
23 trend test.)] Incidences of total lung tumors and lung carcinomas were significantly
24 increased in rats exposed to 10 mg/m³ chrysotile or crocidolite asbestos (Table 4-4). The
25 authors reported that many rats in the control and exposed groups showed evidence of
26 mononuclear-cell leukemia involvement of the lung after 24 months, [but incidence data
27 were not provided, and no analyses were reported] (Hesterberg *et al.* 1993). The authors
28 noted that this is a common spontaneous cancer in F344 rats and also occurred in rats that
29 died or were killed in a moribund condition during the study. [Refractory ceramic fibers
30 also were tested in these studies at similar fiber concentrations and dimensions as

1 MMVF10 and MMVF11 (data not shown), and induced significantly increased
2 incidences of lung tumors and mesotheliomas.]

3 Infante *et al.* (1994) conducted a reanalysis of the Hesterberg *et al.* (1993) data in an
4 attempt to increase the statistical power. Data for the unexposed control group in the
5 glass wool study were pooled with data for unexposed controls from a study of refractory
6 ceramic fibers that overlapped with the study reported by Hesterberg *et al.* for 24 months
7 of a 28-month study (Rossiter and Chase 1995). Data also were combined across all three
8 dose groups within each glass-wool type or within dose groups for the two insulation
9 glass wools (MMVF10 combined with MMVF11). Results of pairwise comparisons
10 (Fisher's exact test performed by Infante *et al.*) indicated that rats exposed to MMVF11,
11 but not MMVF10, had significantly increased incidences ($P = 0.027$) of lung tumors
12 (16/350, 4.6%) compared with the pooled controls (7/382, 1.8%). In addition, significant
13 dose-related trends (Cochran-Armitage) were reported for rats exposed to MMVF10 ($P =$
14 0.01) or MMVF10 and MMVF11 combined ($P = 0.016$). However, Chase and colleagues
15 (Hesterberg and Chase 1996, Rossiter and Chase 1995) have questioned the validity of
16 these statistical reanalyses, arguing that it is inappropriate to ignore inter-study variability
17 and to pool tumor incidences from concurrent and non-concurrent controls and that the
18 lung tumor incidence observed in the concurrent controls was consistent with NTP
19 historical control data.

20 Davis *et al.* (1996) exposed groups of male Wistar rats to JM100/475 fibers (mean
21 diameter of 0.32 μm) or amosite asbestos. Exposures occurred in inhalation chambers for
22 7 hours per day, 5 days per week for one year, and the animals were followed for their
23 full life-span. The target concentrations were 1,000 fibers/ $\text{m}^3 > 5 \mu\text{m}$ in length. Four
24 animals from each group were sacrificed after 12 months and examined for lung
25 pathology and fiber burdens. Fewer long fibers ($> 20 \mu\text{m}$) remained in the glass fiber-
26 exposed group compared with the amosite group after 12-months exposure. Amosite
27 produced rapid pulmonary inflammation and marked fibrosis and was carcinogenic (7
28 carcinomas, 9 adenomas, and 2 mesotheliomas). Glass fibers produced less inflammation
29 and very little fibrosis. Animals exposed to JM100/475 developed lung tumors (11%,
30 adenomas), but the increase was not statistically significant (Table 4-4). The adenomas

1 were small (< 1 mm in diameter) and were found only by microscopic examination
2 following layered sectioning of the lung. In a subsequent study from the same group
3 (Cullen *et al.* 2000), exposure to E-glass microfiber (104E) resulted in 23% total lung
4 tumors (7 lung carcinomas and 3 adenomas) and 2 mesotheliomas (Table 4-4). One lung
5 adenoma and one lung carcinoma occurred in the controls (5.3%). The number of fibers
6 (length 15 to 20 μm and > 20 μm) present in the lung after 12 months of exposure was
7 lower in the 100/475 group than in the 104E group (11×10^6 fibers/lung and 83×10^6
8 fibers/lung, respectively). The authors noted that the latency period for mesothelioma was
9 shorter with 104E fibers than with amosite asbestos fibers tested in this study.

10 *Hamster*

11 The inhalation carcinogenicity of MMVF10a, MMVF33, and amosite asbestos was
12 investigated in male Syrian golden hamsters (Hesterberg *et al.* 1997, McConnell *et al.*
13 1999). (Hesterberg *et al.* presented the preliminary data through 12 months, and
14 McConnell *et al.* presented the final data.) Groups of 125 male hamsters were exposed to
15 the respirable fraction of Manville 901 insulation glass wool (MMVF10a) at 30 mg/m^3
16 (~ 300 WHO fibers/ cm^3 and ~ 100 fibers longer than 20 μm per cm^3), 6 hours per day, 5
17 days per week for 78 weeks. MMVF10a was a mixture of two types of 901 fiberglass;
18 one of the 901 glasses contained fluorine and was the same as the one used in previous
19 studies while the other did not contain fluorine. The average aerosol fiber diameter
20 (arithmetic mean \pm SD) was $0.95 \pm 0.45 \mu\text{m}$, and the average length was $19.4 \pm 20.8 \mu\text{m}$.
21 Five animals per group were sacrificed at 13, 26, 52, and 78 weeks to assess gross and
22 microscopic changes in the lung and lung fiber burdens. Recovery groups were removed
23 from exposure after 13 weeks and 52 weeks and held until 78 weeks. Animals remaining
24 after 78 weeks were maintained for a recovery period of about 6 weeks, or until 20%
25 survival. The average diameters of MMVF10a and MMVF33 (0.9 μm) were 1.5 times
26 greater than that of amosite (0.6 μm). Moreover, asbestos fibers form bundles of fibrils
27 that may split longitudinally in the lung, while glass fibers do not [increased fiber burden
28 after recovery might be accounted for by this process.] The initial lung deposition of long
29 fibers (> 20 μm) was similar for glass wool and asbestos, but at the end of the study the
30 lung burden was much less for the MMVF10a group compared with the asbestos groups.
31 After a 6-week recovery period, lung fiber burdens of MMVF10a had declined to near

1 control levels, while amosite fiber burdens had remained the same or increased. Hamsters
2 exposed to MMVF10a showed inflammation which regressed in recovery groups, but no
3 pulmonary or pleural fibrosis or neoplasms. Amosite asbestos induced dose-related
4 inflammation and fibrosis by 13 weeks, which progressed until the end of the study. No
5 lung tumors were observed in the asbestos-treated groups, but incidences of
6 mesotheliomas were increased [no statistical comparisons reported]. Data are
7 summarized in Table 4-5.

Table 4-4. Tumor incidences in male rats exposed to glass fibers and asbestos by inhalation

Test animal	Exposure group ^a		Lung fiber burden ^b × 10 ⁵	Tumor incidence (%)				Reference(s)
	(mg/m ³)	WHO fibers/cm ³		Lung adenoma	Lung carcinoma	Total lung tumors	Mesothelioma (%)	
F344 ^c	Controls	0	0	3/123 (2.4)	1/123 (0.8)	4/123 (3.3)	0/123 (0)	Hesterberg <i>et al.</i> 1993 McConnell 1994
	Chrysotile (10)	10,600	28.1 ± 7.8	7/69 (10.1)	6/69 (8.7) ^{[*]d}	13/69 (18.9)*	1/69 (1.4)	
	Crocidolite (10)	1,600	NR	10/106 (9.4)	6/106 (5.7) ^{[*]d}	15/106 (14.2)*	1/106 (0.9)	
	MMVF10 (3)	29	0.24 ± 0.08	0/117 (0)	0/117 (0)	0/117 (0)	0/117 (0)	Hesterberg <i>et al.</i> 1995
	MMVF10 (16)	145	1.85 ± 0.53	1/118 (0.8)	0/118	1/118 (0.8)	0/118 (0)	
	MMVF10 (30)	232	2.88 ± 0.56	6/119 (5.0)	1/119 (0.8)	7/119 (5.9)	0/119 (0)	
	<u>Trend^e</u>							
	one-sided <i>P</i>			[0.041*]	[0.499]	[0.047*]	[No trend]	
	two-sided <i>P</i>			[0.072]	[0.878]	[0.084]	[No trend]	
	MMVF11 (3)	41	0.48 ± 0.11	3/118 (2.5)	1/118 (0.9)	4/118 (3.4)	0/118 (0)	
	MMVF11 (16)	153	2.35 ± 0.63	6/120 (5.0)	3/120 (2.5)	9/120 (7.5)	0/120 (0)	
	MMVF11 (30)	246	5.03 ± 2.9	3/112 (2.7)	0/112	3/112 (2.7)	0/112 (0)	
	<u>Trend^e</u>							
	one-sided <i>P</i>			[0.323]	[0.467]	[0.375]	[No trend]	
two-sided <i>P</i>			[0.647]	[0.912]	[0.753]	[No trend]		
Wistar	Controls	0	0	1/38 (2.6)	1/38 (2.6)	2/38 (5.3)	0/38 (0)	Davis <i>et al.</i> 1996 Cullen <i>et al.</i> 2000
	Amosite (NR)	980	1,230 ± 180	9/42 (21) ^{*c}	7/42 (17) ^{[*]d}	16/42 (38) ^{***}	2/42 (4.8)	
	JM100/475 (NR)	1,100	110 ± 110	4/38 (11)	0/38 (0)	4/38 (11)	0/38 (0)	
	104E (NR)	1,000	830 ± 220	3/43 (7)	7/43 (16) ^{[*]d}	10/43 (23)*	2/43 (4.7)	

* *P* < 0.05 vs. controls; *** *P* < 0.001 vs. controls (Fisher's exact test).

NR = not reported; WHO fibers/cm³ = the number of fibers ≥ 5 μm in length, < 3 μm in diameter, with an aspect ratio ≥ 3:1.

^aNose only exposure in studies with F344 rats and whole-body exposures with Wistar rats.

^bNumber of WHO fibers per mg dry lung at 24 months for F344 rats; total lung fiber burden > 20 μm at 12 months in Wistar rats.

^cWHO fibers in the F344 study were similar to total exposure mass of fibers in fibers/cm³.

^d[Statistics were not reported by the study authors; Fisher's exact test conducted by NTP.]

^e[Cochran-Armitage test conducted by NTP; control group in first line of table included with all data sets.]

1 No lung tumors were observed in groups of hamsters similarly exposed to MMVF33
2 (special-purpose glass fibers prepared by mixing three types of commercially
3 manufactured 475 glass [codes 104, 108B, and 110]) (McConnell *et al.* 1999). Exposure
4 groups included 125 animals each. The unexposed chamber control group included 140
5 animals. Fiber concentrations were comparable in all groups (~250 to 300 WHO
6 fibers/cm³) with two lower exposure groups for amosite. Lung clearance was suppressed
7 in the amosite-exposed groups but not in the MMVF33-exposed group. The number of
8 WHO fibers and fibers > 20 µm in length increased in the lung during the 18-month
9 exposure period but were higher in the mid- and high-dose amosite groups than in the
10 MMVF33 group. After 6 weeks of recovery, lung fiber burdens decreased by about 40%
11 in the MMVF33 group compared with a 21% decrease in the high-dose amosite group.
12 Fiber burdens measured in the diaphragm or thoracic wall were lower in the MMVF33
13 group than in any of the amosite-exposed groups, but were higher than with MMVF10a.
14 [This may be linked to a higher fiber deposition.] A six-hour deposition study showed a
15 greater deposition of MMVF33 compared with MMVF10a. MMVF33 did produce more
16 severe inflammation than MMVF10a and some mild fibrosis that progressed in severity
17 from week 26 to 52 before leveling off. Lung fiber burden with MMVF33 was higher
18 than with MMVF10a. Incidences of mesothelioma in positive controls were 22 of 85 and
19 17 of 87 (mid- and high-dose amosite, respectively) compared with 1 of 83 in the
20 MMVF33 group (Table 4-5). Mesothelial hyperplasia was found in 21.7% of hamsters
21 after exposure to MMVF33 compared with 1.2% in both control and MMVF10a groups.
22 [Differences between MMVF33 compared with MMVF10a (more severe inflammation,
23 some mild fibrosis, one mesothelioma) might be related to the different deposition.
24 Hyperplasia may reflect early signs of cell transformation.]

Table 4-5. Tumor incidences in male hamsters exposed to glass wool, special-purpose fibers and asbestos by inhalation

Test animal	Exposure group		Number of animals	Lung fiber burden ^a × 10 ⁶ (WHO)	Mesothelioma (%)
	(mg/m ³)	WHO fibers/cm ³			
Syrian golden hamsters	Controls	0	83	< 0.01 ± 0.01	0
	Amosite (0.8)	36	83	98 ± 20	3/83 (3.6)
	Amosite (3.7)	165	85	356 ± 99	22/85 (25.9) ^{[**]b}
	Amosite (7)	263	87	612 ± 147	17/87 (19.5) ^{[**]b}
	MMVF10a (30)	339	81	76.7 ± 20.5	0
	MMVF33 (37)	310	83	234 ± 521	1/83 (1.2)

Source: Hesterberg *et al.* 1997, McConnell *et al.* 1999.

^[**] $P < 0.01$ vs. controls (Fisher's exact test performed by NTP).

^a Number of fibers per mg dry lung at 78 weeks; arithmetic mean ± SD.

^b Statistics were not reported by the study authors, but results are significant compared with controls by Fisher's exact test [test performed by NTP].

WHO fibers/cm³ = the number of fibers ≥ 5 μm in length, < 3 μm in diameter, with an aspect ratio ≥ 3:1.

1 4.1.3 Studies in primates

2 Goldstein *et al.* (1983, 1984) compared the effects of inhaled fibrous-glass dust and
3 crocidolite in baboons. Ten male baboons were exposed to 7.5 mg/m³ (1,100 fibers/cm³)
4 of glass fibers (a blend of Johns-Manville sample references C102 and C104) or 15.8
5 mg/m³ crocidolite. Animals were exposed 7 hours per day, 5 days per week for up to 35
6 months. Lung biopsies were taken in two animals after 8-, 18-, and 30-months exposure
7 and after 6-, 8-, and 12-months postexposure. Surviving animals were kept under
8 observation. The dimensions of the glass fibers were log-normally distributed and were
9 similar to the dimensions of the crocidolite fibers. The diameters ranged from about 0.06
10 to 8 μm (mean < 1 μm) and lengths ranged from about 0.8 to 58 μm (mean > 5 μm). Fiber
11 content of lung tissue was much higher in crocidolite-exposed baboons (5.6×10^{10}
12 fibers/g) than in glass fiber-exposed baboons (5.0×10^7 fibers/g). Baboons exposed to
13 fibrous-glass dust developed focal peribronchiolar fibrosis with scant ferruginous body
14 formation, but the lesions were much less extensive than observed in the crocidolite-
15 exposed animals. No neoplasms were observed in either group, but the authors noted the
16 relatively short exposure and observation periods.

17 Mitchell *et al.* (1986) and Moorman *et al.* (1988) reported results from a chronic
18 inhalation study using commercial grade Owens-Corning insulation fiberglass with binder
19 or Tempstran Code 100/475 special-purpose glass fibers without binder (results for

1 studies in F344 rats with the same fibers are reported in Section 4.1.1). Groups of 15 male
2 cynomolgus monkeys were exposed 7 hours/day, 5 days/week for 72 weeks and held until
3 80% mortality. The target concentrations were 15 mg/m³ for the Owens-Corning
4 fiberglass and 5 mg/m³ for the 475 glass. Two exposure groups for each glass fiber type
5 were used. Pulmonary macrophage aggregates and granulomas that contained glass fibers
6 were observed in treatment groups, but no pleural plaques were observed. There was no
7 evidence of fibrosis or neoplastic lesions in the respiratory tract of any treatment group.

8 **4.2 Intraperitoneal administration**

9 Many studies (Cullen *et al.* 2000, Grimm *et al.* 2002, Lambré *et al.* 1998, Miller *et al.*
10 1999b, Pott 1987, 1989, Pott *et al.* 1974, 1976a, Roller *et al.* 1996, 1997) in which fibers
11 were administered by intraperitoneal injection were described by their authors as designed
12 to examine the relationship between fiber characteristics and tumorigenicity. The results
13 for glass fibers reported from those studies are discussed in Section 4.4 and Table 4-9,
14 and results for all fiber types are discussed in Section 5.3.2 and Tables 5-2 through 5-10.
15 Other studies with intraperitoneal injection of glass fibers are reported below.

16 Two of the studies that reported results for inhalation exposure to glass fibers tested the
17 same fibers by intraperitoneal injections (Muhle *et al.* 1987, Pott *et al.* 1987, Smith *et al.*
18 1987). These studies are reviewed in this section, along with a study by Pott *et al.*
19 (1976a), which is reported based on the English abstract [paper published in German],
20 and a study by Pott *et al.* (1984a) that reported results for JM100 and JM104 (several
21 preparations, including some ball milled for 1 to 4 hours) but with limited data on fiber
22 characteristics. Data for JM104/1974 fibers from two separate experiments reported by
23 Pott *et al.* (1987) are also reported in Table 4-6 because the experiments with those fibers
24 did not include any comparison with other glass fibers or vary the fiber characteristics.

25 Most studies included both saline-injected controls and asbestos-exposed groups;
26 however, since high-tumor incidences were observed in glass fiber-exposed groups,
27 tumor incidences for asbestos-treatment groups are not shown in the tables in Section 4,
28 but they are reported in Tables 5-2 through 5-10. The test fibers were administered in 1 to
29 2.5 mL of saline in the studies reported here. In most cases, tumor incidences in asbestos-
30 exposure groups were similar to those reported for glass fiber-treated animals with two

1 notable exceptions. Muhle *et al.* (1987) [Pott *et al.* 1987 reported the same tumor data
2 with an additional dose (2 mg) for JM104/475]] and Smith *et al.* (1987) reported tumor
3 incidences in asbestos-treatment groups that were about 2.5- to 5-fold higher than in glass
4 fiber-treatment groups. Mesotheliomas were the most common tumor type, but some
5 studies reported sarcomas and carcinomas in a few animals. In many cases, doses
6 exceeded one billion fibers. The strain, sex, number of animals, fiber types, dose and
7 dosing schedule, and results are provided in Table 4-6. Animals were held until their
8 death (generally within 1 to 2.5 years), or sacrificed when moribund.

9 Smith *et al.* (1987) injected groups of 25 female Osborne-Mendel rats with JM100 and
10 crocidolite asbestos. Test animals received a single injection of 25 mg and were then held
11 until their death. Abdominal mesothelioma occurred in 32% of the animals injected with
12 JM100 and in 80% of the asbestos group. No tumors occurred in the untreated cage
13 controls or saline controls.

14 The details for the materials and methods used in the Pott *et al.* (1976a) study are limited
15 because the paper was published in German, but the results shown in Table 4-6 are highly
16 significant ($P < 0.001$) for S&S106 fibers (up to 72% tumor incidence) compared with the
17 saline control and for the trend for increasing tumor incidence with dose. The results for
18 MN104 (up to 71% tumor incidence) and MN112 fibers (38% tumor incidence at a single
19 dose) were not reported with concurrent controls, but the tumor incidences were similar to
20 those for S&S106 fibers.

21 Pott *et al.* (1984a) reported results for JM100 and JM104 glass fibers, as well as other
22 synthetic and natural fibers injected intraperitoneally to female Wistar and Sprague-
23 Dawley rats, but the authors described most of the results as either unfinished
24 experiments (data after 15 months) or as possibly having a reduced tumor rate due to an
25 infection in the twenty-first month of the experiment. Due to these limitations and the
26 lack of sufficient information on the materials and methods used [published in German in
27 Pott *et al.* 1976a], the results are not reported in Table 4-6 or 4-9. Results for three groups
28 of Wistar rats unaffected by either of the limitations noted above had tumor incidences for
29 JM104 fibers that decreased as the time of milling (in a ball mill in distilled water)

1 increased. Wistar rats injected with 10 mg of JM104 fibers after 1 hour of milling had a
 2 73% (27/37) incidence of sarcoma or mesothelioma, while a 66% (29/44) incidence was
 3 observed with 2 hours of milling, and 49% (19/39) with 4 hours of milling.

Table 4-6. Tumor incidences in rats treated with glass wool fibers by i.p. injection

Strain (Sex)	Treatment group	Dose		No. doses	Tumor incidence (%) ^a	Reference
		mg	% Fibers > 5 µm long			
Wistar (F)	Saline (1 mL)	0	0	1	2/32 (6.3)	Muhle <i>et al.</i> 1987 Pott <i>et al.</i> 1987
	TiO ₂	10	0	1	0/32 (0)	
	JM104/475	0.5	28%	1	5/30 (16.7) ^[*]	
		2.0		1	8/31 (25.8) ^[*]	
Wistar (F)	TiO ₂	5	0	1	0/47 (0)	Pott <i>et al.</i> 1987
	JM104/1974	5	NR	1	20/45 (44.4) ^[***]	
Wistar (M)	JM104/1974	10	NR	1	13/26 (50) ^b	Pott <i>et al.</i> 1987
Wistar (F)		10	NR	1	18/33 (54.6) ^b	
Osborne-Mendel (F)	Untreated	0	0	0	0/125 (0)	Smith <i>et al.</i> 1987
	Saline (0.5 mL)	0	0	1	0/25 (0)	
	JM100	25	56%	1	8/25 (32) ^[**]	
Wistar (F)	Saline (2 mL)	0	0	4	0/72 (0)	Pott <i>et al.</i> 1976a
	German glass wool (S&S106)	2	0.024	1	1/34 (3)	
		10	0.12	1	4/36 (11) ^[*]	
		25	1.2	4	23/32 (72) ^[***]	
		<u>Trend^e</u>				
	one-sided <i>P</i>				[< 0.001]	
	two-sided <i>P</i>				[< 0.001]	
	MN104 [JM104]	2	NR	1	20/73 (28) ^{b,c}	
		10		1	41/77 (53) ^b	
		25		2	55/77 (71) ^b	
MN112 [JM112]	20	NA	1	14/37 (38) ^b		

* *P* < 0.05, compared with combined saline and TiO₂ control groups; χ^2 -test reported by authors.

[*] *P* < 0.05, [**] *P* < 0.01; [compared with saline control by NTP, Fisher's exact test].

[***] *P* < 0.001; [compared with TiO₂ control by NTP, Fisher's exact test].

NR = not reported.

^a Most tumors were abdominal sarcomas or mesotheliomas. Pott *et al.* (1987) also reported a few carcinomas.

^b No concurrent controls reported by study authors, but results highly significant (*P* < 0.001) compared with other controls in the same paper.

^c The trend for tumor incidence for MN104 fibers was highly significant (*P* < 0.001) compared with the saline control for S&S106 from the same paper.

4 4.3 Other exposure routes

5 Glass fibers also have been tested for carcinogenicity in experimental animals through
 6 several other parenteral exposure routes. These include intratracheal instillation,
 7 intrathoracic implantation, and intrapleural inoculation. All but one of these studies was
 8 conducted in the 1970s and 1980s. Studies were available in rats, hamsters, guinea-pigs,
 9 mice, and rabbits. [Results from these studies provide further support for the hypothesis

1 that fiber dimension and durability are important factors in fiber-induced neoplasms.]
2 Studies in rats are summarized in Section 4.3.1. Section 4.3.2 includes studies in
3 hamsters, guinea-pigs, mice, and rabbits. The data from all studies are summarized in
4 Table 4-7.

5 4.3.1 Rats

6 In addition to the inhalation study reviewed in Section 4.1.1, Gross *et al.* (1970) exposed
7 groups of 15 to 30 rats and 12 hamsters (discussed in Section 4.3.2) to uncoated, phenol-
8 formaldehyde-coated, or starch-binder-coated glass dust by intratracheal injection.
9 Untreated control groups included 20 rats. Fiber dimensions, dosing, and study duration
10 are described in Table 4-7. No differences in pulmonary reaction to coated and uncoated
11 glass dust were noted, and no tumors were observed. Furthermore, no alveolar fibrosis or
12 other significant septal changes in rat lung were reported.

13 Schepers (1974) summarized about three decades of work investigating the comparative
14 pathogenicity of glass fibers derived from a number of sources. Many of these studies
15 used fiberglass plastic dust where the polymerized resin accounted for 60% to 65% of the
16 total material, while only about 25% of the material was glass fibers. The studies with
17 fiberglass plastic dust are not included in this review. However, several intratracheal
18 injection studies of glass wool or fibrous glass in rats, guinea-pigs, and rabbits were
19 included. These studies used 10 to 21 animals in the exposed groups. No tumors were
20 reported after 12 or 20 months, and the average lung reactions were considered mild in
21 rats.

22 Pott *et al.* (1987) treated a group of 34 female Wistar rats with 20 intratracheal
23 instillations of 0.5 mg JM104/475 glass fibers. Treatments were given weekly, and the
24 animals were followed for life. A control group of 40 female rats was treated with saline,
25 and another group was treated with crocidolite. Lung tumors (1 adenoma, 2
26 adenocarcinomas, and 2 squamous-cell carcinomas) occurred in the treatment group but
27 not in the controls. The tumor incidence in the crocidolite group was about 43%, or about
28 three times higher than in the glass-fiber-exposed group. In a similar experiment, 5
29 weekly intratracheal instillations of 2 mg JM475 glass fibers did not produce tumors in
30 female Osborne-Mendel rats (Smith *et al.* 1987).

1 Two studies by Stanton *et al.* (1977, 1981) evaluated synthetic glass fibers of different
2 dimensions implanted intrathoracically on the pleural surface, and these studies are
3 discussed in Section 4.4 with other studies that examined a range of fiber characteristics
4 in relation to tumorigenicity. Some, but not all, fibers induced tumors in these studies.

5 Four intrapleural injection studies in rats were reviewed (Monchaux *et al.* 1981, Wagner
6 *et al.* 1973, 1976, 1984a). No tumors occurred in Wistar rats administered a single
7 injection of 20 mg of JM110 fibers in two experiments; however, 4 of 32 rats injected
8 with 20 mg of JM100 fibers developed mesothelioma (Wagner *et al.* 1976, Wagner *et al.*
9 1973). Because the JM110 fibers were thicker than the JM100 fibers, the number of
10 injected fibers was about 30 million for JM110 compared with 30 billion for JM100
11 (Wagner *et al.* 1976). Wagner *et al.* (1984a) treated groups of 48 Sprague-Dawley rats
12 [sex not specified] by intrapleural injection of resin-coated or uncoated English glass
13 wool and JM100 glass microfiber. Rats received a single injection of 20 mg dispersed in
14 0.5 mL saline, and a control group of 24 rats was injected with saline. Incidences of
15 mesothelioma were 1 of 48 (glass wool group) and 4 of 48 (JM100 group) (Wagner *et al.*
16 1984a). Six (6) of 45 Sprague-Dawley rats given a 20-mg dose of JM104 fibers developed
17 mesothelioma (Monchaux *et al.* 1981). Tumor incidences were generally higher in
18 asbestos-exposed groups in each of these studies and ranged from 12.5% to 66%.

19 4.3.2 *Hamsters, guinea-pigs, mice, and rabbits*

20 Vorwald *et al.* (1951) primarily studied the effects of asbestos in long-term inhalation
21 studies using rats, mice, guinea-pigs, rabbits, cats, and dogs, but one intratracheal
22 injection study included a small group of guinea-pigs (6 to 9 [exact number not specified
23 by authors]) exposed to two injections of 25 mg of glass wool. Most of the fibers were 20
24 to 50 μm in length and were about 3 μm in diameter. Neither lung fibrosis nor tumors
25 were reported after 12 months. [This study did not include positive controls, the number
26 of animals was limited, the fiber diameter was large, and the delay post inoculation was
27 limited to 12 months.]

28 Gross *et al.* (1970) also exposed groups of 12 hamsters to uncoated, phenol-
29 formaldehyde-coated, or starch-binder-coated glass dust by intratracheal injection.
30 Untreated control groups included 20 hamsters. There were no apparent differences in the

1 pulmonary reaction following exposure to coated or uncoated glass dust, and no tumors
2 were observed. A diffuse, acellular, collagenous pleural fibrosis was noted in some
3 hamsters. [This study did not include positive controls, and the number of animals was
4 limited.]

5 No tumors were reported in guinea-pigs following three intratracheal injections of 75 mg
6 of glass wool, or in rabbits following three intratracheal injections of 300 mg of fibrous
7 glass (Schepers 1974). However, the average lung reactions were considered mild to
8 moderately severe in guinea-pigs and mild in rabbits. No tumors were observed after
9 single intrapleural injections of 10 mg of borosilicate fibers of varying diameters and
10 lengths in groups of 25 mice (Davis 1976, as cited in IARC 2002).

11 Kushner and Wright (1976) and Wright and Kushner (1977) treated groups of 30
12 guinea-pigs by intratracheal injection of glass fibers of different dimensions. The number
13 of injections varied from two to six, and the total amount injected varied from 12 to 25
14 mg. Glass fibers were sorted into six groups: short, thin fibers; long, thin fibers; short,
15 very thin fibers; long, very thin fibers; short, thick fibers; and long, thick fibers. The
16 animals were observed for 24 months. No tumors were reported in any of the groups, but
17 the authors noted that the long glass fibers were fibrogenic.

18 Two intratracheal instillation studies of JM104 fibers were conducted in hamsters. Pott *et*
19 *al.* (1984b) and Mohr *et al.* (1984) reported increased incidences of lung carcinoma,
20 mesothelioma, and thoracic sarcoma following eight weekly treatments with 1 mg, while
21 Feron *et al.* (1985) reported no increase in tumors in hamsters receiving 1 mg every 2
22 weeks for one year.

Table 4-7. Carcinogenicity studies of glass wool administered by intrapleural or intratracheal inoculation

Test animal (sex)	Fiber type	Fiber dimensions (μm)		Dose (mg \times no.)	Route	Study duration	Tumor incidence (%) ^a	Reference
		diameter	length					
Rat- strain								
NR (NR)	Uncoated glass dust	1 (mean)	≤ 50	3.5×3 3.5×10	i.t.	24 mo	0/15 (0) 0/30 (0)	Gross <i>et al.</i> 1970
	Phenol-formaldehyde-coated glass dust	1 (mean)	≤ 50	3.5×3 3.5×10	i.t.	24 mo	0/30 (0) 0/30 (0)	
	Starch-binder-coated glass dust	1 (mean)	≤ 50	3.5×3 3.5×10	i.t.	24 mo	0/15 (0) 0/30 (0)	
NR (NR)	Controls	NA	NA	0	i.t.	24 mo	0/56 (0)	Schepers 1974
	Fiber glass	< 2 (20%)	> 20 (51%)	3.5×3		12 mo	0/10 (0)	
	Glass wool	$< 3-8$	20-50	3.5×3		20 mo	0/21 (0)	
Wistar (F)	Saline JM104/475	0	0	$0.3 \text{ mL} \times 20$	i.t.	life	0/40 (0) 5/34 (14.7)	Pott <i>et al.</i> 1987
		< 0.18 (50%)	> 3.2 (50%)	0.5×20				
Osborne-Mendel (F)	JM100	0.45 (mean)	≤ 20 (94%)	2×5	i.t.	life	0/22 (0)	Smith <i>et al.</i> 1987
Wistar (M/F)	JM110	1.5-2.5 (30%)	> 20 (60%)	20×1	i.pl.	life	0/35 (0)	Wagner <i>et al.</i> 1973
Wistar (M/F)	Saline	0	0	$0.4 \text{ mL} \times 1$	i.pl.	life	0/32 (0) 0/32 (0) 4/32 (12.5)	Wagner <i>et al.</i> 1976
	JM110	< 1 (17%)	> 50 (10%)	20×1				
	JM100	< 0.5 (99%)	> 20 (2%)	20×1				
Sprague-Dawley (M)	Saline JM104	0	0	$2 \text{ mL} \times 1$	i.pl.	life	0/32 (0) 6/45 (13.3)	Monchaux <i>et al.</i> 1981
		0.23 (mean)	5.9 (mean)	20×1				
Sprague-Dawley (NR)	Saline Resin-coated Non-coated	0	0	$0.5 \text{ mL} \times 1$	i.pl.	life	0/24 (0) 1/48 (2) 1/47 (2)	Wagner <i>et al.</i> 1984a
		< 1 (85%)	< 5 (70%)	20×1				
		< 1 (85%)	< 5 (57%)	20×1				
Sprague-Dawley (NR)	Saline JM100	0 < 0.6 (95%)	0 < 5 (88%)	$0.5 \text{ mL} \times 1$ 20×1	i.pl.	life	0/48 (0) 4/48 (8.3)	Wagner <i>et al.</i> 1984a

Test animal (sex)	Fiber type	Fiber dimensions (μm)		Dose (mg \times no.)	Route	Study duration	Tumor incidence (%) ^a	Reference
		diameter	length					
Hamster- strain								
NR (NR)	Uncoated glass dust	1 (mean)	≤ 50	3.5×3	i.t.	24 mo	0/12	Gross <i>et al.</i> 1970
	Phenol-formaldehyde-coated glass dust	1 (mean)	≤ 50	3.5×1 1.75×2 3.5×3	i.t.	24 mo	0/12 0/12 0/12	
	Starch-binder-coated glass dust	1 (mean)	≤ 50	3.5×3	i.t.	24 mo	0/12	
Syrian golden (M)	Titanium dioxide (granular dust as control)	0	0	1×8	i.t.	113 wk	2/135 (1.5) ^b 0/135 ^c 0/135 ^d	Pott <i>et al.</i> 1984b
	JM104	< 0.3 (50%)	> 7 (50%)	1×8	i.t.	113 wk	6/136 (4.4) ^b 37/136 (27.2) ^c 5/136 (3.7) ^d	
	JM104	< 0.3 (50%)	< 4.2 (50%)	1×8	i.t.	113 wk	6/138 (4.3) ^b 26/138 (18.8) ^c 6/138 (4.3) ^d	
Syrian golden (M/F)	JM104	< 1 (88%)	< 5 (58%)	1×26 1×26	i.t.	85 wk	0/34 0/30	Feron <i>et al.</i> 1985
Guinea pigs								
Guinea-pigs (NR)	Glass wool	3	20-50	25×2	i.t.	12 mo	0	Vorwald <i>et al.</i> 1951
Guinea-pigs (NR)	Glass fibers	< 0.6 (95%) < 1 (84%) < 0.3 (100%) < 0.3 (99.7%) > 1 (61%) > 1 (78%)	> 10 (92%) < 10 (93%) < 5 (100%) > 10 (50%) < 10 (87%) > 10 (75%)	4×3 12.5×2 12.5×2 2×6 12.5×2 12.5×2	i.t.	24 mo	0/30 0/30 0/30 0/30 0/30 0/30	Kuschner and Wright 1976 Wright and Kuschner 1977
Guinea-pigs (NR)	Controls Glass wool Fiber glass	0 $< 3-8$ < 2 (20%)	0 20-50 20-50	0 75×3 75×3	i.t.	24 mo 12 mo 12 mo	0/150 0/20 0/20	Schepers 1974

Test animal (sex)	Fiber type	Fiber dimensions (µm)		Dose (mg × no.)	Route	Study duration	Tumor incidence (%) ^a	Reference
		diameter	length					
Mouse and rabbit								
BALB/c (NR)	Glass fibers	0.05 (mean)	> 20	10 × 1	i.pl.	≤ 18 mo	0/25	Davis 1976 (cited in IARC 2002)
		0.05 (mean)	< 20	10 × 1			0/25	
		3.5 (mean)	> 20	10 × 1			0/25	
		3.5 (mean)	< 20	10 × 1			0/25	
Rabbits (NR)	Controls	0	0	0	i.t.	24 mo	0/20	Schepers 1974
	Fiberglass	< 2 (20%)	> 20 (51%)	300 × 3		8 mo	0/5	

i.t.= intratracheal instillation, i.pl. = intrapleural injection, NA = not applicable; NR = not reported.

^a Primarily mesothelioma.

^b Incidence of thoracic sarcoma.

^c Incidence of mesothelioma.

^d Incidence of lung carcinoma.

1 **4.4 Studies of fiber characteristics and tumorigenicity for glass wool fibers**

2 A number of studies have been carried out to compare various fiber types in order to
3 determine how characteristics of fiber dimensions and durability/biopersistence relate to
4 tumorigenicity. The data from these studies of glass fibers are reported in this section and
5 in Tables 4-8 and 4-9, while the data for all fiber types, which included natural fibers like
6 asbestos and other synthetic mineral fibers like stone wools, that were tested in these
7 studies are reported in Section 5.2. When the chemical compositions of fibers were
8 reported by the authors, the Z-score or Soluble Components Index (K_{NB}) was calculated
9 using the formula reported in Section 1.4. In addition, data on either the biopersistence of
10 fibers, expressed as the half-life *in vivo*, or the dissolution coefficient (K_{dis}) determined *in*
11 *vitro* and reported in units of ng/cm² per hour are reported in Tables 4-8 and 4-9 when
12 available.

13 The studies by Stanton and Wrench (1972) in the early 1970s compared the
14 tumorigenicity of glass fibers and asbestos applied directly to the lung pleura of rats.
15 Based on incidences of mesotheliomas in the range of 12% to 18% for rats exposed to an
16 especially fine fibrous glass, compared with tumor incidences of 58% to 75% for
17 standard reference samples of amosite, chrysotile, and crocidolite, the authors concluded
18 that long, thin glass fibers were as carcinogenic as similarly sized asbestos.

19 Stanton *et al.* (1977, 1981) extended these studies with experiments testing the
20 tumorigenicity of 22 glass fiber preparations and other fiber types (see description below
21 and in Section 5.2.1). Based on induction of significant numbers of pleural sarcomas by
22 fine, durable fibers of glass and other fiber types, Stanton *et al.* concluded that fiber
23 dimensions and durability were important in determining the tumorigenicity of the
24 material. [The parameters used to define durability in these studies were not reported.]

25 Stanton *et al.* implanted one of either 18 (1977 study) or 22 (1981 study) types of
26 synthetic glass fibers on the pleural surface of the thoracic cavity in groups of 30 to 50
27 female Osborne-Mendel rats. Other experiments conducted with various natural and
28 synthetic fibers are reviewed in Section 5.2.1. A standard dose of 40 mg of fibers was
29 suspended in gelatin and spread over the surface of flat, 45-mg pledgets composed of
30 autoclaved, binder-coated, coarse fibrous glass (designated as glass #17), which also

1 served as a control treatment. [This sample was designated glass #18 in Stanton *et al.*
2 (1981).] The pledgets were implanted on the pleural surface via a left-sided open
3 thoracotomy. Most of the glass fibers were flame-attenuated or rotary-processed
4 borosilicate fibrous glasses and were derived from commercial products as received from
5 the manufacturers. The numbers of animals, fiber characteristics, and results are reported
6 in Table 4-8. The samples are identified according to the numbering reported in Stanton
7 *et al.* (1981), which differed slightly from the numbering reported in Stanton *et al.* (1977)
8 because of the addition of a new glass fiber sample identified as Glass #2 in the later
9 paper. The reported tumor incidences were the same in both studies. Tumor incidences
10 were adjusted for survival based on a life-table analysis. Rats were killed when moribund
11 or at 25 months. Incidences of pleural sarcoma were based on animals surviving the first
12 52 weeks after treatment and ranged from 0% to 85%.

13 The statistical comparisons were different in the two studies, in part because the first
14 study examined only glass fibers, while the later study also included a large number of
15 other natural and synthetic mineral fibers. Stanton *et al.* (1977), which examined only
16 glass fibers, divided their experiments into three groups: high-risk, intermediate-risk, and
17 low-risk groups. Incidences of pleural sarcoma in the low-risk group were significantly
18 different from untreated controls, but the authors considered the data to be insufficient to
19 distinguish differences from the treated control group (Glass #18 in Table 4-8). The low-
20 risk group included experiments 9 to 16 (glasses 10 to 17 in Table 4-8). Tumor
21 incidences in the high-risk group (glasses 1, 3, 4, 5, and 6) and intermediate-risk group
22 (glasses 7, 8, and 9) were significantly higher than in the control group ($P < 0.001$ and P
23 < 0.01 , respectively). Since the authors drew conclusions based on the dimensions
24 (diameter and length) of the fibers, the fibers are listed in Table 4-8 by decreasing
25 percentage of fibers with diameter $> 1.5 \mu\text{m}$ or $> 2.5 \mu\text{m}$.

26 The results for the 18 glass fiber types tested in the 1977 paper were reported again in
27 Stanton *et al.* (1981) together with one additional glass fiber (designated #2 in that paper)
28 and ~50 additional natural and synthetic fibers (see Section 5.3 and Table 5-2). Stanton *et*
29 *al.* (1981) concluded that the best fit for probability of tumor formation was found for
30 fibers $< 0.25 \mu\text{m}$ in diameter and $> 8 \mu\text{m}$ in length. Another correlation was found for

1 fibers with a diameter of up to 1.5 μm and $> 4 \mu\text{m}$ in length. Experimental data from the
2 Stanton *et al.* publications were re-analyzed by other authors. Bertrand and Pezerat
3 (1980) confirmed the dependence with fiber dimensions. Oehlert (1991) also confirmed
4 the hypothesis that the logarithm of the number of fibers $< 0.25 \mu\text{m}$ in diameter and > 8
5 μm in length were predictive of tumor yield. Stanton *et al.* acknowledged that some
6 samples did not fit well, especially some asbestos samples. This point was studied by
7 Wylie *et al.* (1987). These authors first confirmed that the number of index fibers
8 (defined as those $< 0.25 \mu\text{m}$ in diameter and $> 8 \mu\text{m}$ in length) reflected differences in
9 carcinogenic potency, but that the outliers were related to the mathematical calculations
10 when samples contained a low number of fibers of such dimensions (see Section 5.3.2 for
11 further discussion of these studies).

Table 4-8. Carcinogenicity studies of glass wool (40 mg per animal^a) administered by intrathoracic inoculation with results arranged by percent of fibers below the cutoff values for diameter

Fiber Type	Z-score ^b	Diameter, μm	Length, μm	Tumor Incidence (mesothelioma) ^c (%)
Glass 1 (SPF)	[23.4]	< 1.5 (100%)	> 8 (99%)	9/17 (85)
Glass 17 (SPF)	[23.4]	< 1.5 (93%)	> 8 (24%)	0/28 (0)
Glass 4 (SPF)	[23.4]	< 1.5 (67%)	> 8 (99%)	18/29 (71)
Glass 6 (SPF)	[23.4]	< 1.5 (64%)	> 8 (95%)	7/22 (64)
Glass 3 (SPF)	[23.4]	< 1.5 (49%)	> 8 (97%)	20/29 (74)
Glass 12 (Ins)	[42.05]	< 1.5 (34%)	> 8 (84%)	1/25 (7)
Glass 5 (SPF)	[23.4]	< 1.5 (32%)	> 8 (98%)	16/25 (69)
Glass 8 (SPF)	[23.4]	< 1.5 (25%)	> 8 (76%)	3/26 (19)
Glass 9 (NR)	NR	< 1.5 (19%)	> 8 (95%)	2/28 (14)
Glass 16 (NR)	NR	< 1.5 (16%)	> 8 (62%)	1/29 (5)
Glass 10 (SPF)	[23.4]	< 1.5 (14%)	> 8 (49%)	2/27 (8)
Glass 7 (SPF)	[23.4]	< 1.5 (13%)	> 8 (88%)	5/28 (21)
Glass 13 (SPF)	[23.4]	< 1.5 (4%)	> 8 (60%)	1/27 (6)
Glass 2 (NR)	NR	NR	NR	12/31 (77)
Glass 18 ^c (Ins)	[23.5]	> 2.5 (100%)	> 64 (100%)	0/115 (0)
Glass 11 (SPF)	[23.4]	> 2.5 (96%)	> 8 (14%)	1/27 (8)
Glass 15 (Ins)	[23.5]	> 2.5 (98%)	> 8 (96%)	1/24 (6)
Glass 14 (pyrex)	[29.4]	> 2.5 (98%)	> 8 (90%)	1/25 (6)

Source: Stanton *et al.* 1977, 1981.

Ins = insulation glass wool; NR = not reported; SPF = special-purpose fiber.

^aNumber of fibers administered not reported; no data reported for biopersistence or dissolution rate.

^bZ-score calculated from glass composition reported by authors (see Section 1 for formula).

^cAdjusted for survival by life-table analysis. Animals were followed for up to two years, and tumor incidences were based on animals surviving at least one year.

^eGlass 18 served as the control group and was the vehicle for the implants.

1 Following the studies by Stanton and co-workers, most investigators studying the
2 relationship between fiber characteristics (diameter, length, and durability or
3 biopersistence) have tested fibers by intraperitoneal injection. The authors of these
4 studies generally agreed with the concept put forward by Stanton and co-workers that
5 carcinogenicity is related to fiber dimensions and biopersistence, but the authors'
6 conclusions are discussed further below and in Section 5.2.2. The results of the studies
7 with glass fibers are reported in Table 4-9.

8 Pott *et al.* (1974) investigated the tumorigenic effects of various fibrous dusts, including
9 sodium-calcium borosilicate glass fibers, in Wistar rats. About 73% of the fibers were < 5
10 μm in length and the average diameter was about 0.5 μm . A group of 40 rats [sex not
11 specified] was given four weekly injections of 25 mg of glass fibers. The control group
12 received four injections of saline. No tumors occurred in the control group, but more than
13 half of the treatment group (23/40) developed mesotheliomas. Based on their results the
14 authors suggested that fibers less than 10 μm in length could still be carcinogenic, and
15 similarly, they proposed that carcinogenicity could not be limited to fibers with diameter
16 less than 0.5 μm .

17 Pott *et al.* (1976a) investigated the carcinogenicity of a number of fibrous dusts in groups
18 of female Wistar rats. [The paper was published in German with an English abstract.]
19 Rats were administered single injections of 2 or 10 mg of S&S106 glass fibers (59%
20 fibers < 3 μm long) or MN104 [identified as JM104 by IARC 2002] (mean fiber
21 dimensions 10 $\mu\text{m} \times 0.2 \mu\text{m}$). [The S&S 106 glass fibers were identified as German glass
22 wool by IARC 2002 and reported in a section with insulation glass wools; however, the
23 source of these fibers was the German company, Schleicher and Schuell, of Dassell,
24 Germany, which is now part of the Whatman Group and manufactures glass fibers for
25 filtration (i.e., special-purpose fibers). No other information on the characteristics of
26 these fibers was identified.] Other groups were treated with four weekly injections of 25
27 mg of glass wool, two weekly injections of 25 mg of MN104, or a single injection of 20
28 mg of MN112 [identified as JM112 by IARC 2002] (mean fiber dimensions 30 $\mu\text{m} \times 1$
29 μm). In addition, several groups were treated with various doses of chrysotile asbestos.
30 Hamsters were administered single injections of 2 or 10 mg of glass wool. The animals

1 were held until natural death. Dose-dependent increases in incidences of mesothelioma
2 were reported, ranging from 3% to 72% in glass wool treatment groups, 27% to 71% in
3 MN104 treatment groups, and 38% in the MN112 group. Other tumor types also were
4 reported. Spindle-cell sarcoma was the most common tumor type, occurring in most
5 treatment groups at 4% to 8% incidence. Tumor incidences in asbestos-treated groups
6 ranged from about 16% to 81%. No tumors were reported in 72 saline-treated rats. [The
7 English abstract reported that i.p. injection of fibrous dusts also induced mesothelioma in
8 mice, but not in Syrian golden hamsters or guinea-pigs. However, no data were presented
9 for these species.]

10 Pott *et al.* (1984a) tested some of the same fibers as in their previous publications, but
11 they also injected JM100 and JM104 glass fibers into female Wistar or Sprague-Dawley
12 rats. The percentage of either Wistar or Sprague-Dawley rats that developed abdominal
13 tumors after i.p. injection of JM104 glass fibers decreased after pretreatment of the fibers
14 for 2 or 24 hours with 1.4 N NaOH, which resulted in loss of 1.7% to 6.8% of the starting
15 weight of the fibers. Pretreatment with 1.4 N HCl for 24 hours, which resulted in the loss
16 of approximately one third of the starting weight of the fibers, almost totally eliminated
17 tumor development in either strain of rats followed for more than 450 days after injection
18 (see Figure 4-1). The fiber dimensions were affected only slightly by the pretreatments,
19 and the authors reported that the loss of fiber weight was not associated with any
20 discernible corrosion of the fibers examined by scanning electron microscopy. (The
21 authors noted that two different batches of JM104 fibers differed in the amount of weight
22 lost after treatment with hydrochloric acid, which led them to conclude that the two
23 samples must have had different chemical compositions.) Pott *et al.* did propose that the
24 considerable reduction in carcinogenicity with HCl pretreatment might have been due to
25 alterations in the rate of dissolution or disintegration of the fibers or their migration
26 within tissues, but they did not consider these hypotheses as proven by their data.

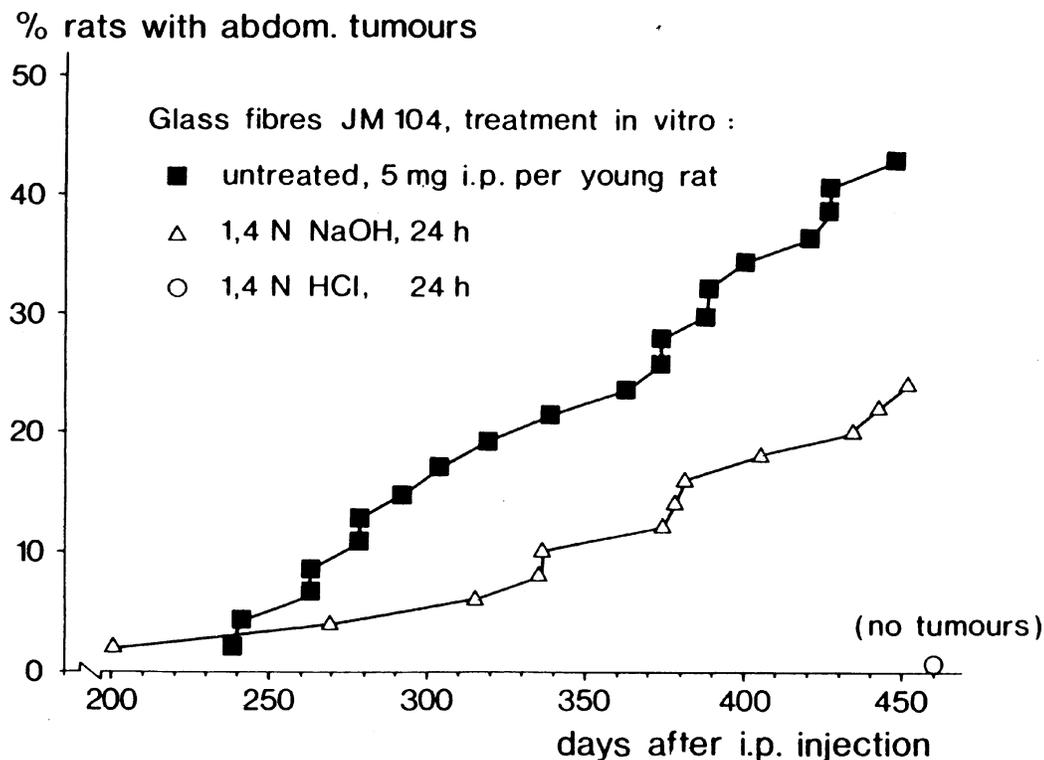


Figure 4-1. Effects of fiber pretreatment with sodium hydroxide (NaOH) or hydrochloric acid (HCl) on tumorigenicity

Source: Pott *et al.* 1984a, used with permission.

1 A series of other experiments by Pott and co-workers (Muhle *et al.* 1987, Pott 1989, Pott
 2 *et al.* 1984a, 1987) was conducted specifically to investigate the relationship of fiber
 3 dimensions and durability with carcinogenic potency. These studies examined the
 4 carcinogenicity of JM100 and JM104 microfibers as well as several other types of
 5 mineral fibers, including asbestos. In the first study, groups of 37 to 45 female Wistar rats
 6 were given single i.p. injections of 2 mg of JM100 or JM104 microfibers (Pott *et al.*
 7 1984a). Other groups received 10 mg of JM104. Two batches of JM100 fibers were used
 8 that had slightly different size distributions. Several batches of JM104 fibers that were
 9 used were subjected to 1 to 4 hours of milling in a ball mill before use. The authors
 10 reported incidences of mesothelioma and sarcoma combined. JM100 fibers induced a low
 11 incidence of tumors (5%). The authors noted that these fibers were relatively short (90%
 12 were < 7.3 μm in one batch and < 3.1 μm in the other batch). Tumor incidences were
 13 higher in the JM104-treatment groups, presumably due to longer fibers. The lowest tumor

1 incidence in rats treated with JM104 (9%) occurred with shorter and thicker fibers
2 relative to the other JM104 groups. The authors also noted in a footnote to one table that
3 the tumor incidence could have been reduced in this group due to an infection at 21
4 months, but no other details were provided. Subsequent studies with JM104 fibers in
5 male and female Wistar rats and female Sprague-Dawley rats resulted in tumor
6 incidences of about 17% to more than 80%. Tumor incidences in the saline controls
7 ranged from about 2% to 6%. All abdominal tumors (including mesothelioma, sarcoma,
8 and carcinoma) were combined; however, very few carcinomas occurred. The authors
9 noted that the three tumor types could not always be differentiated.

10 Pott *et al.* (1991) conducted a comparative carcinogenicity study of some experimental
11 fibers having a relatively low biodurability (B-1 and B-2) and fibers having greater
12 biodurability (B-3 and M-475 code 104). The mean half-lives were 38 days for B-2 glass
13 wool, 107 days for B-1 glass wool, and 238 days for B-3 glass wool. [No half-life was
14 reported for M-475 fibers.] Female Wistar rats received one to three injections of
15 experimental fibers (B-1, B-2, and B-3) at the doses and numbers of fibers shown in
16 Table 4-9, or a single injection of 2 mg of M-475. The median diameters of the fibers
17 were 0.14 μm (M-475), 0.35 μm (B-3), 0.5 μm (B-2), and 1.5 μm (B-1). Both the dose
18 and length of the fibers were varied, with fibers designated either as K (kurz, German for
19 short), M (medium), or L (lange, German for long). The Z-scores calculated for the fibers
20 were lowest for B-3 fibers (20.7) and highest for B-1 and B-2 fibers (35.8), which had the
21 same chemical composition (see Section 1, Table 1-4). The authors concluded that a
22 carcinogenic effect could be detected only in groups injected with durable glass fibers (B-
23 3 or M-475), and that slightly durable glass fibers (B-1 and B-2) did not induce a
24 carcinogenic effect at the doses and fiber sizes tested, which included up to 5.80×10^9 B-
25 2 fibers with median length of 6 μm and median diameter of 0.51 μm . [The most
26 carcinogenic B-3 fibers were also the thinnest.]

27 Roller *et al.* (1996) conducted a study designed to examine the dose-response relationship
28 for fiber types of different dimensions and *in vivo* durabilities. Incidences of
29 mesothelioma ranged from 3% to 70% for glass fibers, while incidences of mesothelioma
30 in asbestos-treated groups ranged from 23% to 80%. These studies investigated several

1 types of SVFs, including samples from at least four commercial insulation wools, and an
2 experimental glass fiber type (B-01) of low biodurability (mean $T_{1/2} = 32$ days). Each of
3 these studies followed the same general design. Groups of at least 32 Wistar rats (usually
4 female) were given single or multiple i.p. injections of $\sim 10^7$ to $> 10^{10}$ fibers (length > 5
5 μm) and were observed for 30 months. Results are reported in Table 4-9, and discussed
6 below.

7 The relationships between fiber dimensions and tumorigenicity were discussed in Roller
8 *et al.* (1997). The fibers were divided into groups of relatively long, thick fibers (aspect
9 ratio $> 5:1$, median length 8–17 μm , median diameter 0.7–1.2 μm) and short, thin fibers
10 (aspect ratio $> 5:1$, median length 2–4 μm , median diameter 0.2–0.5 μm). The long, thick
11 fibers included the following glass fiber types: B-09-0.9, B-09-2.0, B-20-2.0, and
12 MMVF11. The short, thin fibers included the following glass fiber types: B-09-0.6, B-20-
13 0.6 [reported as B-0.9-0.6 in Table #1 in Roller *et al.* (1997), but the doses matched the
14 results reported for fiber type B-20-0.6 in Table #4 in Roller *et al.* (1996)] and M-753-
15 105. The overall conclusion by Roller *et al.* (1997) was that the mechanism responsible
16 for mesotheliomas in their experimental system was specific to the fibrous shape of the
17 particles administered based on parallelism of the probit lines calculated for each fiber
18 type (see Section 5.3.1 and Figure 5-3).

19 Lambré *et al.* (1998) evaluated the carcinogenic potential of two glass wools (Fiber A
20 and Fiber C) described as sodium-modified borosilicates (see Tables 1-4 and 4-9). The
21 samples had been specially manufactured and processed to produce fibers in the size
22 range with median diameter less than 1 μm and median length between 10 and 15 μm .
23 Fiber durability (K_{dis}) was 129 ng/cm^2 per hour for Fiber A and 309 ng/cm^2 per hour for
24 Fiber C. Both fiber types had a Z-score of 26.7. These fibers were administered to groups
25 of 51 female Wistar rats by i.p. injection (one or two injections) at 0.7, 2.1, 7, or 17.5
26 mg/dose . Crocidolite (0.005, 0.05, or 0.5 mg) was used as a positive control. The study
27 was stopped at week 130 when the survival rate had reached 20% in the control groups.
28 Survival was the same in groups injected with glass fibers as in the negative control
29 groups. Adhesions involving various abdominal organs were noted in the treatment
30 groups. Fibrosis increased with dose, and a few mesotheliomas occurred in the groups

1 treated with Fiber A or Fiber C. Incidences of mesothelioma in asbestos-treated groups
2 ranged from 7.8% to 39.2%. (Tumors were induced by several stone wools tested in the
3 same study [see Section 5.3.1]). The authors concluded that the glass fibers tested in this
4 study did not show a carcinogenic potential at the tested doses, and their general
5 conclusion was that fibers with a high dissolution rate *in vitro* at pH 7.4 along with low
6 biopersistence for fibers with length > 20 µm tended to have a low carcinogenic potency
7 in the i.p. assay. [This study was initiated when the recommended dose was 0.5×10^9
8 critical fibers (defined by length > 5 µm, diameter < 2 µm, and an aspect ratio (L/D) > 5);
9 however, this recommendation was subsequently increased to 5×10^9 critical fibers (see
10 Grimm *et al.* 2002).]

11 Miller *et al.* (1999b) and Cullen *et al.* (2000) investigated the carcinogenic effects of a
12 number of SVFs, including MMVF10 glass wool and two special-purpose glass
13 microfibers (JM100 and 104E) (see Table 4-9). Durability (K_{dis}) was 122.4 ng/cm² per
14 hour for MMVF10 and 9.1 ng/cm² per hour for JM100. The i.p. dose was selected as a
15 mass sufficient to contain 10^9 fibers > 5 µm in length. Treatment groups consisted of 18
16 to 24 male Wistar rats. Positive controls were treated with 6.1 mg of amosite asbestos.
17 These studies did not include negative controls. Animals were maintained until they
18 showed signs of debilitation. Miller *et al.* (1999b) reported that carcinogenicity was
19 linked to the number of injected fibers > 20 µm in length and the biopersistence of fibers
20 > 5 µm in length. The incidence of mesotheliomas was 59% in the glass wool group, 33%
21 in the JM100 group, 88% in the 104E group, and 88% in the asbestos group. Although
22 tumor incidences were similar for the 104E and asbestos groups, tumors appeared earlier
23 in the 104E group. In particular, Cullen *et al.* (2000) speculated that differences in
24 surface properties (i.e., selective leaching of some glass components) might also be
25 important for explaining the greater effect of 104E glass compared with 100/475 fibers.

26 Adachi *et al.* (2001) administered glass wool or micro glass fibers to groups of female
27 F344 rats by i.p. injection (10 to 20 mg) and observed the animals for 2 years. Chrysotile
28 asbestos and several SVFs were included in this study. No tumors were reported for the
29 groups exposed to glass wool or micro glass fiber, but very few details were provided,
30 and this study is not included in Table 4-9.

1 In the most recent study, Grimm *et al.* (2002) investigated the carcinogenic potential of
2 three newly developed biosoluble insulation glass wool fibers (designated M, P, and V)
3 and compared these with a previously developed soluble B glass fiber (reported by the
4 authors as non-carcinogenic by the German TRGS 905 fiber regulations) (see Table 4-9).
5 The dissolution coefficients (K_{dis}) for the fibers were 580 ng/cm² per hour for B, 103.7
6 ng/cm² per hour for M, 610 ng/cm² per hour for P, and 450 ng/cm² per hour for V.
7 Calculated Z-scores are 34.42 for B fibers, 30.04 for M, 45.45 for P, and 26.35 for V.
8 Prior to administration, the fibers were processed to reduce the amount of non-WHO
9 fibers and nonfibrous particles. Groups of 50 to 53 female Wistar rats were given 2, 8, or
10 20 i.p. injections of the various glass fibers. Crocidolite (0.5 or 5 mg) was used as a
11 positive control. The study was terminated after 123 weeks. Fiber M did not show a
12 carcinogenic response, while Fibers P and V showed a slight carcinogenic response
13 similar to that for B fibers. The high doses of fibers B (17%), P (15%), and V (27%)
14 significantly increased tumor levels [statistical test and level of significance not reported
15 by the study authors]. [However, according to Fisher's exact test, *P* values for the high-
16 dose were 0.0016 for B fibers, 0.003 for P, and < 0.001 for V (see Table 4-9). Hence,
17 fiber B cannot be considered as non-carcinogenic in this study.] Incidences of
18 mesotheliomas in the asbestos groups were about 53% to 88%.

Table 4-9. Tumor incidences in rats treated with glass wool fibers by i.p. injection

Strain (Sex)	Treatment group	Biopersistence, T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diam. (median) µm	Length (median) µm	Dose		No. doses	Tumor incidence (%) ^a	Reference	
						mg	Fibers × 10 ⁹ or % > 5 µm long				
Wistar (NR)	Saline (2 mL)	–	–	–	–	0	0	4	0/80 (0)	Pott <i>et al.</i> 1974 (see Table 5-3)	
	Glass fiber	NA	NA	0.5 (avg.)	72.6% < 5	25	~27%	4	23/40 (57.5) ^[***]		
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	5	2/102 (2)	Pott <i>et al.</i> 1989 (see Table 5-5)	
	JM104	NA	NA	0.15	2.6	1	0.68	5	34/53 (64) ^[***]		
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	5	2/50 (4)	Pott <i>et al.</i> 1991 ^c (see Table 5-6)	
	B-1K	107	[35.8]	1.06	7.4	20	0.24	3	3/46 (7)		
	B-1K	(98–119)		1.06	7.4	50	0.60	3	1/32 (3)		
	B-1M			1.68	10.7	20	0.05	1	1/48 (2)		
	B-1M			1.68	10.7	20	0.16	3	1/46 (2)		
	B-1ML			1.19	11.0	50	0.51	2	1/39 (2)		
	B-1L			1.40	17.8	20	0.04	1	1/48 (2)		
	B-1L			1.40	17.8	20	0.11	3	5/46 (11)		
	B-2K	38	[35.8]	0.49	4.2	6.7	0.29	1	0/48 (0)		
	B-2K	(35–41)		0.49	4.2	20	0.86	1	0/46 (0)		
	B-2L			0.51	6.0	6.7	0.39	1	0/45 (0)		
	B-2L			0.51	6.0	20	1.16	1	2/44 (5)		
	B-2L			0.51	6.0	50	5.8	2	1/35 (3)		
			<u>B-2L Trend^c</u> one-sided <i>P</i> two-sided <i>P</i>								[0.44] [0.94]
	B-3K	238	[20.7]	0.37	3.3	6.7	0.38	1	10/48 (21) ^[**]		
	B-3K	(183–340)		0.37	3.3	20	1.14	1	30/47 (64) ^[***]		
B-3L			0.34	5.6	6.7	0.15	1	19/48 (40) ^[***]			
B-3L			0.34	5.6	20	0.46	1	31/47 (66) ^[***]			
JM104	NR	[21.0]	0.40	10.60	2	0.32	1	8/48 (17) ^[*]			

Strain (Sex)	Treatment group	Bioper-sistence, T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%) ^a	Reference
						mg	Fibers × 10 ⁹ or % > 5 μm long			
Wistar (F)	Saline (2 mL) MMVF11	–	–	–	–	0	0	3	0/38 (0)	Roller <i>et al.</i> 1996, 1997 (see Table 5-7)
		199 (172–235)	[27.1]	0.77	14.6	35	0.4	2	12/40 (30) ^[***]	
						30	1.0	6	16/23 (70) ^[***]	
	Saline (2 mL) M 753	–	–	–	–	0	0	3	0/38 (0)	
		NA	[24.8]	0.22	~3.3	17	1	1	30/40 (75) ^[***]	
						50	2.9	1	36/40 (90) ^[***]	
Wistar (F)	Untreated Saline (2 mL) B-01-0.9	–	–	–	–	0	0	0	0/37 (0)	
		–	–	–	–	0	0	20	0/93 (0)	
		32 (26–45)	[35.8]	~0.7	9.60	25	2.5	5	3/39 (8) ^[*]	
						25	5.0	10	4/37 (11) ^[**]	
						25	10	20	3/36 (8) ^[*]	
								[0.019] [0.024]		
Wistar (M)	Saline (2 mL) B-01-0.9	–	–	–	–	0	0	0	1/69 (1)	
		32 (26–45)	[35.8]	~0.7	9.60	25	10	20	10/48 (21) ^[***]	
						25	20	40	33/50 (66) ^[***]	
Wistar (F)	Saline (2 mL) B-09-0.6	–	–	–	–	0	0	3	0/38 (0)	
		NA	[26.7]			50	2.0	2	1/40 (3)	
						50	6.1	6	4/39 (10)	
	Saline (2 mL) B-09-2.0	–	–	–	–	0	0	3	0/38 (0)	
		NA	[26.7]	0.49	3.3	50	1.1	3	9/40 (23) ^[**]	
				50	3.2	9	21/40 (53) ^[***]			

Strain (Sex)	Treatment group	Bioper-sistence, T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%) ^a	Reference
						mg	Fibers × 10 ⁹ or % > 5 μm long			
Wistar (F)	Saline	–	–	–	–	0	0	0	0/102 (0)	Lambré <i>et al.</i> 1998 (see Table 5-8)
	Fiber A	129 (K _{dis}) ^d	[26.7]	0.70	24.6	0.7	0.009	1	2/51 (4)	
						2.1	0.027	1	0/51 (0)	
						7.0	0.092	1	0/51 (0)	
						17.5	0.460	2	1/51 (2)	
									[0.31]	
									[0.73]	
Wistar (F)	Saline	–	–	–	–	0	0	0	0/102 (0)	
	Fiber C	309 (K _{dis})	[26.74]	0.69	27.2	0.7	0.013	1	1/51 (2)	
						2.1	0.038	1	1/51 (2)	
						7.0	0.126	1	0/51 (0)	
						17.5	0.630	2	0/51 (0)	
									[0.46]	
									[0.72]	
Wistar (M)	MMVF10	122.4 (K _{dis})	NA	NA	> 5	144	0.66	1	13/22 (59) ^b	Miller <i>et al.</i> 1999b (see Table 5-9) ^f
	JM100/475	9.1 (K _{dis})	[22.9]	NA	> 5	8.3	1.87	1	8/24 (33) ^b	
Wistar (M)	104E	NA	NA	NA	NA	12.6	~1	1	21/24 (88) ^b	Cullen <i>et al.</i> 2000 (see Table 5-9)

Strain (Sex)	Treatment group	Bioper-sistence, T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%) ^a	Reference		
						mg	Fibers × 10 ⁹ or % > 5 μm long					
Wistar (F)	Untreated	–	–	–	–	0	0	0	0/51 (0)	Grimm <i>et al.</i> 2002 (see Table 5-10)		
	Saline (2.5 mL)	–	–	–	–	0	0	20	0/51 (0)			
	B glass	580 (K _{dis})	[34.42]	0.52	8.90	216	2	8	3/51 (2)			
						541	5	20	9/53 (17) ^[**]			
	M glass	103.7 (K _{dis})	[30.04]	0.41	7.70	41	0.5	2	0/50 (0)			
						164	2	8	0/51 (0)			
						410	5	20	0/52 (0)			
	P glass	610 (K _{dis})	[45.45]	0.40	9.60	51	0.5	2	0/51 (0)			
						205	2	8	4/51 (8)			
						512	5	20	8/52 (15) ^[**]			
	<u>P glass Trend^e</u>											
	one-sided <i>P</i>										[< 0.001]	
	two-sided <i>P</i>										[< 0.001]	
V glass	450 (K _{dis})	[26.36]	0.80	9.90	72	0.5	2	2/51 (4)				
					290	2	8	1/51 (2)				
					724	5	20	14/51 (27) ^[***]				
<u>V glass Trend^e</u>												
one-sided <i>P</i>									[< 0.001]			
two-sided <i>P</i>									[< 0.001]			

[*] *P* < 0.05; [**] *P* < 0.01; [***] *P* < 0.001; [compared with controls by NTP, Fisher's exact test].

NR = not reported; Z-score = sum of the percent composition of alkali and alkaline earth oxides (Na₂O + K₂O + CaO + MgO + BaO) (see Section 1.3.1 and Table 1-4) [calculated by NTP].

^a Most tumors were abdominal mesotheliomas or carcinomas. Some studies (Pott *et al.* 1976a, 1984a, 1987, 1989, 1991) also reported a few carcinomas.

^b No concurrent controls.

^c B-1 and B-2 are experimental low-durability glass wool; B-3 is an experimental durable glass fiber. K, M, and L designate short, medium, and long fiber ranges, respectively.

^d K_{dis} = dissolution coefficient *in vitro*, reported in units of ng/cm² per hour.

^e [Cochran-Armitage test performed by NTP.]

^f Data also reported by Davis *et al.* (1996) and Cullen *et al.* (2000).

1 **4.5 Routes of exposure**

2 Three primary test models have been used to evaluate the toxicity and carcinogenicity of
3 fibers in rodents: inhalation exposure, intratracheal instillation of fiber suspensions, and
4 direct exposure of the pleura or peritoneum by injection of fiber suspensions into the
5 thoracic or abdominal cavity (see Sections 4.1, 4.2, and 4.3). IARC (2002) acknowledged
6 that “there is no general agreement on which of these routes of administration best
7 predicts human cancer risk.” However, the available data demonstrate that chronic i.p.
8 injection studies and inhalation toxicity studies provide the same relative ranking of fiber
9 pathogenic potential (Bernstein 2001a,b, 2007a). This section discusses interspecies
10 comparisons between rats and humans, and the different types of animal models used to
11 test for carcinogenicity.

12 *4.5.1 Interspecies comparison*

13 There is debate on whether humans are more sensitive to fiber carcinogenicity (from
14 inhalation exposure) than rats (Maxim and McConnell 2001, Muhle and Pott 2000, Roller
15 and Pott 1998). This debate stems from evaluation of the body of literature on asbestos.
16 Various investigators have compared the sensitivity of humans and rats to asbestos-
17 induced carcinogenicity and have arrived at different conclusions. Muhle and Pott (2000)
18 and Roller and Pott (1998) compared cancer risks for humans using the epidemiologic
19 data (primarily from Health Effect Institute-Asbestos Research and Doll and Peto (1985);
20 data from U.S. EPA and U.S. OSHA provide a similar risk estimate) and animals using
21 data on asbestos inhalation studies. They concluded that rats required more than 100
22 times higher fiber concentrations to match the lung cancer risk (Figure 4-2) of asbestos
23 workers and 1,000 times higher to match the mesothelioma risk. In a later publication
24 (Wardenbach *et al.* 2005), these authors created a scatterplot of the tumor response in rat
25 inhalation studies from several studies and human and epidemiological data from
26 multiple studies (in response to criticism for using a single point, see below) for
27 amphibole and chrysotile asbestos. According to the authors, this analysis still showed a
28 greater sensitivity for humans compared with rats for both amphibole asbestos and
29 chrysotile asbestos (when compared with textile studies, which were considered by the
30 authors to have the purest asbestos exposure). They did not think that the shorter
31 exposure duration in the animal studies should be taken into account when comparing

1 sensitivities since comparisons should be based on lifespan rather than absolute time
 2 units. These authors concluded that the rat inhalation model is not sufficiently sensitive to
 3 show a carcinogenic response for fibers.

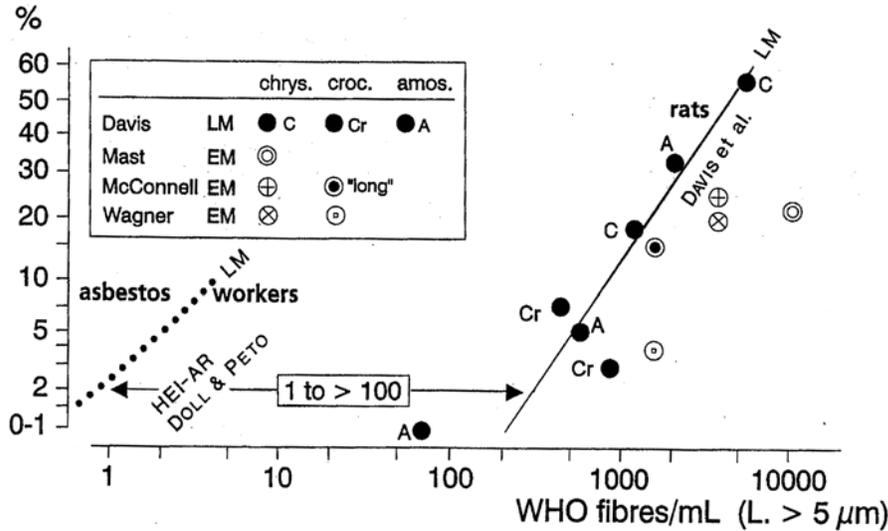


Figure 4-2. Tumor incidence for epidemiologic studies (humans) and chronic inhalation studies (rats) for exposure to asbestos.

Source: Muhle and Pott (2000), used with permission.

Dotted curve on the left-hand side = increasing tumor risk from asbestos fibers for workers (excluding mining and milling) after 25-years occupational exposure when the fiber concentration increases from 1 to 5 fibers per mL (Doll and Peto 1985, HEI-AR 1991). Measurement points on the right-hand side = association between much higher fiber concentrations in the air of chronic inhalation studies with rats and tumor response. Exposure in the majority of the experiments: 35 hours/week for one year. Data of Davis *et al.* (1986a, 1978), Davis and Jones (1988), Mast *et al.* (1995a, 1995b), McConnell *et al.* (1994, 1984), Wagner *et al.* (1984b, 1985). The fiber concentration in the workplace atmosphere and in the inhalation chambers of Davis and co-workers are related to light microscopical (LM) measurements; electron microscopy (EM) has been used in the other inhalation experiments. The regression line has been calculated from the results of Davis *et al.* (black dots).

4 In contrast to this conclusion, Maxim and McConnell (2001) conducted an interspecies
 5 comparison of the toxicity of asbestos and SVF and concluded that “there is no reason to
 6 conclude that humans are more sensitive to fibers than rats with respect to the
 7 development of lung cancer.” They stated that a comparison of tumor data from several
 8 animal studies with only one estimate of potency in humans could be misleading, given
 9 that potency estimates in human epidemiologic studies vary substantially, and that some
 10 of the apparent differences in sensitivity might be explained by the synergistic effects of

1 asbestos exposure and smoking. They also thought exposure duration should be
2 considered when conducting interspecies analyses. They cited an analysis conducted by
3 Rowe and Springer (1986) that used data from 5 epidemiologic studies and animal data
4 from one publication (Wagner *et al.* 1974) in an analysis that included exposure duration
5 (working lifetime of 45 years with 8 hours per day and 250 days per year). This analysis
6 found that risks estimated by the animal study were within the range of the risk estimates
7 from the human studies. [Wardenbach *et al.* criticized the use of only the Wagner data in
8 this analysis since the study provided mass concentrations rather than fiber number, and
9 in general the high tumor incidences in this study have not been replicated in other
10 studies in experimental animals.]

11 Maxim and McConnell (2001) also discussed factors related to dosimetry (exposure and
12 lung burden) and fiber toxicity and concluded that the rat is preferable as a model for
13 lung cancer. In addition to the points discussed above, they drew the following
14 conclusions:

- 15 1. Deposition and clearance: Modeling studies that normalize for lung weight show
16 that the relative deposition of SVFs (number of fibers per unit time) in humans is
17 smaller than that for rats, and that fiber clearance (based on models and data using
18 refractory ceramic fiber) is faster in rats than humans. The authors also pointed
19 out that clearance can be reduced by high particle overload, which has been
20 demonstrated in rats.
- 21 2. The sensitivities of human and rodent cells appear to have comparable sensitivity
22 with regard to fiber-induced cytotoxicity, production of inflammatory components
23 (i.e., cytokines), transformation, and proliferation.
- 24 3. The available data suggest that lung fiber burdens associated with fibrosis are
25 similar in rats and humans, although exact comparisons are limited by the paucity
26 of information on the [asbestos] fibers' length, diameter, and distribution in the
27 lung.
- 28 4. Humans and rats are equally sensitive to development of fiber-induced lung
29 cancer based on studies with asbestos and refractory ceramic fibers (see above).

1 5. Lifespan of animals: The authors stated that the rate of dissolution of fibers is
2 similar in rats and humans, and since humans live longer, the rat model might not
3 take into account the effects of clearance.

4 4.5.2 *Animal models*

5 *Inhalation studies*

6 In principle, the most relevant route of administration used in animal studies is the route
7 that mimics human exposure. Inhalation is the primary route of exposure to fibers;
8 however, inhalation experiments with fibers present some unique challenges. These
9 include sample preparation, size selection, and aerosol generation methods; determination
10 of the MTD; whole-body or nose-only exposure; differences in the respiratory tract and
11 respiration in rodents and humans; differences in respirable fiber dimensions, deposition,
12 clearance, and retention in rodents and humans; selecting the best animal model; and
13 sensitivity and potency issues. All of these are relevant factors for interpreting results
14 from the available inhalation studies (Oberdörster 1996).

15 The primary advantages of fiber inhalation studies include use of a natural route of
16 exposure: lung defenses are not bypassed, and lung biopersistence and toxicity and
17 mechanisms for lung tumor induction can be examined. The disadvantages are that
18 inhalation studies are complex, time-consuming, costly, and may lack sufficient
19 sensitivity for detecting fiber-induced cancers under experimental conditions.
20 Furthermore, there is no general consensus on which animal species is (are) best for
21 predicting effects in humans (Oberdörster 1996). Although the rat model is the most
22 common, there is some evidence that the hamster might be more appropriate for detecting
23 mesotheliomas (Kane 1996a).

24 A number of problems with the early inhalation studies (generally those conducted prior
25 to 1988) were identified by IARC (2002) (see Section 4.1 and Table 4-3), but these
26 problems were generally addressed in later studies. Nevertheless, several questions
27 remain regarding respirability, dosing, and sensitivity. Biopersistence of fibers can be
28 affected by the presence of particles in the exposure dose, leading to particle overload.
29 Particle overload is a condition noted primarily from inhalation studies in the rat and
30 occurs when the deposition rate of poorly-soluble, low toxicity particles exceeds the

1 normal macrophage-mediated clearance rate (ILSI 2000). Clearance mechanisms can
2 become impaired under high-exposure conditions resulting in chronic alveolar
3 inflammation, fibrosis, and lung tumors. IARC (2002) reported that overload occurs in
4 the rat when 1 to 3 mg of particles are deposited per gram of lung tissue. This condition
5 leads to non-specific lung injury and possibly lung tumors (Hesterberg and Hart 2001,
6 IARC 2002).

7 Oberdörster (1996) noted two important differences between humans and rats that relate
8 to respiratory tract dosimetry: (1) most of the lung tumors develop in the conducting
9 airways of humans but develop only in the peripheral region in rats; therefore, respirable
10 fibers appear to be more important in the rat; and (2) because of the differences in
11 respiratory physiology, respirable fibers represent very different fractions in humans and
12 rats (see Section 5.1). Therefore, Oberdörster recommended enrichment of the inhaled
13 aerosol with long fibers in order to deposit enough of them into the respiratory tract of the
14 rat. Pertinent questions for inhalation studies of fiber carcinogenicity were also addressed
15 and included the following: (1) should rat respirable or human respirable samples be
16 used, (2) is it possible to test the longer human respirable fibers (*i.e.*, the most potent
17 fibers) in the rat inhalation model, and (3) are chronic inhalation studies in rats sensitive
18 enough to detect lung tumors below the MTD for any fiber type?

19 The conventional definition of the MTD is *a dose that produces no increased mortality*
20 *compared with controls, no shortening of life span other than that resulting from tumor*
21 *development and no more than a 10% weight gain reduction compared with controls*
22 (Kane *et al.* 1996b). However, the conventional definition might not be adequate for fiber
23 studies. Muhle *et al.* (1990) introduced the concept of the *maximal functionally tolerated*
24 *dose* (MFTD) for particulates. The MFTD was defined as the lung burden associated with
25 a two- to four-fold decrease in particle clearance. Other indicators that could be useful in
26 identifying the MTD for fiber inhalation studies include the following: increased lung
27 weight, increased inflammatory parameters, increased target cell proliferation, altered
28 histopathology other than carcinogenicity, impaired lung clearance function, and non-
29 linear fiber retention kinetics (Greim 2004, Oberdörster 1996). Hesterberg *et al.* (1996a)
30 used lung toxicity and particle clearance to estimate the MTD for glass wool and

1 concluded that 30 mg/m³ (~230 to 300 fibers/cm³) was an appropriate MTD for
2 MMVF10 in their chronic inhalation studies (see Section 4.1.1).

3 Ellouk and Jaurand (1994) noted that for animal models to be relevant to human
4 exposures, inhalation studies require the use of fibers or particles that are respirable in the
5 species tested. However, it may not be possible to increase the respirable dose beyond the
6 MTD for an animal model. Therefore, investigations by the inhalation route should be
7 reserved for respirable fibers, i.e., thin fibers of a diameter allowing lung deposition.

8 Wardenbach *et al.* (2005) noted that humans are more sensitive to asbestos-induced
9 carcinogenicity by inhalation than rats (see above for a discussion of this opinion and
10 opposing views) and presented arguments in favor of using intraperitoneal injection to
11 test for fiber carcinogenicity. In a comparison of recent chronic rat inhalation studies
12 using special-purpose fibers and insulation wool fibers, differences between the exposure
13 concentrations of these two types of fibers decreased with fiber length and barely existed
14 for fiber lengths > 20 µm (Figure 4-3). However, at every length category examined
15 (total, > 5 µm, > 20 µm) special-purpose fibers had a higher concentration of lung fibers
16 (per dry lung weight) as compared with insulation glass wool fibers (Figure 4-4). The
17 special-purpose fibers induced tumors, whereas the glass wool fibers did not. These
18 results suggested that special-purpose fibers are more respirable than glass wool fibers.
19 Previous studies had shown that almost all of the special-purpose fibers were respirable;
20 however, data were not available on the respirability of insulation glass wool fibers.
21 [Table 4-4 reports data that show that for glass wool fiber exposure concentrations of 3 to
22 30 mg/m³, there are 29 to 232 WHO fibers/cm³. In these studies, these fibers were
23 approximately 81% to 90% of the total mass of fibers in the exposure aerosol. No lung
24 tumors were detected above control values. These exposure concentrations are in contrast
25 to the crocidolite positive control (10 mg/m³), which had an exposure concentration of
26 1,600 WHO fibers/cm³ and a significant increase in lung tumors.] Because of the low
27 sensitivity of the inhalation model and the possible differences in respirability and
28 outcome in the rat model, the intraperitoneal model was proposed (see below).

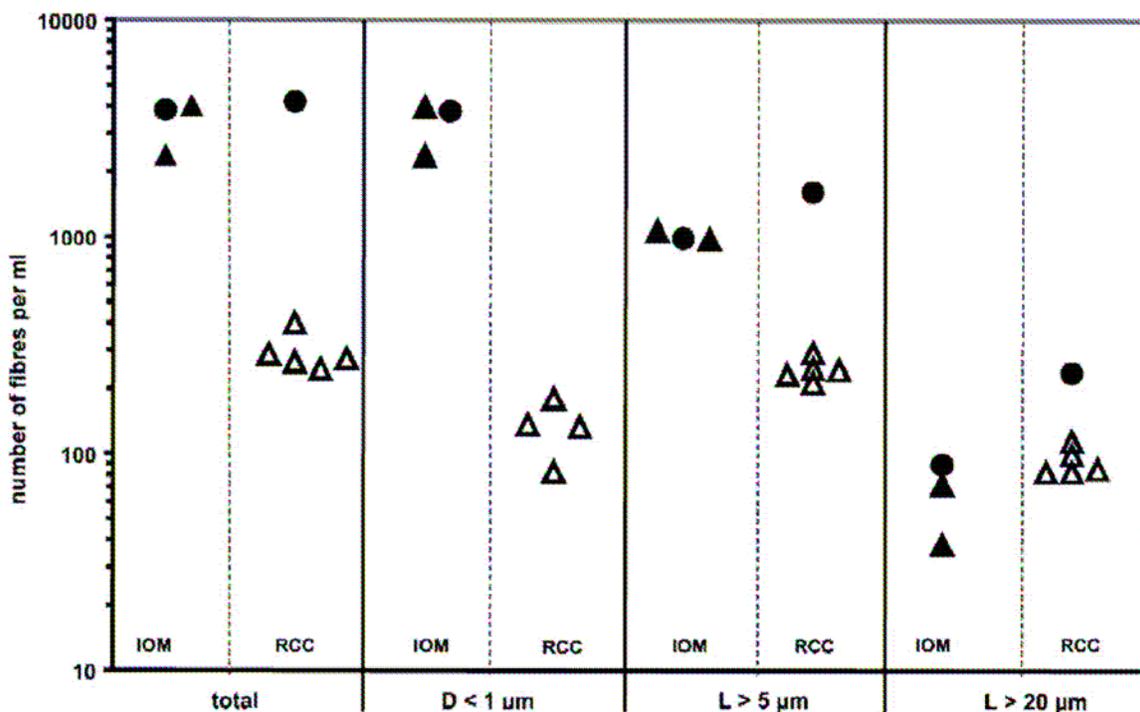


Figure 4-3. Exposure concentration vs. size categories of fibers from rat inhalation studies conducted at two different laboratories

Source: Wardenbach *et al.* 2005 (authors reported that some points were estimated from diagrams), used with permission.

Closed symbols = statistically significant induction of lung tumors; open symbols = nonsignificant for lung tumors. Triangles = MMVFs except RCFs, circles = amphibole asbestos. L = Length, D = Diameter.

RCC = Research and Consulting Company (Geneva, Switzerland) experiments with insulation glass fibers; IOM = Institute of Occupational Medicine (Edinburgh, Scotland) experiments with special-purpose fibers.

[The data for 104/475 fibers > 20 µm in length from Davis *et al.* 1996 do not appear in the figure. It should be an open triangle. In addition, the closed triangle at 38 fibers/mL and L > 20 µm likely refers to the 100/475 fibers in Cullen *et al.* 2000 and should be an open triangle.]

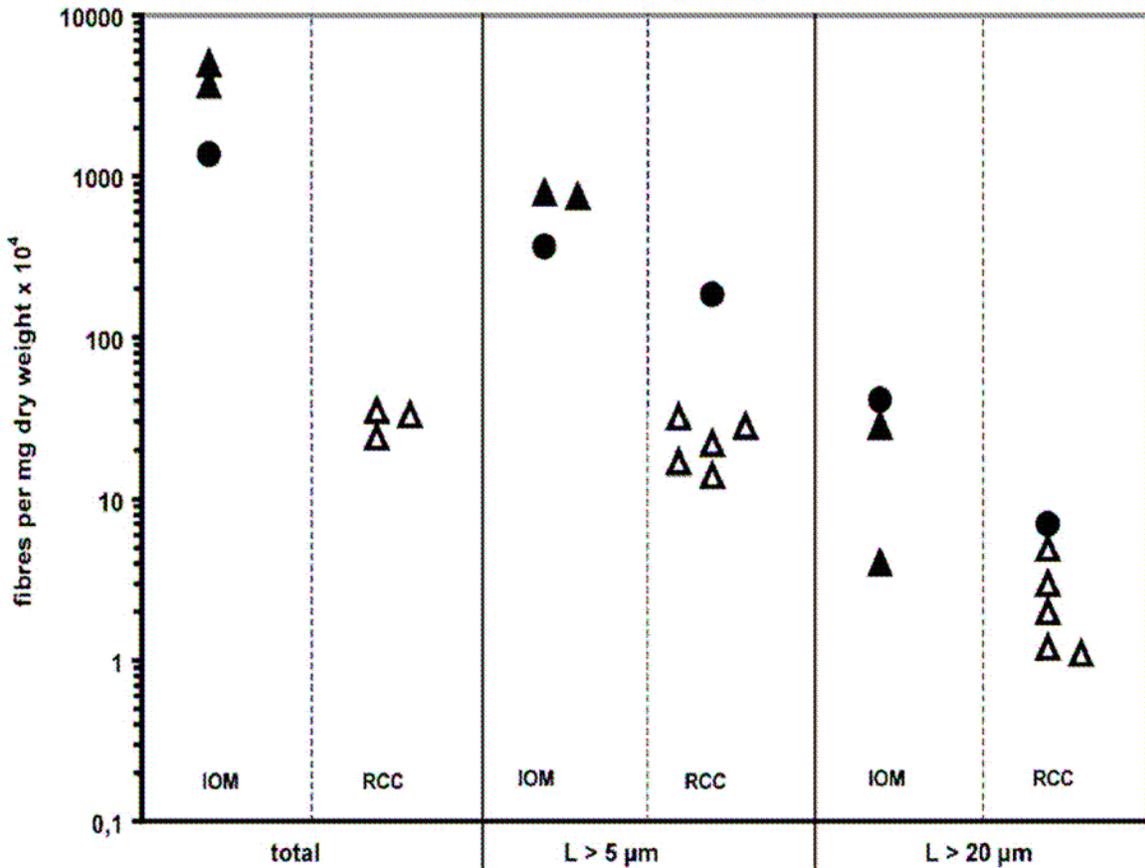


Figure 4-4. Concentration of fibers in lung tissue vs. size categories of fibers from rat inhalation studies conducted at two different laboratories

Source: Wardenbach *et al.* 2005 (authors reported that some points were estimated from diagrams), used with permission.

Concentration of fibers is in mg/dry weight of tissue.

Closed symbols = statistically significant induction of lung tumors; open symbols = nonsignificant for lung tumors. Triangles = MMVFs except RCFs, circles = amphibole asbestos. L = Length, D = Diameter.

RCC = Research and Consulting Company (Geneva, Switzerland) experiments with insulation glass fibers; IOM = Institute of Occupational Medicine (Edinburgh, Scotland) experiments with special-purpose fibers.

1 *Intratracheal instillation*

2 One of the advantages of intratracheal instillation is that selected doses of human
 3 respirable fibers can be delivered directly to the lung (Oberdörster 1996). Although the
 4 delivered fibers are then subject to the lung's normal defense mechanisms, these
 5 mechanisms might be adversely affected if the doses were too high. The primary
 6 differences between intratracheal instillation and inhalation studies are the delivery of the
 7 entire dose in seconds rather than over several hours, bypassing of the defense

1 mechanisms of the extrathoracic region, and the lack of even distribution of the dose
2 within the lung. Although multiple treatments are generally used, the dosing interval is
3 typically one week. Therefore, the exposure protocol does not mimic normal human
4 exposure. Careful selection of dose is required because high local doses can cause an
5 acute inflammatory effect (bolus effect) that would likely not occur during inhalation
6 exposure. Oberdörster (1996) concluded that this method was well suited for comparative
7 studies of dose response and toxicity ranking of different fiber types, but a well-
8 conducted multidose asbestos study is needed to validate this method for carcinogenicity
9 assessment.

10 *Intracavity injection*

11 Intracavity injection studies, particularly i.p., are commonly used to evaluate the
12 carcinogenicity of fibers. The primary advantages of these studies are that they are less
13 labor intensive, are easy to perform, and have been successfully used to investigate the
14 carcinogenic potential and potency of fibers (Oberdörster 1996). Repeated injections at
15 weekly intervals over several months have been performed, but most studies used single
16 injections. The disadvantages of intracavity injection studies are similar to those
17 mentioned above for intratracheal instillation studies and include the following: (1) these
18 methods are nonphysiological in that the lung is completely bypassed, (2) the peritoneal
19 and pleural cavities do not have the same defense mechanisms as the lungs and might be
20 overwhelmed following intracavity injections of large doses, and (3) intracavity injection
21 completely circumvents the fiber selection process that occurs during translocation of
22 fibers from the alveolar region of the lung to the pleura (Kane 1996a). Further, the
23 relationship of fiber durability to the incidence of peritoneal tumors needs to be addressed
24 (Ellouk and Jaurand 1994).

25 Oberdörster (1996) noted the importance of the MTD in intracavity injection studies, as
26 the bolus delivery of fibers to the peritoneal cavity can result in toxicity due to high local
27 doses.

28 Wardenbach *et al.* (2005) supported the use of the intraperitoneal injection model
29 because the carcinogenic potency of various MMVF can differ by three orders of
30 magnitude. The increased sensitivity of the i.p. route would enable the selection of less

1 potent MMVFs [see Table 4-6 for i.p. doses (in mg) of glass wool fibers (which have a
2 ten-fold dose range) and tumor incidences]. They also stated that there was no evidence
3 that i.p. injection studies would be biased towards producing false positive results since
4 no mesotheliomas were induced in rats given a high mass of granular silicon carbide dust
5 by i.p. injection.

6 **4.6 IARC evaluations**

7 The IARC (1988) review concluded that there was *sufficient evidence* for the
8 carcinogenicity of glass wool in experimental animals. Later, IARC (2002) evaluated
9 insulation glass wools and special-purpose glass fibers separately as part of a review of
10 man-made vitreous fibers and concluded that there was *limited evidence* in experimental
11 animals for the carcinogenicity of insulation glass wools but *sufficient evidence* in
12 experimental animals for the carcinogenicity of special-purpose glass fibers. The data and
13 findings from these reviews and publicly available, peer-reviewed carcinogenicity studies
14 in experimental animals were summarized in this section.

15 **4.7 Summary**

16 Numerous studies of various types of commercial insulation glass wools, special-purpose
17 glass fibers, and some experimental fibers have been conducted for carcinogenicity in
18 experimental animals by inhalation, i.p. injection, intrapleural injection, intratracheal
19 instillation, and intrathoracic injection or implantation. Findings from these studies are
20 summarized by fiber type, species, and route of exposure in Table 4-10.

21 Although all inhalation studies conducted prior to the late 1980s were negative, the
22 results were considered inconclusive because of various study limitations recognized by
23 researchers in the field, including a failure in some studies to produce tumors in positive
24 control groups exposed to asbestos fibers. A series of long-term inhalation studies were
25 conducted in rats and hamsters in the late 1980s and early 1990s to address the
26 limitations of the earlier studies. Two glass wool fibers (MMVF10 and MMVF11) and
27 two special-purpose fibers (JM100/475 and 104E) were tested in separate studies.
28 Significantly increased incidences of lung carcinomas combined with adenomas occurred
29 in male Wistar rats exposed to 104E microfibers but not to JM100/475 fibers; no
30 significant increases in lung tumors or mesotheliomas were reported for male F344 rats

1 exposed to MMVF10, or MMVF11. However, there were apparent positive trends for
2 both adenomas and combined tumors in male F344 rats exposed to MMVF10.
3 Mononuclear-cell leukemia incidence was statistically significant for F344 rats exposed
4 to Owens-Corning or JM100/475 glass fibers for 86 weeks. In the most recent inhalation
5 study in male hamsters, a mesothelioma was observed in 1 of 83 animals exposed to
6 JM100/475 glass fibers for 78 weeks. Although this result was not statistically
7 significant, the authors considered it treatment related.

8 Significantly increased incidences of peritoneal tumors (primarily mesothelioma) were
9 reported in almost all i.p. injection studies in rats using different types of fibers including
10 insulation fibers such as MMVF10 and MMVF11 and special-purpose fibers such as
11 JM475 (various diameters), M753, and E glass. However, no tumors were observed in
12 some studies testing experimental fibers that have low biodurability. In most cases, tumor
13 incidences were similar to those seen in the asbestos treatment groups. In addition,
14 increased incidences of pleural sarcomas occurred in rats following intrathoracic
15 implantation of some glass fibers (depending on the fiber dimensions) but not others.
16 Increased incidences of neoplasms (mesothelioma, pleural sarcoma, and lung carcinoma)
17 were observed in some intrapleural or intratracheal instillation studies in rats exposed to
18 JM100 or JM104 microfibers and in intratracheal instillation studies in hamsters exposed
19 to JM104 microfibers. No tumors were reported following intrapleural or intratracheal
20 instillation of glass wool in mice, guinea-pigs, or rabbits.

21 A number of studies, including both intrathoracic implantation and i.p. injection of fibers,
22 have been conducted with the intent of comparing fibers with different characteristics,
23 such as differing fiber dimensions and biopersistence/durability. The earliest of these
24 studies by Stanton and co-workers using intrathoracic implantation of glass fibers and
25 other natural and synthetic fibers led the authors to conclude that fiber dimensions and
26 durability were important in determining the tumorigenicity of the material. Later studies
27 using i.p. injection reached similar conclusions in many cases, but some data suggest that
28 the relationship might not be completely defined by those fiber characteristics.

Table 4-10. Summary of carcinogenicity studies of glass wool fibers in experimental animals

Fiber type/source	Species, strain	Results, tumor type				
		Inhalation	Intraperitoneal	Intratracheal	Intrathoracic	Intrapleural
Insulation wool	rat, not specified			–		
	rat, Wistar		Mesothelioma			
	rat, Sprague-Dawley					–
	rat, Osborne-Mendel				Pleural sarcoma	
	rat, F344	MCL	–			
	hamster, Syrian golden	–		–		
	guinea-pig			–		
	mouse, BALB/c					–
	rabbit			–		
475 glass	rat, Wistar	–	Mesothelioma, spindle-cell sarcoma, carcinoma combined	Lung adenoma, adenocarcinoma, squamous-cell carcinoma		Mesothelioma
	rat, Sprague-Dawley		Mesothelioma, spindle-cell sarcoma, carcinoma combined			Mesothelioma
	rat, Osborne-Mendel		Mesothelioma	–		
	rat, F344	MCL	–			
	hamster, Syrian golden	Mesothelioma ^a		Mesothelioma, pleural sarcoma, lung carcinoma		
E glass	rat, Wistar	Lung carcinoma	Mesothelioma			
753 glass	rat, Wistar		Mesothelioma			
Experimental fibers	rat, Wistar		Mesothelioma,			

Fiber type/source	Species, strain	Results, tumor type				
		Inhalation	Intraperitoneal	Intratracheal	Intrathoracic	Intrapleural
			peritoneal sarcoma			

– = Negative studies; MCL – mononuclear-cell leukemia.

^a The only positive study (reported by both Hesterberg *et al.* 1997 and McConnell *et al.* 1999) reported that 1 of 83 hamsters developed a mesothelioma. Although this result was not statistically significant, the authors considered it treatment related.

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5 Other Relevant Data

1 This section discusses the respirability, deposition, clearance, and retention of glass fibers
2 (Section 5.1); their durability and biopersistence (Section 5.2); studies of fiber
3 characteristics and tumorigenicity of synthetic vitreous fibers (SVF) (Section 5.3);
4 toxicity (Section 5.4); genetic and related effects (Section 5.5); and the mechanisms of
5 potential fiber-induced carcinogenesis (Section 5.6). A summary is provided in Section
6 5.7. Much of what is known about fiber carcinogenicity was discovered in studies with
7 asbestos, and the general principles are relevant for glass fibers. Therefore, this section
8 includes some discussion of asbestos carcinogenicity with comparisons to glass fibers.

9 5.1 Respirability, deposition, clearance, and retention

10 Two important concepts relating to exposure to airborne particulates are *inhalability* and
11 *respirability*. Inhalability is the ratio of the particle concentration in the inhaled air to that
12 in the ambient air and decreases with increasing particle size. Larger particles settle out
13 of the air faster and are more readily deposited in the extrathoracic region. Respirability
14 refers to the relative amount of airborne particles reaching the alveolar region of the lung
15 and generally increases with decreasing particle size (Hesterberg and Hart 2001).
16 Variations in fiber density, length, and diameter can be normalized using the equivalent
17 aerodynamic diameter (D_A) for D_{AS} above $0.5 \mu\text{m}$. D_A is expressed as the diameter of a
18 spherical particle that has the same terminal settling velocity in still air as the fiber and is
19 calculated as follows: $D_A = 1.3p^{1/2}d^{5/6}L^{1/6}$ (where D_A = aerodynamic diameter, p =
20 density, d = diameter, L = length) (Hesterberg and Hart 2001). In humans, fibers with a
21 $D_A < 1 \mu\text{m}$ are 100% respirable, fibers with a D_A of about $4 \mu\text{m}$ are 50% respirable, and
22 fibers with a D_A of 9 to $10 \mu\text{m}$ are non-respirable (Hesterberg and Hart 2001). Morgan *et*
23 *al.* (1980) reported that respirability in the rat peaked at a D_A of approximately $2 \mu\text{m}$ and
24 decreased markedly between 2 and $3 \mu\text{m}$, with $D_A < 6 \mu\text{m}$ being the limit of respirability
25 (no fiber alveolar deposition). Dai and Yu (1998) calculated respirability of inhaled fibers
26 in rats based on deposition models. They reported the limit of respirability in the rat at
27 $D_A > 3.5 \mu\text{m}$ and aspect ratios (L/D) > 10 , and noted that there was appreciable fiber
28 deposition in humans at this fiber size. Respirable fibers can cause adverse effects in the
29 lung such as pulmonary inflammation, cell proliferation, pulmonary fibrosis (collagen

1 deposition) and neoplasia (Oberdörster 2000). Fibers that are inhalable but non-respirable
2 can deposit in the extrathoracic and tracheobronchial regions and can cause adverse
3 effects including acute nasal effects, chronic inflammation, and bronchogenic carcinoma
4 (Churg 1988).

5 There are marked species differences in the amount of fibers retained in the airway for a
6 given exposure concentration with both anatomic and physiologic factors influencing the
7 dose retained (IARC 2002, Oberdörster 2000). It is important to note that exposure
8 concentration in ambient air is not equivalent to the dose deposited in the lung.

9 Deposition is the actual dose deposited in the lung from the inspired air as a result of
10 inelastic encounters of the particles with the respiratory epithelium and is influenced by
11 the anatomy and physiology of the airway, respiratory rate, and physical properties of the
12 fiber. Once deposited, fibers can be removed or cleared from the respiratory tract.

13 Clearance is defined as the amount of fibers eliminated (cleared) from the lung over a
14 time period and is influenced by both the physical properties of the fiber and the
15 physiologic response of the host. Retention is defined as the dose retained within the lung
16 and is equal to deposition minus the amount cleared. This section briefly reviews some of
17 the primary concepts relating to deposition, clearance, and retention of fibers in the
18 respiratory tract.

19 There are three general anatomic regions of the respiratory tract where inhaled particles
20 deposit. These are the extrathoracic region (mouth, nose, pharynx, and larynx), the
21 tracheobronchial region (trachea, bronchi, and ciliated bronchioles), and the alveolar-
22 interstitial region (respiratory bronchioles, alveolar ducts, alveoli, and pulmonary
23 interstitium) (IARC 2002).

24 *5.1.1 Deposition*

25 Respirability determines the concentration of particles in the air reaching the alveolar
26 interstitial region, whereas deposition is the actual dose deposited in the lung. In humans,
27 40% to 80% of fibers with $D_A < 1 \mu\text{m}$ that are inhaled into the alveolar interstitial region
28 are not deposited and are subsequently exhaled from the lung (Hesterberg and Hart
29 2001). Deposition is a function of the physical characteristics of the particle, such as size,
30 shape, and density, and the anatomical and physiological parameters of the respiratory

1 tract. Distribution of fibers within an alveolar interstitial region is dependent on airway
2 geometry and the composition and physical properties of alveolar fluid. Alveolar fluid
3 consists of an aqueous layer over the pulmonary epithelium covered by a surfactant layer
4 at the air-liquid interface (Geiser *et al.* 2003).

5 Fibers deposit in the respiratory tract by impaction, sedimentation, diffusion, and
6 interception (see Glossary for definitions). All four deposition mechanisms occur in
7 humans and experimental animals. Impaction and sedimentation are most effective for
8 particles with D_A of 0.5 to 1 μm . Deposition due to aerodynamic behavior becomes less
9 important as particle size decreases below 1 μm , and for particles with D_A less than 0.5
10 μm , deposition is mainly determined by diffusional displacement induced by Brownian
11 motion. Interception is more important for deposition of fibrous particles than of
12 spherical particles because it occurs when one end of the particle touches the epithelium
13 of the airway (Bernstein *et al.* 2005).

14 Although mechanisms of deposition are similar between humans and experimental
15 animals, there are some important interspecies differences that can influence fiber
16 deposition (IARC 2002, Maxim and McConnell 2001):

- 17 • Rats are obligate nose breathers; humans can breathe through the mouth and nose.
- 18 • Nasal turbinates in rodents are more complex than in humans and deposit fibers
19 more efficiently; this, along with other differences in size and physiology, results
20 in more and larger fibers depositing in human extrathoracic airways than in the
21 rodent.
- 22 • The conducting airways in humans are more dichotomous and symmetrical
23 resulting in greater impaction of fibers at branch points, while in rodents they are
24 monopodial and asymmetrical favoring a more uniform airflow resulting in more
25 distal deposition of fibers.
- 26 • In humans, the deposition fraction in the extrathoracic and tracheobronchial
27 regions increases with workload (minute ventilation), and deposition increases
28 when switching from nose to mouth breathing.

1 Dai and Yu (1998) studied alveolar deposition in rodents and humans and found that
2 aerodynamic fiber diameters between 1 and 2 μm result in peak lung deposition in
3 rodents and humans and that increasing the aspect ratio (ratio of fiber length to fiber
4 diameter) of the fibers decreases the peak deposition. Further, alveolar deposition in
5 rodents does not occur when D_A is greater than 3.5 μm and the aspect ratio is greater than
6 10. Considerable alveolar deposition occurs in humans with particles having aerodynamic
7 diameters less than 5 μm .

8 5.1.2 Clearance

9 Clearance mechanisms vary from region to region within the respiratory tract. Ciliary
10 movement in the extrathoracic region clears deposited particles cranially, primarily
11 towards the pharynx where they may be swallowed or cleared by coughing. Particles
12 within the anterior nasal cavity may be cleared by nose-blowing or sneezing. Ciliated
13 epithelial cells line the lung conductive airways from the pharynx caudally to the terminal
14 (respiratory) bronchioles and clear the airway by moving particles, fibers, cells, and
15 fluids back to the pharynx where they can be swallowed or coughed out. This system,
16 known as the mucociliary escalator, is an important clearance mechanism for the
17 tracheobronchial region. Mucociliary clearance usually takes less than 24 hours. Airway
18 macrophages can clear many particles through phagocytosis and subsequent mucociliary
19 clearance. Phagocytosis is the primary clearance mechanism in the alveolar region and is
20 slower than clearance from other regions of the respiratory tract. The presence of fibers
21 on the lung epithelium stimulates the release of chemotactic factors that attract alveolar
22 macrophages, neutrophils, and other cells involved in inflammation (Wilson and Wynn
23 2009). These activated cells also release chemotactic, inflammatory, and other factors.
24 Fiber length is known to be an important factor for effective phagocytosis, and there are
25 species differences in alveolar macrophage size and number. Fibers that are too long to
26 be fully phagocytized and too durable to be broken down may remain in the alveolar
27 region with macrophages attached to the fibers (a phenomenon called “frustrated
28 macrophages”) or can translocate to interstitial and pleural sites (Oberdörster 1996). In
29 general, small particles in the alveoli are phagocytized, but they have also been found in
30 alveolar capillaries (Geiser *et al.* 2003).

1 The clearance of fibers in the lung over time has been studied by Bernstein *et al.* (2001a).
2 Tracking percent fiber retention in the lung over time (days following cessation of
3 exposure) resulted in a bi-phasic clearance curve. The rate of fiber clearance (slope of the
4 line) is initially fast and then decreases markedly, resulting in a bi-exponential curve. The
5 fast clearance phase is proposed to represent clearance of short fibers from either the
6 tracheobronchial or alveolar regions, and clearance of long fibers ($> 20 \mu\text{m}$) from the
7 tracheobronchial region. The slow clearance phase is proposed to describe dissolution of
8 shorter fibers that have accumulated in microgranulomas or the bronchial-associated
9 lymphoid tissue and lymph nodes, or dissolution of fibers that were too long to be
10 phagocytized by macrophages. Because of the importance of alveolar macrophages,
11 species differences in macrophage size and number might affect fiber clearance.
12 Macrophages in humans have an average diameter of about $21 \mu\text{m}$ compared with about
13 13 to $14 \mu\text{m}$ in rats and hamsters (Hesterberg and Hart 2001).

14 Zeidler-Erdely *et al.* (2006) investigated the influence of JM100 fiber length on lactate
15 dehydrogenase release in primary cultures of human alveolar macrophages. Human
16 macrophages completely engulfed glass fibers up to $20 \mu\text{m}$ in length, with no evidence of
17 incomplete phagocytosis or length-dependent toxicity. However, in a study of
18 cytotoxicity using code 100 (JM100) glass fibers and rat alveolar macrophages (Blake *et*
19 *al.* 1998), evidence of a length-related toxicity was seen with fibers of 17 and $33 \mu\text{m}$. (see
20 Section 5.4.3 for study details.)

21 Differences in the phagocytic response of rat and hamster alveolar macrophages to SVFs
22 have been investigated by Dörger *et al.* (2000). Alveolar macrophages were obtained by
23 bronchoalveolar lavage, and macrophage-enriched cell cultures were exposed to either
24 MMVF10 (glass wool, median length $16.3 \mu\text{m}$) or MMVF21 (rock wool, median length
25 $19.4 \mu\text{m}$) for 20 hours. The phagocytic response was video recorded. Rat macrophages
26 had a significantly ($P < 0.05$) greater percentage of cells with partial phagocytosis than
27 hamster macrophages for MMVF10 (27% for rats vs. 2% for hamsters) and MMVF21
28 (30% for rats vs. 1% for hamsters). Also, a higher percentage of hamster macrophages
29 completely phagocytized both types of fibers compared with rat macrophages (18% vs.
30 9% for MMVF10 and 33% vs. 16% for MMVF21 for hamsters and rats, respectively).

1 After a 2-hour exposure to the fibers, superoxide anion production was also measured by
2 a cytochrome c reduction assay. Rat alveolar macrophages released significantly higher
3 amounts of super oxide anion than hamster macrophages with MMVF21 exposure, but
4 not with MMVF10 exposure. The authors concluded that there were species differences
5 in the phagocytic response that could result in more efficient clearance of inhaled fibers
6 from hamster lung than from rat lung.

7 Using the same methods and fibers, Dörger *et al.* (2001) also compared superoxide anion
8 production and phagocytic response of rat alveolar macrophages with rat peritoneal
9 macrophages. Alveolar macrophages had a greater number of partly incorporated fibers
10 than peritoneal macrophages (41% vs. 10%, respectively, for MMVF10; 34% vs. 12%,
11 respectively, for MMVF21) and had a lower percentage of fiber-free macrophages (9%
12 vs. 50%, respectively, for MMVF10, 9% vs. 29%, respectively, for MMVF21). Alveolar
13 macrophages produced significantly greater amounts of superoxide anion than peritoneal
14 macrophages when exposed to MMVF21 (approximately 150 vs. 10 nmol/mg protein per
15 2 hours), but exposure of alveolar or peritoneal macrophages to MMVF10 did not result
16 in production of superoxide anions. The authors concluded that these data are consistent
17 with a higher biopersistence of mineral fibers in the peritoneal cavity as compared with
18 the lung.

19 5.1.3 Retention

20 Retention is defined as deposition minus clearance. Chemical composition, fiber size
21 distribution, number of fibers in the lung, and time since the last exposure are important
22 factors. Based on the experimental data, two possible mechanisms have been proposed to
23 explain the length-related patterns of fiber retention (Oberdörster 2002). Short fibers are
24 expected to be efficiently phagocytized by the alveolar macrophages and transported
25 from the alveoli to bronchioles where they are cleared by the mucociliary escalator. Long
26 fibers are resistant to effective phagocytosis but may be subject to dissolution or
27 transverse breakage. As the long fibers break, the population of short fibers is increased;
28 therefore, the population of long fibers typically decreases faster than the population of
29 short fibers for nondurable types of fibers (see Section 5.2). If long fibers are resistant to
30 transverse breakage or dissolution (*e.g.*, amphibole asbestos), they are retained. The

1 second possible mechanism is based on differences in the intracellular and extracellular
2 compartments of the lung. Long fibers tend to remain in the extracellular compartment
3 because they cannot be completely phagocytized by macrophages. The extracellular
4 compartment is at near-neutral pH, whereas phagocytosis by alveolar macrophages
5 exposes the fibers to the acidic pH and digestive factors within the phagolysosomes.
6 Thus, the solubility of long fibers at neutral pH would be an important factor in retention
7 of the fiber.

8 A limited number of studies are available regarding retention of fibers in humans;
9 however, the average overall retention half-time for poorly soluble fibers has been
10 reported to be hundreds of days. In one study (McDonald *et al.* 1990), which used a
11 subset of the Marsh *et al.* cohort (see Section 3.1.1), analytical transmission electron
12 microscopy was used to determine fiber retention in lung tissue. The selected population
13 consisted of 112 MMVF workers (101 glass wool workers and 11 rock or slag wool
14 workers) that had died between 1952 and 1979, and for whom tissue was available from
15 autopsies. The unexposed group consisted of 112 autopsies from the same hospital. There
16 was no significant difference in retention of fibers in the 112 exposed workers as
17 compared with the unexposed group. The exposed workers had a mean exposure duration
18 of 11 years and a mean elapsed time since last exposure of 12 years. Fibers were detected
19 in 29 of the 112 production workers compared with 28 of 112 in the unexposed group.
20 Fiber numbers detected in the exposed workers and the unexposed group were similar to
21 those found after environmental exposure. However, 10 of the 112 exposed workers and
22 2 of the 112 unexposed group had more than 1 million asbestos fibers/g dry lung tissue.
23 The authors concluded that either the synthetic fibers disappeared from the lung in less
24 than 12 years, or the exposed workers did not inhale enough respirable SVF fibers to
25 show a difference from controls; alternatively, fixative fluids might have altered some
26 retained fibers in the lung.

27 **5.2 Biodurability and biopersistence of glass fibers**

28 This section reviews several studies that illustrate the differences in biodurability and
29 biopersistence among fiber types and the various ways these properties are measured.

1 The relationship between fiber biopersistence and pathogenicity in experimental animal
2 models and humans is also discussed.

3 5.2.1 Definitions

4 Biodurability describes the rate of removal of a fiber from the lungs by dissolution or
5 disintegration, the latter due to partial dissolution. It is assumed that biodurability is
6 similar in rats and humans since the ionic milieu in the lung is also relatively similar. On
7 the other hand, biopersistence also includes the removal of fibers from the lung by
8 physical clearance of entire fibers, *e.g.*, by ciliary or macrophage-mediated clearance.
9 Therefore, biopersistence is equal to biodurability plus physiological clearance and refers
10 to the capacity of a fiber to persist and to conserve its chemical and physical features over
11 time in the lung (Hesterberg and Hart 2001).

12 5.2.2 Fiber dissolution

13 Physico-chemical processes can act on fibers in the lung resulting in chemical
14 dissolution, leaching, and mechanical breaking (IARC 2002). Dissolution occurs when
15 water molecules attack the surface of the fiber. For many SVFs, certain components
16 dissolve more rapidly than others (leaching). Leaching results in changes in fiber
17 composition over time. As the zones of leached-out, lower-density material expand, fiber
18 weakness (*e.g.*, fractures, peeling, and pitting) and breakage occur. Therefore, chemical
19 composition and surface reactivity of the fiber affect its dissolution rate. Maxim *et al.*
20 (2006) reported that fluorine and oxides of boron, magnesium, calcium, sodium, and
21 barium increase the dissolution rate, while aluminum oxide decreases the dissolution rate
22 of borosilicate glass fibers.

23 Experimental dissolution rates of various fibers have been studied in a number of *in vitro*
24 and *in vivo* systems. Cell-free systems typically use balanced salt solutions to simulate
25 lung fluids and are conducted at near neutral pH (to simulate the pH of extracellular
26 fluid) or at a pH of 4.5 (to simulate the pH of the phagolysosomes of macrophages).
27 Results with cell-culture studies are generally consistent with results from the cell-free
28 systems, but dissolution of glass wool is faster in cell-free systems. Reported *in vitro*
29 dissolution rate constants in cell-free systems at neutral pH are $< 1 \text{ ng/cm}^2$ per hour for
30 crocidolite, 8 to 12 ng/cm^2 per hour for E-glass and 475 glass, and 100 to 300 ng/cm^2 per

1 hour for building insulation glass wools (Zoitos *et al.* 1997). Although experimental
2 dissolution rates for glass fibers show considerable variability (up to a 30-fold range),
3 they generally show some correlation with clearance rates of long fibers from the lung in
4 short-term biopersistence studies (see next section). Therefore, *in vitro* dissolution tests
5 have been used to screen for toxicity.

6 Luoto *et al.* (1994, 1995b) studied the effect of fiber length on the dissolution of
7 commercial glass wool and rock wool fibers in cell-culture medium with and without rat
8 alveolar macrophages present. Atomic absorption spectroscopy was used to determine the
9 amount of iron, aluminum, or silicon remaining in original and tested fibers. More iron
10 and aluminum dissolved from fibers in culture with macrophages, while more silicon was
11 dissolved from fibers in culture medium without cells. Further, they found that glass wool
12 fibers (MMVF10, MMVF11) dissolved more readily at pH 7 in culture medium alone
13 than did rock wool fibers, whereas rock wool fibers dissolved more readily when
14 macrophages were present in the culture medium (Luoto *et al.* 1995a). These authors
15 concluded that the intracellular and the extracellular dissolution of the fibers differ, and
16 that cell-culture systems were preferable to cell-free systems for assessing *in vivo* fiber
17 durability and dissolution.

18 The *in vivo* clearance of fibers > 20 μm in length from the lungs of F344 rats has been
19 reported to result from the dissolution of the fibers in extracellular fluid at approximately
20 the same rate as the dissolution rate (k_{dis}) measured in simulated lung fluid *in vitro*, a
21 process that depends on the chemical composition of the fibers (Eastes and Hadley 1995,
22 Eastes *et al.* 1995). The predicted dissolution rates were similar for inhalation studies of
23 MMVF10 and MMVF11 glass fibers, MMVF21 rock wool, MMVF22 slag wool, and
24 crocidolite asbestos (Eastes and Hadley 1995) and for intratracheal instillation studies of
25 MMVF10 and MMVF11 glass fibers and three experimental glass fibers, X7779, X7753,
26 and X7484, with k_{dis} values of 2, 100, and 600 ng/cm^2 per hour, respectively (Eastes *et*
27 *al.* 1995). For fibers < 20 μm in length they proposed that physical removal occurred by a
28 macrophage-mediated process that did not differ by fiber type. The authors also reported
29 that computer simulations of fiber clearance based on these processes agreed well with *in*
30 *vivo* measurements of fibers remaining in the lung up to a year after exposure.

1 The dependence of the *in vitro* k_{dis} of fibers on their chemical composition was the basis
2 for a method of calculating those rate constants by Eastes *et al.* (2000a). The individual
3 dissolution rates for the oxides were summed based on their weight percent multiplied by
4 a coefficient (P_i) determined by fitting experimental data for k_{dis} measured *in vitro* for a
5 set of 62 fiber types, which resulted in a correlation coefficient (r^2) of 0.96 for the
6 calculated versus the measured values. The authors also calculated k_{dis} values for
7 approximately 30 additional fiber types not used to determine the coefficients for the
8 oxides and reported that they provided “a reasonable estimate of k_{dis} ” over a range of
9 100,000, much larger than the range of approximately 100 for the k_{dis} values on which
10 the coefficients were based. The same authors also estimated dissolution rates from *in*
11 *vivo* biopersistence data obtained from published intratracheal instillation and short-term
12 inhalation studies, as well as for an unpublished inhalation biopersistence study of six
13 fiber types, and they reported good agreement with dissolution constants measured *in*
14 *vitro* for the same fiber types (Eastes *et al.* 2000b). The dissolution rates were estimated
15 from the decrease in diameter of fibers $> 20 \mu\text{m}$ retained in the lungs. The authors noted
16 that the majority of datasets (19 of 31) for different fiber types had r^2 values above 70%,
17 and the overall correlation between *in vivo* k_{dis} and k_{dis} measured *in vitro* for the same
18 fibers was 0.727, which the authors considered to be in reasonably good agreement.

19 Nguea *et al.* (2008) proposed an *in vitro* test for fiber degradation using a human
20 monocytic cell line (U-937). Crocidolite fibers (asbestos), glass wool fibers (CM44), and
21 rock wool fibers (HDN) were tested. After a 24-hour incubation of U-937 cells with each
22 of the fibers, phagocytosis was observed; however, dissolution of the fibers (as observed
23 by scanning electron microscopy) did not occur. Degradation of CM44 and HDN fibers
24 occurred only with activation of the monocytes with *E. coli* bacteria, *E. coli* culture
25 media, IL-6, or TNF-alpha, but not with lipopolysaccharide (LPS), *B. subtilis*, *S. aureus*,
26 or heat-inactivated *E. coli*. Asbestos fibers did not degrade in the presence of *E. coli*. The
27 pattern of HDN fiber degradation observed *in vitro* was in accord with that observed in
28 rats after a one-month intratracheal exposure.

29 In general, biodurability of various fibers in the lung have been ranked as follows: glass
30 fibers $<$ refractory ceramic fibers $<$ chrysotile asbestos $<$ amphibole asbestos (Collier *et*

1 *al.* 1994). Collier *et al.* (1994, 1995) compared the durability of an experimental glass
2 fiber (X7753) of uniform diameter (2 μm) by injecting fibers into the peritoneal cavity
3 and by intratracheal instillation to the lung of female Fischer rats. Scatter plots of fiber
4 diameter vs. fiber length were produced to estimate the injected fiber size distribution and
5 the size distribution for the fibers recovered 150 days after either intratracheal instillation
6 or intraperitoneal injection. After 150 days of exposure, fibers were recovered from the
7 tissues by lavage. Fiber diameters by both routes of exposure had decreased, whereas
8 there was an apparently greater decrease in fiber length by the intratracheal route of
9 exposure. [These conclusions were based on a qualitative assessment of the scatterplots
10 by the authors.] Peak diameters of fibers $> 20 \mu\text{m}$ and $< 20 \mu\text{m}$ in length were plotted
11 against days after administration by both routes. The diameters of long fibers ($> 20 \mu\text{m}$)
12 declined from 2 μm to below 0.4 μm by 50 days after administration by the intratracheal
13 instillation route, but remained above 1 μm for intraperitoneal exposure. Diameters of
14 short fibers ($< 20 \mu\text{m}$) remained above 1 μm for both injection routes [diameters
15 estimated from graphs]. Their results suggested that dissolution rates of long fibers were
16 slower in the peritoneal cavity compared with the lung. In the peritoneal cavity, diameters
17 of both short and long fibers declined at a rate similar to that of short fibers in the lung.
18 Doses greater than 1.5 mg in the peritoneal cavity resulted in clumps of fibers (nodules)
19 that were either free in the cavity or bound to peritoneal organs and were associated with
20 classic foreign body reactions.

21 5.2.3 Biopersistence studies

22 Yu *et al.* (1998) evaluated the biopersistence of MMVF10 glass wool, MMVF11 glass
23 wool, MMVF21 rock wool and MMVF22 slag wool and developed a clearance model in
24 the rat lung using experimental data from short-term, nose-only inhalation biopersistence
25 studies. Crocidolite asbestos was used as a positive control. Their model accounted for
26 differential mechanical clearance by alveolar macrophages, *in vivo* dissolution of fibers,
27 and breakage of long fibers. The *in vitro* dissolution rate was correlated with the *in vivo*
28 dissolution rate, although the *in vivo* rate was much lower. Fiber breakage was related to
29 dissolution. The breakage rate of the more soluble fibers was higher. MMVF10 had the
30 highest dissolution and breakage rate followed closely by MMVF11 and MMVF22.
31 Because crocidolite fibers are highly durable, the authors assumed that removal was by

1 macrophage-mediated mechanical clearance alone. Different half-times were calculated
2 for different fiber lengths. For crocidolite fibers shorter than 5 μm , mechanical clearance
3 was about the same as for nonfibrous particles but decreased with fiber length. For
4 crocidolite fibers longer than 20 μm , the average mechanical clearance rate was 0.001
5 (1/day) and corresponds to a half-time of 693 days (Muhle and Pott 2000).

6 A different approach for the calculation of half-times was used by Bernstein *et al.* (1996).
7 The authors examined the biopersistence of nine SVFs in the rat. These included
8 MMVF11, three experimental glass wools (including B-01-0.9), one commercial stone
9 wool, and four experimental stone wools. Groups of 56 male F344 rats were exposed
10 (nose only) to a well-defined, rat-respirable aerosol (mean diameter < 1 μm) at a
11 concentration of 30 mg/m^3 for 6 hours per day for 5 days. Groups of eight animals were
12 sacrificed at 1 hour, 1 day, 5 days, and 4 weeks following the last day of exposure and at
13 13, 26, or 52 weeks following the first day of exposure. Clearance, when modeled with a
14 single exponential curve, did not provide a good fit to the experimental data for many of
15 the fibers. Both a fast-clearance phase and a slow-clearance phase were observed for
16 many of the fibers; therefore, a weighted clearance half-time ($\text{WT}_{1/2}$) was calculated. This
17 method provided a much better fit to the data. The $\text{WT}_{1/2}$ for World Health Organization
18 (WHO) fibers⁴ was 28 days for MMVF11 and ranged from 11 to 15 days for the three
19 experimental glass wools. WHO fiber clearance was shown to represent clearance of
20 shorter fibers (5 to 20 μm) but was not a good indicator of the clearance of the more
21 biologically relevant longer fibers (> 20 μm). The $\text{WT}_{1/2}$ for the longer fibers was 13 days
22 for MMVF11 and only 2 to 4 days for the experimental glass wools, indicating that
23 clearance of long glass fibers was rapid due to dissolution and breakage. For comparison,
24 the $\text{WT}_{1/2}$ for crocidolite fibers longer than 20 μm was 536 days. [This approach uses the
25 fraction of the short half-time that does not contribute to fiber accumulation in the lungs,
26 but some have suggested that only the slow phase of the half-time should be used.]

27 Hesterberg *et al.* (1998) used the rat inhalation model to compare biopersistence of long
28 amosite with five SVFs. The test fibers included two special-purpose fibers, MMVF32 (E

⁴ WHO fibers are respirable fibers with lengths greater than 5 μm , diameters less than 3 μm , and aspect ratios (ratio of fiber length to diameter) $\geq 3:1$ (ATSDR 2004).

1 glass) and MMVF33 (475 glass). Fischer rats were exposed for 6 hours per day for five
2 days and followed for one year. Mass concentrations were adjusted to achieve target
3 concentrations of $150 \text{ fibers/cm}^3 > 20 \mu\text{m}$. Groups of five to eight rats were sacrificed at
4 nine post-exposure time points (1, 2, 7, 14, 30, 60, 90, 180, and 365 days) to evaluate
5 lung fiber burdens, dimensions, and morphology. Lung deposition of fibers $> 20 \mu\text{m}$ was
6 similar for amosite and the five SVFs, while deposition of WHO fibers was more
7 variable. The authors used a two-pool, first-order kinetic model to describe removal of
8 fibers from the lung. Lung burdens for all six fibers were reduced about 35% during the
9 first 90 days compared with day 1 levels. However, during the subsequent slower
10 clearance phase (~ 275 days), the number of long amosite fibers was 80% of the 90-day
11 value while the number of glass fibers was about 25% of the 90-day value. For amosite
12 fibers $> 20 \mu\text{m}$ the half-times of the fast pool and slow pool were 20 and 1,160 days,
13 respectively, while the $WT_{1/2}$ was 418 days. For MMVF32 and MMVF33, the half-times
14 were, respectively, 7 and 5 days (fast pool), 179 and 155 days (slow pool), and 79 and 49
15 days ($WT_{1/2}$). Amosite fibers did not show any surface deterioration during the 365 days
16 of lung residence, while slight surface etching was noted for the glass fibers. The authors
17 noted that in this study (and previous studies) between 20% and 60% of long fibers
18 typically cleared from the lung during the first two weeks regardless of the dissolution
19 rate of the fiber. This rapid removal indicates that these fibers likely deposit in the upper
20 airways and are cleared by ciliary action. The authors noted that the half-times for the
21 slow pool suggest that glass fibers were subject to dissolution and transverse breakage
22 during lung residence while amosite was not.

23 **5.3 Studies of fiber characteristics and tumorigenicity of SVF**

24 **5.3.1 Intrathoracic and intraperitoneal studies**

25 Most studies that have examined fiber characteristics and tumorigenicity have used
26 intrathoracic implantation or i.p. injection. Stanton *et al.* (1977, 1981) conducted
27 experiments testing the tumorigenicity of 22 glass fiber preparations, including 18
28 borosilicate glass fibers, 13 samples of crocidolite, 8 samples of aluminum oxide
29 whiskers, 7 talcs, 7 dawsonites, 4 wollastonites, 2 tremolites, 2 attapulgites, 2 halloysites,
30 2 crystals of silicon carbide and potassium titanate, and 1 crystal of nickel titanate in the
31 same pleural implantation model. [The results for glass fibers were reported in Section 4,

1 and all results are summarized here.] The tumor incidences and percent tumor
 2 probabilities, and common log of the fibers/ μg with diameter $< 0.25 \mu\text{m}$ and length > 8
 3 μm are shown in Table 5-1. Based on induction of significant numbers of pleural
 4 sarcomas by fine, durable fibers of chrysotile, crocidolite, amosite, tremolite, glass,
 5 attapulgite, dawsonite, aluminum oxide, silicon carbide, and potassium titanate, Stanton
 6 *et al.* concluded that “the carcinogenicity of fibers depends on dimension and durability
 7 rather than on physicochemical properties.”

Table 5-1. Fibrous materials tested in Osborne-Mendel rats by intrapleural implantation

Experiment No.	Compound	Tumor incidence	Tumor probability \pm SD (%)	Common log fibers/ μg ($\leq 0.25 \mu\text{m} \times > 8 \mu\text{m}$)
1	Titanate 1	21/29	95 \pm 4.7	4.94
2	Titanate 2	20/29	100	4.70
3	Silicon carbide	17/26	100	5.15
4	Dawsonite 5	26/29	100	4.94
5	Tremolite 1	22/28	100	3.14
6	Tremolite 2	21/28	100	2.84
7	Dawsonite 1	20/25	95 \pm 4.8	4.66
8	Crocidolite 1	18/27	94 \pm 6.0	5.21
9	Crocidolite 2	17/24	93 \pm 6.5	4.30
10	Crocidolite 3	15/23	93 \pm 6.9	5.01
11	Amosite	14/25	93 \pm 7.1	3.53
12	Crocidolite 4	15/24	86 \pm 9.0	5.13
13	Glass 1	9/17	85 \pm 13.2	5.16
14	Crocidolite 5	14/29	78 \pm 10.8	3.29
15	Glass 2	12/31	77 \pm 16.6	4.29
16	Glass 3	20/29	74 \pm 8.5	3.59
17	Glass 4	18/29	71 \pm 9.1	4.02
18	Aluminum oxide 1	15/24	70 \pm 10.2	3.63
19	Glass 5	16/25	69 \pm 9.6	3.0
20	Dawsonite 7	16/30	68 \pm 9.8	4.71
21	Dawsonite 4	11/26	66 \pm 12.2	4.01
22	Dawsonite 3	9/24	66 \pm 13.4	5.73
23	Glass 6	7/22	64 \pm 17.7	4.01
24	Crocidolite 6	9/27	63 \pm 13.9	4.60
25	Crocidolite 7	11/26	56 \pm 11.7	2.65
26	Crocidolite 8	8/25	53 \pm 12.9	0
27	Aluminum oxide 2	8/27	44 \pm 11.7	2.95
28	Aluminum oxide 3	9/27	41 \pm 10.5	2.47
29	Crocidolite 9	8/27	33 \pm 9.8	4.25
30	Wollastonite 1	5/20	31 \pm 12.5	0
31	Aluminum oxide 4	4/25	28 \pm 12.0	2.60
32	Crocidolite 10	6/29	37 \pm 13.5	3.09
33	Aluminum oxide 5	4/22	22 \pm 9.8	3.73
34	Glass 20	4/25	22 \pm 10.0	0

Experiment No.	Compound	Tumor incidence	Tumor probability \pm SD (%)	Common log fibers/ μ g ($\leq 0.25 \mu\text{m} \times > 8 \mu\text{m}$)
35	Glass 7	5/28	21 \pm 8.7	2.50
36	Wollastonite 3	3/21	19 \pm 10.5	0
37	Halloysite 1	4/25	20 \pm 9.0	0
38	Halloysite 2	5/28	23 \pm 9.3	0
39	Glass 8	3/26	19 \pm 10.3	3.01
40	Crocidolite 11	4/29	19 \pm 8.5	0
41	Glass 19	2/28	15 \pm 9.0	0
42	Glass 9	2/28	14 \pm 9.4	1.84
43	Aluminum oxide 6	2/28	13 \pm 8.8	0.82
44	Dawsonite 6	3/30	13 \pm 6.9	0
45	Dawsonite 2	2/27	12 \pm 7.9	0
46	Wollastonite 2	2/25	12 \pm 8.0	0
47	Crocidolite 12	2/27	10 \pm 7.0	3.73
48	Attapulgit 2	2/29	11 \pm 7.5	0
49	Glass 10	2/27	8 \pm 5.6	0
50	Glass 11	1/27	8 \pm 5.5	0
51	Titanate 3	1/28	8 \pm 8.0	0
52	Attapulgit 1	2/29	8 \pm 5.3	0
53	Talc 1	1/26	7 \pm 6.9	0
54	Glass 12	1/25	7 \pm 5.4	0
55	Glass 13	1/27	6 \pm 5.7	0
56	Glass 14	1/25	6 \pm 5.5	0
57	Glass 15	1/24	6 \pm 5.9	1.30
58	Aluminum oxide 7	1/25	5 \pm 5.1	0
59	Glass 16	1/29	5 \pm 4.4	0
60	Talc 3	1/29	4 \pm 4.3	0
61	Talc 2	1/30	4 \pm 3.8	0
62	Talc 4	1/28	5 \pm 4.9	0
63	Aluminum oxide 8	1/28	3 \pm 3.4	0
64	Glass 21	2/47	6 \pm 4.4	0
65	Glass 22	1/45	2 \pm 2.3	0
66	Glass 17	0/28	0	0
67	Glass 18	0/115	0	0
68	Crocidolite 13	0/29	0	0
69	Wollastonite 4	0/24	0	0
70	Talc 5	0/30	0	0
71	Talc 6	0/30	0	3.30
72	Talc 7	0/29	0	0

Source: Stanton *et al.* 1981.

1 Stanton *et al.* (1981) examined 22 glass fiber types (including the 17 fibers tested in the
2 1977 paper) along with 50 natural and synthetic fibers not tested in the earlier study and
3 reported incidences of pleural sarcomas in various control groups (Table 5-1). These
4 included untreated controls (3 of 488), noncarcinogenic pulmonary implants (9 of 432),
5 and noncarcinogenic pleural implants (17 of 598). The authors reported a combined
6 incidence of pleural sarcomas in all control groups of 7.7% based on the life-table

1 method. Tumor incidences in the individual experiments that exceeded 30% were
2 considered significantly different from the combined controls by the authors. The authors
3 reported that the incidence of malignant mesenchymal neoplasms correlated with fiber
4 dimensions. The correlation coefficient (r^2) was 0.8 for fibers $< 0.25 \mu\text{m}$ in diameter and
5 $> 8 \mu\text{m}$ in length, but high correlations also were noted in categories with diameters < 1.5
6 μm and lengths $> 4 \mu\text{m}$ ($r^2 = 0.45$ to 0.68). The authors also suggested that their
7 experiments could simply be measuring the efficiency of phagocytosis of fibers of
8 different dimensions since short and large-diameter fibers were avidly phagocytosed,
9 while long, thin fibers showed negligible phagocytosis.

10 As noted above and in Section 4.4, Stanton *et al.* (1981) reported correlations between
11 fiber dimensions and the probability of tumor formation, with the best fit for fibers < 0.25
12 μm in diameter and $> 8 \mu\text{m}$ in length and another correlation for fibers with a diameter of
13 up to $1.5 \mu\text{m}$ and $> 4 \mu\text{m}$ in length. Experimental data from the Stanton *et al.* publications
14 were re-analyzed by Bertrand and Pezerat (1980), Oehlert (1991), and Wylie *et al.*
15 (1987).

16 Bertrand and Pezerat (1980) confirmed the dependence with fiber dimensions. Those
17 authors used the data from Stanton *et al.* and looked for other relationships between
18 carcinogenicity and fiber size distribution using a new statistical approach
19 (correspondence analysis, multiple regression on fiber length and diameter, and linear
20 regression on the average aspect ratio). They reported a strong positive correlation
21 between tumor probability and long fibers with a small cross-section, and almost no
22 correlation with small fibers with a large cross-section. Bertrand and Pezeret concluded
23 that the carcinogenicity of fibers is a continuous, increasing function of the aspect ratio,
24 and thus show that it is not possible to separate the effects of length and diameter.

25 Oehlert (1991) also confirmed the hypothesis that the logarithm of the number of fibers $<$
26 $0.25 \mu\text{m}$ in diameter and $> 8 \mu\text{m}$ in length were predictive of tumor yield. Based on a
27 reanalysis of the Stanton *et al.* pleural sarcoma data, Oehlert reported that the log mean
28 aspect ratio was not as good a predictor of tumor incidence as the number of index
29 particles and reconfirmed the number of index particles as the primary dimensional

1 predictor of tumor incidence. However, in contrast to the “Stanton hypothesis,” which
2 states that dimensional properties alone determine carcinogenicity, there was evidence
3 that mineral type is important. Significant improvements in fit were accomplished by
4 allowing separate curves for the different mineral types and by including additional
5 covariates. Thus, using a single criterion (i.e., number of index particles) for all mineral
6 types could result in large overestimates or underestimates of tumor potential. Oehlert
7 concluded that dimensional properties are not the sole determinant of carcinogenicity.

8 Wylie *et al.* (1987) studied a point raised by Stanton *et al.* acknowledging that some
9 samples did not fit well, especially some asbestos samples. Wylie *et al.* first confirmed
10 that the number of index fibers [particles] (defined as those $< 0.25 \mu\text{m}$ in diameter and $>$
11 $8 \mu\text{m}$ in length) reflected differences in carcinogenic potency, but that the outliers were
12 related to the mathematical calculations when samples contained a low number of fibers
13 of such dimensions. They then determined the frequency distributions of length and
14 width of seven crocidolite samples that were used by Stanton *et al.* to evaluate possible
15 sources of measurement error, and to discuss the effects of these errors on the utility and
16 reliability of using the number of index particles as a measure of mineral fibrosity and
17 carcinogenicity. Although there were some differences in the frequency distributions
18 compared with Stanton *et al.*, the authors concluded that the index number (log of the
19 number of index particles) was reproducible and relatively insensitive to variations in
20 technique using the same instrumentation. The population of mineral fibers studied by
21 Stanton fell into two groups: those whose index number was indeterminate (no index
22 particles) and those whose index numbers fell between 2.5 and 6.0. Wylie *et al.* noted
23 that Stanton assigned an index number of 0 to those populations without index particles,
24 thus creating a bimodal distribution rather than a continuous function throughout the
25 range of the independent variable. Therefore, Wylie *et al.* reanalyzed the data using only
26 those populations that contained index particles. The correlation coefficient of logit of
27 tumor probability with index number was 0.307 ($r^2 = 0.094$) and was not significant.
28 However, the correlation coefficient derived from a linear regression of tumor probability
29 with index number was 0.53 ($r^2 = 0.281$), which was significant but lower than reported
30 by Stanton. Wylie *et al.* concluded that the correlation coefficients were low enough to

1 suggest the possibility that factors other than size and shape play a role in mineral fiber
2 carcinogenicity.

3 Many studies have investigated the tumorigenic properties of fibers in rats by i.p.
4 injection and are reviewed below. Where possible, the tables include information on fiber
5 dimensions (diameter and length), durability (*in vitro* dissolution rates, k_{dis} , or *in vivo*
6 half-lives, $T_{1/2}$), dose (in mg and number of fibers) and Z-scores [calculated by NTP
7 based on the reported composition (see Section 1.3.1)].

8 Pott *et al.* (1974) compared the carcinogenic effects of glass fibers (average diameter of
9 0.5 μm) with chrysotile, gypsum, nemalite, and palygorskite following i.p. injection into
10 Wistar rats [sex not specified] (Table 5-2). Based on their results they suggested that
11 fibers less than 10 μm in length could still be carcinogenic. Similarly, they proposed that
12 carcinogenicity could not be limited to fibers with diameter less than 0.5 μm based on the
13 size distribution of fibers in their sample.

Table 5-2. Fibers tested by Pott *et al.* (1974)^a

Fiber type	Diameter (μm)	Length (% < 5 μm)	Dose (mg)	Tumor incidence (mesothelioma) (%)
Chrysotile A, milled	NR	99.8%	100 (25 \times 4)	12/40 (30.0)
Nemalite	NR	96.4%	100 (25 \times 4)	25/40 (62.5)
Chrysotile A	NR	93.9%	6	27/40 (67.5)
			25	26/40 (65.0)
			100 (25 \times 4)	15/40 (37.5)
Gypsum	NR	75.0%	100 (25 \times 4)	2/40 (5.0)
Glass fibers	0.5 (average)	72.6%	100 (25 \times 4)	23/40 (57.5)
Palygorskite	NR	70.0%	75 (25 \times 3)	26/40 (65.0)
Saline	–	–	2 mL \times 4	0/80 (0)

NR = not reported.

^aNo information available on durability or number of fibers injected.

14 Pott *et al.* (1987) reported results from 15 different experiments with approximately 50
15 fibrous dusts prepared from synthetic and naturally occurring fibers. Experiments 1
16 through 13 are summarized in Table 5-3. Experiment 14 involved i.p. injections of
17 cadmium and nickel compounds and is not summarized here. Preliminary results from
18 experiment 15 (which was still in progress) were reported through 28 months, but the
19 complete results were reported in a subsequent publication (Pott *et al.* 1989) and are
20 presented below (see Table 5-4). Rats were reported as tumor bearing if they were

1 diagnosed with either sarcoma, mesothelioma, or carcinoma of the abdominal cavity, but
 2 the authors noted that only a few carcinomas were found, and the three tumor types could
 3 not always be differentiated histologically with certainty. The overall conclusion by Pott
 4 *et al.* was that length and durability of fibers are significant determinants of carcinogenic
 5 potency; however, they pointed out that relatively thick rock and ceramic fibers were
 6 “unexpectedly strong” as carcinogens. [The authors did not report any measures of
 7 durability for the fibers that they tested, however.] They did recommend re-measuring
 8 several of the fiber samples tested to confirm the relationship between fiber dimensions
 9 and carcinogenic effects.

Table 5-3. Fibers tested by Pott *et al.* (1987)^a

Fiber type	Diameter (µm)	Length (µm)	Dose (mg)	Tumor incidence (sarcoma, mesothelioma, or carcinoma) (%)
Experiment #1 (female Wistar rats, 12 wks old)				
Chrysotile, UICC/A	0.15	9	6	27/34 (77.1)
Chrysotile, UICC/A	0.15	9	25	25/31 (80.6)
Chrysotile, HCl treated	–	–	6	0/38 (0)
Chrysotile, HCl treated	–	–	25	NR
Saline	–	–	–	0/70 (0)
Experiment #2 (female Wistar rats, 12 wks old)				
Glass filaments, ES 5	5.5	39	10	2/50 (4.0)
Glass filaments, ES 5	5.5	39	40 (20 × 2)	5/46 (10.9)
Glass filaments, ES 7	7.4	46	40 (20 × 2)	1/47 (2.1)
Experiment #3 (female Wistar rats, 15 wks old)				
Slag wool, RH	2.6	26	40 (20 × 2)	6/99 (6.1)
Slag wool, Z1	1.5	14	40 (20 × 2)	2/96 (2.1)
Nemalite, Mg(OH) ₂	0.06	1.3	40 (20 × 2)	43/48 (89.6)
Saline	0.06	1.3	2 mL × 2	48 (0)
Experiment #4 (female Wistar rats, 12 wks old)				
Glass filaments, ES 5	5.5	39	250 ^b	2/28 (7.1)
Experiment #5 (female Wistar rats, 15 wks old)				
Glass filaments, ES 3	3.7	16.5	50 ^b	3/48 (6.3)
Glass filaments, ES 3	3.7	16.5	250 ^b	4/46 (8.7)
Saline	–	–	4 mL ^b	2/45 (4.4)
Experiment #6 (female Wistar rats, 12 wks old)				
Anthophyllite, UICC	0.61	2.6	2	4/37 (10.8)
Anthophyllite, UICC	0.61	2.6	10	17/39 (43.6)
Chrysotile, UICC/A milled	0.02	0.2	10	1/39 (2.6)
Glass fibers, 106	0.47	2.2	10	2/39 (5.1)
Nemalite	0.06	1.3	2	28/37 (75.7)
Nemalite	0.06	1.3	10	32/40 (80.0)

Fiber type	Diameter (µm)	Length (µm)	Dose (mg)	Tumor incidence (sarcoma, mesothelioma, or carcinoma) (%)
Experiment #7 (female and male Wistar rats, 3 wks old)				
Glass fibers, 104/1974, Ch. 2	0.3	3.5	10	13/26 (50.0)
Glass fibers, 104/1974, Ch. 2	0.3	3.5	10	18/33 (54.6)
Experiment #8 (female Wistar rats, 12 wks old)				
Chrysotile, UICC/B milled	0.06	0.56	50	1/41 (2.4)
Actinolite, F.R.G	0.17	1.9	2.5	30/45 (66.7)
Experiment #9 (female Wistar rats, 9 wks old)				
Attapulgitite, Mormoiron	0.07	0.7	60 (12 × 5)	4/114 (3.5)
Attapulgitite, Lebrija	0.07	0.5	60 (12 × 5)	4/115 (3.5)
Attapulgitite, Georgia	0.04	0.8	60 (12 × 5)	4/112 (3.6)
γ-ferric oxide hydrate (1)	0.07	0.5	135 (27 × 5)	21/111 (18.9)
Experiment #10 (female Sprague-Dawley rats, 8 wks old)				
Glass fibers, 104/1974, Ch. 1	4.8	0.29	5	44/54 (81.5)
Glass fibers, HCl-treated, 2 h	–	–	5	32/54 (59.3)
Glass fibers, HCl-treated, 24 h	5.3	0.5	5	4/54 (7.4)
Glass fibers, NaOH-treated, 2 h	–	–	5	42/54 (77.8)
Glass fibers, NaOH-treated, 24 h	5.4	0.5	5	46/53 (86.8)
Erionite, Turkey	2.9	0.38	1.25	38/53 (71.7)
Erionite, Turkey	2.9	0.38	5	43/53 (81.1)
Erionite, Turkey	2.9	0.38	20	37/53 (69.8)
Experiment #11 (female Wistar rats, 4 wks old)				
Glass fibers, 104/1974, Ch. 1	0.29	4.8	5	20/45 (44.4)
Glass fibers, HCl-treated 24 h	0.5	5.3	5	2/45 (4.4)
Glass fibers NaOH-treated 24 h	0.5	5.4	5	27/46 (58.7)
Erionite, Turkey	0.38	2.9	5	34/48 (70.8)
Actinolite, F.R.G.	0.17	1.9	0.5	54/59 (91.5)
Experiment #12 (female Sprague-Dawley rats, 8 wks old)				
Glass fibers, 100/Pen	0.33	2.4	2	21/54 (38.9)
Glass fibers, 100/Pen	0.33	2.4	10	24/53 (45.3)
Glass fibers, 100/L&V	0.32	4.4	2	26/54 (48.1)
Rock wool, Sweden	1.9	23.0	75 (25 × 3)	45/63 (71.4)
Rock wool, Sweden, fine	0.64	4.1	10	6/45 (13.3)
NaCl-sol.	–	–	2 mL × 2	3/54 (5.6)
Experiment #13 (female Wistar rats, 5 wks old)				
Attapulgitite, Caceres	0.07	1.3	10 (2 + 4 + 4)	12/30 (40.0)
Erionite, Oregon	0.21	1.8	0.5	15/31 (48.4)

Fiber type	Diameter (µm)	Length (µm)	Dose (mg)	Tumor incidence (sarcoma, mesothelioma, or carcinoma) (%)
Erionite, Oregon	0.21	1.8	2.0	28/31 (90.3)
Actinolite, F.R.G.	0.17	1.9	0.3	23/29 (79.3)
Actinolite, PVNO separately	0.17	1.9	0.3	21/32 (65.6)
Actinolite, in 1 mL 2% PVNO + PVNO separately	0.17	1.9	0.3	14/29 (48.3)
Chrysotile, UICC/B	0.11	0.9	1.0	27/32 (84.4)
Chrysotile, PVNO separately	0.11	0.9	1.0	24/30 (80.0)
Chrysotile, Calidria	0.03	1.2	0.5	2/32 (6.3)
Crocidolite, South Africa	0.20	2.1	0.5	18/32 (56.3)
Crocidolite, South Africa	0.20	2.1	2.0	28/32 (87.5)
Glass fibers, 104/475	0.18	3.2	0.5	5/30 (16.7)
Glass fibers, 104/475	0.18	3.2	2.0	8/31 (25.8)
Glass fibers, HCl-treated 24 h	–	–	2.0	16/32 (50.0)
Kevlar fibers (1)	–	–	10 (2 + 4 + 4)	4/31 (12.9)
Saline	–	–	1 mL	2/32 (6.3)

F.R.G. = Federal Republic of Germany; HCl = hydrochloric acid; NaOH = sodium hydroxide; NR = not reported; PVNO = polyvinylpyridine-*N*-oxide; UICC = Union Internationale Contre le Cancer (International Union Against Cancer).

^aNo information available on durability or number of fibers injected.

^bRelatively large diameter fibers inoculated in 4 mL saline “by laparotomia [laparotomy] in nembutal anesthesia.”

1 Pott *et al.* (1989) tested 104/475 glass fibers by i.p. injection in female Wistar rats along
2 with 10 other fibrous dusts and 3 granular dusts (not reported here) (Table 5-4). The
3 authors expressed concern about their ability to compare the dose-response relationship
4 between asbestos fibers and man-made mineral fibers because of uncertainty about the
5 number of fibers in each size category, their durability, and their surface properties. They
6 did point out that actinolite and 104/475 glass fibers had similar size distributions based
7 on the available data, and both fibers were durable in rats; however, the number of fibers
8 that induced tumors at approximately a 60% rate was much greater for the glass fibers
9 than for the actinolite fibers. They also found high tumor incidences for the relatively
10 thick basalt fibers and one of the ceramic fibers (Fiberfrax) even though the number of
11 fibers injected per rat was smaller for these fiber types than for the glass fibers. Further,
12 the number of fibers longer than 5 µm was similar in 0.25 mg of actinolite and 75 mg of
13 basalt fibers, and these preparations resulted in similar tumor incidences (56% for
14 actinolite and 57% for basalt). The authors suggested that the carcinogenic potency of the

1 fibers did not decrease with increasing diameter as would have been expected based on
 2 earlier publications, and they proposed that either the percentage of very long (> 20 µm)
 3 fibers in the two preparations or some unknown surface properties might explain the
 4 unexpected results.

Table 5-4. Fibers tested by Pott *et al.* (1989)^a

Fiber type	Diameter (µm)	Length (µm)	Dose (mg)	No. fibers × 10 ⁶	Tumor incidence (mesothelioma) (%)
Actinolite, F.R.G.	50% < 0.10	1.10	0.01	102 ^b	8/35 (23)
			0.05		15/36 (42)
			0.25		20/36 (56)
			0.25 (0.4% PVNO)		8/35 (23)
			0.25 (2% PVNO)		12/36 (33)
Chrysotile, Canadian, UICC	50% < 0.05	0.67	0.05	202 ^b	12/36 (33)
			0.25		23/34 (68)
			1.00		30/36 (83)
Glass fibers, 104/475	50% < 0.15	2.6	5	680	34/53 (64)
Basalt wool	50% < 1.1	17	75 (15 × 5)	59	30/53 (57)
Ceramic wool, Fiberfrax	50% < 0.89	13	45 (9 × 5)	150	33/47 (70)
Ceramic wool, Manville	50% < 1.4	16	75 (15 × 5)	21	12/54 (22)
Wollastonite, India	50% < 1.1	8.1	100 (20 × 5)	430	0/54 (0)
γ-Ferric oxide	50% < ~0.03	~0.5	250 (50 × 5)	NR	8/49 (16)
α-Ferric oxide	50% < ~0.01	~0.1	250 (50 × 5)	NR	2/51 (4)
Kevlar fibers	50% < 0.48	4.9	20 (4 × 5)	1260	3/53 (6)
Polypropylene fibers	50% < 1.1	10	50 (10 × 5)	409	2/51 (2)
Sodium chloride solution	–	–	10 mL (2 mL × 5)	–	2/102 (2)

F.R.G. = Federal Republic of Germany; NR = not reported; PVNO = polyvinylpyridine-*N*-oxide; UICC = Union Internationale Contre le Cancer (International Union Against Cancer).

^aNo information available on durability of fibers injected.

^bOnly a single value was reported for fiber number, and the authors did not relate that number to the dose in mg.

5 Pott *et al.* (1991) injected female Wistar rats with 3 different glass fibers with different
 6 half-lives *in vivo* (Table 5-5). The mean half-lives ranged from 38 days for B-2 glass
 7 wool to 107 days for B-1 glass wool and 238 days for B-3 glass wool. Pott *et al.* noted
 8 that only the most durable of the fibers caused tumors. Both the dose and length of the
 9 fibers were varied, with fibers designated as either K (kurz, German for short), M
 10 (medium), or L (lange, German for long). In the additional experiments reported in Table

1 5-5, Pott *et al.* injected a number of different fibrous dusts i.p. They summarized the main
2 results of these experiments for glass fibers as demonstrating that slightly durable glass
3 fibers (B-1 and B-2) did not induce a carcinogenic effect at the doses and fiber sizes
4 tested, which included up to 5.80×10^9 B-2 glass fibers with median length of 6 μm and
5 median diameter of 0.51 μm .

Table 5-5. Fibers tested by Pott *et al.* (1991)^a

Fiber type	T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diameter (µm)	Length (µm)	Dose (mg)	No. fibers × 10 ⁹	Tumor incidence (mesothelioma) (%)
B-3K	238 (183– 340)	[20.7]	0.37	3.3	6.7	0.38	10/48 (20.8)
B-3K			0.37	3.3	20	1.14	30/47 (63.8)
B-3L			0.34	5.6	6.7	0.15	19/48 (39.6)
B-3L			0.34	5.6	20	0.46	31/47 (66.0)
B-1K	107 (98– 119)	[35.8]	1.06	7.4	60 (20 × 3)	0.24	3/46 (6.5)
B-1M			1.68	10.7	20	0.05	1/48 (2.1)
B-1M			1.68	10.7	60 (20 × 3)	0.16	1/46 (2.2)
B-1L			1.40	17.8	20	0.04	1/48 (2.1)
B-1L			1.40	17.8	60 (20 × 3)	0.11	5/46 (10.9)
B-1K	107 (98– 119)	[35.8]	1.06	7.4	150 (50 × 3)	0.60	1/32 (3.1)
B-1ML			1.19	11.0	100 (50 × 2)	0.51	1/39 (2.6)
B-2K	38 (35–41)	[35.8]	0.49	4.2	6.7	0.29	0/48 (0)
B-2K			0.49	4.2	20	0.86	0/46 (0)
B-2L			0.51	6.0	6.7	0.39	0/45 (0)
B-2L			0.51	6.0	20	1.16	2/44 (4.5)
B-2L	38 (35–41)	[35.8]	0.51	6.0	100 (50 × 2)	5.80	1/35 (2.9)
JM475	NR	[21.0]	0.40	2.3	2	0.32	8/48 (16.7)
Ca-Na- metaphosphate	NA	NA	0.30	2.8	50	0.26	3/17 (17.6)
			0.30	2.8	250 (50 × 5)	1.29	4/16 (25.0)
Gypsum A 30	NA	NA	1.34	11.2	250 (50 × 5)	0.19	1/24 (4.2)
Gypsum H 30	NA	NA	0.98	9.7	250 (50 × 5)	0.16	0/12 (0)
Mg-oxide- sulphate	NA	NA	0.19	2.2	50	5.98	1/21 (4.8)
			0.19	2.2	150 (15 × 10)	17.9	0/10 (0)
Sepiolite, Uicaluaro	NA	NA	0.06	1.0	50	7.56	0/23 (0)
			0.06	1.0	250 (50 × 5)	37.8	2/21 (9.5)
Basalt	NA	NA	1.08	13.8	25	0.005	1/38 (2.6)
			1.08	13.8	150 (30 × 5)	0.030	15/21 (71.4)
Slag	NA	NA	1.21	9.0	150 (30 × 5)	0.25	2/28 (7.1)

Fiber type	T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diameter (μm)	Length (μm)	Dose (mg)	No. fibers × 10 ⁹	Tumor incidence (mesothelioma) (%)
Silicon carbide	NA	NA	0.31	3.1	0.05	0.005	2/16 (12.5)
			0.31	3.1	0.25	0.27	5/23 (21.7)
			0.31	3.1	1.25	0.13	13/21 (61.9)
			0.31	3.1	6.25	0.67	23/30 (76.7)
			0.31	3.1	25	2.68	36/37 (97.3)
Carbon	NA	NA	17.7	193	50	0	0/25 (0)
			17.7	193	250 (50 × 5)	0	0/20 (0)
NaCl solution	–	–	–	–	2 mL × 5	–	2/50 (4.0)
Al-silicate “Fiberfrax” I	NA	NA	0.47	5.5	12	0.029	15/35 (42.9)
Al-silicate “Fiberfrax” II	NA	NA	0.84	13.1	12	0.021	17/36 (47.2)
			0.84	13.1	40 (20 × 2)	0.069	29/36 (80.6)
Al-silicate, Manville5	NA	NA	1.35	16.4	40 (20 × 2)	0.009	6/36 (16.7)
Potassium titanate	NA	NA	0.22	3.2	0.5	0.045	1/34 (2.9)
			0.22	3.2	2	0.18	11/36 (30.6)
NaCl solution	–	–	–	–	1 mL × 50	–	0/34 (0)

NA = not available; NR = not reported; Z-score = sum of the percent composition of alkali and alkaline earth oxides (Na₂O + K₂O + CaO + MgO + BaO) (see Section 1.3.1 and Table 1-4) [calculated by NTP].

^aNo information available on *in vitro* dissolution rate of fibers injected.

- 1 They illustrated the relationship between fibers with long half-life that induced tumors
- 2 compared with fibers with short half-life that were not carcinogenic after i.p. injection
- 3 (Figure 5-1).

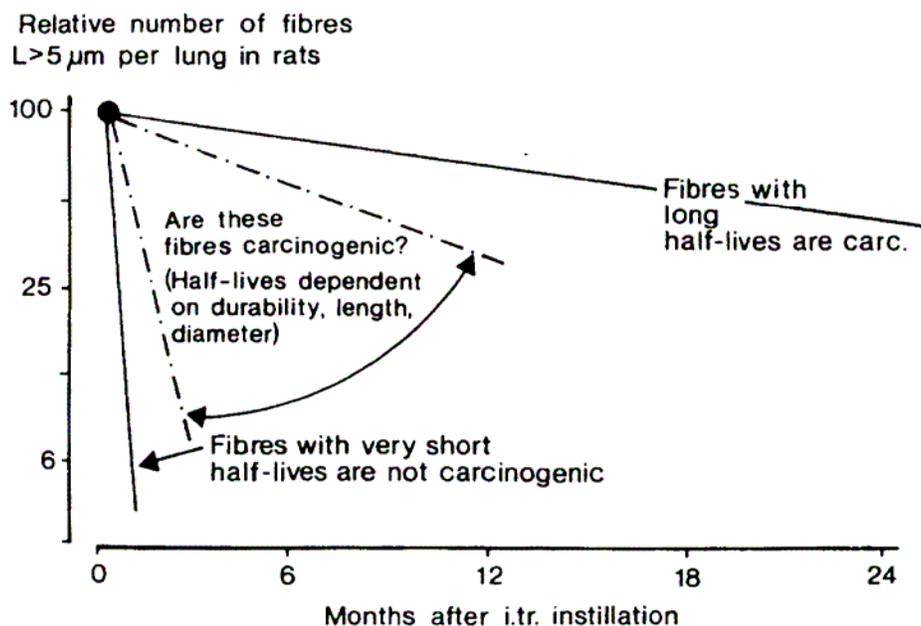


Figure 5-1. Diagram depicting relative difference in fiber half-lives and carcinogenicity

Source: Pott *et al.* 1991, used with permission.

Data shown are relative percentage of fibers $> 5 \mu\text{m}$ long vs. time after intratracheal instillation.

- 4 Pott *et al.* also plotted the dose-response relationship between fiber types and percent
- 5 tumor incidence as shown in Figure 5-2. They noted that the regression lines for the
- 6 amphibole fibers (actinolite and crocidolite) differed in dose by a factor of about 20
- 7 compared with the regression line for the 6 different glass fibers tested, but they did not
- 8 have an explanation for the difference.

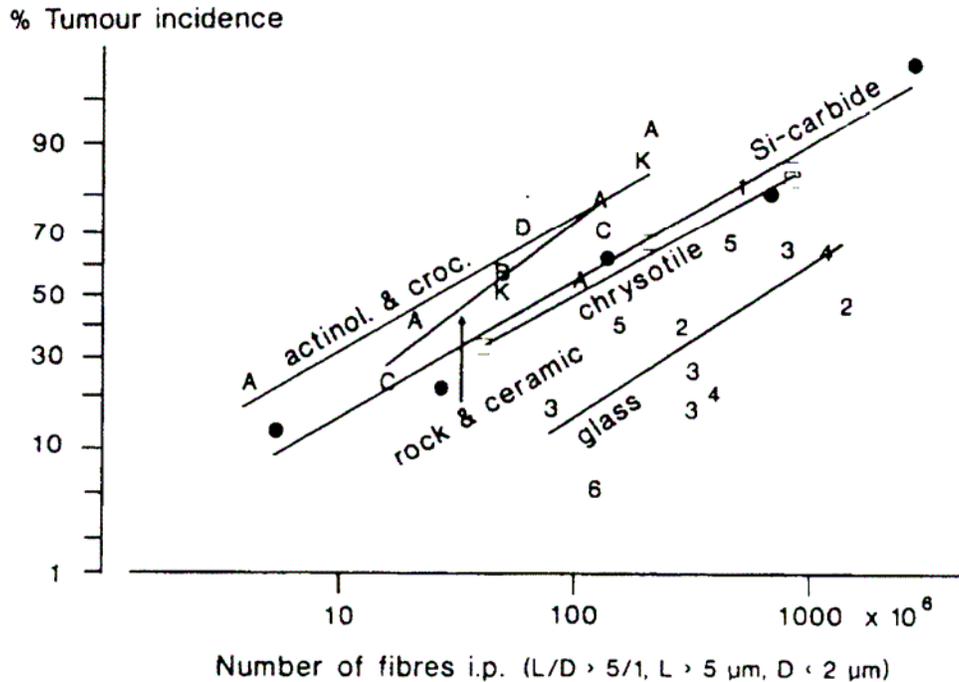


Figure 5-2. Exposure dose by i.p. injection of different fiber types and percent tumor incidence

Source: Pott *et al.* 1991, used with permission.

A = actinolite, K = crocidolite, B = basalt, D = diabase, C = ceramic (2 types); open squares = chrysotile, closed circles = silicon carbide, 1-6 = glass microfibers (1-3 & 6 = Manville; 4 & 5 = Bayer): 1 = M-104/E, 2 = M-100/475, 3 = M-104/475; 4 = B-3K, 5 = B-3L, 6 = M 106.

1 Roller *et al.* (1996) conducted a study designed to examine the dose-response relationship
 2 for fiber types of different dimensions and *in vivo* durabilities (Table 5-6). The
 3 relationships were discussed in Roller *et al.* (1997). The fibers were divided into groups
 4 of relatively long, thick fibers (aspect ratio > 5:1, median length 8 to 17 μm, median
 5 diameter 0.7 to 1.2 μm) and short, thin fibers (aspect ratio > 5:1, median length 2 to 4 μm,
 6 median diameter 0.2–0.5 μm). The long, thick fibers included the following: fibers B-01-
 7 0.9, B-09-2.0, B-20-2.0, glass wool fibers MMVF11, stone wool fibers MMVF21, slag
 8 wool fibers MMVF22, M-stone 3, and R-stone-E3. The short, thin fibers included the
 9 following: glass fibers B-09-0.6, B-20-0.6 [reported in Table 1 of Roller *et al.* (1997) as
 10 B-0.9-0.6, but the doses matched the B-20-0.6 fiber type], glass fibers M-753-104, and
 11 crocidolite and tremolite asbestos. The probit model was fitted to the data, and each data
 12 set was constrained to a common slope (Figure 5-3).

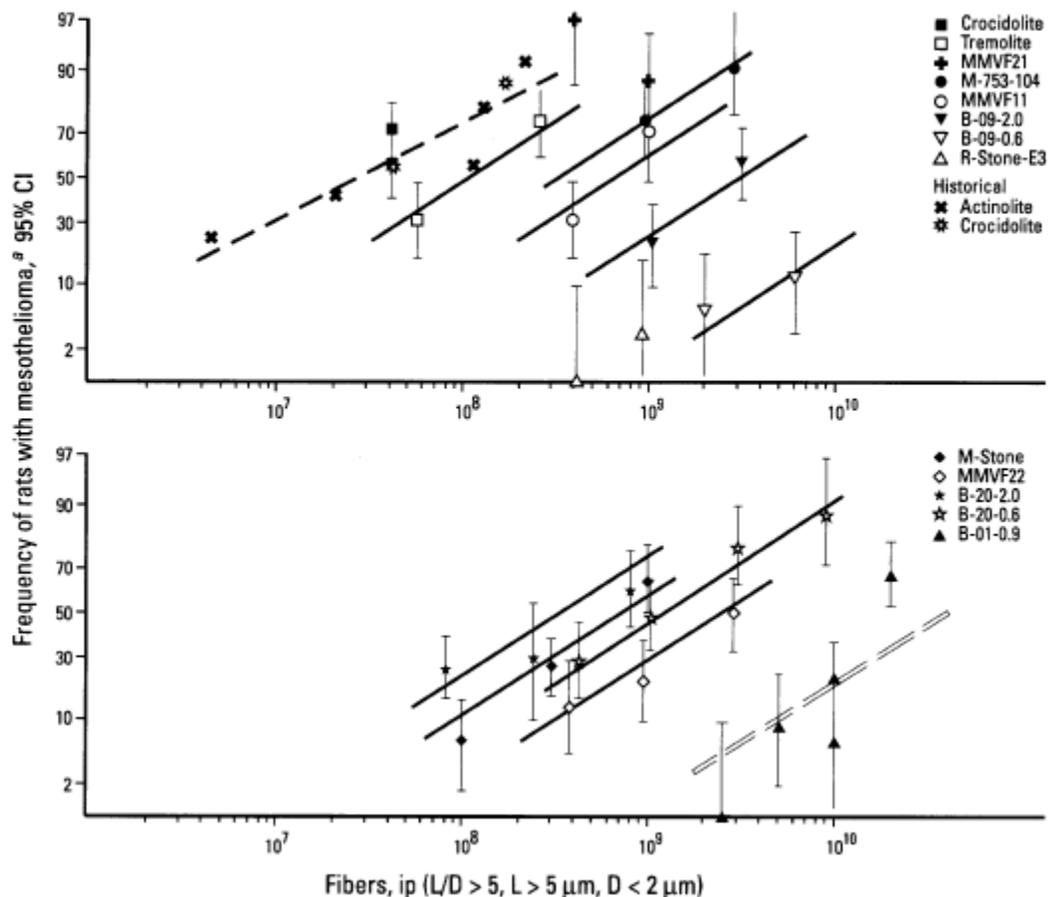


Figure 5-3. Probit analysis of the number of fibers injected (i.p.) and the frequency of peritoneal mesothelioma in rats

Source: Roller *et al.* 1997, reproduced with permission from *Environmental Health Perspectives*.

Combined data from three experiments (1990–1992). Combined results of asbestos studies (actinolite and crocidolite; combined historical data) are presented in the top panel, broken line. Data are presented in 2 panels for clarity.

L = length, D = diameter.

^a Historical data for mesothelioma/sarcoma.

- 1 Data from crocidolite, R-Stone-E3, and MMVF21 were not included in the probit
- 2 analysis because the results for these fibers were at the extremes of either no response for
- 3 R-Stone-E3 or a near maximal response at the lowest dose tested for MMVF21 and
- 4 crocidolite. The normalized data for the various dusts also were plotted with a linear scale
- 5 for frequency of mesothelioma, which resulted in a slightly superlinear curve (Figure 5-
- 6 4). The authors fitted a curve separately to the data for the B-01-0.9 data, which resulted

- 1 in a sublinear shape. The authors noted that this dust has a relatively low durability and
- 2 was tested with the highest dose of 1,000 mg.

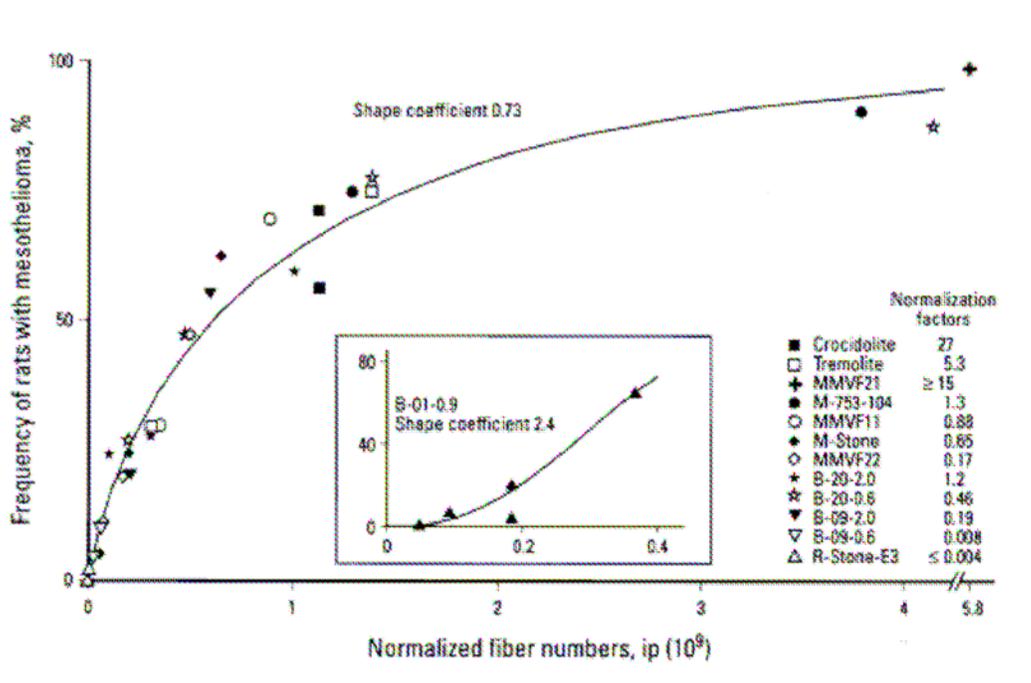


Figure 5-4. Percent incidence of mesothelioma after i.p. injection of various fiber dusts

Source: Roller *et al.* 1997, reproduced with permission from *Environmental Health Perspectives*.

Shape coefficient is calculated from the Weibull model and fitted to normalized data. Insert is for B-01-0.9 fiber (sublinear curve; dose values normalized so that scale of the x-axis is comparable with the larger plot).

- 3 The overall conclusion by Roller *et al.* (1997) was that the mechanism responsible for
- 4 mesotheliomas in their experimental system was specific to the fibrous shape of the
- 5 particles administered based on parallelism of the probit lines calculated for each fiber
- 6 type.

Table 5-6. Fibers tested by Roller *et al.* (1996, 1997)^a

Fiber type	T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diameter (μm)	Length (μm)	Sex	Dose (mg)	No. fibers \times 10 ⁹	Tumor incidence (mesothelioma) (%)
Untreated	NA	NA	NA	NA	F	0	0	0/37 (0)
Saline	NA	NA	NA	NA	F	2 mL \times 20	0	0/93 (0)
					M	2 mL \times 20		1/69 (1)
					F	2 mL \times 20		0/38 (0)
MMVF-21	326 (266–421)	[30.2]	1.02	16.9	F	60 (30 \times 2)	0.4	37/38 (97)
					F	150 (30 \times 5)	1.0	33/38 (87)
MMVF-11	199 (172–235)	[27.1]	0.77	14.6	F	70 (35 \times 2)	0.4	12/40 (30)
					F	180 (30 \times 6)	1.0	16/23 (70)
M-stone	116 (108–126)	[37.1]	0.84	10.1	F	8.5	0.1	2/32 (6)
					M	8.5	0.1	2/36 (6)
					F	25.5	0.3	9/32 (28)
					M	25.5	0.3	8/36 (22)
					M	85 (42.5 \times 2)	1.0	22/35 (63)
MMVF-22	81 (75–89)	[48.2]	0.77	8.7	F	20	0.4	4/40 (10)
					F	50	1.0	8/40 (20)
					F	150 (50 \times 3)	2.9	18/38 (47)
B-01-0.9	32 (26–45)	[35.8]	~0.7	~9	F	125 (25 \times 5)	2.5	3/39 (8)
					F	250 (25 \times 10)	5.0	4/37 (11)
					F	500 (25 \times 20)	10.0	3/36 (8)
					M	500 (25 \times 20)	10.	10/48 (21)
					M	1,000 (25 \times 40)	20.0	33/50 (66)
R-stone-E3	32 (29–36)	[47.3]	1.03	16.9	F	114 (28.5 \times 4)	0.4	0/38 (0)
					F	256.5 (28.5 \times 9)	0.9	4/35 (11)
Crocidolite	NA	[4.3–14.6]	0.19	1.8	F	0.5 (0.1 \times 5)	0.042	25/32 (78)
					M	0.5 (0.1 \times 5)	0.042	32/48 (67)
					F	0.5 (0.1 \times 5)	0.042	20/39 (51)
Tremolite	NA	[32–41.1]	0.29	3.4	F	3.3	0.057	9/40 (23)
					M	15	0.26	30/40 (75)
M-753-104	NA	[24.8]	0.22	~3.3	F	17	1.0	30/40 (75)
					F	50	2.9	36/40 (90)

Fiber type	T _{1/2} , days (95% CI) <i>in vivo</i>	Z-score	Diameter (μm)	Length (μm)	Sex	Dose (mg)	No. fibers × 10 ⁹	Tumor incidence (mesothelioma) (%)
B-09-0.6	NA	[26.7]	0.49	3.3	F	100 (50 × 2)	2.0	1/40 (3)
					F	300 (50 × 6)	6.1	4/39 (10)
B-09-2.0	NA	[26.7]	1.19	10.5	F	150 (50 × 3)	1.1	9/40 (23)
					F	450 (50 × 9)	3.2	21/40 (53)
B-20-0.6	NA	[38]	0.30	3.6	F	3.5	0.4	12/40 (30)
					F	8.5	1.0	17/40 (43)
					F	25	3.0	30/40 (75)
					F	75 (25 × 3)	9.0	27/32 (87)
B-20-2.0	NA	[38]	0.77	7.8	F	6	0.08	2/32 (6)
					M	6	0.08	15/36 (42)
					F	18	0.24	7/32 (22)
					M	18	0.24	12/34 (35)
					M	60 (30 × 2)	0.8	21/35 (60)

NA = not available; Z-score = sum of the percent composition of alkali and alkaline earth oxides (Na₂O + K₂O + CaO + MgO + BaO) (see Section 1.3.1 and Table 1-4) [calculated by NTP].

^aNo information available on *in vitro* dissolution rate of fibers injected.

1 Lambré *et al.* (1998) conducted a study to evaluate five newly developed MMVFs, two
2 glass wools (A and C) and three stone wools (F, G, and H) (Table 5-7) using a testing
3 protocol and dose selections ($0.5\text{--}2.0 \times 10^9$ Pott fibers [defined as $L > 5 \mu\text{m}$, $D < 2 \mu\text{m}$
4 and $L/D > 5$]) recommended by the German MAK (Maximale Arbeitsplatz Konzentration
5 [maximum workplace concentration]) Commission (intraperitoneal test in female Wistar
6 rats using a single injection, for a long duration). [The highest dose technically injectable
7 for glass and stone fibers was 35 mg and 55, which was the lower limit of the MAK
8 Commission requirement, so two successive injections were required.] The fibers were
9 characterized by high dissolution rates (k_{dis}) *in vitro* and short biopersistence ($t_{1/2}$ in the
10 inhalation test from 3.5 up to 13 days for fibers with length $> 20 \mu\text{m}$. The samples had
11 been specially manufactured and processed to enrich for fibers with lengths (median
12 length between 10 and 15 μm) and diameters (medium less than 1 μm) that are
13 considered to be the most toxic. The stone wool fibers designated H had the highest
14 weighted half-time (13 days) for persistence for fibers $> 20 \mu\text{m}$, although only slightly
15 higher than the range of the other 4 fibers, which was 3.5 to 8.5 days (Bernstein *et al.*
16 1996). The H fibers caused 7/51 (14%) mesotheliomas and 9/51 (17.6%) intra-abdominal
17 tumors with serosal spread [IATSS], which included all malignant tumors (mesothelioma,
18 carcinoma, and sarcoma beginning and/or spreading in the abdominal cavity) at the
19 highest dose (55 mg) tested, while none of the other fibers caused more than 2/51 (4%)
20 mesothelioma at any dose tested. The positive control, crocidolite, caused 20/51 (39%)
21 mesothelioma and 25/51 (49%) IATSS at the highest dose of 0.5 mg, and showed a dose
22 response relationship with tumor development. The authors summarized the findings as
23 showing that the i.p. test tended to demonstrate a low carcinogenic potency (except for
24 fiber H) for the fibers that they studied, which all had high dissolution rates *in vitro* at pH
25 7.4 along with low biopersistence for fibers with length $> 20 \mu\text{m}$.

Table 5-7. Fibers tested by Lambré *et al.* (1998)^a

Fiber type	W-T _{1/2} ^a , days (fibers > 20 µm)	k _{dis} , SiO ₂ , ² ng/cm ² -h	Z- score	Diameter, µm	Length, µm	Dose, mg	No. critical fibers ^b × 10 ⁶	Tumor incidence	
								Mesothelioma (%)	IATSS ^c (%)
Saline	NA	NA	NA	NA	NA	NA	0 0	0/51 (0) 0/51 (0)	NR NR
Crocidolite	NA	< 1	[9.81]	0.29	9.4	0.005 0.050 0.500	1.1 11 110	4/51 (7.8) 8/51 (15.7) 20/51 (39.2)	4/51 (7.8) 10/51 (19.6) 25/51 (49.0)
Fiber A (glass wool)	3.5	129	[26.7]	0.70	24.6	0.7 2.1 7.0 35 (17.5 × 2)	9.2 27 92 460	2/51 (3.9) 0/51 (0) 0/51 (0) 1/51 (1.9)	3/51 (5.9) 1/51 (1.9) 1/51 (1.9) 3/51 (5.9)
Fiber B ^d (glass wool)	17	580	[34.42]	0.52	8.90	0.7 2.1 7.0 35 (17.5 × 2)	8.6 25.8 86.1 430	1/51 (1.9) 0/51 (0) 0/51 (0) 0/51 (0)	4/51 (7.8) 2/51 (3.9) 1/51 (1/9) 2/51 (3.9)
Fiber C (glass wool)	4.1	309	[26.74]	0.69	27.2	0.7 2.1 7.0 35 (17.5 × 2)	12.6 38 126 630	1/51 (1.9) 1/51 (1.9) 0/51 (0) 0/51 (0)	5/51 (9.8) 4/51 (7.8) 1/51 (1.9) 1/51 (1.9)
Fiber F (stone wool)	8.5	96	[36.35]	0.72	15.8	1.1 7.7 55.0	11 77 550	2/51 (3.9) 0/51 (0) 1/51 (1.9)	3/51 (5.9) 1/51 (1.9) 3/51 (5.9)
Fiber G (stone wool)	5.4	129	[32.75]	0.74	16.0	1.1 7.7 55.0	9.2 64.4 460	1/51 (1.9) 0/51 (0) 1/51 (1.9)	2/51 (3.9) 1/51 (1.9) 2/51 (3.9)
Fiber H (stone wool)	13	169	[35.27]	0.79	17.1	1.1 7.7 55.0	5.2 36.4 260	1/51 (1.9) 0/51 (0) 7/51 (13.7)	3/51 (3.9) 1/51 (1.9) 9/51 (17.6)

k_{dis} = *in vitro* dissolution rate, measured at pH = 7.4; NA = not available; NR = not reported; Z-score = sum of the percent composition of alkali and alkaline earth oxides (Na₂O + K₂O + CaO + MgO + BaO) (see Section 1.3.1 and Table 1-4) [calculated by NTP].

^aWeighted half-life reported by Bernstein *et al.* 1996.

^bCritical fibers (also called Pott fibers by some authors) are defined by $L > 5 \mu\text{m}$, $D < 2 \mu\text{m}$, $L/D > 5$.

^cIATSS are defined by the authors as intra-abdominal tumors with serosal spread, which included all malignant tumors (mesothelioma, carcinoma, and sarcoma) beginning and/or spreading in the abdominal cavity.

^dResults for Fiber B were reported by Grimm *et al.* (2002) who noted that the fiber type was used in the Lambré study as an internal comparison, but the results were not published by Lambré *et al.* “due to the commercial competitive situation at that time.”

1 Miller *et al.* (1999b) tested the carcinogenicity of 100/475 glass microfibers, amosite,
2 MMVF10 glass wool, MMVF21 and MMVF22 stone wool, and RCF1, RCF2, and RCF3
3 refractory ceramic fibers by i.p. injection to male Wistar rats. The authors stated that the
4 objectives of their study included comparing the abilities of a range of mineral fibers to
5 produce mesothelioma in rats by i.p. injection and to relate the dimensions and durability
6 of the fibers with their carcinogenic potential. The set of fiber samples was selected to
7 represent a range of physico-chemical properties. [A silicon carbide whisker was also
8 tested, but the results are not reported here; no control group was included.] The fiber
9 characteristics and the tumor incidences resulting from the i.p. injections are reported in
10 Table 5-8. No statistical comparisons were reported, but the highest tumor rate was
11 reported for MMVF21 (19/20) followed by amosite and RCF1 (21/24 for both fiber
12 types). Tumor rates for the glass wool-treated groups were 13/22 for MMVF10 and 8/24
13 for 100/475 glass. One refractory ceramic fiber (RCF4) produced no tumors (0/22), and
14 the authors noted that this sample, which was derived from RCF1 by heat treatment, had
15 “many fewer long fibres than RCF1.” The authors used stepwise regression models with
16 mass dose injected, estimated numbers of injected fibers for various length and diameter
17 categories, estimated rates of biopersistence in the lung after intratracheal injection, and
18 estimated coefficients of dissolution *in vitro*. At step 2, the model predicted decreasing
19 survival (the response variable was median lifetime) with increasing numbers of longer
20 fibers and increasing biopersistence (the authors noted that the model preference for
21 biopersistence over *in vitro* dissolution rate was “consistent with the belief that
22 dissolution is not the sole factor governing biopersistence”). However, at step 3, the
23 model predicted increasing survival with increasing fiber numbers over 10 µm in length,
24 which the authors considered “more problematic” because of the direction of the effect.
25 The authors noted that they preferred the first model on the basis of plausibility, but they
26 also suggested that step 3 might represent “overfitting” based on the size of the dataset
27 and the fact that step 2 represented the largest gain in variance explained for the model.

Table 5-8. Fibers tested by Miller *et al.* (1999b) (sorted by k_{dis} in descending order)^a

Fiber type	k_{dis} , SiO ₂ (ng/cm ² -h)	Z-score	Diameter class (μ m)	Length (μ m)	Dose (mg) ^b	No. fibers ^c $\times 10^6$	Tumor incidence (mesothelioma) (%)
MMVF10	122.4 ^d	NA	< 0.95 > 0.95	> 5	144.4	314 659	13/22 (59)
MMVF22 (stone wool)	52.8	NA	< 0.95 > 0.95	> 5	129.6	671 544	13/24 (54)
MMVF21 (stone wool)	28.9	NA	< 0.95 > 0.95	> 5	183.1	1,012 644	19/20 (95)
100/475	9.1	[22.9]	< 0.95 > 0.95	> 5	8.3	1,868 12	8/24 (33)
RCF 1	4.4	NA	< 0.95 > 0.95	> 5	110.9	394 374	21/24 (88)
RCF 2	3.1	NA	< 0.95 > 0.95	> 5	188.8	619 550	13/18 (72)
RCF 4	0.5	NA	< 0.95 > 0.95	> 5	90.4	264 466	0/22 (0)
Amosite	0.2	[1.8]	< 0.95 > 0.95	> 5	6.1	402 8	21/24 (88)

k_{dis} = *in vitro* dissolution rate; NA = not available; RCF = refractory ceramic fiber; Z-score = sum of the percent composition of alkali and alkaline earth oxides (Na₂O + K₂O + CaO + MgO + BaO) (see Section 1.3.1 and Table 1-4) [calculated by NTP].

^a No information available on *in vivo* half-life ($T_{1/2}$) of fibers injected.

^b Injected doses were selected to provide an estimated 10^9 fibers > 5 μ m in length.

^c Fiber numbers provided for each diameter class (reported separately for < 0.95 μ m and > 0.95 μ m); target dose was a total of $1,000 \times 10^6$ fibers.

^d Different k_{dis} values for MMVF10 were reported by Hesterberg and Hart (2001) (300 ng/cm² per hour) and McConnell *et al.* (1999) (259 ng/cm² per hour).

1 Grimm *et al.* (2002) tested 3 newly developed biosoluble insulation glass wool fibers (M,
2 P, and V) and 1 newly developed biosoluble insulation stone wool fiber along with a
3 previously developed biosoluble glass fiber (B) (Table 5-9). Values for the biopersistence
4 of three of the glass wool fibers (B, M, P) and the stone wool fibers (O) were reported,
5 with P fibers having the longest biopersistence (21 days), followed by B fibers (17 days),
6 and the M and O fibers (8.5 days). [No biopersistence data were reported for V glass
7 fibers.] The authors considered that, “the physical-chemical properties and biopersistence
8 of these fibers are similar and therefore little difference in the fundamental biological
9 reactions would be expected;” [however, the highest tumor incidences among the B, M,
10 P, and O fibers were for the P and B fibers, which have the longest biopersistence.]
11 Grimm *et al.* suggested that fiber length as well as biopersistence could help explain the
12 increased tumorigenic response in their study. Tumor levels were increased significantly
13 [statistical test and level of significance not reported by the study authors] for the high
14 doses of fibers B (17%), P (15%), and V (27%). [According to Fisher’s exact test
15 performed by NTP, *P* values were 0.0016 for the high-dose B fibers, 0.003 for P, and <
16 0.001 for V (see Table 4-9). Hence, fiber B cannot be considered as non-carcinogenic in
17 this study.] Incidences of mesothelioma in the asbestos groups were about 53% to 88%.

Table 5-9. Fibers tested by Grimm *et al.* (2002) (arranged by *in vivo* clearance rate in descending order)

Study design	Fiber type	T _{1/2} , days (95% CI) <i>in vivo</i>	k _{dis} , SiO ₂ (ng/cm ² -h)	Z-score	Diameter (median)	Length (median)	Dose, mg	No. WHO fibers × 10 ⁶	Tumor incidence (mesothelioma) (%)
Female Wistar rats	Untreated	–	NA	NA	NA	NA	0	0	0/51 (0)
	Saline	–	NA	NA	NA	NA	2.5 mL × 20	0	0/51 (0)
i.p. injection	P (glass wool)	21	610	[45.45]	0.40	9.60	51.15	500	0/51 (0)
							204.6	2000	4/51 (8)
							511.5	5000	8/52 (15)
123 wk of observation	B (glass wool)	17	580	[34.42]	0.52	8.90	216.4	2000	3/51 (6)
							541.0	5000	9/53 (17)
	M (glass wool)	8.5	1,037	[30.04]	0.41	7.70	41.0	500	0/50 (0)
							164.0	2000	0/51 (0)
							410.0	5000	0/52 (0)
	O (stone wool)	8.5	523	[26.67]	0.40	10.60	53.65	500	0/51 (0)
							214.6	2000	1/51 (2)
536.5							5000	0/51 (0)	
V (glass wool)	NA	450	[26.36]	0.80	9.90	72.4	500	2/51 (4)	
						289.6	2000	1/51 (2)	
						724.0	5000	14/51 (27)	
Crocidolite	NA	~1	[9.81]	0.30	6.90	0.5	100	27/51 (53)	
						5.0	1000	45/51 (88)	

k_{dis} = *in vitro* dissolution rate; NA = not available.

Z-score = sum of the percent composition of alkali and alkaline earth oxides (Na₂O + K₂O + CaO + MgO + BaO) (see Section 1.3.1 and Table 1-4) [calculated by NTP].

1 5.3.2 Inhalation studies

2 Chronic inhalation studies with glass wool fibers (microfibers and insulation glass wool
3 fibers) were described in detail in Section 4.4. Several of these studies also evaluated
4 fiber characteristics, such as fiber length, *in vitro* dissolution, and biopersistence and
5 tumorigenicity (see Section 5.3.4 for modeling studies).

6 Cullen *et al.* (2000) and Davis *et al.* (1996) reported results of a chronic inhalation study
7 with an E-glass microfiber (104E) and another microfiber type (JM100/475). The 104E
8 fibers caused increased incidences of lung carcinoma and adenoma combined compared
9 with controls, but the JM100/475 fibers did not (see Section 4.1.2 and Table 4-4). The
10 authors reported that long fibers (15 to 20 μm and $> 20 \mu\text{m}$) of the JM100/475 sample
11 persisted longer than those of 104E. However, fiber analyses after 12-months exposure
12 and 12-months recovery periods showed a decrease in Ba, Ca, K in JM100/475. These
13 elements were not present in native 104E fibers. The authors suggested that the different
14 pathogenicity between the two fiber types was partly due to differences in numbers of
15 long fibers and to differences in surface properties, possibly due to dissolution of 100/475
16 fibers. The authors also noted that the latency period for mesotheliomas was shorter with
17 104E fibers than with amosite asbestos fibers tested in this study.

18 In an inhalation carcinogenicity study conducted in male Syrian golden hamsters,
19 McConnell *et al.* (1999) presented data for MMVF10a, MMVF33 (special-purpose glass
20 fibers prepared by mixing three types of commercially manufactured 475 glass [codes
21 104, 108B, and 110]), and amosite asbestos. The aerosol dimensions and lung doses of
22 the asbestos (0.6 μm diameter) and the test fibers (MMVF10a and MMVF33) (0.9 μm
23 diameter) were comparable (Hesterberg and Hart 2001). No lung tumors were observed
24 in any group, but incidences of mesothelioma were increased in positive controls
25 (amosite asbestos; 22/85 for mid-dose and 17/87 for high-dose) compared with 1 of 83 in
26 the MMVF33 group (see Section 4.1.2 and Table 4-5). McConnell *et al.* concluded that
27 the severity of the lung and pleural lesions in their study increased as the cumulative fiber
28 burden (particularly fibers $> 20 \mu\text{m}$ in length) increased in the lung, thoracic wall, and
29 diaphragm. The severity of the lesions also was inversely related to the *in vitro*
30 dissolution rates, i.e., the faster the dissolution, the lower the cumulative fiber burden.

1 Accordingly, dissolution rates (in this study) for MMVF10, MMVF33, and amosite were
2 259, 12, and 0.2 ng/cm² per hour, respectively. [However, it should be noted that
3 dissolution rates for the same fibers can vary between researchers, depending on the
4 methodology used. For example, Hesterberg and Hart (2001) reported the dissolution rate
5 for MMVF10 fibers as 300 ng/cm² per hour, McConnell *et al.* (1999) reported a rate of
6 259 ng/cm² per hour, and for Miller *et al.* (1999b) the rate was 122.4 ng/cm² per hour
7 (see Tables 5-8 and 5-10). The dissolutions rates also vary depending on the pH at which
8 the assay is performed.]

9 Hesterberg and Hart (2001) reviewed data from various inhalation studies in rats and
10 compared lung deposition, biopersistence, and *in vitro* dissolution with pathogenicity of
11 various fiber types. The authors reported that the results of these studies clearly indicated
12 a relationship between biopersistence in the lung and pathogenicity (see Table 5-10).
13 Characteristics of the more pathogenic fibers included little or no change in chemical
14 composition, morphology, or fiber dimensions (which the authors interpreted as
15 suggesting no significant dissolution or transverse fragmentation), and preferential
16 clearance of shorter fibers. The nonpathogenic fibers showed chemical composition and
17 surface changes, a decrease in average fiber dimensions, and a more rapid decrease in the
18 number of long fibers compared with short fibers. Data from the biopersistence studies
19 for amosite and crocidolite asbestos are compared with special-purpose fibers (MMVF32
20 and MMVF33), glass wool (MMVF10 and MMVF11), refractory ceramic fibers
21 (RCF1a), rock wool (MMVF21), slag wool (MMVF22), HT stonewool (MMVF34), and
22 a hybrid fiber (X607) in Table 5-10. The clearance half-times for insulation glass fibers
23 MMVF10 and MMVF11, slag wool MMVF22, stone wool MMVF34, and hybrid fiber
24 X607 are faster than special-purpose glass fibers MMVF32 and MMVF33, and RCF1a,
25 and rock wool MMVF 21; clearance half-times for asbestos are slower than for the SVFs.
26 The fibers had different *in vitro* dissolution rates; the lowest dissolutions rates were found
27 for asbestos, and the highest for the hybrid fiber. However, as noted above, dissolution
28 rates for the same fibers can vary between researchers, depending on the methodology
29 used, and three different estimates were identified for MMVF10 fibers.

Table 5-10. Comparison of the lung deposition, biopersistence, *in vitro* dissolution, and lung pathogenicity in rats of synthetic vitreous fibers and asbestos

Fiber type	Exposure (fibers/cm ³)		Lung deposition ^a			Clearance half-time, fibers > 20 µm (days)	<i>In vitro</i> dissolution ^b		Chronic inhalation lung pathogenicity	
	> 5 µm	> 20 µm	Total	> 5 µm	> 20 µm		pH 7.4 k _{dis}	pH 4.5 k _{leach}	Fibrosis	Tumors
Crocidolite	2,600	290	99.6	29.8 ± 7.1	1.0 ± 1.0	817	< 1	nd	+	+
Amosite	700	235	22.6	10.9 ± 1.0	1.6 ± 0.3	418	< 1	nd	+	+
MMVF32 E glass	400	150	7.6	5.7 ± 1.3	1.3 ± 0.3	79	9	7	+	+
MMVF 21 rock wool	250–400	100–150	11.9	7.7 ± 1.0	1.1 ± 0.1	67	20	72	+	–
RCF1a	400	150	13.4	8.3 ± 2.0	1.5 ± 0.2	55	3	nd	+	+
MMVF33 475 glass	400	150	9.8	7.1 ± 0.6	1.4 ± 0.3	49	12	13	+	±
MMVF10 glass wool	250–350	100	13.8	8.6 ± 1.6	1.0 ± 0.2	14.5	300	329	–	–
X607 hybrid fiber	nd	nd	5.6	3.6	nd	9.8	990	nd	–	–
MMVF11 glass wool	250–350	100	8.6	5.6 ± 1.2	1.0 ± 0.2	9	100	25	–	–
MMVF22 slag wool	250–350	100	5.8	3.4 ± 0.6	0.4 ± 0.1	9	400	459	–	–
MMVF34 stone wool	400	150	13.9	9.1 ± 1.7	1.5 ± 0.4	6	59	1010	–	–

Source:(Hesterberg and Hart 2001).

nd = no data.

^a Rats were exposed 6 hours/day for 5 days. Reported lung burdens were determined one day after exposure stopped.^b units = ng/cm² per hour.

1 Miller *et al.* (1999a) examined the influence of fiber characteristics on tumor
2 development in rat lungs for inhalation studies with the same set of nine fiber types that
3 they reported on for intraperitoneal studies (Miller *et al.* 1999b) (see Table 5-9). Data for
4 modeling was obtained from studies carried out by the Colt Fibre Research Programme
5 and reported by Davis *et al.* (1996) (see Section 5.3.2), and by the Thermal Insulation
6 Manufacturers Association and reported by Bunn *et al.* (1993) [an interim report of
7 separate studies for refractory ceramic fibers, fibrous glass, and rock and slag wool],
8 Hesterberg *et al.* (1993, 1995), Mast *et al.* (1995b) [studies on ceramic fibers only], and
9 McConnell *et al.* (1994) (see Section 4.1.2 and Table 4-4 for results of Hesterberg *et al.*
10 [1993, 1995] and McConnell *et al.* [1994]). The factors of fiber dimensions, persistence
11 in the lung, dissolution *in vitro*, and cell toxicity *in vitro* were assessed. In the inhalation
12 studies, the determining factors were the number of long, thin fibers (> 20 µm long and <
13 1 µm in diameter) and the dissolution rate adjusted for mass lost per unit initial mass.
14 Short-term cell toxicity tests *in vitro* were not significantly related to cancer risks in any
15 model tested. The authors noted that the effect of dissolution rate rather than
16 biopersistence in the lung was contrary to expectations, but they suggested that larger
17 measurement error for *in vivo* biopersistence compared with *in vitro* dissolution might be
18 responsible. The authors noted that overall the results for modeling of inhalation studies
19 were “broadly consistent” with the studies for intraperitoneal injection of the same fibers.

20 5.3.3 Modeling studies: inhalation or intraperitoneal injection

21 A model designed to predict the development of fibrosis or tumors after inhalation or
22 intraperitoneal injection of fibers was developed based on the hypothesis that the effect of
23 a rapidly dissolving fiber (> 20 µm in length) is equivalent to a smaller dose of a durable
24 fiber (Eastes and Hadley 1996). As discussed in Section 5.2 fibers > 20 µm in length have
25 been proposed to be cleared by dissolution in extracellular fluid, and Eastes and Hadley
26 considered the dose of a fiber that dissolves in 1 year to have the same effect as half that
27 dose for a fiber that dissolves in 2 years or more, which the authors considered the
28 approximate lifespan for the rat. The authors noted that their model did not rely on
29 adjustable parameters, but only on the dissolution rate constant (k_{dis}), which could be
30 measured *in vitro* and used to estimate the lifetime for the fibers. An adjustment factor
31 (α) was calculated as the ratio of the time the fiber would remain in the lung compared

1 with the lifetime of the animal and introduced into the dose-response relation. The
2 predictions of the model were compared with *in vivo* results obtained by the Research and
3 Consulting Company in Geneva, Switzerland for seven fiber types, i.e., crocidolite
4 asbestos, chrysotile asbestos, kaolin refractory ceramic fibers, MMVF10 and MMVF11
5 glass wools, MMVF21 rock wool, and MMVF22 slag wool, with endpoints of fibrosis
6 and lung cancer after inhalation, and mesothelioma after intraperitoneal injection. The
7 k_{dis} values for these seven fiber types ranged from 0.1 ng/cm² per hour for crocidolite to
8 400 ng/cm² per hour for MMVF22 slag wool. The authors noted that the predicted
9 response depended only on the dissolution rate of the fibers, and not on the fiber family,
10 but they felt the model was limited in its ability to predict results for different durable
11 fibers, which might differ in their tumorigenicity despite being similarly durable. When
12 the predictions of the model with adjustments for dose were compared with the observed
13 incidences of fibrosis or tumors, the values of χ^2 were 109 ($P = 0.62$) for fibrosis by
14 inhalation, 17 ($P = 0.16$) for lung tumors by inhalation, and 35 ($P = 0.051$) for
15 mesothelioma by i.p. injection. The authors considered a P value greater than about 0.05
16 to be good evidence that the model predicted the observed values to within the error
17 involved in the experimental data.

18 In a review of the characteristics of various SVFs (including glass wool, stonewool,
19 slagwool, and refractory ceramic fibers) and their influence on biopersistence and
20 toxicity, Bernstein *et al.* (2001a) reported that biopersistence clearance half-time is a
21 good predictor of both the pathological response (collagen deposition) observed in
22 chronic inhalation studies and the tumor response observed in i.p. injection studies. In
23 previous studies, Bernstein *et al.* (2001a, 2001b) investigated the relationship of fiber
24 biopersistence with pathogenicity. Biopersistence clearance half-times (for fibers > 20
25 μm) from both inhalation and intratracheal instillation studies were used. Weighted half-
26 times and slow clearance half-times were evaluated from inhalation biopersistence
27 studies, while clearance half-times for various categories of fiber dimensions, including
28 WHO fibers and fibers longer than 20 μm , were evaluated from intratracheal instillation
29 biopersistence studies. One study examined the relationship of biopersistence with
30 chronic inhalation toxicity in rats at 24 months (collagen deposition at the broncho-
31 alveolar junction) while the other study used tumor response data from chronic i.p.

1 studies in rats. Collagen deposition was selected because it is a precursor to fibrosis,
2 which is associated with tumor response. Five SVFs (including MMVF10 and MMVF11)
3 from 15 exposure groups were available from inhalation studies, while 9 SVFs from 24
4 exposure groups were available from i.p. studies. Both weighted and slow-phase
5 clearance times of long fibers from inhalation biopersistence studies were equally good
6 predictors of lung fiber burdens and collagen score (Bernstein *et al.* 2001a). Clearance
7 half-times of WHO fibers and long fibers from intratracheal instillation studies also were
8 good predictors of collagen scores. The authors reported an apparent threshold for
9 collagen formation of approximately 500,000 long fibers in the lung. Most of the animals
10 examined (42 of 48) that had fewer fibers in the lung had a collagen score of 0.

11 Biopersistence half-times determined from inhalation or intratracheal instillation studies
12 were equally good predictors of tumor response in chronic intraperitoneal injection
13 studies (Bernstein *et al.* 2001b). The logistic regression analysis included median fiber
14 length, number of fibers injected, and biopersistence half-times. The authors calculated r^2
15 (a measure of goodness of fit of the model) values for individual data and grouped
16 (mean) data. The ranges of values reported for r^2 (grouped) were 0.860 to 0.901 for
17 grouped data and 0.471 to 0.494 for individual data. Because the only difference between
18 the models was whether intratracheal or inhalation measurements of WHO or fibers with
19 length $> 20 \mu\text{m}$ (L20) were used, and the r^2 values were very similar, the authors
20 concluded that the models are equally as good in predicting intraperitoneal results. The
21 data demonstrated that there was little difference in the various measures of
22 biopersistence and that fiber length and number were important to the analysis. Therefore
23 the authors concluded that comparisons of potency between different fiber types must be
24 based on studies that use fibers of the same length and that, unlike inhalation studies,
25 there was no apparent threshold for intraperitoneally injected fibers.

26 Berry (1999) developed a model for cumulative mesothelioma incidence as it related to
27 fiber biopersistence in humans and rats. The predicted effect of biopersistence was
28 investigated using a mesothelioma incidence model that included an exponential term
29 representing elimination over time. The incidences generated by the model were then
30 applied over the lifetime of reference groups with mortality from other causes. For

1 humans, occupational exposure was taken as continuous from age 20 to 60 years or until
2 death, if earlier, and the cumulative incidence of mesothelioma was calculated to 100
3 years for various elimination rates. For rats, exposure was a single injection [site of
4 injection not stated] of fibers at 6 weeks of age and cumulative incidence of
5 mesothelioma was calculated up to 160 weeks post injection. The model was
6 standardized for cumulative incidence of mesothelioma for a durable fiber (elimination
7 constant, 0.01/year) at 50% for 75-year-old men and 110 weeks post-injection for rats.
8 The author reported that the predicted carcinogenic effect in humans dropped off rapidly
9 as the dissolution rate increased, whereas the decrease only occurred with the least
10 durable fibers in rats. The effect of fiber elimination rate on the mesothelioma rate was 17
11 times higher in humans than in rats. Berry concluded that relatively soluble fibers (*e.g.*,
12 glass wool) that do not produce disease in rats are even less likely to produce disease in
13 humans, most likely because rats age and develop cancer at a much quicker rate than
14 humans and further, that the influence of fiber dissolution is less in rats compared with
15 humans.

16 Rödelsperger (2004) further evaluated the extrapolation of the carcinogenic potency of
17 fibers from rats to humans. Using the Berry model, he compared predicted mesothelioma
18 incidences in humans (at 85 years of age) and rats (at 136 weeks of age) from graphs of
19 percent mesothelioma vs. elimination constant for highly durable crocidolite fibers
20 (elimination constant of 0.1/year) with less durable refractory ceramic fibers (elimination
21 constant of 1.0/year). The predicted tumor incidence for crocidolite was about 4,750
22 times higher than for the less durable fiber in humans but only about 3.2 times higher in
23 rats; however, Rödelsperger noted that the uncertainty in the estimate for rats was large
24 due to the life-span of rats being too short to measure the elimination rate of biopersistent
25 fibers sufficiently. Rödelsperger also noted that the carcinogenic potency of refractory
26 ceramic fibers and crocidolite were similar in rats when administered by inhalation or i.p.
27 injection but concluded that this similarity cannot be assumed for humans because of the
28 greater effect of the dissolution rate in humans compared with rats.

1 5.3.4 Summary of studies

2 The early studies with glass fibers and asbestos applied directly to the lung pleura
3 (intrapleural implantation) of rats were interpreted by their authors as supporting the
4 conclusion that long, thin glass fibers induced tumor formation as well as similarly sized
5 asbestos. Based on induction of significant numbers of pleural sarcomas by fine, durable
6 glass fibers and several other fiber types, including asbestos fibers, it was concluded that
7 fiber dimensions and durability were important determinants of tumorigenicity.
8 Following these early studies, most investigators have tested fibers by intraperitoneal
9 injection, but several studies also have been published in which fibers with different
10 physico-chemical characteristics were tested by inhalation exposure. The authors of many
11 of these studies concluded that there was a relationship between fiber dimensions
12 (particularly fibers $> 20 \mu\text{m}$ in length with diameters $< 1 \mu\text{m}$) and durability and
13 tumorigenicity; [however, several studies have reported results that suggested that the
14 relationship might not completely explain the data.]

15 Among the studies whose results suggested that the relationship between fiber
16 dimensions and durability might not completely explain the tumorigenicity of various
17 fibers, the authors of one that compared glass fibers with asbestos and other natural fibers
18 suggested that fibers $< 10 \mu\text{m}$ in length (with diameters $< 0.5 \mu\text{m}$) could still cause
19 tumors by i.p. injection. Another set of studies reported “unexpectedly strong”
20 tumorigenic effects of relatively thick rock and ceramic fibers even though the number of
21 fibers injected per rat in one of the studies was smaller for these fiber types than for the
22 glass fibers. The authors of another of the same set of studies also pointed out that
23 actinolite and 104/475 glass fibers had similar size distributions based on the available
24 data and that both fibers were durable in rats; however, the number of fibers that induced
25 tumors at approximately a 60% rate was much greater for the glass fibers than for the
26 actinolite fibers. In addition, the number of fibers longer than $5 \mu\text{m}$ was similar in 0.25
27 mg of actinolite and 75 mg of basalt fibers, and these preparations resulted in almost
28 identical tumor incidences. In another study, pretreatment of fibers with HCl decreased
29 the weight of glass fibers without changing the physical dimensions of the fibers
30 measurably or visibly corroding them, but tumorigenicity was decreased markedly, which

1 the authors suggested might be due to alterations in the rate of dissolution or
2 disintegration of the fibers or their migration within tissues.

3 The conclusions reached by the authors of studies on inhalation studies with fibers with
4 different physical and chemical characteristics generally confirmed the interpretations of
5 the i.p. studies. The number of long fibers (particularly fibers > 20 µm in length) was
6 considered important as a determinant of pathogenicity, and the biopersistence of the
7 fibers as reflected in the *in vitro* dissolution rate and the resulting effect of biopersistence
8 on cumulative fiber burden in the lung, thoracic wall, and diaphragm were also critical
9 factors. Modeling studies that looked at inhalation and intraperitoneal injection studies
10 separately came to similar conclusions that tumor incidence depended on the number of
11 long, thin fibers (> 20 µm long and < 1 µm in diameter), and that biopersistence can
12 predict pathological responses, such as collagen deposition or tumor response.

13 [The concept that fiber dimensions and durability/biopersistence are related to the
14 potential tumorigenicity of those fibers was developed using data from a broad range of
15 fiber types as summarized here, and that concept continues to be generally accepted. The
16 results summarized above that do not appear to fit neatly within that relationship are
17 possibly due to the difficulty of applying the general principle to data sometimes obtained
18 with a relatively narrow range of fiber characteristics under different experimental
19 conditions.]

20 **5.4 Toxic effects**

21 This section describes toxicity studies in humans and experimental animals.

22 *5.4.1 Humans*

23 Mortality from non-malignant diseases was also evaluated in some of the cohort and
24 nested case-control mortality studies of glass fiber production workers discussed in the
25 human cancer studies. (See Section 3.1 for a detailed description of the study population
26 and methodology). In addition several other studies evaluated respiratory disease
27 morbidity and are discussed below.

1 *Respiratory effects: mortality studies*

2 No significant increase in mortality from non-malignant respiratory disease (NMRD),
3 excluding influenza and pneumonia, was observed among the 32,110 fiberglass and
4 mineral production workers followed until 1992 (SMR = 0.92, 95% CI = 0.84 to 1.02,
5 440 deaths compared with local rates) or 4,008 female workers (SMR = 1.02, 95% CI =
6 0.74 to 1.37, 44 deaths) in the 10-plant U.S. cohort established by Marsh and colleagues
7 (Marsh *et al.* 2001a, Stone *et al.* 2004). Earlier publications of an overlapping cohort
8 (16,661 male mineral wool and fiberglass workers at 17 plants, and followed until 1977,
9 1982, or 1985) found significant SMRs for NMRD (excluding influenza and pneumonia)
10 (SMR = 1.30, $P < 0.01$, 129 deaths for the 1977 follow-up, SMR = 1.32, $P < 0.01$, 230
11 deaths for 1982, and SMR = 1.29, $P < 0.01$, 281 deaths for 1985); however, no
12 relationship was observed with cumulative exposure to respirable fibers (Enterline *et al.*
13 1983, 1987, Marsh *et al.* 1990). Among workers employed at the three plants
14 manufacturing fine fibers, higher SMRs were found for ever-exposed workers (at each
15 plant) compared with non-exposed workers. In a case-control study of employees at the
16 Owens-Corning Fiberglass plant in Newark, Ohio (1 of the 10 plants in the Marsh
17 cohort), a non-significantly increased risk (OR = 1.50, 95% CI = 0.55 to 4.08) of NMRD
18 was observed among workers with cumulative exposure of > 300 respirable fibers/cm³ in
19 conditional regression analyses (Chiazze *et al.* 1993); however, no increased risk in
20 mortality was found in a smaller case-control study (30 cases and 103 matched controls)
21 at another plant in Kansas City, Kansas (Chiazze *et al.* 2002).

22 Nonsignificantly increased SMRs for respiratory disease were reported in the Canadian
23 cohort (SMR = 1.19, 95% CI = 0.74 to 1.82; 21 deaths (Shannon *et al.* 2005) and among
24 5,275 glass wool workers in the European cohort (SMR = 1.18, 95% CI = 0.98 to 1.40;
25 127 deaths) (Sali *et al.* 1999).

26 *Respiratory effects: morbidity studies*

27 Several studies have evaluated adverse respiratory effects and exposure to glass wool
28 fibers; these include studies measuring respiratory symptoms, lung abnormalities
29 (monitored by chest radiographs), and pulmonary function. The findings from IARC

1 (1988) are summarized, and studies published after the IARC (1988) review on exposures
2 specific to glass fibers are described in detail.

3 The IARC (1988) review stated that numerous studies have reported that exposure to
4 SVF causes irritation and inflammation of the upper respiratory tract. Bronchitis was also
5 associated with exposure to SVFs in one study. Abnormalities on chest X-rays were
6 reported in some (Nasr *et al.* 1971, Valentin *et al.* 1977), but not all studies (Wright
7 1968). Pathological changes in the lung (parenchymal involvement or pulmonary
8 fibrosis) or respiratory distress were reported in workers with prolonged exposure to glass
9 fibers in one study (Chiappino *et al.* 1981), but not in another study (Gross *et al.* 1971).
10 No effects on pulmonary function were found in a study of six workers exposed to glass
11 wool or rockwool or in two studies of sheet-metal workers (Bjure *et al.* 1964, Hill *et al.*
12 1984, Hill *et al.* 1973, Sixt *et al.* 1983).

13 Moulin *et al.* (1988a) conducted a respiratory health assessment of 2,024 workers in three
14 glass wool (1,041 from Plant A) and two rock wool production plants in France. A
15 standardized questionnaire that covered occupational history, smoking habits, respiratory
16 symptoms, and upper airway irritation was administered by industrial physicians. After
17 adjusting for age and current smoking, significantly elevated ORs related to exposure to
18 fibers were observed for cough, phlegm, and symptoms of the pharynx-larynx among
19 workers at Plant A, but not among workers at the other two glass wool plants. ORs
20 increased with exposure duration for symptoms of the pharynx-larynx (not statistically
21 significant) and for sinus and nasal cavity complaints (e.g., sinusitis, nasal congestion,
22 and nosebleed) ($P = 0.02$); however, no exposure response was observed for cough and
23 phelgm. IARC (2002) reported that a nested case-control study (Moulin *et al.* 1987,
24 published in French) did not confirm these results

25 Hunting and Welch (1993) investigated the occurrence of lung disease among sheet metal
26 workers from the United States and Canada exposed to asbestos and fiberglass. The
27 workers were selected from a larger study of workers with 20 years of experience with
28 high use of fiberglass. The selection criteria for this study were workers who had
29 participated in medical screening, worked in the sheet metal industry for at least 70% of

1 their working career (or removal for 40% of their career) and were not welders for more
2 than 20% of their career. Occupational exposure history was obtained by telephone
3 interview for 333 workers (out of 407 who met the selection criteria), and cumulative
4 exposure models were developed for high-, medium-, and low-intensity exposure to
5 fiberglass. In multiple logistic regression analyses, smoking, years of asbestos exposure,
6 and high intensity exposure to fiberglass (OR = 2.28, 95% CI = 1.07 to 4.86) were
7 associated with chronic bronchitis risk, but only smoking and welding were risk factors
8 for obstructive lung disease.

9 Kilburn and Warshaw (1991) investigated respiratory effects in 175 fiberglass production
10 workers (12 women and 163 men) from a group of 500 U.S. workers who underwent
11 medical examination. Most of the workers (137/175, 78%) reported a history of asbestos
12 exposure, but 38 workers were identified without known asbestos exposure; however, all
13 had worked in a facility where ovens insulated with asbestos were cleaned, repaired,
14 dismantled, and rebuilt. Chest radiographs, lung function measurements, and
15 occupational and medical histories were taken. Pulmonary flows and volumes were
16 adjusted for age, height, ethnicity, and smoking. Chest radiographs revealed small,
17 irregular opacities in 31 men; 16.8% (23/137) of the workers were exposed to asbestos
18 and fiberglass, and 21% (8/38) to fiberglass only. After adjusting for age and smoking,
19 workers with abnormal radiographs (31/175) had greater functional pulmonary
20 impairment than workers with normal radiographs (63/175). [No unexposed control
21 group was included in this study.] The authors concluded that it was possible that the men
22 who did not report exposure to asbestos were actually exposed since they shared a similar
23 air environment, and thus the effects of fiberglass exposure could not be estimated
24 independently of the effects from asbestos exposure.

25 Kilburn *et al.* (1992) examined pulmonary effects in 284 (182 men and 102 women) of
26 500 workers (end-users) who had worked for at least 20 years and completed medical
27 examinations. The workers were employed in fiberglass sheeting and rotary spun
28 fiberglass insulation. Pulmonary effects were determined using spirometry, lung volumes,
29 chest radiographs, and occupational questionnaires. Air sampling showed that 49% to
30 83% of the fibers had diameters < 5 μm and 23% to 71% were < 3 μm ; no asbestos fibers

1 were identified. Chest radiographs revealed abnormalities in 43 workers; 17 reported
2 previous exposures to asbestos and 26 were without reported exposure to asbestos.
3 Pulmonary function was reduced in the workers with abnormalities (detected by
4 radiographs) attributed to glass fiber exposure compared with workers without
5 abnormalities and who were not exposed to asbestos. [There was no unexposed control
6 group in this study.] The authors concluded that exposure to commercial rotary spun
7 fiberglass used for insulating appliances appeared to produce pulmonary effects similar to
8 asbestosis.

9 Hughes *et al.* (1993) also conducted a study of SVF workers at seven plants (five fibrous
10 glass and two mineral wool manufacturing plants) in the United States. [These plants
11 might be the same plants studied by Marsh and colleagues.] Workers underwent a chest
12 X-ray (1,449), interview, and spirometry (1,030). Comparison (blue collar) workers were
13 identified for each plant from the communities where the plants were located and
14 participated in the spirometry (386), interview, and chest X-ray (305, no radiographs
15 were available for comparison workers for two plants). The prevalence of respiratory
16 symptoms (such as chronic bronchitis and cough) was higher in three of the seven plants
17 (one glass and two mineral wool) than in the comparison group. Among SVF workers,
18 there were significant differences in pulmonary function (spirometric measurements)
19 across the plants (highest for the very fine fiber plant); however, when asthmatic workers
20 or workers with previous chest surgery were omitted from the analyses, no significant
21 differences in pulmonary function were observed compared with the comparison group.
22 The prevalence of small opacities (detected by radiographs) was higher among SVF
23 workers (23/1435) than the comparison groups (2/305), and most (98%) of the opacities
24 were found at two glass fibers plants with the highest average and cumulative exposures;
25 one of these plants made small fibers. Analyses of all workers (controlling for film
26 quality, smoking, and age) found a significant association for opacities with cumulative
27 exposure, average exposure, and time in job, although only duration of exposure was
28 significant after allowing for plant effect. Phase two of the study evaluated workers (157)
29 at the two plants with the higher prevalence of opacities using pre-employment
30 radiographs of each worker as the comparison; none of the workers with pre-employment
31 radiographs had participated in the main part of the study. No significant differences in

1 opacities were found between pre-employment and workers' films, and the prevalence of
2 opacities was not significantly related to any exposure indices in regression analyses.

3 Guber *et al.* (2006) reported a case of pulmonary fibrosis in a patient with exposure to
4 glass wool fibers; the patient denied exposure to asbestos and did not smoke. Fibers with
5 a chemical composition consistent with typical glass wool insulation were identified in
6 sputum and biopsy samples.

7 Abbate *et al.* (2006) investigated changes in the respiratory system induced by
8 occupational exposure to production dust from glass fiber-reinforced plastics. This study
9 included 29 male subjects with a mean length of employment of 11 years. Heavy smokers
10 (> 15 cigarettes/day) were excluded from the study. The subjects were given a medical
11 examination, chest X-rays, and spirometric and other tests. Bronchoalveolar lavage fluid
12 was submitted for microscopic and biochemical analysis. The respiratory function tests
13 confirmed obstructive syndromes in the workers. There were qualitative and quantitative
14 alterations of the alveolar macrophages and evidence of intense and active phlogosis
15 (external inflammation). Biochemical analysis indicated an increase in protein content
16 that was associated with a significant decrease in glutathione, suggesting alterations of
17 the lung oxidant/antioxidant status. Antioxidant enzymes (catalase [CAT] and superoxide
18 dismutase [SOD]) were increased three to five fold. Alterations of the cellular and
19 humoral components of the pulmonary interstitium were identified as acute alveolitis.

20 *Other effects*

21 Several studies have also evaluated non-respiratory effects and exposure to glass wool. In
22 the cohort mortality studies, no significant increases in SMRs from non-malignant
23 diseases were observed in the latest update of the U.S. workers (Marsh *et al.* 2001a,
24 Stone *et al.* 2004), glass wool workers in the European cohort (Sali *et al.* 1999) or in the
25 Canadian cohort (Shannon *et al.* 2005). In an earlier update of the U.S. glass wool cohort
26 (16,661 workers followed until 1985), a significantly increased SMR for nephritis and
27 nephrosis was observed (SMR = 1.46, $P < 0.01$, 56 deaths) (Marsh *et al.* 1990). In a case-
28 control study of glass wool workers from three plants (Newark, Ohio; Kansas City,
29 Kansas; and Santa Clara, California) in the U.S. cohort assembled by Marsh, no
30 association between exposure to respirable fibers and mortality from nephritis or

1 nephrosis was reported. This study used two case-control analyses that evaluated deaths
 2 from nephritis or nephrosis as the underlying cause only (15 deaths) or underlying and
 3 contributing cause (47 deaths) (Chiazze *et al.* 1999).

4 IARC (2002) also reviewed several morbidity studies showing an association between
 5 mineral fiber exposure and dermal irritation and skin disease. One of these studies
 6 reported that 25% of 259 workers in a manufacturing and processing plant for mineral
 7 wool insulation presented with a skin disease that was attributed to an allergy related to
 8 MMVF additives. Other studies reported high incidences of skin and eye irritation or
 9 positive patch tests with mineral fibers among construction workers or workers
 10 investigated for sick-building syndrome.

11 **5.4.2 Experimental animals**

12 Toxic effects in experimental animals that are potentially important to the carcinogenic
 13 process include inflammation and fibrosis (IARC 2002). These effects are commonly
 14 graded according to the Wagner scale (Table 5-11). Other effects, such as genotoxic or
 15 mitogenic affects are discussed in Section 5.6 as they relate to potential mechanisms of
 16 carcinogenicity.

Table 5-11. Wagner grading scale for lung pathology

Description	Wagner score	Pathology
<i>Cellular change</i>		
Normal	1	no lesion
Minimal	2	macrophage response
Mild	3	bronchiolization, inflammation
<i>Fibrosis</i>		
Minimal	4	minimal fibrosis
Mild	5	linking of fibrosis
Moderate	6	consolidation
Severe	7	marked fibrosis and consolidation
	8	complete obstruction of most airways

Source: Hesterberg *et al.* 1993.

17 Studies with MMVF10 and MMVF11 in F344 rats exposed 6 hours/day, 5 days/week for
 18 up to 24 months have shown exposure-dependent responses in lung pathology that

1 peaked at a Wagner score of 3 (Hesterberg *et al.* 1993). In this same study, a Wagner
2 score of 4 was observed in rats exposed to chrysotile asbestos for only three months.

3 Cullen *et al.* (2000) reported on the pathogenicity of 104E-glass fibers, code 100/475
4 microfibers, and amosite asbestos in Wistar rats exposed 7 hours/day, 5 days/week for
5 one year. Fibrosis (Wagner score of 4) was evident in four rats exposed to 104E fibers
6 after the 12-months exposure period, but the lesions were small and only 0.3% of the
7 lung parenchyma was involved. In the nine animals that survived for another 10 to 12
8 months without further exposure, significant areas of advanced fibrosis and
9 bronchoalveolar hyperplasia were evident. Instead of Wagner scores, the authors reported
10 the mean level of advanced fibrosis as the percentage of lung area affected. The values
11 were 0.08% (controls), 0.2% (100/475 glass), 8.0% (104E glass), and 7.6% (amosite).
12 The authors noted that there were greater numbers of long fibers in the lungs of animals
13 exposed to 104E glass for 12 months compared with the other fiber types.

14 Hesterberg *et al.* (1999, 1997) investigated the effects of inhalation exposure in Syrian
15 golden hamsters. Animals were exposed for 6 hours/day, 5 days/week for periods of 13 to
16 52 weeks. MMVF10a, MMVF33, and amosite asbestos were used in the studies. Time-
17 dependent increases in pathology were noted with Wagner scores after 52 weeks of 0
18 (controls), 2.3 (MMVF10a), 4.0 (MMVF33 and low-dose amosite), and 6.0 (high-dose
19 amosite). McConnell *et al.* (1999) reported on a similar study design in Syrian golden
20 hamsters exposed to these same test fibers for 78 weeks. The fibrosis index in hamsters
21 exposed to MMVF10a or MMVF33 was not significantly different from controls but was
22 significantly elevated in hamsters exposed to amosite.

23 Hesterberg *et al.* (2002) used a short-term assay to evaluate the toxicity of MMVF10,
24 JM475, amosite asbestos and two new biosoluble glass wool fibers (JM902 and JM901F).
25 MMVF10 and JM902 were tested concurrently, while JM901F, JM475, and amosite
26 asbestos were tested in a separate study. Size-separated fiber samples were tested for lung
27 biopersistence and their potential to induce persistent pulmonary inflammation in rats.
28 Groups of 82 to 105 male F344 rats were exposed by nose-only inhalation for 6
29 hours/day for 5 days. The control groups included 45 to 55 rats exposed to filtered air.

1 The geometric mean dimensions of the fibers were similar, and the mean concentrations
2 of WHO fibers ranged from 321 to 443 fibers/cm³. In addition, intratracheal instillation
3 biopersistence studies were conducted with JM902 fibers. Dissolution rate constants were
4 measured *in vitro*. Histopathological effects were limited to fiber-containing
5 microgranulomas and alveolar macrophage aggregation in rats exposed to JM902,
6 JM901F, or MMVF10 on recovery day 1. After 30 days recovery, no adverse symptoms
7 were noted, while some inflammatory symptoms were still present in rats exposed to
8 JM475 or amosite.

9 Bellmann *et al.* (2003) conducted a subchronic inhalation study in male Wistar rats to
10 investigate the biological effects of E-glass microfiber, stone wool (MMVF21), and a
11 new high-temperature application fiber (calcium-magnesium-silicate fiber). Results are
12 reported here for the E-glass microfiber. Rats were exposed 6 hours/day, 5 days/week for
13 3 months to aerosol concentrations of approximately 15, 50, and 150 fibers/cm³ (fiber
14 length > 20 µm). For the E-glass microfiber, the highest gravimetric concentration was
15 17.2 mg/m³. Recovery effects were studied during a 3-month postexposure period. The
16 lung burden of the long-fiber fraction of E-glass declined 38.4% after 3 months recovery.
17 The estimated half-times were 55 to 157 days for WHO fibers and 57 to 63 days for
18 fibers > 20 µm in length. Dose-dependent effects included an increase in lung weight in
19 the mid- and high-dose groups at 1, 7, and 14 weeks after exposure. Biochemical analysis
20 of bronchoalveolar lavage fluid indicated a significant increase in lactate dehydrogenase,
21 β-glucuronidase, and total protein after 1 and 7 weeks in the mid- and high-dose groups;
22 however, at 14 weeks, total protein was the only parameter that remained elevated.
23 Cytokine analysis (TNF-α and IL-6) did not show any significant changes.
24 Histopathological findings included accumulation of fiber-laden macrophages,
25 bronchoalveolar hyperplasia, microgranulomas, and interstitial fibrosis in all exposure
26 groups. The authors concluded that the effects induced by E-glass were more pronounced
27 than those induced by the other fibers.

28 Bermudez *et al.* (2003) investigated toxicity of MMVF10a fiberglass in male F344 rats
29 and Syrian golden hamsters using pleural dosimetry. Animals were exposed (nose-only)
30 to a target concentration of 45 mg/m³ for 4 hours/day, 5 days/week for up to 12 weeks.

1 Animals were killed following 4 or 12 weeks of exposure or after 12 weeks of exposure
2 followed by a 12-week recovery period. The geometric mean length and diameter of the
3 fiber samples were 12.5 μm and 0.93 μm , respectively. Lung fiber burdens (calculated as
4 total number of fibers per lung, averaged over the three time points) were greater in rats
5 (50.1×10^6 fibers/lung) than in hamsters (6.4×10^6 fibers/lung). When lung fiber burdens
6 were normalized based on lung surface area, rats had significantly higher lung burdens
7 than hamsters. Fibers recovered from the lungs of both species were shorter and thinner
8 than those in the aerosol. Lung fiber burdens decreased about 90% in hamsters following
9 12 weeks of postexposure recovery compared with 44% in rats. Average fiber burdens in
10 the pleural compartment were about the same in rats and hamsters but were at least three
11 orders of magnitude lower than found in the lung. When normalized based on surface
12 area, pleural fiber burdens $> 5 \mu\text{m}$ in length were significantly higher in the hamster at 12
13 weeks of exposure. Fibers in the pleural compartment were longer than those found in the
14 lung but were about the same diameter. Mild pulmonary inflammation was observed in
15 both species and characterized by increased numbers of macrophages and neutrophils,
16 and an increase in mesothelial cell replication. The neutrophil response was correlated
17 with lung fiber burdens in the rat but not in the hamster. All the biochemical markers
18 examined in the rat bronchoalveolar lavage fluid were elevated after 4-weeks exposure,
19 and lactate dehydrogenase (LDH) and alkaline phosphatase levels remained elevated and
20 unchanged through 12-weeks recovery. There were no significant increases in the
21 biochemical markers of toxicity in bronchoalveolar lavage fluid in hamsters.

22 *5.4.3 Cytotoxicity*

23 Similar to the IARC (2002) review, this section is limited to studies that met several
24 criteria, including: (1) the dose was expressed as number of fibers administered, (2) fiber
25 length was specified so that false-negative results from preparations of short fibers could
26 be excluded, (3) adequate documentation of fiber source was supplied, (4) studies
27 involving instillation of fibers directly into the lungs were screened to exclude those with
28 excessive doses, and (5) control fibers were used or different categories of fiber length
29 were used.

1 One study used Chinese hamster ovary cells to assess cytostatic effects of MvL 901 glass
2 fibers (Hart *et al.* 1994). Fibers with an average length of 25 μm inhibited cell
3 proliferation to approximately 25% of control levels, whereas fibers with an average
4 length of 3.5 μm did not inhibit cell proliferation. A modest effect was also seen for fiber
5 thickness, with thinner fibers being more effective inhibitors of cell proliferation than
6 thicker fibers. The authors noted that this study showed that long fibers were toxic *per se*,
7 in addition to their ability to accumulate in the lung due to slower clearance rates.

8 Blake *et al.* (1998) assessed the ability of code 100 glass fibers, at varying lengths, to
9 inhibit lucigenin chemiluminescence and to cause release of LDH from rat alveolar
10 macrophages. A length-related toxicity was seen, with fibers of 17 μm and 33 μm
11 showing similar high potency, while fibers less than or equal to 7 μm showed markedly
12 lower potency. The authors suggested that the increased toxicity of long fibers was due to
13 frustrated phagocytosis leading to leakage of oxidants and enzymes from a macrophage
14 trying to engulf a fiber.

15 Zeidler-Erdely *et al.* (2006) investigated the influence of fiber length on primary human
16 alveolar macrophages. JM100 glass fibers were sorted into four length categories (8, 10,
17 16, and 20 μm). Macrophages were obtained by bronchoalveolar lavage of healthy, non-
18 smoking volunteers and treated with three different concentrations of the sized fibers *in*
19 *vitro*. Cytotoxicity was determined by monitoring cytosolic lactate dehydrogenase release
20 and loss of function (decrease in zymosan-stimulated chemiluminescence). In contrast to
21 the study in rats (Blake *et al.* 1998), human macrophages completely engulfed glass
22 fibers of all length categories with no evidence of incomplete phagocytosis or length-
23 dependent toxicity. All fiber length fractions exhibited equal cytotoxicity on a per fiber
24 basis in a dose-dependent manner.

25 **5.5 Genetic and related effects**

26 This section reviews the available genetic and related effect studies for glass fibers,
27 including those reviewed by IARC (2002) and those published subsequent to the IARC
28 review. This review includes studies of oxidative and genetic damage (such as mutations,
29 micronucleus formation, DNA damage) and also studies of related effects, such as
30 production of reactive oxygen species and changes in gene expression. Some of the

1 studies were designed to evaluate the effects of fiber characteristics (diameter and length
2 and sometimes fiber composition) on the genotoxic endpoint. Some of the fibers used in
3 these studies were used in animal cancer studies or were manufactured to be similar to a
4 fiber used in the animal studies. These include the special-purpose fibers (e.g. Manville
5 codes JM100, JM100/475) and insulation glass wool fibers (e.g., MMVF10, MMFV11,
6 and Owens Corning general insulation fibers). However, as IARC noted, no studies are
7 available that correlated genotoxic endpoints and pathogenic effects in the same
8 experimental animal system.

9 *5.5.1 Production of reactive oxygen species*

10 The following sections discuss studies that investigated reactive oxygen species produced
11 by exposure to glass wool. Although ROS are not necessarily associated with
12 genotoxicity, they may damage DNA or chromosomes. This section discusses studies
13 conducted in cell-free systems, cultured cells, or experimental animals.

14 *Cell-free systems*

15 The ability of glass wool to produce reactive oxygen has been studied in cell-free systems
16 by measuring guanine hydroxylation in DNA or deoxyguanosine (an indication of
17 hydroxyl radical formation), studies using the salicylate assay to measure hydroxyl
18 radical formation, and studies measuring scission of plasmid DNA after incubation with
19 glass wool. These studies are summarized in Table 5-12.

20 All of the guanine hydroxylation studies were positive; [however, most studies did not
21 provide detailed information on fiber characteristics] (Adachi *et al.* 1992, Leanderson *et*
22 *al.* 1988, Leanderson and Tagesson 1992). Glass wool and JM100 glass fibers induced
23 hydroxyl radical formation in the presence of hydrogen peroxide (Maples and Johnson
24 1992). These authors reported a significant correlation between the capacity of natural
25 fibers (asbestos and erionite) to initiate hydroxyl radical formation and tumor rates in rat
26 i.p. studies or literature values for human mesothelioma mortality rates; however, no
27 correlations were found with glass fibers. In another study, JM100/475 and an insulation
28 glass wool fiber (MMVF10) did not induce hydroxyl radical formation; however, this
29 study was conducted at a lower pH (3.9) than the Maples and Johnson study (neutral pH)
30 and did not use hydrogen peroxide (Brown *et al.* 1998).

1 Several studies were conducted that reacted glass fibers with plasmid DNA and measured
 2 oxidative DNA damage to the plasmid (as assessed by a reduction in the percentage of
 3 supercoiled DNA) (Brown *et al.* 1998, Donaldson *et al.* 1995b, Gilmour *et al.* 1995,
 4 1997). All of these studies were negative. However, Gilmour *et al.* (1995, 1997) reported
 5 that MMVF10 and MMVF11 did have a detectable, although not statistically significant,
 6 effect on plasmid DNA. In contrast, there was significant free radical damage with
 7 amosite asbestos. There was no correlation between iron release from the fibers and free
 8 radical activity. Although the authors demonstrated that iron at the surface of asbestos
 9 fibers had a role in generating hydroxyl radicals, some fibers released large quantities of
 10 iron without causing free radical damage. Thus, the exact role of iron in fiber reactivity is
 11 not completely understood.

Table 5-12. Oxidative damage studies in cell-free systems

End point	Test system	Result	Fiber type (dose)	Fiber length & diameter (µm)	Reference
Guanine hydroxylation in DNA or deoxyguanosine (dG) or hydroxyl radical studies					
Hydroxylation of deoxyguanosine	deoxyguanosine	+	Glass wool (NR)	NR	Leanderson <i>et al.</i> 1988
8-OHdG formation (hydroxylation of guanine in DNA)	calf-thymus DNA	+	Glass wool (20 mg)	NR	Leanderson <i>et al.</i> 1988
8-OHdG formation (hydroxylation of deoxyguanosine)	calf-thymus DNA	+	Glass wool (10 mg)	NR	Leanderson and Tagesson 1989
8-OHdG formation (hydroxylation of deoxyguanosine)	calf-thymus DNA	+	Glass wool (10 mg)	NR	Leanderson <i>et al.</i> 1989
8-OHdG formation (5.0 mg)	calf-thymus DNA	+	Fiberglass	L = 16.8 D = 0.65	Adachi <i>et al.</i> 1992
Hydroxyl radical formation	hydrogen peroxide	+	Manville code 100/SPF (1 mg/mL)	NR	Maples and Johnson 1992

End point	Test system	Result	Fiber type (dose)	Fiber length & diameter (μm)	Reference
Hydroxyl radical formation	hydrogen peroxide	+	Owens Corning glass wool/IGW (1 mg/mL)	NR	Maples and Johnson 1992
Hydroxyl radical formation	cell-free system	-	Manville code 100/475/SPF 8.24×10^7 fibers	NR	Brown <i>et al.</i> 1998
Hydroxyl radical formation	cell-free system	-	MMVF10/IGW 8.24×10^7 fibers	NR	Brown <i>et al.</i> 1998
Plasmid DNA scission studies					
Reduction of supercoiled DNA	plasmid DNA	-	code 100/475/SPF ($46.25 \times 10^6/\text{mL}$ WHO fibers ^a)	NR	Brown <i>et al.</i> 1998
Reduction of supercoiled DNA	plasmid DNA	-	MMVF10/IGW ($46.25 \times 10^6/\text{mL}$ WHO fibers ^a)	NR	Brown <i>et al.</i> 1998
Reduction of supercoiled DNA	plasmid DNA	-	MMVF10/IGW ($46.5 \times 10^6/\text{mL}$ WHO fibers ^a)	NR	Gilmour <i>et al.</i> 1997
Reduction of supercoiled DNA	plasmid DNA	-	MMVF10 MMVF11/IGW ($30.8 \times 10^6/\text{mL}$ WHO fibers ^a)	NR	Donaldson <i>et al.</i> 1995b
Reduction of supercoiled DNA	plasmid DNA	-	MMVF10 MMVF11/IGW ($61.7 \times 10^6/\text{mL}$ WHO fibers ^a)	NR	Gilmour <i>et al.</i> 1995)

+ = positive; - = negative; L = length, D = diameter; NR = not reported; SPF = special-purpose glass fibers; IGW = Insulation glass wool fibers.

^aWHO fibers are longer than 5 μm and less than 3 μm in diameter, with aspect ratio (ratio of fiber length to fiber diameter) > 3, defined as respirable fibers.

1 *Cultured cells*

2 Most studies have reported that glass fibers cause oxidative damage in cultured cells.
3 These studies have used different types of fibers (varying in length and diameter) and
4 assessed oxidative damage by different endpoints. These studies are summarized in Table
5 5-13.

6 Superoxide production induced by glass fibers (code 100/475 – either uncoated or coated
7 with rat immunoglobulin [IgG]), was studied in rat alveolar macrophages (Donaldson *et*
8 *al.* 1995b, Hill *et al.* 1996), and glass fiber code 100 was studied in rat alveolar

1 macrophages and hamster alveolar macrophages (Hansen and Mossman 1987, Mossman
2 and Sesko 1990). Dörger *et al.* (2000, 2001) investigated the responses of rat alveolar and
3 peritoneal macrophages and hamster alveolar macrophages exposed to MMVF10. All
4 studies except Dörger *et al.* (2000, 2001) reported increased superoxide production in
5 alveolar macrophages exposed to glass fibers. IgG opsonization of code 100/475 did not
6 increase superoxide production.

7 Gilmour *et al.* (1997) reported that intracellular glutathione levels were significantly
8 decreased in rat alveolar macrophages exposed to MMVF10; however, glutathione
9 depletion was not related to free radical activities of the fibers (see “*in vivo studies*” in
10 Section 5.5.1). The authors concluded that the decrease in glutathione was likely a result
11 of exportation as a stress response rather than a direct free radical oxidation of
12 glutathione. Wang *et al.* (1999b) reported that both a long glass fiber (GW1) and a
13 microfiber (MG1) increased superoxide anion (as measured by cytochrome C reduction)
14 and hydrogen peroxide production, and depleted glutathione in guinea-pig alveolar
15 macrophages. GW1 induced levels of hydrogen production similar to that of asbestos
16 (chrysotile). Glass wool also increased hydrogen peroxide production in human
17 polymorphonuclear leukocytes (Leanderson and Tagesson 1992).

18 Nishiike *et al.* (2005) investigated the effects of asbestos and SVFs on nitrosothiol
19 formation and glutathione levels in the murine macrophage cell line (RAW264.7). J774
20 cells were also used in some experiments. Glass wool and chrysotile asbestos
21 significantly increased nitric oxide and superoxide anion production and decreased
22 glutathione levels in RAW264.7 cells. S-nitrosothiol formation was increased in both cell
23 lines by all fiber types tested.

24 Brown *et al.* (1986) reported no increase of malondialdehyde production (an indicator of
25 lipid peroxidation) in human A549 cells exposed to 50 $\mu\text{g}/\text{cm}^2$ glass fibers; however,
26 malondialdehyde was significantly increased in cell cultures treated with crocidolite
27 asbestos. MMVF10 and MMVF11 (insulation glass wool fibers) caused dose-dependent
28 increases in reactive oxygen species in human polymorphonuclear cells (Luoto *et al.*
29 1997). Fibers of different lengths (MG1, a short micro fiber; and GW1, a longer glass
30 fiber) induced reactive oxygen species in human monocytes (Ohyama *et al.* 2000) and

1 guinea-pig alveolar macrophages (Wang *et al.* 1999b); however, the longer fiber (GW1)
2 was more effective in inducing ROS than the shorter fiber (MG1) in human monocytes.
3 Ruotsalainen *et al.* (1999) reported that fiber size did not appear to be important in
4 inducing reactive species in human polymorphonuclear leukocytes; dose-dependent
5 increases in production of reactive oxygen were induced by two glass fibers of different
6 sizes. A similar observation was made between fiber lengths of other types of fibers (e.g.,
7 refractory ceramic fibers, rock wool). However, the glass wool fibers in the Ruotsalainen
8 *et al.* (1999) study appeared to have a more heterogeneous size distribution than the GW1
9 and MG1 fibers in the Ohyama *et al.* study (2000). Ruotsalainen *et al.* (1999) also
10 included other types of synthetic fibers and suggested that fiber composition might
11 mediate production of reactive oxygen species because the amount of ROS production
12 differed according to fiber types of similar dimensions.

13 Zoller and Zeller (2000) investigated the potential for four SVFs (including glass wool
14 code A) and two natural mineral fibers (crocidolite and erionite) to induce ROS in a
15 differentiated human promyelocytic cell line (HL-60-M cells). ROS production was
16 measured by lumino-enhanced chemiluminescence. The influence of fiber preincubation
17 in unbuffered saline also was investigated. Cell cultures exposed to 250 µg of glass fibers
18 showed increased chemiluminescence; however, decreased ROS-generating potential was
19 observed after preincubation in saline for 4 weeks. The authors thought that the decreased
20 ROS-generating potential of code A fibers was likely due to surface alterations (leaching
21 and initiation of dissolution).

22 In contrast to the cell-free studies using calf-thymus DNA, Murata-Kamiya *et al.* (1997)
23 reported no increase in 8-OHdG formation when the DNA of a reticulum-cell sarcoma
24 line (J774) was incubated with glass fibers (100 µg/mL).

Table 5-13. Oxidative damage in cultured cells

End point	Test system	Result	Fiber type (dose)	Fiber length & diameter (μm)	Reference
Superoxide production	rat alveolar macrophages	+	Manville code 100/475/SPF (3 million fibers)	L = > 5	Donaldson <i>et al.</i> 1995b
Superoxide production	rat alveolar macrophages	+	Manville code 100/475/SPF (12.5–2000 μg) 121,742 WHO fibers/ μg	L = > 5	Hill <i>et al.</i> 1996
Superoxide production	rat alveolar macrophages	+	Manville code 100/SPF (5 $\mu\text{g}/\text{cm}^2$)	L = 1–100 D = 0.2–2.9	Hansen and Mossman 1987, Mossman and Sesko 1990
Intracellular glutathione	rat alveolar macrophages	+	MMVF10 (8.2 $\times 10^6$ fibers/mL)	NR	Gilmour <i>et al.</i> 1997
Superoxide production	hamster alveolar macrophages	+	Manville code 100/SPF (0.01–20 $\mu\text{g}/\text{cm}^2$)	L = 1–100 D = 0.2–2.9	Hansen and Mossman 1987, Mossman and Sesko 1990
Superoxide anion production (cytochrome C reduction) Hydrogen peroxide production	guinea-pig alveolar macrophages	+	MG1 micro glass fibers, (200 $\mu\text{g}/\text{mL}$)	L = 3.0 D = 0.24	Wang <i>et al.</i> 1999b
Superoxide anion production (cytochrome C reduction) Hydrogen peroxide production	guinea-pig alveolar macrophages	+	GW1 glass wool fibers (200 $\mu\text{g}/\text{mL}$)	L = 20 D = 0.88	Wang <i>et al.</i> 1999b
Superoxide anion production (cytochrome C reduction)	rat and hamster alveolar macrophages	–	MMVF10 (12 μg)	L = 16.3 D = NR	Dörger <i>et al.</i> 2000
Superoxide anion production (cytochrome C reduction)	rat alveolar and peritoneal macrophages	–	MMVF10 (100 $\mu\text{g}/\text{mL}$)	L = 16.3 D = NR	Dörger <i>et al.</i> 2001
Nitric oxide and superoxide anion production	murine RAW264.7 and J774 cells	+	glass wool (100 μg)	L = 20 D = 0.88	Nishiike <i>et al.</i> 2005
Malondialdehyde production	human A549 cells	–	glass fibers (50 $\mu\text{g}/\text{cm}^2$)	NR	Brown <i>et al.</i> 1986

End point	Test system	Result	Fiber type (dose)	Fiber length & diameter (µm)	Reference
Reactive oxygen species production	human polymorphonuclear leukocytes	+	MMVF10, (100 µg/mL)	L = 23.21 D = 1.42	Luoto <i>et al.</i> 1997
Reactive oxygen species production	human polymorphonuclear leukocytes	+	MMVF11 (200 µg/mL)	L = 15.65 D = 1.12	Luoto <i>et al.</i> 1997
Reactive oxygen species production (chemiluminescence)	human polymorphonuclear leukocytes	+	two glass wool fibers (2 and 3) of different chemical composition (100–1000 µg/mL)	D = < 5 L = 10–50 (~70% of fibers); ~25 % fibers 2 were > 50, and ~25% of fiber 3 were ,10.	Ruotsalainen <i>et al.</i> 1999
Reactive oxygen species production (chemiluminescence)	human monocytes	+	MG1 micro glass fibers, (5 × 10 ⁵ fibers)	L = 3.0 D = 0.24	Ohyama <i>et al.</i> 2000
Reactive oxygen species production (chemiluninescence)	human monocytes	+	GW1 glass wool fibers (5 × 10 ⁵ fibers)	L = 20 D = 0.88	Ohyama <i>et al.</i> 2000
Reactive oxygen species production (chemiluninescence)	human HL-60 cells	+	code A glass wool (250 µg)	L = > 5 (87.5%) D = < 1 (84%)	Zoller and Zeller 2000
Hydrogen peroxide production	human polymorphonuclear leukocytes	+	glass wool	NR	Leanderson and Tagesson 1992
8-OHdG formation	human polymorphonuclear leukocytes	+	glass wool (50–1,000 µg/mL)	NR	Leanderson and Tagesson 1992
8-OHdG formation	J774 cells Heticulum-cell sarcoma line	–	glass fibers (100 µg/mL)	L = 12.8 D = 0.54	Murata-Kamiya <i>et al.</i> 1997

+ = positive; – = negative; NR = not reported; L = length, D = diameter; IGW = insulation glass wool fibers; SPF = special-purpose glass fibers.

1 *In vivo*

2 Schürkes *et al.* (2004) investigated the role of indirect (inflammation-driven)
 3 genotoxicity in fiber-induced carcinogenicity. Induction of the pre-mutagenic DNA-
 4 adduct 8-OHdG by MMVF11 or crocidolite asbestos (with and without reduced iron
 5 content) was measured and correlated with parameters of inflammation. Groups of female
 6 Wistar rats were injected i.p. with crocidolite (1 or 2 mg) or MMVF11 (14.7, 29.4, 50,
 7 and 100 mg). Previous i.p. carcinogenicity studies with these fibers (Roller *et al.* 1996),
 8 indicated that 1 mg of crocidolite and 50 mg of MMVF11 were associated with a

1 theoretical lifetime tumor risk of 25%. The two lower doses of MMVF11 were chosen to
2 give comparable fiber numbers relative to crocidolite. All fiber suspensions were given in
3 a single injection in a volume of 2 mL of PBS [not defined by the authors, but most likely
4 phosphate-buffered saline] except the high dose for MMVF11, which was given in two
5 injections. The control group was injected with 2 mL of PBS. There were significant
6 comparable increases in 8-OHdG in the greater omentum for all fiber treatment groups.
7 The percentage of macrophages and TNF- α secretion was significantly correlated with
8 induction of 8-OHdG 10 weeks after treatment. The authors concluded that this study
9 supported the hypothesis of persisting inflammation as an important parameter for fiber-
10 induced mutagenesis.

11 Kováčiková *et al.* (2004) investigated the antioxidant status of the lung in male F344 rats
12 administered stone wool or glass fibers by intratracheal instillation. Animals were
13 exposed to 2 mg or 8 mg of fibers for 4 or 16 weeks. The high dose was administered in 4
14 doses at weekly intervals. All doses were administered in 0.2 mL of saline, and control
15 groups were administered saline. The activity of superoxide dismutase, glutathione
16 peroxidase, and total glutathione was measured in lung tissue and in cell-free fractions of
17 bronchoalveolar lavage fluid. Ascorbic acid was measured in lung tissue. In rats exposed
18 to glass fibers, there were no statistically significant differences in lung tissue except an
19 increase in ascorbic acid in the group exposed to 8 mg for 4 weeks. Superoxide dismutase
20 also was significantly decreased in bronchoalveolar lavage fluid from this group. Only
21 mild dose-dependent histological alterations were seen in the exposed groups.

22 5.5.2 Genetic damage: prokaryotic systems

23 Manville code 100 glass fiber (JM100) and code 110 coarse glass fiber (JM110) did not
24 cause reverse mutations in *Salmonella typhimurium* TA1535 and TA1538 or in
25 *Escherichia coli* B/r, WP2, WP2 *uvrA* and WP2 *uvrA polA* (Chamberlain and Tarmy
26 1977). These fibers differ in both length and diameter (code 110 are much longer and
27 thicker than code 100) (see Table 5-14).

Table 5-14. Summary of prokaryotic studies

Test system	End point	Result	Fiber type/Fiber class (Dose)	Fiber length & diameter (μm)
<i>Salmonella typhimurium</i> TA1535, 15388	reverse mutations (NR)	–	Manville code 100 (JM100) SPF	L = 2.7 D = 0.12
<i>Salmonella typhimurium</i> TA1535, 15388	reverse mutations (NR)	–	Manville code 110 coarse glass fibers (JM110)	L = 26 D = 1.9
<i>Escherichia coli</i> B/r, WP2, WP2 <i>uvrA</i> , WP2 <i>uvrA polA</i>	reverse mutations (1–1,000 $\mu\text{g}/\text{plate}$)	–	Manville code 100 (JM100) SPF	L = 2.7 D = 0.12
<i>Escherichia coli</i> B/r, WP2, WP2 <i>uvrA</i> , WP2 <i>uvrA polA</i>	reverse mutations (1–1,000 $\mu\text{g}/\text{plate}$)	–	Manville code 110 coarse glass fibers (JM110)	L = 26 D = 1.9

Source: Chamberlain and Tarmy 1997.

– = negative; L = length; D = diameter; NR = not reported; SPF = special-purpose glass fibers.

1 5.5.3 Genetic damage: mammalian in vitro systems

2 DNA damage, repair, and cross linking

3 Several studies, using different types of glass fibers (which varied in fiber length and
4 diameter), were conducted to evaluate whether glass fibers could damage DNA. Most of
5 these studies assessed DNA damage by the single-cell gel/comet assay and most studies
6 were positive (see Table 5-15).

7 Zhong *et al.* (1997b) used the alkaline single-cell gel/comet assay to compare DNA
8 damage in Chinese hamster V79 cells with human embryonic lung fibroblasts (Hel 299
9 cells) exposed to Owens-Corning AAA-10 glass fibers (1.7, 3.4, 6.9, and 27.6 $\mu\text{g}/\text{cm}^2$).
10 Significant DNA damage was reported in V79 cells at all four concentrations tested and
11 in human embryonic lung fibroblasts (Hel 299 cells) at the three highest doses. Wang *et*
12 *al.* (1999a) reported that both long glass wool fibers (GW1, length = 20 μm) and
13 microfibers (MG1, length = 3 μm) induced DNA damage (as assessed by the comet
14 assay), inhibited DNA repair and caused DNA-DNA intrastrand cross links in human
15 epithelial cells. Cavallo *et al.* (2004) exposed human mesothelial cells (Me-T-5A) to four
16 concentrations of glass wool (1, 2, 5 and 10 $\mu\text{g}/\text{cm}^2$ for 2 hours and measured DNA

1 damage (as assessed by the comet assay) and oxidative DNA damage (assessed by the
2 comet assay with formamidopyrimidine DNA-glycosylase [Fpg]). Glass wool caused
3 non-significant dose-related increases in direct DNA damage and a slight increase in
4 oxidative damage at the highest dose. Kováčiková *et al.* (2004) isolated and cultured
5 alveolar macrophages and type II cells from F344 rats. After a 20-hour incubation, the
6 cells were exposed to various concentrations of glass fibers, rockwool, wollastonite, and
7 amosite. The comet assay was used to detect DNA damage. DNA strand breaks were
8 enhanced in both cell types by exposure to all fibers in a dose-dependent manner. The
9 highest level of damage was seen in cells exposed to amosite. Type II cells exposed to
10 glass fibers showed the lowest level of damage.

Table 5-15. DNA damage and repair in mammalian cells

End point (dose)	Test system	Result	Fiber type/class (dose)	Fiber length & diameter (μm)	Reference
DNA damage (comet assay)	Chinese hamster V79 cells	+	Owens-Corning AAA-10 (1.7–27.6 $\mu\text{g}/\text{cm}^2$)	L = 2.0, D = 0.18	Zhong <i>et al.</i> 1997b
DNA damage (comet assay)	human embryonic lung fibroblasts (Hel 299)	+	Owens-Corning AAA-10 (1.7–27.6 $\mu\text{g}/\text{cm}^2$)	L = 2.0, D = 0.18	Zhong <i>et al.</i> 1997b
DNA damage (comet assay)	human epithelial cells (A549)	+	MG1 micro glass fibers (40 $\mu\text{g}/\text{cm}^2$)	L = 3.0, D = 0.24	Wang <i>et al.</i> 1999a
DNA damage (comet assay)	human epithelial cells (A549)	+	GW1 glass wool fibers (40 $\mu\text{g}/\text{cm}^2$)	L = 20, D = 0.88	Wang <i>et al.</i> 1999a
DNA damage (comet assay)	human mesothelial cells (MeT-5A)	+/-	Glass wool; 1–10 $\mu\text{g}/\text{cm}^2$ (0.5 $\times 10^3$ fibers/ μg , WHO ^a = 0.19 $\times 10^3$ fibers/ μg , WHO < 20 μm = 0.14 $\times 10^3$ fibers/ μg)	L = 57.3, D = 4.3	Cavallo <i>et al.</i> 2004
Oxidative DNA damage (comet assay with Fpg enzyme)	human mesothelial cells (MeT-5A)	+/-	Glass wool; 1–10 $\mu\text{g}/\text{cm}^2$ (0.5 $\times 10^3$ fibers/ μg , WHO ^a = 0.19 $\times 10^3$ fibers/ μg , WHO < 20 μm = 0.14 $\times 10^3$ fibers/ μg)	L = 57.3, D = 4.3	Cavallo <i>et al.</i> 2004
DNA damage (comet assay)	F344 alveolar macrophages and type II cells	+	Glass fibers: 1–15 $\mu\text{g}/\text{cm}^2$	NR	Kovacikova <i>et al.</i> 2004
DNA repair	human epithelial cells (A549)	+	MG1 micro glass fibers, GW1 glass wool fibers (40 $\mu\text{g}/\text{cm}^2$)	L = 3.0, D = 0.24	Wang <i>et al.</i> 1999a
DNA repair	human epithelial cells (A549)	+	GW1 glass wool fibers (40 $\mu\text{g}/\text{cm}^2$)	L = 20, D = 0.88	Wang <i>et al.</i> 1999a
DNA-DNA intrastrand crosslinks	human epithelial cells (A549)	+	MG1 micro glass fibers (40 $\mu\text{g}/\text{cm}^2$)	L = 3.0, D = 0.24	Wang <i>et al.</i> 1999a
DNA-DNA intrastrand crosslinks	human epithelial cells (A549)	+	GW1 glass wool fibers (40 $\mu\text{g}/\text{cm}^2$)	L = 20, D = 0.88	Wang <i>et al.</i> 1999a

+ = positive; - = negative, L = length; D = diameter; NR = not reported.

^aWHO fibers are longer than 5 μm and less than 3 μm in diameter with aspect ratio (ratio of fiber length to fiber diameter) > 3, defined as respirable fibers.

1 *Chromosomal or chromatid-related effects*

2 It has been proposed that mineral fibers, including asbestos and synthetic fibers, can enter
3 cells and physically interfere with chromosome segregation during mitosis, possibly
4 resulting in aneuploidy and chromosomal translocation. Numerous studies have been
5 conducted to evaluate nuclear abnormalities (including micronuclei and polynuclei) and
6 chromosomal aberrations (including polyploidy and structural aberrations). There has
7 also been one study evaluating sister-chromatid exchange. Many of these studies
8 evaluated the effect of fiber characteristics (e.g., composition, length, and diameter) on
9 the genotoxic endpoint. The results from these studies are summarized in Table 5-16.

10 Hart *et al.* (1994) evaluated the effects of fiber length, fiber diameter, and composition of
11 asbestos and vitreous fibers on cytotoxicity and induction of nuclear abnormalities
12 (micronuclei and polynuclei) in Chinese hamster ovary cells. Cells were exposed to MvL
13 475 glass fibers of similar lengths but different diameters (ranging from 0.3 to 7 μm) and
14 MvL 901 glass fibers of different lengths (ranging from 3.5 to 31 μm) and similar
15 diameters. Fiber length but not fiber diameter (when calculated as the number of
16 fibers/unit area) affected induction of nuclear abnormalities; longer fibers caused a
17 greater percentage of abnormalities than shorter fibers. Hesterberg *et al.* (1986) reported
18 that unmilled glass fibers were more effective (almost 7-fold) in inducing micronucleus
19 formation than milled fibers. Milling decreases fiber length, thus supporting the findings
20 of Hart *et al.* that longer fibers are more potent inducers of micronuclei. Milling of fibers
21 also affected phagocytosis, cytotoxicity, and transformation frequency. However, another
22 study reported two microfibers (Manville 100 microfiber and Owens AAA-10
23 microfiber), but not Owens-Corning general insulation fibers, induced multinucleated and
24 micronucleated cells in a concentration-dependent manner in Chinese hamster lung
25 fibroblast cells (V79) (Ong *et al.* 1997). Most of the micronuclei were kinetochore
26 positive, which is an indicator of aneuploidy. The microfibers were short and thin,
27 whereas the general insulation fibers were thicker and longer. Zhong *et al.* (1997a) also
28 reported that Owens AAA-10 microfibers induced micronuclei in Chinese hamster lung
29 fibroblasts (V79 cells). Significant concentration-related increases in frequencies of
30 micronucleated and multinucleated cells were observed when the cells were exposed to
31 concentrations of 1.7 to 27 $\mu\text{g}/\text{cm}^2$.

1 Thin glass wool fibers induced bi- and multinucleated cells in rat liver cells, human
2 primary mesothelial cells (PL-102), and an immortal, non-tumorigenic human
3 mesothelial cell line (MeT-5A). Significant increases in the percentage of binucleated
4 cells were observed at all doses (1, 2, 5 $\mu\text{g}/\text{cm}^2$) in the two types of human mesothelial
5 cells but only at the highest dose in rat liver cells. Thin glass fibers appeared to be as
6 effective as asbestos (when doses were expressed as the number of fibers per culture
7 area) in inducing binucleated cells in human mesothelial cells. Milled glass wool caused
8 significant increases in binucleated cells in MeT-5A cells (highest dose only) but not in
9 PL-102 or rat liver cells (Pelin *et al.* 1995).

10 Sincock *et al.* (1982) reported that fine glass fibers (Manville code 100) but not thick
11 glass fibers (Manville code 110) caused chromosomal aberrations (breaks and
12 rearrangements) in Chinese hamster ovary cells (CHO). However, a respirable fraction of
13 the thick glass fibers (but not the total sample) caused a significant increase in
14 chromosomal aberrations (chromatid and isochromatid gaps) in Chinese hamster V79-4
15 cells in another study (Brown *et al.* 1979). Koshi *et al.* (1991) tested three glass fibers
16 (Manville codes 100, 104, and 108A) of different fiber dimensions for chromosomal
17 aberrations in Chinese hamster lung cells. None of the fibers caused significant increases
18 in structural chromosome aberrations, but all three types of fibers caused an increase in
19 polyploidy; however, the thinner fibers (codes 100 and 104) caused increases at lower
20 doses (10 $\mu\text{g}/\text{cm}^2$) than the thicker fiber (code 108A). In general, the clastogenic activity
21 of glass fibers was mild compared with that of asbestos. An increase in structural
22 chromosome aberrations was observed in human embryo lung cells treated with a
23 microfiber (MG1) and a glass wool fiber (GW1) (Wang *et al.* 1999a).

24 Two insulation glass wool fibers (MMVF10 and MMVF11) did not induce anaphase or
25 telophase aberrations (as assessed by lagging chromatin, bridge, or asymmetric
26 segregation) in rat pleural mesothelial cells when exposed to less than 2.5×10^5 Stanton
27 fibers/ cm^2 [Stanton fibers are defined as fibers with length $< 8 \mu\text{m}$ and diameter ≤ 0.25
28 μm], which are poorly represented in MMVF10 and MMVF11 fibers (Yegles *et al.*
29 1995).

1 Casey *et al.* (1983) reported that neither coarse glass nor fine glass fibers caused sister
 2 chromatid exchange in CHO-K1 cells, human fibroblasts (primary cells) or human
 3 lymphoblastoid cells. However, both fiber types caused mitotic delay (as measured by the
 4 number of second metaphase cells) in CHO-K1 cells, and human fibroblasts; the fine
 5 glass fibers caused a greater inhibition than the coarse glass fibers.

Table 5-16. Chromosomal or chromatid-related effects

End point (dose)	Test system	Result	Fiber type/class (dose)	Fiber length & diameter (μm)	Reference
Nuclear abnormalities (micronuclei and ploidy)	Chinese hamster ovary cells	+ No diameter-dependent differences	diameter study: five fibers of MvL475 glass/SPF (codes 90, 108, 110, 112) with a range of diameters (NA)	L = 16–27 D = 0.3–7	Hart <i>et al.</i> 1994
Nuclear abnormalities (micronuclei and ploidy)	Chinese hamster ovary cells	+	length study: eight subpopulations size selected from MvL 901/IGW with a range of lengths (NA)	L = 3.5–31.4 D = 0.5–1.3	Hart <i>et al.</i> 1994
Micronuclei	Chinese hamster V79 cells	+	Owens-Corning AAA-10 (1.7–27.6 $\mu\text{g}/\text{cm}^2$)	L = 2.0 D = 0.18	Zhong <i>et al.</i> 1997a
Micronuclei	Chinese hamster V79 cells	+	Owens-Corning AAA-10, (10–80 $\mu\text{g}/\text{mL}$)	L = 2.0 D = 0.18	Ong <i>et al.</i> 1997
Micronuclei	Chinese hamster V79 cells	+	Manville100 microfiber (10–80 $\mu\text{g}/\text{mL}$)	L = 3.5 D = 0.2	Ong <i>et al.</i> 1997
Micronuclei	Chinese hamster V79 cells	–	general purpose Building insulation/IGW 10–160 $\mu\text{g}/\text{mL}$	L = 98 D = 7.3	Ong <i>et al.</i> 1997

End point (dose)	Test system	Result	Fiber type/class (dose)	Fiber length & diameter (µm)	Reference
Micronuclei	Syrian hamster embryo cells	+	Manville code 100 (unmilled)/SPF (1 µg/cm ²)	L = 9.5 D = 0.13	Hesterberg <i>et al.</i> 1986
Bi- and multinucleated cells	rat liver cells	+ (only at lowest dose)	thin glass wool (1–5 µg/cm ²)	L = 3.8 D = 0.21	Pelin <i>et al.</i> 1995
Bi- and multinucleated cells	human mesothelial cells MeT-5A, PL102	+ +	thin glass wool (1–5 µg/cm ²)	L = 3.8 D = 0.21	Pelin <i>et al.</i> 1995
Bi- and multinucleated cells	rat liver cells	–	milled glass wool (1–5 µg/cm ²)	NR Milling reduces fiber length	Pelin <i>et al.</i> 1995
Bi- and multinucleated cells	human mesothelial cells: MeT-5A PL102	+ (highest dose) –	milled glass wool (1–5 µg/cm ²)	NR Milling reduces fiber length	Pelin <i>et al.</i> 1995
Chromosomal aberrations	Chinese hamster V79-4 cells	– 110 T + 110 R	Manville code 110 T 110 R (respirable)	L = < 200 D = 1.5–2.49	Brown <i>et al.</i> 1979
Chromosomal aberrations	Chinese hamster ovary cells (CHO) primary human fibroblasts or lymphoblaoid lines	+ CHO – Human cells	Manville code 100 (fine glass)/SPF	L = 2.7–26 D = 0.12–1.9	Sincock <i>et al.</i> 1982
Chromosomal aberrations	Chinese hamster ovary cells (CHO)	– CHO – Human cells	Manville code 110 (coarse glass)	L = 2.7–26 D = 0.12–1.9	Sincock <i>et al.</i> 1982
Chromosomal aberrations (structural)	Chinese hamster lung cells	–	Manville codes 100, 104, 108A, 108B (10–300 µg/mL)	L: 90% < 5, 95% < 10 D: code 100 0.29–0.32 code 104 0.39–0.53 code 108A 0.69–1.1 code 108B 1.2–2.4	Koshi <i>et al.</i> 1991

End point (dose)	Test system	Result	Fiber type/class (dose)	Fiber length & diameter (µm)	Reference
Chromosomal aberrations (polyploidy)	Chinese hamster lung cells	+ 100, 104 all doses + 108A (100, 300)	Manville codes 100, 104, 108A (10, 30, 100,-300 µg/mL)	All fibers L: 90% < 5, 95% < 10 D: code 100 0.29–0.32 code 104 0.39–0.53 code 108A 0.69–1.1	Koshi <i>et al.</i> 1991
Chromosomal aberrations	human embryo lung cells	+	JFMRA ^a MG1 micro glass fibers (1.0 µg/cm ²)	L = 3.0 D = 0.24	Wang <i>et al.</i> 1999a
Chromosomal aberrations	human embryo lung cells	+	JFMRA ^a GW1 glass wool fibers (1.0 µg/cm ²)	L = 20 D = 0.88	Wang <i>et al.</i> 1999a
Anaphase/telophase aberrations	rat pleural mesothelial cells	–	MMVF10/IGW (6-10 × 10 ³ fibers/µg)	L = 21.5 D = 0.55	Yegles <i>et al.</i> 1995
Anaphase/telophase aberrations	rat pleural mesothelial cells	–	MMVF11/IGW (6-10 × 10 ³ fibers/µg)	L = 16.7 D = 1.10	Yegles <i>et al.</i> 1995
Sister-chromatid exchange	CHO-K1, human fibroblast (primary culture), human lymphoblastoid cell line	–	Manville code 100/SPF (0.01 mg/mL)	L = 2.7 D = 0.12	Casey 1983
Sister-chromatid exchange	CHO-K1, human fibroblast (primary culture), human lymphoblastoid cell line	–	Manville code 110 coarse glass fibers (JM110) 0.01 mg/mL)	L = 26 D = 1.9	Casey 1983
Mitotic inhibition	CHO-K1, human fibroblast (primary culture)	–	Manville code 100/SPF (0.01 mg/mL)	L = 2.7 D = 0.12	Casey 1983
Mitotic inhibition	CHO-K1, human	+	Manville code	L = 26	Casey 1983

End point (dose)	Test system	Result	Fiber type/class (dose)	Fiber length & diameter (µm)	Reference
	fibroblast (primary culture)		110 coarse glass fibers 0.01 mg/mL)	D = 1.9	

+ = positive; - = negative; +/- = slight effect at highest dose, non-significant dose-response (comet).

NA = not available; NR = not reported; L = length; D = diameter.

^aJFMRA = Japan Fibrous Material Research Association.

1 *Cell transformation and transfection studies*

2 The probable mechanism of asbestos-mediated carcinogenesis involves mutation and/or
3 activation of proto-oncogenes, inhibition of tumor-suppressor genes, and activation of
4 transcription factors controlling the production of cytokines, cell transformation, and cell
5 growth. A number of studies have investigated these endpoints in glass fibers and are
6 reviewed in this section. The data are summarized in Table 5-17.

7 Gene amplification was determined by a Southern blot analysis of *K-ras*, *H-ras*, *c-myc*,
8 and *c-fos* proto-oncogenes in nine BALB-c-3T3 cell lines transformed by Owens-Corning
9 AAA-10 glass fiber (Whong *et al.* 1999). Mutational spectra of the p53 tumor-suppressor
10 gene and the *K-ras* proto-oncogene were also determined. Gene amplification was found
11 in five of nine transformed cell lines for *K-ras*, five of nine for *c-myc*, and six of nine for
12 *c-fos* proto-oncogenes, and all transformed cell lines showed *H-ras* gene amplification.
13 Point mutations (transitions or transversions) were found in *K-ras* (exon 2) in two of nine
14 of the transformed cell lines and p53 (exons 2-5) in six of nine. The authors stated that
15 the results show the possibility of genomic instability originating from chromosomal
16 alterations induced by glass fibers, followed by gene amplification and/or gene mutations
17 in proto-oncogenes and/or tumor suppressor genes.

18 Various types of glass wool fibers, including insulation glass wool and special-purpose
19 glass wool fibers, have been shown to transform mammalian cells; however,
20 transformation efficiency appeared to be affected by fiber length and diameter.

21 Gao *et al.* (1995) investigated cell transformation in NIH-c-3T3 cells and cytotoxicity in
22 BALB/c-3T3 cells with three fibers: Owens-Corning insulation glass wool, Owens-
23 Corning AAA-10, and JM100 fibers. All fiber types induced cytotoxicity (measured by
24 relative cloning efficiency) and dose-related increases in cell transformation, and

1 anchorage-independent growth of the transformed cells. The authors concluded that cell
2 transformation was inversely related to size, with the shortest fibers (AAA-10) having the
3 highest transforming potency and the longest and thickest fibers (insulation glass wool)
4 having the lowest potency. A similar relationship between fiber size and cytotoxicity (as
5 measured by survival) was observed. In contrast to this, Hesterberg *et al.* (1986) reported
6 that unmilled glass fibers induced greater toxicity and higher transformation efficiency
7 than milled glass fibers in Syrian hamster embryo cells similar to that observed for
8 micronuclei induction (see above). [However, in the study reported by Gao *et al.*, AAA-
9 10 and JM100 fibers were also smaller in diameter besides being shorter than the
10 insulation glass wool fibers, thus diameter size might also have contributed to differences
11 in cell transformation.] In another study in Syrian hamster embryo cells, thinner glass
12 fibers (Manville code 100) were more potent in inducing cell transformation and
13 cytotoxicity (relative survival) than thicker glass fibers (Manville code 110). Fiber length
14 also affected transformation efficiency; transformation efficiency was reduced 10 fold
15 when the length of the thin fibers was decreased from 9.5 μm to 1.7 μm , and was absent
16 when the length was reduced to 0.95 μm (Hesterberg and Barrett 1984).

17 Glass fibers did not mediate transfection with plasmids and DNA replication in human
18 MeT-5A mesothelial cells (Gan *et al.* 1993). Several asbestos fibers were positive in this
19 assay.

Table 5-17. Gene mutation and amplification, cell transformation and DNA transfection studies

End point	Test system	Result	Fiber type/class (dose)	Fiber length & diameter (µm)	Reference
Gene amplification, : <i>K-ras</i> , <i>H-ras</i> , <i>c-myc</i> , and <i>c-fos</i>	9 glass fiber-induced transformed BALB-c-3T3 cells	+	Owens-Corning AAA-10	L = 0.5–9 D = 0.08–0.8	Whong <i>et al.</i> 1999
Gene mutations: p53 and <i>K-ras</i>	9 glass fiber-induced transformed BALB-c-3T3 cells	+	Owens-Corning AAA-10	L = 0.5–9 D = 0.08–0.8	Whong <i>et al.</i> 1999
Cell transformation, cytotoxicity	Syrian hamster embryo cells	+ (code 100 more potent)	Manville code 100 (thin)/SPF Manville code 110 (thick) (0.1–10 µg/cm ²)	code 100: L = 9.5 D = 0.13 code 110: L = 10–140 D = 0.8	Hesterberg and Barrett 1984
Cell transformation	Syrian hamster embryo cells	+	code 100 (unmilled) (1 µg/cm ²)	L = 9.5 D = 0.13	Hesterberg <i>et al.</i> 1986
Cell transformation	NIH-3T3, BALB/c-3T3 cells	+	Owens-Corning AAA-10 (1–150 µg/cm ²)	L = 0.5–0.9 D = 0.08–0.8	Gao <i>et al.</i> 1995
Cell transformation	NIH-3T3, BALB/c-3T3 cells	+	Manville code 100/SPF (1–150 µg/cm ²)	L = 1–10 D = 0.05–0.5	Gao <i>et al.</i> 1995
Cell transformation	NIH-3T3, BALB/c-3T3 cells	+	Owen-Corning general purpose insulation/IGW	L = 25–200 D = 4–10	Gao <i>et al.</i> 1995
Transfection of plasmid, DNA replication	Human mesothelial cells (MeT-5A)	–	glass fibers prepared by milling Pyrex wool filtering fiber/IGW (2, 20 µg/plate)	L = 30–60 D = 15–30	Gan <i>et al.</i> 1993

L = length; D = diameter; + = positive; – = negative; SPF = special purpose glass fibers; IGW = insulation glass wool fibers.

1 5.5.4 Genetic damage: mammalian in vivo systems

2 Bottin *et al.* (2003) exposed transgenic male *LacI* F344 rats (lambda LIZ, BigBlue) by
3 nose only to CM44 glass fibers (mean length = 5.0 µm and mean diameter = 0.37 µm) at
4 a concentration of 6.3 mg/m³ (601 WHO fibers) for 5 days and examined mutations in

1 lung DNA 1, 3, 14, 28, and 90 days following exposure. No significant differences in
2 mutant frequencies between the exposed and control rats were observed. This fiber was
3 also rapidly cleared from the lungs. Schürkes *et al.* (2004) investigated the induction of 8-
4 OHdG in female Wistar rats exposed to MMVF11 (see Section 5.5.1), since the
5 production of hydroxyl radicals in cells treated with fibers may result in the formation of
6 pre-mutagenic DNA bases. MMVF11 (14.7, 29.4, 50, and 100 mg MMVF; diameter =
7 0.08 to 4.20 μm , length = 1.7 to 98.8 μm) was administered to female rats for 10 or 20
8 weeks. TNF- α released by macrophages from peritoneal lavages and the induction of 8-
9 OHdG were measured. A dose of 14.7 mg resulted in significant increases in
10 macrophages, while 100 mg resulted in decreased relative macrophage numbers. 8-OHdG
11 was increased with increasing doses of MMVF. Percentages of macrophages correlated
12 with the induction of 8-OHdG 10 weeks after treatment.

13 Topinka *et al.* (2006b, 2006a) investigated mutagenesis and DNA damage induced by
14 SVFs alone or combined with exposure to benzo[*a*]pyrene in the lung of male
15 homozygous λ -*lacI* transgenic F344 rats (Big Blue rats). Rats were administered by
16 intratracheal instillation either single doses of 1 or 2 mg, or four weekly consecutive
17 doses of 2 mg of MMVF10 or rock wool fibers alone, the fibers combined with a 10-mg
18 dose of benzo[*a*]pyrene, 10 mg of benzo[*a*]pyrene alone, or vehicle (0.2 mL of
19 physiological saline). The added exposure to benzo[*a*]pyrene was designed to model the
20 interaction between fibers and tobacco smoke, which the authors suggested might act
21 synergistically to amplify weak mutagenic and carcinogenic effects of fibers. DNA strand
22 breaks (measured by the comet assay) were increased in macrophages and lung epithelial
23 cells in treated rats, but no increase in mutant frequency was observed with MMVF10
24 fibers alone (Topinka *et al.* 2006b). The rock wool fibers caused more extensive
25 inflammation than glass wool fibers. There were only minor differences in the extent of
26 inflammation in rats given single or multiple doses. There was some evidence of
27 oxidative damage in rats that had received multiple doses of MMVF10 based on
28 increased levels of malondialdehyde, a marker for oxidative stress, in lung tissue after 16
29 weeks.

30 The simultaneous administration of benzo[*a*]pyrene with rock wool fibers resulted in an
31 increased mutant frequency that was more than three-fold higher than the sum of the

1 mutant frequencies induced by benzo[*a*]pyrene and fibers separately and was observed
2 after only 4 weeks compared with 16 weeks for the fibers alone (Topinka *et al.* 2006a).
3 The authors reported a super-additive mutagenic effect for combined exposure to
4 benzo[*a*]pyrene and MMVF10 fibers only at the highest dose of fibers tested (4 × 2 mg).
5 Neither rock wool nor MMVF10 fibers co-administered with benzo[*a*]pyrene caused any
6 significant difference in the levels of benzo[*a*]pyrene-specific DNA adducts in lung tissue
7 compared with benzo[*a*]pyrene treatment alone.

8 **5.6 Mechanisms of fiber carcinogenicity**

9 The mechanisms of fiber-induced carcinogenicity are not completely understood, but
10 several hypotheses have been proposed and are discussed below. The pathogenicity of
11 fibers appears to depend on multiple factors, including fiber dimensions, location of
12 deposition, biopersistence, uptake by macrophages or other target cells, migration into the
13 interstitium and pleura, and induction of persistent inflammation and fibrosis. The
14 German Commission for the Investigation of Health Hazards of Chemical Compounds in
15 the Work Area (DFG 2002) concluded that: “in principle, all kinds of elongated dust
16 particles have the potential, like asbestos fibers, to cause tumors if they are sufficiently
17 long, thin and durable *in vivo*.” However, the definition of pathogenic fiber properties
18 “sufficiently long, thin and durable” is still under discussion. Clearance of the shorter
19 fibers is similar to or faster than clearance of insoluble nuisance dusts (Bernstein 2006,
20 Muhle *et al.* 1987); however, long fibers are not as easily cleared from the lungs and
21 induce inflammation and fibrosis (Davis and Cowie 1990). Since much of what is known
22 about mechanisms of fiber carcinogenesis comes from studies of asbestos and other
23 SVFs, the following discussion is not limited to glass fibers.

24 Nguea *et al.* (2008) proposed that fiber-induced lung carcinogenesis, [which included
25 discussion of fiber interactions with both lung epithelial cells and mesothelial cells,]
26 could be explained by two different mechanisms relating to the physical properties of the
27 fibers *in situ* and the effects of the fibers on macrophages (Figure 5-5). The potential for
28 harm from inhaled fibers is dependent upon the following physicochemical properties:
29 fiber dimension, biopersistence, surface reactivity, and chemical composition. The fibers
30 can interact directly with target cells (epithelial cells, mesothelial cells, fibroblasts)
31 leading to an inflammatory response and/or genotoxicity. Alveolar macrophages provide

1 an early immune response through phagocytosis of inhaled foreign bodies and
2 amplification of the inflammatory response through the release of cytokines, reactive
3 oxygen and nitrogen species, interleukins, mitogenic factors, and chemotactic factors.
4 These inflammatory mediators would affect the local cell environment, leading to
5 genotoxicity, proliferation and/or apoptosis. Depending on the properties of the fibers,
6 incomplete phagocytosis (frustrated phagocytosis) can occur, leading to further
7 amplification of the inflammatory response.

8 The potential mechanisms of fiber carcinogenesis have also been reviewed by others
9 (Fubini and Fenoglio 2007, Hesterberg and Hart 2001, IARC 2002, Kane *et al.* 1996b,
10 Nguea *et al.* 2008). The available reviews identify the following mechanisms as having
11 important roles in the development of fiber-induced diseases: production and release of
12 ROS and DNA damage, genotoxicity, chronic inflammation with release of cytokines and
13 growth factors, cytotoxicity and increased cell proliferation, and co-carcinogenicity. In
14 addition, Christensen *et al.* (2008, 2009) recently investigated the role of gene silencing
15 through DNA hypermethylation in asbestos carcinogenesis.

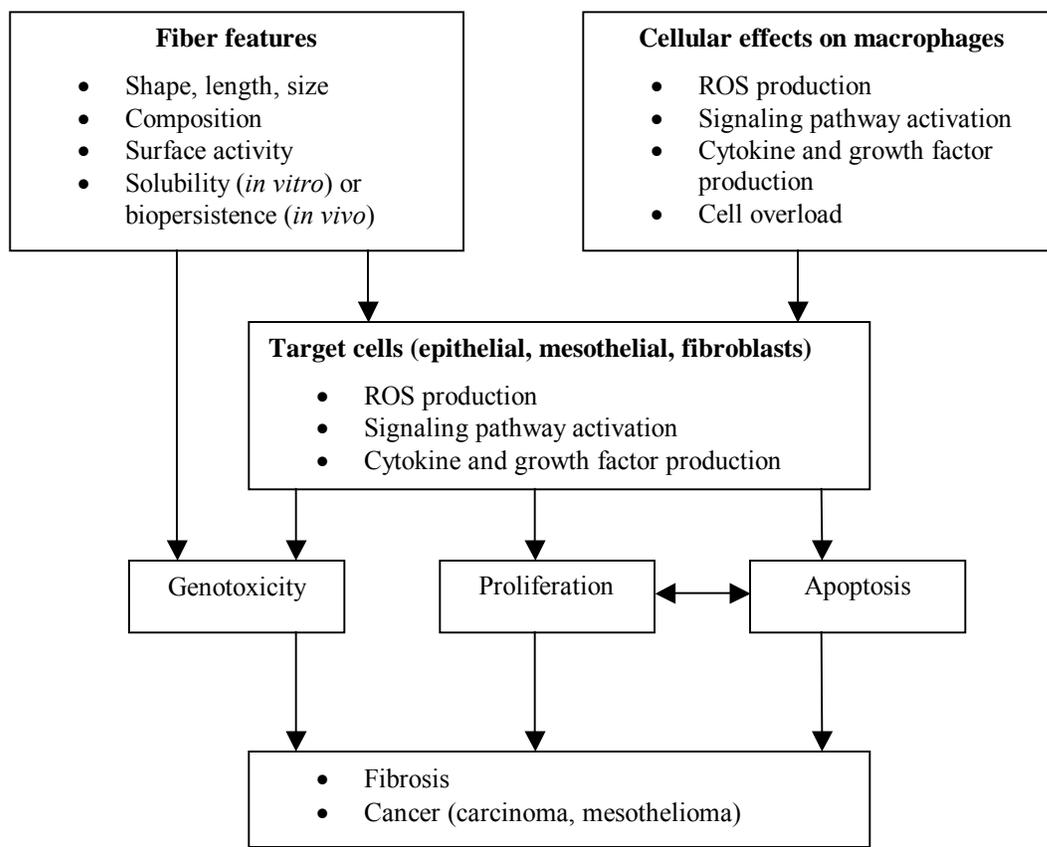


Figure 5-5. Mechanisms of fiber-induced toxicity and carcinogenicity

Source: adapted from Nguea 2008.

1 5.6.1 Release of reactive oxygen species

2 Both natural fibers and SVFs have generated ROS and reactive nitrogen species (RNS) in
 3 cell-free or *in-vitro* model systems (Nguea *et al.* 2008). Proposed mechanisms include
 4 iron-catalysed generation of the hydroxyl radical in the presence of molecular oxygen,
 5 superoxide anion, or hydrogen peroxide or release of ROS/RNS (hydrogen peroxide,
 6 superoxide anion, nitric oxide, hydroxyl radical, peroxyxynitrite, or nitronium ions) from
 7 macrophages during incomplete phagocytosis (frustrated phagocytosis) of long fibers
 8 (Kane 1996a). Biopersistent fibers deposited in the lung cause chronic inflammatory
 9 reactions leading to generation of free radicals that mediate DNA damage and mutations
 10 in oncogenes, growth regulatory genes, and tumor-suppressor genes. Thus, inflammatory
 11 reactions induced by persistent fibers in the lung are thought to be important genotoxic
 12 mediators that accelerate tumor development and progression (Nguea *et al.* 2008, Okada
 13 2007) (see Section 5.6.3 for DNA damage).

1 Alveolar macrophages are the first line of defense in the alveolar environment and play a
2 central role in recruiting and activating other inflammatory cells (Nguea *et al.* 2008).
3 Rihn *et al.* (2000) demonstrated that inhaled crocidolite induced the release of ROS and
4 RNS resulting in oxidation and nitrosylation of protein and DNA, and lipoperoxidative
5 damage of type II pneumocytes, fibroblasts, and mesothelial cells. Thus, cell injuries
6 caused by release of these reactive species contribute to the pathogenesis of fiber-related
7 lung disease and indicate that oxidative stress is a basic mechanism of the carcinogenic
8 effect (Nguea *et al.* 2008). Zeidler-Erdely *et al.* (2006) showed that increasing the dose of
9 JM100 glass fibers resulted in an increase in reactive species production by human
10 alveolar macrophages. However, there was no effect of fiber length over the range of 8 to
11 20 μm . Ohyama *et al.* (2000, 2001) investigated the chemiluminescent response (an
12 indicator of reactive oxygen species production) from human monocyte-derived
13 macrophages exposed to glass wool, rock wool, refractory ceramic fibers, and others.
14 These authors reported that there was a strong correlation between geometric-mean
15 length and the ability to induce chemiluminescence for various fiber samples longer than
16 6 μm in length. There was no correlation with geometric-mean width; however, between
17 two refractory fiber samples with similar lengths, the narrower width sample induced
18 more chemiluminescence.

19 5.6.2 *Chronic inflammation*

20 A potential indirect mechanism of fiber carcinogenesis involves the release of cytokines
21 and growth factors from inflammatory cells in the lungs (Kane 1996a). Macrophages are
22 activated in response to particulates deposited in the lung resulting in increased release of
23 ROS, chemical mediators, and cytokines. Cytokines sustain and amplify the
24 inflammatory reaction. Thus, persistent fibers in the lung, interstitium, or subpleural
25 connective tissue may cause a sustained chronic inflammatory reaction. A chronic
26 imbalance between cytokines and growth factors may contribute to tissue injury and
27 proliferation of epithelial and mesenchymal cells. Injury to the alveolar epithelial lining
28 and basement membranes could enhance translocation of fibers and inflammatory
29 mediators to the interstitium of the lung.

30 Poland *et al.* (2008) reported that concerns over the potential pathogenicity of carbon
31 nanotubes had been raised because their needle-like fiber shape was similar to asbestos.

1 Therefore, the pathogenicity of multiwalled carbon nanotubes was compared with long-
2 fiber and short-fiber amosite asbestos (used as positive and negative controls,
3 respectively). Four samples of carbon nanotubes were prepared. Two of the samples
4 contained a substantial proportion of straight fibers that were longer than 20 μm while the
5 other two samples consisted of nanotubes that were arranged in low-aspect-ratio tangled
6 aggregates. Each material was injected i.p. into mice (50 μg), and the peritoneal cavity
7 was washed out either 24 hours or 7 days post exposure with physiological saline. The
8 authors reported that carbon nanotubes produced an asbestos-like, length-dependent,
9 pathogenic response, which included inflammation and formation of granulomas.
10 Polymorphonuclear leukocytes, protein exudation, and granulomas were observed only in
11 samples that contained long fibers.

12 *Cytokines and growth factors*

13 The roles of NF- κB , tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β) in
14 fiber-induced disease have been the focus of several studies (Brown *et al.* 1999, Cullen *et al.*
15 *et al.* 1997, Dostert *et al.* 2008, Fisher *et al.* 2000, Fujino *et al.* 1995, Gilmour *et al.* 1997,
16 Murata-Kamiya *et al.* 1997, Schins and Donaldson 2000, Xie *et al.* 2000, Ye *et al.* 1999,
17 2001).

18 Results for production of TNF- α in response to exposure to glass fibers are variable.
19 Fujino *et al.* (1995) tested the toxicity of several SVFs and natural fibers by measuring
20 TNF- α production and release of lactate dehydrogenase (LDH) and β -glucuronidase
21 (BGU) from rat alveolar macrophages *in vitro*. Cell cultures were incubated for 24 hours
22 with the various fibers (100 $\mu\text{g}/\text{mL}$). There was a significant increase in TNF- α , LDH,
23 and BGU in cell cultures exposed to glass fibers (specified as $\text{SiO}_2 \cdot \text{Na}_2\text{O}$ with a median
24 length of 12.8 μm and diameter of 0.54 μm). The results were similar to the responses
25 reported for chrysotile, crocidolite, and amosite. Murata-Kamiya *et al.* (1997) reported
26 the TNF- α production was slightly increased (not significant compared with controls) in
27 a murine macrophage cell line (J774 cells) exposed to 100 $\mu\text{g}/\text{mL}$ of glass fibers for 18
28 hours. Cell cultures exposed to chrysotile asbestos showed a significant increase in
29 TNF- α production. The glass fibers used in this study had the same geometric mean
30 length and diameter as those tested by Fujino *et al.* (1995). Cullen *et al.* (1997) tested the

1 effects of MMVF10, MMVF11, 100/475, 104E, amosite, crocidolite, and other SVFs on
2 TNF- α production in rat alveolar macrophages. MMVF10 and MMVF11 did not
3 stimulate TNF- α production, whereas the effects of 100/475 and 104E glass were
4 intermediate. [No statistics were reported, but values were less than twice the control
5 values.] Values for amosite and crocidolite asbestos were about 2.5 to 3.2 times greater
6 than controls. Fisher *et al.* (2000) investigated TNF- α production in four different cell
7 types: primary rat alveolar macrophages, human peripheral blood monocytes, Thp-1 cells
8 (derived from the peripheral blood of a 1-year-old boy with acute monocytic leukemia),
9 and J774.2 cells (recloned from J774.1 cells that were recovered from a Balb C mouse).
10 Fibers tested included amosite (35.3% > 20 μ m), 100/475 glass (19.3% > 20 μ m), and
11 MMVF10 (67.2% > 20 μ m). Cells were incubated with the various fiber types for 16
12 hours. None of the fiber types resulted in a significant increase in TNF- α production for
13 any of the cell types. The authors concluded that TNF- α release did not equate to fiber
14 pathogenicity in this study.

15 The glass fiber-induced expression of TNF- α likely involves several different
16 transcription factors, including NF- κ B, which is involved in the activation of a variety of
17 proinflammatory genes (Schins and Donaldson 2000). Mechanisms involved in NF- κ B
18 activation by fibers include ROS, arachidonic acid metabolism, physicochemical
19 properties of the fibers (e.g., fiber dimensions, transition metals), lipid peroxidation, and
20 frustrated phagocytosis. Gilmour *et al.* (1997) reported that MMVF10 upregulated the
21 nuclear translocation of AP-1 transcription factor in rat alveolar macrophages by about
22 12% compared with untreated controls but did not affect NF- κ B. In the same study, AP-1
23 was upregulated by 37.4% and NF- κ B by about 20% by amosite. Brown *et al.* (1999)
24 investigated the effects of fiber exposure on NF- κ B nuclear translocation in A549 human
25 alveolar epithelial cells. Asbestos fibers caused a dose-dependent increase in NF- κ B
26 nuclear translocation, but MMVF10 and code 100/475 fibers did not. When the fiber dose
27 was doubled from 8.24×10^6 to 16.48×10^6 , MMVF10 caused a significant increase in
28 the nuclear translocation of NF- κ B. Doubling the dose of 100/475 fibers had no effect.

29 In other studies, a substantial increase in TNF- α production and the DNA-binding
30 activity of NF- κ B in RAW 264.7 mouse monocytes (Ye *et al.* 1999) and NR8383 rat

1 alveolar macrophages (Ye *et al.* 2001) was observed when exposed to code 100 fibers.
2 These studies compared the effects of long fibers (17 μm) and short fibers (7 μm) after
3 exposure for 3, 6, or 16 hours. TNF- α production was not induced after a 3-hour
4 exposure, but a significant induction was observed after 6 or 16 hours. The TNF- α gene
5 promoter was activated after exposure to both short and long fibers; however, the long
6 fibers showed a 100% increase in stimulatory activity compared with short fibers. The
7 increase in DNA binding activity of NF- κB indicated that this transcription factor was
8 responsible for activation of the gene promoter. On a fiber-per-fiber basis, long glass
9 fibers were two to four times more potent than short fibers in inducing NF- κB , the gene
10 promoter activity, and production of TNF- α .

11 Ye *et al.* (2001) also demonstrated that glass fibers induced phosphorylation of MAP
12 kinases, p38, and ERK in primary rat alveolar macrophages exposed to code 100 fibers
13 and that this phosphorylation was associated with TNF- α gene expression. When
14 transcription factor inhibitors were included in the assays, release of TNF- α was almost
15 completely inhibited by SN50 (an inhibitor of NF- κB), 70% by SB203580 (an inhibitor
16 of p38), and 50% by PD98059 (which prevents phosphorylation of ERK by MEK). Xie *et*
17 *al.* (2000) conducted a study to determine if TNF- α affected binding (defined as
18 resistance to removal by a simple washing technique) of fibers to epithelial cells. Rat
19 tracheal explants were exposed to TNF- α , or to culture medium alone, followed by a
20 suspension of amosite or MMVF10. Exposure to TNF- α increased epithelial fiber
21 binding, but higher TNF- α doses were needed to show an effect with MMVF10. This
22 effect was abolished by an anti-TNF- α antibody and an NF- κB inhibitor indicating that
23 fiber binding was controlled by a NF- κB -dependent mechanism.

24 Interleukin-1 beta (IL-1 β) is a cytokine released from activated macrophages and, like
25 TNF- α , is a mediator of inflammation, cell proliferation/differentiation, and apoptosis. It
26 is involved in recruitment of inflammatory cells and has been shown, along with TNF- α ,
27 to regulate mesothelial cell proliferation (Wang *et al.* 2004).

28 Dostert *et al.* (2008) has studied the proinflammatory response of macrophages to
29 asbestos and silica particles. Using a macrophage-like cell line, THP1, mature IL-1 β was

1 released after 6-hour exposure to asbestos or silica particles, but not to cigarette smoke or
2 diesel exhaust particles. Further experiments demonstrated that ROS generated upon
3 actin-mediated phagocytosis activated the Nalp3 inflammasome within the macrophage.
4 Caspase-1 within this multiprotein complex then cleaved pro-IL-1 β releasing mature IL-
5 1 β . Inhibitors of NADPH oxidase decreased IL-1 β production, providing evidence in
6 support of activation of ROS through generation of NADPH oxidase. Using a mouse
7 model, the role of Nalp3 inflammasome in asbestos-induced inflammation was further
8 investigated. Nalp3^{-/-} and Nalp3^{+/+} mice were exposed for 9 days to chrysotile asbestos,
9 and markers of inflammation were analyzed. Lymphocyte, eosinophil, and neutrophil
10 infiltrations were decreased in the lungs of Nalp3^{-/-} mice, as were the levels of IL-1 β and
11 KC [keratinocyte chemoattractant], a neutrophil chemokine. These data support the role
12 of the Nalp3 inflammasome in particulate-induced pulmonary inflammation.

13 *Inflammation and fibrosis*

14 Chronic inflammation also is known to be an important factor for fibrosis. In rodent
15 inhalation studies of fibers and other particulates, lung cancer is almost always preceded
16 by chronic inflammation and fibrosis (IARC 2002). Although high levels of pulmonary
17 fibrosis have been found in studies showing significant lung tumor incidences, a direct
18 cause and effect relationship has not been established (Kane 1996a). Nevertheless, IARC
19 (2002) concluded that the proposed mechanistic links between chronic inflammation,
20 fibrosis, and cancer are biologically plausible.

21 *5.6.3 Genotoxic effects*

22 Genotoxic effects include oxidized bases, DNA breaks, aneuploidy, and mutations and
23 may result from three possible mechanisms: (1) direct interaction of fibers with the
24 spindle apparatus, (2) release of fiber components that directly damage DNA, and (3)
25 indirect damage resulting from chemical species released during chronic inflammation.
26 As discussed previously (see Section 5.5.3, “*Chromosomal or chromatid-related*
27 *effects*”), phagocytized fibers might interfere with chromosome segregation during
28 mitosis. Some studies using light microscopy on fixed cells have suggested that long
29 fibers can interfere with the mitotic spindle, causing lagging chromosomes and
30 subsequent aneuploidy (Kane 1996a). Aneuploidy, polyploidy, and binucleated cells have
31 been observed in a wide variety of rodent and human cell types *in vitro*; however, it has

1 not yet been established *in vivo* whether fibers are internalized by the target cells that are
2 responsible for bronchogenic carcinoma or malignant mesothelioma.

3 Physical interference with chromosomal segregation is not the only way fibers might
4 disrupt mitosis (Kane 1996a). Disruption of the cytoskeletal organization of the cell could
5 enhance the interaction of fibers with the mitotic spindle, and interference with the
6 cleavage furrow might result in binucleated daughter cells.

7 Johnson and Jaramillo (1997) examined expression of p53, Cip1, and Gadd153 proteins
8 following treatment of A549 cells with crocidolite and JM100 fibers. These proteins are
9 associated with DNA damage and cell-cycle arrest. A dose-dependent toxicity was
10 observed with both fiber types, but the cytotoxic effects were more marked with JM100
11 when compared with crocidolite on an equal mass/unit area basis. There was a dose-
12 dependent increase in expression of all three proteins in cells exposed to crocidolite, but
13 not to JM100 fibers. Pache *et al.* (1998) exposed a human mesothelial cell line (MET5A)
14 or A549 cells to various concentrations of crocidolite and MMVF10 and measured the
15 intensity and distribution of epidermal growth factor receptor (EGF-R) protein.
16 Crocidolite asbestos, but not MMVF10, caused an increase in the number of EGF-R-
17 positive MET5A cells. No increase in EGF-R-positive A549 cells was observed with
18 either fiber type.

19 Most of the studies of DNA damage were conducted with target cell populations *in vitro*.
20 Important factors include the fiber source and preparation, cell type, species, and assay
21 conditions. Several natural and synthetic fibers (i.e., SVFs) have caused DNA damage in
22 rodent and human cells. Studies with asbestos indicate that mesothelial cells might be
23 more sensitive to DNA damage than epithelial cells or fibroblasts (Kane 1996a). Ngueta *et*
24 *al.* (2008) reviewed SVF-induced genotoxicity and reported that asbestos fibers
25 (including amosite, chrysotile, and crocidolite) appeared to be more genotoxic than glass
26 fibers based on higher levels of DNA base oxidation (i.e., 8-OHdG). *In vivo* studies using
27 Big Blue transgenic rats indicated that glass fibers of low biopersistence were not
28 mutagenic for lung DNA (see Section 5.5.4); however, asbestos fibers caused an increase
29 in mutant frequency (Bottin *et al.* 2003, Rihn *et al.* 2000). Although a number of studies
30 (see Section 5.5.3) have shown that glass fibers can cause DNA damage, micronuclei,

1 and chromosomal aberrations *in vitro*, relatively few *in vivo* studies have been conducted.
2 The exact genotoxic mechanisms initiated and sustained by SVF are not well understood
3 and further study is needed to distinguish between direct and indirect DNA damage
4 (Greim 2004).

5 Schürkes *et al.* (2004) investigated the role of inflammation-driven genotoxicity in fiber-
6 induced carcinogenesis (MMVF11 glass fibers and crocidolite) (see Section 5.5.1) and
7 reported a correlation between parameters of inflammation and the induction of 8-OHdG.

8 5.6.4 Epigenetic effects

9 Malignant pleural mesothelioma is highly associated with asbestos exposure, which
10 occurs in 70% to 80% of cases of this type of mesothelioma (Christensen *et al.* 2008,
11 Christensen *et al.* 2009). Christensen *et al.* (2008) noted that asbestos is a nonmutagenic
12 carcinogen, and they focused their investigations on the epigenetic mechanism of gene
13 silencing through hypermethylation of cytosines in CpG islands in tumor-suppressor
14 genes. Using a biochemical pathway-based approach, they examined promoter
15 hypermethylation of an array of genes involved in cell-cycle control. One or more of
16 these genes was methylated in 60% of a set of 70 cases of pleural mesothelioma. In a
17 larger study of 158 pleural mesotheliomas and 18 non-tumorigenic parietal pleura
18 samples, the methylation patterns of 1,505 CpG loci associated with 803 cancer-related
19 genes were determined (Christensen *et al.* 2009). The number of asbestos bodies, which
20 reflects the exposure to asbestos, was significantly ($P < 0.03$) associated with the pattern
21 of methylation, and there was a clear distinction between the methylation patterns for
22 malignant versus normal pleura ($P < 0.0001$). The lung burden of asbestos bodies also
23 was found to be significantly ($P < 0.02$) associated with methylation of any of the six
24 cell-cycle genes in the earlier paper by Christensen *et al.* (2008). A significant ($P < 0.05$)
25 trend between increasing asbestos body count and increasing number of methylated cell-
26 cycle pathway genes remained after controlling for age, gender, and tumor histology,
27 consistent with the hypothesis that asbestos body burden contributes to epigenetic
28 dysregulation of cell-cycle genes. Gender was associated with asbestos body count, with
29 significantly ($P < 0.001$, more than 5-fold) higher asbestos body count in males compared
30 with females. The authors of these papers suggested that methylation could represent a
31 novel tumorigenic mechanism of action for asbestos as an epigenetic cause for malignant

1 mesothelioma. That is, mesotheliomas are driven by both genetic and epigenetic
2 alterations (Tsou *et al.* 2007).

3 *5.6.5 Cytotoxicity and proliferation of target cells*

4 High concentrations of asbestos fibers are toxic to target cell populations *in vitro*;
5 however, under certain conditions, asbestos fibers induce cell proliferation (Kane 1996a).
6 Kane (1996a) identified four potential mechanisms of growth stimulation based on
7 studies with asbestos fibers. Each mechanism requires direct interaction with target cells
8 and includes the following: (1) compensatory cell proliferation in response to toxicity, (2)
9 stimulation of intracellular signal transduction pathways, (3) direct mitogenesis, and (4)
10 induction of growth factor and growth factor receptor expression.

11 *Cell proliferation*

12 Cell proliferation is triggered as part of the healing response to tissue injury.
13 Intraperitoneal injection of asbestos has caused injury to the mesothelial lining of the
14 parietal pleura (diaphragm) in mice, and localized damage to the alveolar epithelium
15 following inhalation or intratracheal administration is believed to facilitate translocation
16 of fibers into the interstitium of the lungs (Kane 1996a). Hart *et al.* (1994) evaluated MvL
17 901 glass fibers and Blake *et al.* (1998) evaluated code 100 glass fibers. Both studies
18 showed length-related toxicity. Fibers of lengths 17 to 33 μm showed marked increases in
19 toxicity, while fibers less than 7 μm in length showed significantly less, or no toxicity.
20 Fiber thickness also had a modest effect on toxicity in one study. It was concluded that
21 long fibers were toxic *per se*, in addition to their ability to accumulate in the lung due to
22 slower clearance rates. It was suggested that the increased toxicity of long fibers was due
23 to frustrated phagocytosis leading to leakage of oxidants and enzymes.

24 *Signal transduction pathways*

25 Intracellular signal transduction pathways are commonly triggered in response to tumor
26 promoters and asbestos fibers (Kane 1996a). Experimental evidence demonstrates that
27 asbestos fibers can act as a tumor promoter, activate protein kinase C, cause increased
28 expression of ornithine decarboxylase, and cause hydrolysis of inositol phospholipids.

1 *Mitogenic effects*

2 Evidence for the mitogenic effects of fibers is based on *in vitro* studies that show
3 induction of the proto-oncogenes *c-fos* and *c-jun* following exposure to asbestos (Gao *et al.*
4 *al.* 1997, Janssen *et al.* 1994). Prolonged expression of proto-oncogenes may result in
5 growth stimulation of target cells.

6 The induction of proto-oncogenes (Gao *et al.* 1997, Janssen *et al.* 1994), expression of
7 DNA-damage-inducible genes (Johnson and Jaramillo 1997), and epidermal growth
8 factor-receptor (Pache *et al.* 1998) by glass wool has also been investigated. Janssen *et al.*
9 (1994) examined the effects of crocidolite, chrysotile, MMVF10, and other fibers and
10 particulates on mRNA levels of *c-fos*, *c-jun*, and ornithine decarboxylase in hamster
11 tracheal epithelial (HTE) cells and rat pleural mesothelial (RPM) cells. These cells were
12 selected because they are the progenitor cells of bronchogenic carcinoma and
13 mesothelioma, respectively. MMVF10 was less cytotoxic than asbestos, and RPM cells
14 were more susceptible to cytotoxicity than HTE cells. There was an increase in *c-jun*
15 mRNA levels in HTE cells after exposure to asbestos or MMVF10; however, increases
16 were less after exposure to MMVF10 compared with asbestos. No alterations in *c-fos*
17 mRNA levels were observed in HTE cells. Ornithine decarboxylase mRNA levels also
18 were increased in HTE cells after exposure to asbestos or MMVF10. Crocidolite asbestos
19 caused increases in *c-fos*, *c-jun*, and ornithine decarboxylase in RPM cells, but MMVF10
20 did not when added at nontoxic concentrations ($< 10 \mu\text{g}/\text{cm}^2$). At a higher concentration
21 of MMVF10 ($25 \mu\text{g}/\text{cm}^2$), *c-fos* and *c-jun* mRNA levels were increased. Gao *et al.* (1997)
22 investigated the relationship between silica and glass fiber-induced cell transformation
23 and oncoprotein expression (protein products from seven proto-oncogenes), and p53 in
24 BALB/c-3T3 cells. All transformants induced by glass fibers were positive for *c-jun*
25 protein expression. The other proto-oncogene proteins or tumor suppressor genes (*c-K-*
26 *ras*, *c-H-ras*, *c-myc*, *c-sis*, *c-erb B1*, *c-myb*, and p53) were either not detectable or were
27 not significantly different between transformed and non-transformed cells.

28 *Growth factors*

29 Increased expression of platelet-derived growth factor (PDGF-AA) and its receptor was
30 demonstrated *in vitro* in rat lung fibroblasts exposed to asbestos fibers (Lasky *et al.*
31 1995). Increased expression of growth factors and their receptors may trigger cell

1 proliferation by activating an autocrine growth-stimulatory pathway. However, the
2 mechanism responsible for turning on transcription factors that regulate specific genes
3 has not been identified. One possibility is oxidant stress from generation of ROS and
4 activation of NF- κ B.

5 *Cytotoxicity*

6 Nguea *et al.* (2005) reported that cell viability was inversely related to fiber concentration
7 regardless of the type and size of fibers. These authors concluded that cell overloading
8 may be responsible for the cytotoxicity of fibers, because cytotoxicity was observed only
9 when the ratio of fibers to cells was high. Castranova *et al.* (1996) reported that long and
10 thick fibers designed for building insulation had only a weak effect on cell viability of rat
11 alveolar macrophages and did not affect macrophage function.

12 Extracellular release of cytoplasmic LDH and BGU can result from cytotoxicity (Nguea
13 *et al.* 2008). Release of LDH indicates loss of membrane integrity, and BGU is a
14 lysosomal enzyme biomarker of phagocyte damage or activation. Castranova *et al.*
15 (1996) reported that glass microfibers induced a dose-dependent release of both LDH and
16 BGU from rat alveolar macrophages. Blake *et al.* (1998) reported that cytotoxicity in rat
17 alveolar macrophages was directly related to glass fiber length over 17 μ m; however,
18 chemical composition also had some influence.

19 5.6.6 *Co-carcinogenesis*

20 Lung cancer risk is enhanced in asbestos workers who smoke (Hesterberg and Hart
21 2001). Although a small excess of lung cancer occurs in non-smokers exposed to
22 asbestos, most cases of lung cancer occur in people exposed to asbestos who are smokers
23 (Kane *et al.* 1996b). It is not known if the mechanisms leading to lung cancer are the
24 same for smokers and non-smokers exposed to asbestos. However, there is experimental
25 evidence that asbestos fibers enhance the delivery of the carcinogens in cigarette smoke
26 and increase their metabolic activation (Kane 1996a). Furthermore, cigarette smoking
27 reduces ciliary action in the tracheobronchial region and enhances fiber penetration into
28 the bronchial epithelium. Topinka *et al.* (2006a) administered benzo[*a*]pyrene
29 simultaneously with rock wool fibers to model the interaction between fibers and tobacco
30 smoke (see Section 5.5.4). Intratracheal instillation of benzo[*a*]pyrene and fibers

1 combined in Big Blue rats resulted in mutant frequencies that were higher and occurred
2 earlier than those with benzo[*a*]pyrene or fibers alone.

3 Exposure to SVFs generally consists of a mixture of non-fibrous and fibrous particulates.
4 Several of the mechanisms described in this section (e.g., cell proliferation and chronic
5 inflammation) are responses to particulate exposure in general and not just to fibers.

6 Little is known about the interactions of fibers with non-fibrous particles, particularly the
7 less toxic particulates. However, increased incidences of lung tumors and mesotheliomas
8 have been reported in rats exposed by inhalation to a mixture of chrysotile asbestos and
9 non-fibrous dust (Kane 1996a).

10 Another possible, yet controversial, co-carcinogenic interaction is with SV40 virus.
11 SV40-like DNA sequences have been identified in human mesothelioma tissue samples
12 but not in adjacent lung tissue (Carbone *et al.* 1994, Rivera *et al.* 2008). The origin of the
13 viral DNA and its relationship to malignant mesothelioma is unknown. The viral
14 oncoprotein can bind to p53 and inhibit its activity (IARC 1999). Rivera *et al.* (2008)
15 reported that co-carcinogenesis between SV40 and asbestos in causing malignant
16 mesothelioma has been demonstrated in three separate laboratories using different
17 experimental approaches; however, epidemiological evidence is lacking due “to
18 unattainable identification of infected from noninfected cohorts.”

19 **5.7 Summary**

20 *5.7.1 Deposition, clearance, and retention*

21 Fibers that are carried in the inhaled air to the tracheobronchial region are considered
22 *inhalable* while those that reach the alveolar region are considered *respirable*. Fibers that
23 are inhalable but non-respirable can deposit in the extrathoracic and tracheobronchial
24 regions and can cause adverse effects. Deposition refers to the actual dose deposited in
25 the lung and is influenced by the anatomy and physiology of the airway, respiratory rate,
26 and physical properties of the fiber. Deposition occurs by impaction, sedimentation,
27 interception, and diffusion. Peak deposition occurs in rodents and humans for fibers with
28 aerodynamic diameters of 1 to 2 μm .

29 Clearance and retention of fibers are affected by chemical composition, size distribution,
30 number of fibers deposited, and time since last exposure. Clearance mechanisms also

1 depend on the region of deposition. Short fibers are readily phagocytized by alveolar
2 macrophages and transported from the lower lung to the upper airways and cleared
3 through the mucociliary escalator, or they can be cleared via lymphatics. Long fibers are
4 not effectively cleared by phagocytosis, and can effectively kill the phagocyte, but
5 depending on the fiber type, may be subject to dissolution and transverse breakage.
6 Particle overload (which has been observed in rats) occurs when the deposition rate of
7 poorly-soluble, less toxic particles exceeds the normal clearance rate, and can result in
8 adverse effects.

9 *5.7.2 Dissolution, biodurability, and biopersistence of glass fibers*

10 Dissolution occurs when water molecules attack the surface of the fiber and remove
11 material. Biodurability describes the rate of removal through dissolution or
12 disintegration; biopersistence includes biodurability plus physiological clearance and
13 refers to the capacity of a fiber to persist and to conserve its chemical and physical
14 features over time in the lung. Biodurability is expected to be similar in rats and humans,
15 but biopersistence may be substantially different due to differences in the physiological
16 clearance mechanisms. In general, biodurability of various fibers in the lung has been
17 ranked as follows: glass fibers < refractory ceramic fibers < chrysotile asbestos <
18 amphibole asbestos. Highly durable fibers, such as asbestos, are resistant to dissolution
19 and transverse breakage. Although experimental dissolution rates for glass fibers show
20 variability (up to a 30-fold range), they generally show some correlation with clearance
21 rates of long fibers in short-term biopersistence studies. Certain components of SVFs are
22 subject to leaching resulting in changes in composition over time. The literature indicates
23 that the special-purpose fibers cited in this document tend to have greater biopersistence
24 than the insulation glass wools. The fibers become weaker from fractures, peeling, and
25 pitting and may break.

26 *5.7.3 Toxic effects*

27 Several studies have evaluated mortality from non-malignant respiratory disease or
28 morbidity related to the respiratory system among workers exposed to glass wool. A
29 significantly elevated SMR for non-malignant respiratory disease was found in the earlier
30 updates, but not the most recent update of the large U.S. cohort study. Mixed findings

1 have also been observed for adverse respiratory symptoms, pulmonary function, and lung
2 abnormalities (detected on chest radiographs); workers in some studies were also exposed
3 to asbestos.

4 Various types of glass wool fibers (MMVF10, MMVF11, 104E glass fibers, JM100/475
5 microfibers) caused adverse lung effects (such as inflammation and fibrosis) in rats
6 exposed by inhalation (Bellmann *et al.* 2003, Bermudez *et al.* 2003, Cullen *et al.* 1997,
7 Hesterberg *et al.* 1993, 2002). In hamsters, inhalation of MMVF10 fibers caused
8 inflammatory effects, but not fibrosis (Bermudez *et al.* 2003, Hesterberg *et al.* 1993). In
9 cytotoxicity studies, longer fibers induced greater toxicity in rat alveolar macrophages
10 (Blake *et al.* 1998, Hart *et al.* 1994).

11 5.7.4 Genetic and related effects

12 Glass fibers were shown to induce production of reactive oxygen species in cell-free
13 systems and cultured cells, to damage DNA, and to cause chromosomal aberrations,
14 nuclear abnormalities, mutations, gene amplification in proto-oncogenes, and cell
15 transformation in mammalian cells. However, glass wool fibers did not cause mutations
16 in bacteria or cause sister chromatid exchange in mammalian cells, but only two types of
17 fibers were tested in each of these assays. Glass wool fibers also induced DNA strand
18 breaks (measured by the comet assay) in macrophages and lung epithelial cells, and
19 oxidative stress in rats, but did not induce mutations *in vivo*. An increase in mutant
20 frequencies was reported for benzo[*a*]pyrene and rock wool fibers instilled
21 simultaneously in Big Blue rats.

22 Further, fiber persistence may also lead to inflammation-driven (indirect) genotoxicity, as
23 reactive inflammatory cells release reactive oxygen species, growth factors, and
24 cytokines. Fiber characteristics did not appear to be important in the production of
25 reactive oxygen species, and studies assessing oxidative damage by different endpoints
26 were positive for both special-purpose fibers and insulation glass wool fibers. Similarly,
27 fibers of different lengths and diameters were able to cause DNA damage in mammalian
28 cells. However, effects on chromosomes and nuclear abnormalities might be related to
29 fiber characteristics; longer fibers appeared to be more potent in causing these genotoxic
30 effects. Some studies suggested that thinner fibers were also more effective. Results from

1 cell transformation studies also suggested that longer and thinner fibers produced higher
2 transformation efficiency.

3 *5.7.5 Mechanisms of fiber carcinogenicity*

4 Several investigators have evaluated fiber characteristics (dimensions and durability or
5 biopersistence) and tumorigenicity in studies in experimental animals. These studies (by
6 i.p. injection and intrathoracic implantation) show that fiber dimensions and durability
7 were important determinants of tumorigenicity. In intrathoracic implantation studies,
8 pleural sarcomas were correlated with fiber dimensions; long, thin fibers were associated
9 with the highest tumor incidence. Fibers with a high dissolution rate tended to have a low
10 potency in the i.p. assay. A relationship between biopersistence in the lung and pathology
11 was also observed in inhalation studies in rats. Clearance half-times of long fibers (> 20
12 μm) were approximately 400 to 800 days for two types of asbestos, 80 days for E glass,
13 50 days for JM100/475 glass, 15 days for MMVF10, and 9 days for MMVF11.

14 The major proposed mechanisms of fiber-induced carcinogenicity are related to the
15 physical and chemical properties (such as size or dimensions, durability, surface
16 reactivity, and chemical composition) of the fibers and to the inflammatory response that
17 results from the inhalation of fibers. Fiber size affects deposition and clearance, and
18 biodurability and biopersistence are related to biological effects. Fibers can directly
19 interact with target cells (epithelial cells, mesothelial cells, fibroblasts) leading to an
20 inflammatory response and/or genotoxicity. Fibers may induce genotoxic effects by
21 interacting with the spindle apparatus of chromosomes, directly damaging DNA, or
22 indirectly damaging DNA through chronic inflammation. Fibers may also induce
23 epigenetic changes. Alveolar macrophages are activated in response to particulates or
24 fibers deposited in the lung, resulting in increased release of reactive oxygen species,
25 chemical mediators, and cytokines (such as $\text{TNF-}\alpha$) and activation of signalling
26 pathways. A sustained inflammatory reaction may result from incomplete phagocytosis
27 and prolonged interaction of persistent fibers with the cell surface. Chronic imbalance
28 between cytokines and growth factors may contribute to tissue injury, proliferation,
29 and/or apoptosis, which may lead to fibrosis and tumors.

References

1. Abbate C, Giorgianni C, Brecciaroli R, Giacobbe G, Costa C, Cavallari V, Albiero F, Catania S, Tringali MA, Martino LB, Abbate S. 2006. Changes induced by exposure of the human lung to glass fiber-reinforced plastic. *Environ Health Perspect* 114(11): 1725-1729. (Support not reported. Authors affiliated with Messina University, Italy; AOU (Concern Hospital University) Polyclinic G. Martino, Italy.)
2. ACGIH. 2001. *Synthetic Vitreous Fibers: TLV Chemical Substances 7th Edition Documentation*. American Conference of Governmental Industrial Hygienists. 16 pp.
3. Adachi S, Kawamura K, Yoshida S, Takemoto K. 1992. Oxidative damage on DNA induced by asbestos and man-made fibers in vitro. *Int Arch Occup Environ Health* 63(8): 553-557. (Support not reported. Authors affiliated with Saitama Medical School, Japan.)
4. Adachi S, Kawamura K, Takemoto K. 2001. A trial on the quantitative risk assessment of man-made mineral fibers by the rat intraperitoneal administration assay using the JFM standard fibrous samples. *Industrial Health* 39(2): 168-174. (Supported by the Ministry of Education, Science, Sports and Culture, Japan. Authors affiliated with Saitama Medical School, Japan; Kagawa Nutrition University, Japan.)
5. Andersen A, Langmark F. 1986. Incidence of cancer in the mineral-wool producing industry in Norway. *Scand J Work Environ Health* 12(Suppl 1): 72-77. (Support not reported. Authors affiliated with Cancer Registry of Norway.)
6. Armstrong BK, de Klerk NH, Musk AW, Hobbs MS. 1988. Mortality in miners and millers of crocidolite in Western Australia. *Br J Ind Med* 45(1): 5-13. (Supported by the National Health and Medical Research Council of Australia, CSR, Ltd., and the Sir Charles Gairdner Hospital Research and Special Purposes Fund. Authors affiliated with University of Western Australia, Australia; Sir Charles Gairdner Hospital, Australia.)
7. ATSDR. 2004. *Toxicological Profile for Synthetic Vitreous Fibers*. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. 332 pp.
8. Axelson O. 1978. Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health* 4: 98-102. (Support not reported. Author affiliated with Regional Hospital, Sweden.)
9. Baccarelli A, Khmelnitskii O, Tretiakova M, Gorbanev S, Lomtev A, Klimkina I, Tchibissov V, Averkina O, Rice C, Dosemeci M. 2006. Risk of lung cancer from exposure to dusts and fibers in Leningrad Province, Russia. *Am J Ind*

- Med* 49(6): 460-467. (Supported by NCI. Authors affiliated with NCI; University of Milan, Italy; Medical Academy of Postgraduate Education, Russia; Regional Center of Hygiene and Sanitation, Russia; Leningrad Oblast Pathological Bureau, Russia; University of Cincinnati, OH.)
10. Balzer JL, Cooper WC, Fowler DP. 1971. Fibrous glass-lined air transmission systems: an assessment of their environmental effects. *Am Ind Hyg Assoc J* 32(8): 512-518. (Supported by the National Insulation Manufacturer's Association. Authors affiliated with University of California Berkeley, CA.)
 11. Baron PA. 1996. Application of the thoracic sampling definition to fiber measurement. *Am Ind Hyg Assoc J* 57(9): 820-824. (Support not reported. Author affiliated with NIOSH.)
 12. Bayliss DL, Dement JM, Wagoner JK, Blejer HP. 1976. Mortality patterns among fibrous glass production workers. *Ann N Y Acad Sci* 271: 324-335. (Support not reported. Authors affiliated with NIOSH.)
 13. Bellmann B, Muhle H, Pott F, Konig H, Kloppel H, Spurny K. 1987. Persistence of man-made mineral fibres (MMMMF) and asbestos in rat lungs. *Ann Occup Hyg* 31(4B): 693-709. (Supported by the Bundesminister für Forschung und Technologie. Authors affiliated with Fraunhofer-Institut für Toxicologie und Aerosolforschung, Germany; Universität Dusseldorf, Germany; Fraunhofer-Institut für Umweltchemie und Ökotoxikologie, Germany.)
 14. Bellmann B, Muhle H, Creutzenberg O, Ernst H, Müller M, Bernstein DM, Riego Sintes JM. 2003. Calibration study on subchronic inhalation toxicity of man-made vitreous fibers in rats. *Inhal Toxicol* 15(12): 1147-1177. (Support not reported. Authors affiliated with Fraunhofer Institute of Toxicology and Experimental Medicine, Germany; European Chemicals Bureau, Italy.)
 15. Bermudez E, Mangum JB, Moss OR, Wong BA, Everitt JI. 2003. Pleural dosimetry and pathobiological responses in rats and hamsters exposed subchronically to MMVF 10a fiberglass. *Toxicol Sci* 74(1): 165-173. (Supported by the North American Insulation Manufacturer's Association and CIIT member companies. Authors affiliated with CIIT Centers for Health Research, NC; GlaxoSmithKline, NC.)
 16. Bernstein. 2006. Fiber Toxicology. In *Toxicology of the Lung*. 4th ed. Gradnes DE, ed. Boca Raton, FL: CRC Press, Taylor and Francis Group. (Support and author affiliations not reported.)
 17. Bernstein D, Castranova V, Donaldson K, Fubini B, Hadley J, Hesterberg T, Kane A, Lai D, McConnell EE, Muhle H, Oberdörster G, Olin S, Warheit DB. 2005. Testing of fibrous particles: short-term assays and strategies. *Inhal Toxicol* 17(10): 497-537. (Supported by the U.S. EPA. Authors affiliated with NIOSH; University of Edinburgh, UK; University of Torino, Italy; Owens

- Corning Science and Technology Center, OH; International Truck and Engine Corp., IL; Brown University School of Medicine, RI; U.S. EPA; ToxPath Inc., NC; Fraunhofer Institute of Toxicology and Experimental Medicine, Germany; University of Rochester, NY; ILSI Risk Science Institute, Washington, D.C.; DuPont Haskell Laboratory for Health and Environmental Sciences, DE.)
18. Bernstein DM, Morscheidt C, Grimm HG, Thévenaz P, Teichert U. 1996. The evaluation of soluble fibers using the inhalation biopersistence model, a nine-fiber comparison. *Inhal Toxicol* 8: 345-385. (Support not reported. Authors affiliated with Paris la Defense, France; Research and Consulting Company, Switzerland; Gesellschaft für Staubmesstechnik und Arbeitsschutz GmbH, Germany.)
 19. Bernstein DM, Sintes JMR. 1999. *Methods for the Determination of the Hazardous Properties for Human Health of Man Made Mineral Fibres (MMMMF)*. European Chemicals Bureau. 93 pp. (Support not reported. Authors affiliated with European Chemicals Bureau, Italy.)
 20. Bernstein DM, Sintes JMR, Ersboell BK, Kunert J. 2001a. Biopersistence of synthetic mineral fibers as a predictor of chronic inhalation toxicity in rats. *Inhal Toxicol* 13(10): 823-849. (Support not reported. Authors affiliated with European Chemicals Bureau, Italy; Technical University of Denmark, Denmark; Universität Dortmund, Germany.)
 21. Bernstein DM, Sintes JMR, Ersboell BK, Kunert J. 2001b. Biopersistence of synthetic mineral fibers as a predictor of chronic intraperitoneal injection tumor response in rats. *Inhal Toxicol* 13(10): 851-875. (Support not reported. Authors affiliated with European Chemicals Bureau, Italy; Technical University of Denmark, Denmark; Universität Dortmund, Germany.)
 22. Bernstein DM. 2007a. Synthetic vitreous fibers: a review toxicology, epidemiology and regulations. *Crit Rev Toxicol* 37(10): 839-886. (Support not reported. Author consultant in toxicology.)
 23. Berrigan D. 2002. Respiratory cancer and exposure to man-made vitreous fibers: a systematic review. *Am J Ind Med* 42(4): 354-362. (Supported by NCI. Authors affiliated with NCI.)
 24. Berry G. 1999. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. *Inhal Toxicol* 11(2): 111-130. (Support not reported. Author affiliated with University of Sydney, Australia.)
 25. Bertazzi PA, Zocchetti C, Riboldi L, Pesatori A, Radice L, Latocca R. 1986. Cancer mortality of an Italian cohort of workers in man-made glass-fiber production. *Scand J Work Environ Health* 12(Suppl 1): 65-71. (Support not reported. Authors affiliated with University of Milan, Italy.)

26. Bertrand R, Pezerat H. 1980. Fibrous glass: carcinogenicity and dimensional characteristics. *IARC Sci Publ*(30): 901-911. (Support not reported. Authors affiliated with Centre Universitaire Jussieu, France.)
27. Bjure J, Soederholm B, Widimsky J. 1964. Cardiopulmonary function studies in workers dealing with asbestos and glasswool. *Thorax* 19: 22-27. (Supported by Statens Medicinska Forskningsrad. Authors affiliated with University of Goteborg, Sweden; Institute for Cardiovascular Diseases, Czechoslovakia.)
28. Blake T, Castranova V, Schwegler-Berry D, Baron P, Deye GJ, Li C, Jones W. 1998. Effect of fiber length on glass microfiber cytotoxicity. *J Toxicol Environ Health A* 54(4): 243-259. (Support not reported. Authors affiliated with NIOSH.)
29. BLS. 2009. *Occupational Employment Statistics: Industry - Drywall and Insulation Contractors (NAICS Code 238310). Period: May 2007*. Bureau of Labor Statistics. <http://www.bls.gov/OES/>. Accessed on 3/27/09.
30. Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Ferro G, Fletcher AC, Frentzel-Beyme R, Gardner MJ, Olsen JH, Simonato L, Teppo L, Westerholm P, Winter P, Zocchetti C. 1992. Lung cancer mortality among workers in the European production of man-made mineral fibers--a Poisson regression analysis. *Scand J Work Environ Health* 18(5): 279-286. (Supported by the Joint European Medical Research Board. Authors affiliated with IARC; Norwegian Cancer Registry, Norway; University of Milan, Italy; German Cancer Research Center, Germany; MRC Environmental Epidemiology Unit, UK; Danish Cancer Registry, Denmark; Veneto Cancer Registry, Italy; Finnish Cancer Registry, Finland; National Institute of Occupational Health, Sweden.)
31. Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, Ferro G, Frentzel-Beyme R, Hansen J, Olsen J, Plato N, Teppo L, Westerholm P, Winter PD, Zocchetti C. 1997. Cancer mortality among man-made vitreous fiber production workers. *Epidemiology* 8(3): 259-268. (Supported by the Joint European Medical Research Board and the European Insulation Manufacturer's Association. Authors affiliated with IARC; National Research Council, Italy; Norwegian Cancer Registry, Norway; University of Milan, Italy; German Cancer Research Center, Germany; University of Aberdeen and Institute of Occupational Medicine, UK; Institute of Preventive and Social Medicine, Germany; Danish Cancer Society, Denmark; Karolinska Hospital, Sweden; Finnish Cancer Registry, Finland; National Institute for Working Life, Sweden; Medical Research Council Environmental Epidemiology Unit, UK.)
32. Boffetta P, Andersen A, Hansen J, Olsen JH, Plato N, Teppo L, Westerholm P, Saracci R. 1999. Cancer incidence among European man-made vitreous fiber production workers. *Scand J Work Environ Health* 25(3): 222-226. (Supported by the Joint European Medical Research Board. Authors affiliated with IARC; Norwegian Cancer Registry, Norway; Danish Cancer Society, Denmark;

Karolinska Hospital, Sweden; Finnish Cancer Registry, Finland; National Institute for Working Life, Sweden; National Research Council, Italy.)

33. Bottin MC, Vigneron JC, Rousseau R, Micillino JC, Eypert-Blaison C, Kauffer E, Martin P, Binet S, Rihn BH. 2003. Man-made mineral fiber hazardous properties assessment using transgenic rodents: example of glass fiber testing. *Inhal Toxicol* 15(10): 1017-1027. (Support not reported. Authors affiliated with Institut National de Recherche et de Sécurité, France.)
34. Breyse PN, Rice C, Aubourg P, Komoroski MJ, Kalinowski M, Versen R, Woodson J, Carlton R, Lees PS. 1990. Cowl rinsing procedure for airborne fiber sampling. *Appl Occup Environ Hyg* 5(9): 619-622. (Support not reported. Authors affiliated with Johns Hopkins University, MD; University of Cincinnati, OH; Owens Corning Fiberglas, OH; Manville Corporation, CO; CertainTeed Corporation, PA.)
35. Breyse PN, Lees PSJ, Rooney BC. 1999. Comparison of NIOSH Method 7400 A and B counting rules for assessing synthetic vitreous fiber exposures. *Am Ind Hyg Assoc J* 60(4): 526-532. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Johns Hopkins University School of Public Health and Hygiene, MD.)
36. Breyse PN, Lees PS, Rooney BC, McArthur BR, Miller ME, Robbins C. 2001. End-user exposures to synthetic vitreous fibers: II. Fabrication and installation fabrication of commercial products. *Appl Occup Environ Hyg* 16(4): 464-470. (Supported by the Thermal Insulation Manufacturers Association [now the North American Insulation Manufacturer's Association.] Authors affiliated with Johns Hopkins University School of Hygiene and Public Health, MD; U.S. Department of Energy, MD; FBI, D.C.; GlobalTox, Inc., WA.)
37. Brown DM, Fisher C, Donaldson K. 1998. Free radical activity of synthetic vitreous fibers: iron chelation inhibits hydroxyl radical generation by refractory ceramic fiber. *J Toxicol Environ Health A* 53(7): 545-561. (Supported by the Health and Safety Executive. Authors affiliated with Napier University, UK.)
38. Brown DM, Beswick PH, Donaldson K. 1999. Induction of nuclear translocation of NF-kappaB in epithelial cells by respirable mineral fibres. *J Pathol* 189(2): 258-264. (Supported by the Health and Safety Executive. Authors affiliated with Napier University, UK.)
39. Brown GM, Cowie H, Davis JM, Donaldson K. 1986. In vitro assays for detecting carcinogenic mineral fibres: a comparison of two assays and the role of fibre size. *Carcinogenesis* 7(12): 1971-1974. (Supported by the Asbestosis Research Council. Authors affiliated with Institute of Occupational Medicine, UK.)

40. Brown RC, Chamberlain M, Davies R, Gaffen J, Skidmore JW. 1979. In vitro biological effects of glass fibers. *J Environ Pathol Toxicol* 2(6): 1369-1383. (Support not reported. Authors affiliated with Llandough Hospital, UK.)
41. Brüske-Hohlfeld I, Möhner M, Pohlabein H, Ahrens W, Bolm-Audorff U, Kreienbrock L, Kreuzer M, Jahn I, Wichmann HE, Jockel KH. 2000. Occupational lung cancer risk for men in Germany: results from a pooled case-control study. *Am J Epidemiol* 151(4): 384-395. (Supported by the Federal Ministry of Education, Science, Research, and Technology. Authors affiliated with National Research Center for Environment and Health, Germany, Federal Institute for Occupational Safety and Health, Germany, Bremen Institute for Prevention Research and Social Medicine, Germany, University Clinics of Essen, Germany, Institute for Medical Informatics, Biometry and Epidemiology, Germany, West-German Cancer Center [WTZ], Germany, Labor Inspection, Occupational Health Division, Wiesbaden, Germany, Ludwig-Maximilians-University, Germany.)
42. Buchanich JM, Marsh GM, Youk AO. 2001. Historical cohort study of US man-made vitreous fiber production workers: V. Tobacco-smoking habits. *J Occup Environ Med* 43(9): 793-802. (Supported by the University of Pittsburgh and the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA.)
43. Bunn WB, 3rd, Bender JR, Hesterberg TW, Chase GR, Konzen JL. 1993. Recent studies of man-made vitreous fibers. Chronic animal inhalation studies. *J Occup Med* 35(2): 101-113. (Support not reported. Authors affiliated with Mobil Corp., NJ; Owens-Corning Fiberglas Corporation, OH; Schuller International, Inc., CO.)
44. Burgess WA. 1995. *Recognition of Health Hazards in Industry - A Review of Materials and Processes*, New York, NY: Wiley Interscience. p. 476.
45. Carbone M, Pass HI, Rizzo P, Marinetti M, Di Muzio M, Mew DJ, Levine AS, Procopio A. 1994. Simian virus 40-like DNA sequences in human pleural mesothelioma. *Oncogene* 9(6): 1781-90. (Supported by the Associazione Italiana per la Ricerca sul Cancro and Il Ministero della Università e della Ricerca Scientifica. Authors affiliated with NIH, Bethesda, MD; Università 'G. D'Annunzio, Chieti, Italy; University of Chicago Hospitals, IL.)
46. Carel R, Olsson AC, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Cassidy A, Mates D, Bencko V, Foretova L, Janout V, Fevotte J, Fletcher T, t Mannelje A, Brennan P, Boffetta P. 2007. Occupational exposure to asbestos and man-made vitreous fibres and risk of lung cancer: a multicentre case-control study in Europe. *Occup Environ Med* 64(8): 502-508. (Supported by the European Commission, the Polish State Committee for Scientific Research and the Roy Castle Foundation. Authors affiliated with IARC; University of Haifa, Israel; Karolinska Institute, Sweden; Institute of

- Carcinogenesis, Russia; Nofer Institute of Occupational Medicine, Poland; National Institute of Environmental Health, Hungary; Cancer Center and Maria Sklodowska-Curie Institute of Oncology, Poland; Specialized State Health Institute, Slovakia; University of Liverpool, UK; Institute of Hygiene, Romania; Charles University, Czech Republic; Masaryck Memorial Cancer Institute, Czech Republic; Universite Claude Bernard, France; London School of Hygiene and Tropical Medicine, UK; Massey University, New Zealand.)
47. Carey T. 2004. Personal communication (letter dated July 16, 2004) from Tim Carey, Manager, Product Stewardship, Johns Manville, Littleton, CO to C.W. Jameson, NTP Report on Carcinogens Project Officer, National Toxicology Program, Research Triangle Park, NC.
 48. Carter CM, Axten CW, Byers CD, Chase GR, Koenig AR, Reynolds JW, Rosinski KD. 1999. Indoor airborne fiber levels of MMVF in residential and commercial buildings. *Am Ind Hyg Assoc J* 60(6): 794-800. (Support not reported. Authors affiliated with North American Insulation Manufacturer's Association, VA; Johns Manville Corporation, CO; USG Corporation, IL; Celotex, FL; CertainTeed Corporation, PA; Owens Corning, OH.)
 49. Casey G. 1983. Sister-chromatid exchange and cell kinetics in CHO-K1 cells, human fibroblasts and lymphoblastoid cells exposed in vitro to asbestos and glass fibre. *Mutat Res* 116(3-4): 369-377. (Supported by the Medical Research Council. Authors affiliated with University College, UK; St. Mary's Hospital Medical School, UK.)
 50. Castranova V, Pailles W, Judy D, Blake T, Schwegler-Berry D, Jones W. 1996. In vitro effects of large and small glass fibers on rat alveolar macrophages. *J Toxicol Environ Health* 49(4): 357-369. (Support not reported. Authors affiliated with NIOSH.)
 51. Cavallo D, Campopiano A, Cardinali G, Casciardi S, De Simone P, Kovacs D, Perniconi B, Spagnoli G, Ursini CL, Fanizza C. 2004. Cytotoxic and oxidative effects induced by man-made vitreous fibers (MMVFs) in a human mesothelial cell line. *Toxicology* 201(1-3): 219-229. (Supported by the Italian Ministry of Health. Authors affiliated with National Institute for Occupational Safety and Prevention, Italy; Dermatologic Institute San Gallicano, Italy.)
 52. Chamberlain M, Tarmy EM. 1977. Asbestos and glass fibres in bacterial mutation tests. *Mutat Res* 43(2): 159-164. (Supported by Gallaher Tobacco Company. Authors affiliated with Llandough Hospital, UK; Royal Cancer Hospital, UK.)
 53. Cherrie J, Dodgson J, Groat S, Maclaren W. 1986. Environmental surveys in the European man-made mineral fiber production industry. *Scand J Work Environ Health* 12(Suppl 1): 18-25. (Support not reported. Authors affiliated with Institute of Occupational Medicine, UK.)

54. Chiappino G, Scotti PG, Anselmino A. 1981. Occupational bronchopulmonary disease due to glass fibres. *Med Lav* 2: 96-101 (as cited in IARC 1988).
55. Chiazze L, Watkins DK, Fryar C, Fayerweather W, Bender JR, Chiazze M. 1999. Mortality from nephritis and nephrosis in the fibreglass manufacturing industry. *Occup Environ Med* 56(3): 164-166. (Supported by Owens Corning. Authors affiliated with Georgetown University Medical Center, Washington, D.C.; Owens Corning, OH.)
56. Chiazze L, Watkins DK, Fryar C, Fayerweather W, Kozono J, Biggs V. 2002. Mortality from non-malignant respiratory disease in the fibreglass manufacturing industry. *Occup Environ Med* 59(6): 369-371. (Supported by Owens-Corning. Authors affiliated with Georgetown University Medical Center, Washington, D.C.; Owens-Corning, OH.)
57. Chiazze L, Jr., Watkins DK, Fryar C. 1992. A case-control study of malignant and non-malignant respiratory disease among employees of a fibreglass manufacturing facility. *Br J Ind Med* 49(5): 326-331. (Supported by Owens-Corning Fiberglas Corporation. Authors affiliated with Georgetown University Medical Center, Washington, D.C.)
58. Chiazze L, Jr., Watkins DK, Fryar C, Kozono J. 1993. A case-control study of malignant and non-malignant respiratory disease among employees of a fibreglass manufacturing facility. II. Exposure assessment. *Br J Ind Med* 50(8): 717-725. (Supported by Owens-Corning Fiberglas Corporation. Authors affiliated with Georgetown University School of Medicine, Washington, D.C.)
59. Chiazze L, Jr., Watkins DK, Fryar C. 1995. Adjustment for the confounding effect of cigarette smoking in an historical cohort mortality study of workers in a fiberglass manufacturing facility. *J Occup Environ Med* 37(6): 744-748. (Supported by Owens-Corning Corporation. Authors affiliated with Georgetown University Medical Center, Washington, D.C.)
60. Christensen BC, Godleski JJ, Marsit CJ, Houseman EA, Lopez-Fagundo CY, Longacker JL, Bueno R, Sugarbaker DJ, Nelson HH, Kelsey KT. 2008. Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. *Carcinogenesis* 29(8): 1555-9. (Supported by the International Mesothelioma Program at Brigham and Women's Hospital, Mesothelioma Applied Research Center, NIH/NIEHS and NCI. Authors affiliated with Harvard School of Public Health, MA; Brown University, RI; University of Massachusetts Lowell, MA; Universidad de Puerto Rico, Puerto Rico; Boston University School of Public Health; Brigham and Women's Hospital, MA; University of Minnesota School of Public Health, MN.)
61. Christensen BC, Houseman EA, Godleski JJ, Marsit CJ, Longacker JL, Roelofs CR, Karagas MR, Wrensch MR, Yeh RF, Nelson HH, Wiemels JL, Zheng S, Wiencke JK, Bueno R, Sugarbaker DJ, Kelsey KT. 2009. Epigenetic

- profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome. *Cancer Res* 69(1): 227-234. (Supported by NCI, NIEHS, the International Mesothelioma Program at Brigham and Women's Hospital and the Mesothelioma Applied Research Foundation. Authors affiliated with Brown University, RI; University of Massachusetts Lowell, MA; Harvard School of Public Health, MA; Boston University School of Public Health, MA; Dartmouth Medical School, NH; University of California San Francisco, CA; University of Minnesota, MN.)
62. Churg A. 1988. Non-neoplastic diseases caused by asbestos. In *Pathology of Occupational Lung Diseases*. Churg A, Green FHY, eds. New York: Igaku-Shoin Medical Publishers. p. 213-277. (Supported by the Medical Research Council and the National Cancer Institute of Canada. Author affiliations not reported.)
63. Collier CG, Morris KJ, Launder KA, Humphreys JA, Morgan A, Eastes W, Townsend S. 1994. The behavior of glass fibers in the rat following intraperitoneal injection. *Regul Toxicol Pharmacol* 20(3 Pt 2): S89-103. (Support not reported. Authors affiliated with AEA Technology, UK; Owens-Corning Fiberglas, OH; Medical Research Council, UK.)
64. Collier CG, Morris KJ, Launder KA, Humphreys JA, Morgan A, Eastes W, Townsend S. 1995. The durability and distribution of glass fibres in the rat following intra-peritoneal injection. *Ann Occup Hyg* 39(5): 699-704. (Support not reported. Authors affiliated with AEA Technology, UK; Owens Corning Fiberglas, OH; Medical Research Council, UK.)
65. Corn M, Sansone EB. 1974. Determination of total suspended particulate matter and airborne fiber concentrations at three fibrous glass manufacturing facilities. *Environ Res* 8(1): 37-52. (Support not reported. Authors affiliated with University of Pittsburgh, PA.)
66. Corn M, Hammad Y, Whittier D, Kotsko N. 1976. Employee exposure to airborne fiber and total particulate matter in two mineral wool facilities. *Environ Res* 12(1): 59-74. (Support not reported. Authors affiliated with University of Pittsburgh, PA.)
67. Crane A. 2004. Personal communication (letter dated February 11, 2004) from Angus Crane, Vice President, General Counsel, North American Insulation Manufacturer's Association, Alexandria, VA to Sanford Garner, Senior Scientist/Technical Manager, Constella Group, LLC., Durham, NC.
68. Cullen RT, Miller BG, Davis JM, Brown DM, Donaldson K. 1997. Short-term inhalation and in vitro tests as predictors of fiber pathogenicity. *Environ Health Perspect* 105(Suppl 5): 1235-40. (Supported by the Colt Foundation, industrial sponsors and the UK Health and Safety Executive. Authors affiliated with Institute of Occupational Medicine, UK; Napier University, UK.)

69. Cullen RT, Searl A, Buchanan D, Davis JM, Miller BG, Jones AD. 2000. Pathogenicity of a special-purpose glass microfiber (E glass) relative to another glass microfiber and amosite asbestos. *Inhal Toxicol* 12(10): 959-977. (Supported by the Colt Foundation, the UK Health and Safety Executive, EURISOL [UK Mineral Wool Association] and the European Ceramic Fibre Industry Association. Authors affiliated with Institute of Occupational Health, UK.)
70. Dai YT, Yu CP. 1998. Alveolar deposition of fibers in rodents and humans. *J Aerosol Med* 11(4): 247-258. (Support not reported. Authors affiliated with State University of New York at Buffalo, NY.)
71. Davis JM, Beckett ST, Bolton RE, Collings P, Middleton AP. 1978. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer* 37(5): 673-688. (Supported by the British Asbestos Research Council. Authors affiliated with Institute of Occupational Medicine, UK.)
72. Davis JM. 1986. A review of experimental evidence for the carcinogenicity of man-made vitreous fibers. *Scand J Work Environ Health* 12(Suppl 1): 12-17. (Support not reported. Author affiliated with Institute of Occupational Medicine, UK.)
73. Davis JM, Addison J, Bolton RE, Donaldson K, Jones AD. 1986a. Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. *Br J Exp Pathol* 67(1): 113-129. (Supported by the British Asbestosis Research Council. Authors affiliated with Institute of Occupational Medicine, UK.)
74. Davis JM, Jones AD. 1988. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol* 69(5): 717-737. (Supported by the Institute for Research and Development of Asbestos (IRDA). Authors affiliated with Institute of Occupational Medicine, UK.)
75. Davis JM, Cowie HA. 1990. The relationship between fibrosis and cancer in experimental animals exposed to asbestos and other fibers. *Environ Health Perspect* 88: 305-309. (Support not reported. Authors affiliated with Institute of Occupational Medicine, Scotland.)
76. Davis JMG. 1976. Pathological aspects of the injection of glass fiber into the pleural and peritoneal cavities of rats and mice. In *Occupational Exposure to Fibrous Glass: Proceedings of a Symposium Presented by the Center of Adult Education, University of Maryland, College Park, Maryland, June 26-27, 1974*. Rockville, MD: U.S. Department of Health, Education and Welfare. p. 141-149. (Support not reported. Author affiliated with Institute of Occupational Medicine, UK.)
77. Davis JMG, Brown DM, Cullen RT, Donaldson K, Jones AD, Miller BG, McIntosh C, Searl A. 1996. A comparison of methods of determining and

- predicting the pathogenicity of mineral fibres. *Inhal Toxicol* 8: 747-770. (Supported by the Colt Fibre Research Programme. Authors affiliated with Napier University, UK; Institute of Occupational Medicine, UK.)
78. De Vuyst P, Dumortier P, Swaen GM, Pairon JC, Brochard P. 1995. Respiratory health effects of man-made vitreous (mineral) fibres. *Eur Respir J* 8(12): 2149-2173. (Support not reported. Authors affiliated with Université Libre de Bruxelles, Brussels, Belgium; University of Limburg, Netherlands; INSERM, France; Université Bordeaux II, France.)
79. Dement JM. 1975. Environmental aspects of fibrous glass production and utilization. *Environ Res* 9: 295-312. (Support not reported. Author affiliated with NIOSH.)
80. DFG. 2002. *MAK- und BAT-Werte-Liste 2002. Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte*. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Mitteilung 38. Weinheim: VCH Verl. Ges.: Deutsche Forschungsgemeinschaft, Hrsg.
81. Doll R, Peto J. 1985. *Asbestos - effects on health of exposure to asbestos*. London, U.K.: Her Majesty's Stationery Office. (Supported by the Health and Safety Executive, the Cancer Research Campaign, and the Imperial Cancer Research Fund. Authors affiliated with University of Oxford, UK; University of London, UK.)
82. Donaldson K, Gilmour PS, Beswick PH. 1995b. Supercoiled plasmid DNA as a model target for assessing the generation of free radicals at the surface of fibres. *Exp Toxicol Pathol* 47(4): 235-237. (Support not reported. Authors affiliated with Napier University, UK.)
83. Dörger M, Münzing S, Allmeling AM, Krombach F. 2000. Comparison of the phagocytic response of rat and hamster alveolar macrophages to man-made vitreous fibers *in vitro*. *Hum Exp Toxicol* 19(11): 635-640. (Supported by the European Insulation Manufacturer's Association. Authors affiliated with University of Munich, Germany.)
84. Dörger M, Munzing S, Allmeling AM, Messmer K, Krombach F. 2001. Differential responses of rat alveolar and peritoneal macrophages to man-made vitreous fibers *in vitro*. *Environ Res* 85(3): 207-214. (Supported by the European Insulation Manufacturer's Association. Authors affiliated with Klinikum der Universität München, Germany.)
85. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. 2008. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 320(5876): 674-677. (Support not reported. Authors affiliated with University of Lausanne, Switzerland; University of

Amsterdam, Switzerland; University of Alabama at Birmingham, AL; University of Vermont College of Medicine, VT.)

86. Dumas S, Parent ME, Siemiatycki J, Brisson J. 2000. Rectal cancer and occupational risk factors: a hypothesis-generating, exposure-based case-control study. *Int J Cancer* 87(6): 874-879. (Support not reported. Authors affiliated with INRS, France; Universite Laval, Canada; McGill University, Canada.)
87. Eastes W, Hadley JG. 1995. Dissolution of fibers inhaled by rats. *Inhal Toxicol* 7: 179-196. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH.)
88. Eastes W, Morris KJ, Morgan A, Launder KA, Collier CG, Davis JA, Mattson SM, Hadley JG. 1995. Dissolution of glass fibers in the rat lung following intratracheal instillation. *Inhal Toxicol* 7: 197-213. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH; AEA Technology, UK.)
89. Eastes W, Hadley JG. 1996. A mathematical model of fiber carcinogenicity and fibrosis in inhalation and intraperitoneal experiments in rats. *Inhalation Toxicology* 8(4): 323-343. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH.)
90. Eastes W, Potter RM, Hadley JG. 2000a. Estimating in vitro glass fiber dissolution rate from composition. *Inhal Toxicol* 12(4): 269-280. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH.)
91. Eastes W, Potter RM, Hadley JG. 2000b. Estimation of dissolution rate from in vivo studies of synthetic vitreous fibers. *Inhal Toxicol* 12(11): 1037-1054. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH.)
92. EIPPCB. 2001. *Integrated Pollution Prevention and Control: Reference Document on Best Available Techniques in the Glass Manufacturing Industry*. European Commission. 323 pp.
93. Ellouk SA, Jaurand MC. 1994. Review of animal/in vitro data on biological effects of man-made fibers. *Environ Health Perspect* 102 Suppl 2: 47-61. (Support not reported. Authors affiliated with INSERM, France.)
94. Engholm G, Englund A, Fletcher AC, Hallin N. 1987. Respiratory cancer incidence in Swedish construction workers exposed to man-made mineral fibres and asbestos. *Ann Occup Hyg* 31(4B): 663-675. (Support not reported. Authors affiliated with the Construction Industry's Organization for Working Environment, Safety, and Health, Sweden; IARC.)
95. Enterline PE, Henderson V. 1975. The health of retired fibrous glass workers. *Arch Environ Health* 30(3): 113-116. (Support not reported. Authors affiliated with University of Pittsburgh, PA.)

96. Enterline PE, Marsh GM. 1980. Mortality of workers in the man-made mineral fibre industry. *IARC Sci Publ* 30: 965-972. (Support not reported. Authors affiliated with University of Pittsburgh, PA.)
97. Enterline PE, Marsh GM, Esmen NA. 1983. Respiratory disease among workers exposed to man-made mineral fibers. *Am Rev Respir Dis* 128: 1-7. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA.)
98. Enterline PE, Marsh GM. 1984. The health of workers in the MMMF industry. In *The Biological Effects of Man-Made Mineral Fibers*, vol. 1. Copenhagen: WHO Regional Office for Europe. p. 311-339 (as cited in Enterline *et al.* 1987).
99. Enterline PE, Marsh GM, Henderson V, Callahan C. 1987. Mortality update of a cohort of U.S. man-made mineral fibre workers. *Ann Occup Hyg* 31(4B): 625-656. (Supported by the U.S. Thermal Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA.)
100. Enterline PE. 1991. Carcinogenic effects of man-made vitreous fibers. *Annu Rev Public Health* 12: 459-480. (Support not reported. Author affiliated with University of Pittsburgh, PA.)
101. Esmen NA, Hammad YY, Corn M, Whittier D, Kotsko N, Haller M, Kahn RA. 1978. Exposure of employees to man-made mineral fibers: mineral wool production. *Environ Res* 15(2): 262-277. (Support not reported. Authors affiliated with University of Pittsburgh, PA; Tulane University, LA; Mellon Institute, PA.)
102. Esmen NA, Corn M, Hammad YY, Whittier D, Kotsko N. 1979. Summary of measurements of employee exposure to airborne dust and fiber in sixteen facilities producing man-made mineral fibers. *Am Ind Hyg Assoc J* 40: 108-117. (Support not reported. Authors affiliated with University of Pittsburgh, PA; Tulane University, LA.)
103. Esmen NA, Sheehan MJ, Corn M, Engel M, Kotsko N. 1982. Exposure of employees to manmade vitreous fibers: installation of insulation materials. *Environ Res* 28(2): 386-398. (Support not reported. Authors affiliated with University of Pittsburgh, PA; West Chester State College, PA; Johns Hopkins School of Hygiene and Public Health, MD; Western Electric Company, NE; Industrial Hygiene Associates, PA.)
104. Feron VJ, Scherrenberg PM, Immel HR, Spit BJ. 1985. Pulmonary response of hamsters to fibrous glass: chronic effects of repeated intratracheal instillation with or without benzo[a]pyrene. *Carcinogenesis* 6(10): 1495-1499. (Supported by the Netherlands Cancer Foundation. Authors affiliated with TNO-CIVO Toxicology and Nutrition Institute, Netherlands.)

105. Fisher CE, Rossi AG, Shaw J, Beswick PH, Donaldson K. 2000. Release of TNFalpha in response to SiC fibres: differential effects in rodent and human primary macrophages, and in macrophage-like cell lines. *Toxicol In Vitro* 14(1): 25-31. (Supported by the U.K. Health and Safety Executive. Authors affiliated with Napier University, UK; University of Edinburgh, UK.)
106. FR. 2004. Call for public comments on 21 substances, mixtures and exposure circumstances proposed for listing in the Report on Carcinogens, Twelfth Edition. *Fed Regist* 69(97): 28940-28944.
107. Fowler DP, Balzer JL, Cooper WC. 1971. Exposure of insulation workers to airborne fibrous glass. *Am Ind Hyg Assoc J* 32(86-91). (Supported by the National Insulation Manufacturer's Association. Authors affiliated with University of California Berkeley, CA.)
108. Fubini B, Fenoglio I. 2007. Toxic potential of mineral dusts. *Elements* 3: 407-414. (Support not reported. Authors affiliated with Universita degli Studi di Torino, Italy.)
109. Fujino A, Hori H, Higashi T, Morimoto Y, Tanaka II, Kaji H. 1995. In-vitro biological study to evaluate the toxic potentials of fibrous materials. *Int J Occup Environ Health* 1(1): 21-28. (Supported by the Ministry of Education. Authors affiliated with University of Occupational and Environmental Health, Japan.)
110. Gan L, Savransky EF, Fasy TM, Johnson EM. 1993. Transfection of human mesothelial cells mediated by different asbestos fiber types. *Environ Res* 62(1): 28-42. (Supported by the American Cancer Society and NIH. Authors affiliated with Mount Sinai School of Medicine, NY.)
111. Gao H, Brick J, Ong S, Miller M, Whong WZ, Ong T. 1997. Selective hyperexpression of c-jun oncoprotein by glass fiber- and silica-transformed BALB/c-3T3 cells. *Cancer Lett* 112(1): 65-69. (Support not reported. Authors affiliated with West Virginia University, WV; NIOSH.)
112. Gao HG, Whong WZ, Jones WG, Wallace WE, Ong T. 1995. Morphological transformation induced by glass fibers in BALB/c-3T3 cells. *Teratog Carcinog Mutagen* 15(2): 63-71. (Support not reported. Authors affiliated with NIOSH.)
113. Gardner MJ, Winter PD, Pannett B, Simpson MJ, Hamilton C, Acheson ED. 1986. Mortality study of workers in the man-made mineral fiber production industry in the United Kingdom. *Scand J Work Environ Health* 12(Suppl 1): 85-93. (Supported by the Joint European Medical Research Board. Authors affiliated with MRC Environmental Epidemiology Unit, UK; The Queen's University of Belfast, UK; Department of Health and Social Security, UK.)
114. Gardner MJ, Magnani C, Pannett B, Fletcher AC, Winter PD. 1988. Lung cancer among glass fibre production workers: a case-control study. *Br J Ind*

- Med* 45(9): 613-618. (Supported by the Health and Safety Executive. Authors affiliated with MRC Environmental Epidemiology Unit, UK.)
115. Geiser M, Matter M, Maye I, Im Hof V, Gehr P, Schurch S. 2003. Influence of airspace geometry and surfactant on the retention of man-made vitreous fibers (MMVF 10a). *Environ Health Perspect* 111(7): 895-901. (Supported by the Swiss National Science Foundation, the Canadian Institutes of Health Research, the Alberta Heritage Foundation for Medical Research and the Silva Casa Foundation. Authors affiliated with University of Bern, Switzerland; University of Calgary, Canada.)
 116. Gilmour PS, Beswick PH, Brown DM, Donaldson K. 1995. Detection of surface free radical activity of respirable industrial fibres using supercoiled ϕ X174 RF1 plasmid DNA. *Carcinogenesis* 16(12): 2973-2979. (Support not reported. Authors affiliated with Napier University, UK.)
 117. Gilmour PS, Brown DM, Beswick PH, MacNee W, Rahman I, Donaldson K. 1997. Free radical activity of industrial fibers: Role of iron in oxidative stress and activation of transcription factors. *Environ Health Perspect* 105(Suppl 5): 1313-1317. (Supported by the Health and Safety Executive. Authors affiliated with Napier University, UK; University of Edinburgh, UK.)
 118. Goldberg MS, Parent ME, Siemiatycki J, Désy M, Nadon L, Richardson L, Lakhani R, Latreille B, Valois MF. 2001. A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. *Am J Ind Med* 39(6): 531-546. (Supported by the National Health Research and Development Program from Health Canada, the National Cancer Institute of Canada, Institut de recherche en sante et securite du travail du Quebec and Fonds de la recherche en sante du Quebec. Authors affiliated with McGill University, Canada; University of Quebec, Canada.)
 119. Goldstein B, Rendall RE, Webster I. 1983. A comparison of the effects of exposure of baboons to crocidolite and fibrous-glass dusts. *Environ Res* 32(2): 344-359. (Support not reported. Authors affiliated with National Center for Occupational Health, South Africa.)
 120. Goldstein B, Webster I, Rendall RE. 1984. Changes produced by the inhalation of glass fibre in non-human primates. In *Biological Effects of Man-Made Mineral Fibres. Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA, Copenhagen, 2-22 April, 1982*, vol. 2. Copenhagen, Denmark: World Health Organization. p. 273-285. (Support and author affiliations not reported.)
 121. Greim HA. 2004. Research needs to improve risk assessment of fiber toxicity. *Mutat Res* 553(1-2): 11-22. (Support not reported. Author affiliated with Technical University of Munich, Germany.)

122. Grimm HG, Bernstein DM, Attia M, Richard J, de Reydellet A. 2002. Experience from a long-term carcinogenicity study with intraperitoneal injection of biosoluble synthetic mineral fibers. *Inhal Toxicol* 14(8): 855-882. (Support not reported. Authors affiliated with International de Toxicologie (CIT), France; Centre Saint-Gobain Insulation, France.)
123. Gross P, Kaschak M, Tolker EB, Babyak MA, de Treville RT. 1970. The pulmonary reaction to high concentrations of fibrous glass dust. A preliminary report. *Arch Environ Health* 20(6): 696-704. (Support not reported. Authors affiliated with University of Pittsburgh, PA; Industrial Hygiene Foundation, PA.)
124. Gross P, Tuma J, DeTreville RT. 1971. Lungs of workers exposed to fiber glass. A study of their pathologic changes and their dust content. *Arch Environ Health* 23(1): 67-76 (as cited in IARC 1988).
125. Gross P. 1986. Man-made vitreous fibers: an overview of studies on their biologic effects. *Am Ind Hyg Assoc J* 47(11): 717-723. (Support not reported. Author affiliated with Industrial Health Foundation, PA.)
126. Guber A, Lerman S, Lerman Y, Ganor E, Trajber I, Edelstein E, Fireman E. 2006. Pulmonary fibrosis in a patient with exposure to glass wool fibers. *Am J Ind Med* 49(12): 1066-1069. (Support not reported. Authors affiliated with Meir General Hospital, Israel; Ben Gurion University of the Negev, Israel; Tel-Aviv University, Israel.)
127. Gustavsson P, Plato N, Axelson O, Brage HN, Hogstedt C, Ringbäck G, Tornling G, Wingren G. 1992. Lung cancer risk among workers exposed to man-made mineral fibers (MMMF) in the Swedish prefabricated house industry. *Am J Ind Med* 21(6): 825-834. (Supported by the Swedish Work Environment Fund. Authors affiliated with Karolinska Institute, Sweden; National Institute of Occupational Health, Sweden; University Hospital, Sweden.)
128. Hammad YY, Esmen NA. 1984. Long-term survey of airborne fibres in the United States. In *Proceedings of a WHO/IARC Conference, April 20-22 1982*, vol. 1. p. 119-132. (Support and author affiliations not reported.)
129. Hansen K, Mossman BT. 1987. Generation of superoxide ($O_2^{\cdot-}$) from alveolar macrophages exposed to asbestiform and nonfibrous particles. *Cancer Res* 47(6): 1681-1686. (Supported by the American Cancer Society, National Cancer Institute and the National Heart, Blood and Lung Institute. Authors affiliated with University of Vermont College of Medicine, VT.)
130. Hardell L, Eriksson M. 1999. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 85(6): 1353-1360. (Supported by the Swedish Work Environment Fund, Swedish Medical Research Council, Orebro County Council Research Committee, and Orebro Medical Center Research

- Foundation. Authors affiliated with Orebro Medical Center, Sweden; University Hospital, Sweden.)
131. Hart GA, Kathman LM, Hesterberg TW. 1994. *In vitro* cytotoxicity of asbestos and man-made vitreous fibers: roles of fiber length, diameter and composition. *Carcinogenesis* 15(5): 971-977. (Supported by Schuller International, Inc. Authors affiliated with Mountain Technical Center, CO.)
 132. Head IW, Wagg RM. 1980. A survey of occupational exposure to man-made mineral fibre dust. *Ann Occup Hyg* 23(3): 235-258. (Support not reported. Authors affiliated with Health and Safety Executive, UK.)
 133. HEI-AR. 1991. *Asbestos in Public and Commercial Buildings: A Literature Review and Synthesis of Current Knowledge*. Cambridge, MA: Health Effects Institute - Asbestos Research.
 134. Hesterberg TW, Barrett JC. 1984. Dependence of asbestos- and mineral dust-induced transformation of mammalian cells in culture on fiber dimension. *Cancer Res* 44(5): 2170-2180. (Support not reported. Authors affiliated with NIEHS.)
 135. Hesterberg TW, Butterick CJ, Oshimura M, Brody AR, Barrett JC. 1986. Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. *Cancer Res* 46(11): 5795-5802. (Support not reported. Authors affiliated with NIEHS.)
 136. Hesterberg TW, Müller WC, McConnell EE, Chevalier J, Hadley JG, Bernstein DM, Thevenaz P, Anderson R. 1993. Chronic inhalation toxicity of size-separated glass fibers in Fischer 344 rats. *Fundam Appl Toxicol* 20(4): 464-476. (Support not reported. Authors affiliated with Schuller International, Inc., CO; Experimental Pathology Services, Sweden; Owens-Corning Technical Center, OH; Research and Consulting Co., Switzerland.)
 137. Hesterberg TW, Hart GA. 1994. A comparison of human exposures to fiberglass with those used in a recent rat chronic inhalation study. *Regul Toxicol Pharmacol* 20(3 Pt 2): S35-46. (Support not reported. Authors affiliated with Schuller International, CO.)
 138. Hesterberg TW, Müller WC, Thevenaz P, Anderson R. 1995. Chronic inhalation studies of man-made vitreous fibres: characterization of fibres in the exposure aerosol and lungs. *Ann Occup Hyg* 39(5): 637-653. (Support not reported. Authors affiliated with Schuller International, Inc., CO; Research and Consulting Company, Switzerland.)
 139. Hesterberg TW, Chase GR. 1996. Commentary on "fibrous glass and lung cancer". *Am J Ind Med* 30(1): 111-112. (Support not reported. Authors affiliated with Schuller International, Inc., CO.)

140. Hesterberg TW, McConnel EE, Miiller WC, Chevalier J, Everitt J, Thevenaz P, Fleissner H, Oberdörster G. 1996a. Use of lung toxicity and lung particle clearance to estimate the maximum tolerated dose (MTD) for a fiber glass chronic inhalation study in the rat. *Fundam Appl Toxicol* 32(1): 31-44. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with Schuller International, Inc., CO; Chemical Industry Institute of Toxicology, NC; Research and Consulting Company, Switzerland; University of Rochester, NY.)
141. Hesterberg TW, Axten C, McConnell EE, Oberdörster G, Everitt J, Müller WC, Chevalier J, Chase GR, Thevenaz P. 1997. Chronic inhalation study of fiber glass and amosite asbestos in hamsters: twelve-month preliminary results. *Environ Health Perspect* 105(Suppl 5): 1223-1229. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with Schuller International, Inc., CO; North American Insulation Manufacturer's Association, VA; University of Rochester, NY; Chemical Industry Institute of Toxicology, NC; Experimental Pathology Services, Switzerland; Research and Consulting Co., Switzerland.)
142. Hesterberg TW, Chase G, Axten C, Miller WC, Musselman RP, Kamstrup O, Hadley J, Morscheidt C, Bernstein DM, Thevenaz P. 1998. Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. *Toxicol Appl Pharmacol* 151(2): 262-275. (Supported by the European Insulation Manufacturer's Association and the North American Insulation Manufacturer's Association. Authors affiliated with Johns Manville Corporation, CO; North American Insulation Manufacturer's Association, VA; USG Corporation, IL; Rockwool International, Denmark; Owens-Corning, OH; Research and Consulting Company, Switzerland.)
143. Hesterberg TW, Axten C, McConnell EE, Hart GA, Miiller W, Chevalier J, Everitt J, Thevenaz P, Oberdörster G. 1999. Studies on the inhalation toxicology of two fiberglasses and amosite asbestos in the Syrian golden hamster. Part I. Results of a subchronic study and dose selection for a chronic study. *Inhal Toxicol* 11(9): 747-784. (Supported by Johns Manville Corporation and the North American Insulation Manufacturer's Association. Authors affiliated with Johns Manville Technical Center, CO; North American Insulation Manufacturer's Association, VA; ToxPath, Inc., NC; Experimental Pathology Services, Switzerland; Chemical Industry Institute of Toxicology, NC; Research and Consulting Company, Switzerland; University of Rochester, NY.)
144. Hesterberg TW, Hart GA. 2001. Synthetic vitreous fibers: a review of toxicology research and its impact on hazard classification. *Crit Rev Toxicol* 31(1): 1-53. (Support not reported. Authors affiliated with Johns Manville Corporation, CO.)

145. Hesterberg TW, Hart GA, Müller WC, Chase G, Rogers RA, Mangum JB, Everitt JI. 2002. Use of short-term assays to evaluate the potential toxicity of two new biosoluble glasswool fibers. *Inhal Toxicol* 14(3): 217-246. (Support not reported. Authors affiliated with Johns Manville Technical Center, CO; Science Writer International, CO; Rogers Imaging Corporation, MA; CIIT Centers for Health Research, NC.)
146. Hill IM, Beswick PH, Donaldson K. 1996. Enhancement of the macrophage oxidative burst by immunoglobulin coating of respirable fibers: fiber-specific differences between asbestos and man-made fibers. *Exp Lung Res* 22(2): 133-148. (Support not reported. Authors affiliated with Napier University, UK.)
147. Hill JW, Whitehead WS, Cameron JD, Hedgecock GA. 1973. Glass fibres: absence of pulmonary hazard in production workers. *Br J Ind Med* 30(2): 174-9 (as cited in IARC 1988).
148. Hill JW, Rossiter CE, Foden DW. 1984. A pilot respiratory morbidity study of workers in a MMMF plant in the United Kingdom. In *Biological Effects of Man-Made Mineral Fibres. Proceedings of a WHO/IARC Conference*, vol. 1. Copenhagen: World Health Organization. p. 413-426. (Support and author affiliations not reported.)
149. Hughes JM, Jones RN, Glindmeyer HW, Hammad YY, Weill H. 1993. Follow up study of workers exposed to man made mineral fibres. *Br J Ind Med* 50(7): 658-667. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Tulane University School of Medicine, LA.)
150. Hunting KL, Welch LS. 1993. Occupational exposure to dust and lung disease among sheet metal workers. *Br J Ind Med* 50(5): 432-442. (Supported by the American Lung Association of the District of Columbia. Authors affiliated with George Washington University Medical Center, Washington, DC.)
151. IARC. 1988. *Man-Made Mineral Fibres*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer. p. 39-171.
152. IARC. 1999. *Surgical Implants and Other Foreign Bodies*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer.
153. IARC. 2002. *Man-Made Vitreous Fibres*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer. 381 pp.
154. ILSI. 2000. The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. ILSI Risk Science Institute Workshop Participants. *Inhal Toxicol* 12(1-2): 1-17. (Supported by the U.S. EPA, Chemical Manufacturer's Association, NIEHS, HEI,

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155. Infante PF, Schuman LD, Dement J, Huff J. 1994. Fibrous glass and cancer. *Am J Ind Med* 26(4): 559-584. (Support not reported. Authors affiliated with Department of Labor, Washington, DC; Duke University Medical Center, NC; NIEHS.)
156. Jacob TR, Hadley JG, Bender JR, Eastes W. 1992. Airborne glass fiber concentrations during installation of residential insulation. *Am Ind Hyg Assoc J* 53(8): 519-523. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH.)
157. Jacob TR, Hadley JG, Bender JR, Eastes W. 1993. Airborne glass fiber concentrations during manufacturing operations involving glass wool insulation. *Am Ind Hyg Assoc J* 54(6): 320-326. (Support not reported. Authors affiliated with Owens-Corning Fiberglas, OH.)
158. Janssen YM, Heintz NH, Marsh JP, Borm PJ, Mossman BT. 1994. Induction of c-fos and c-jun proto-oncogenes in target cells of the lung and pleura by

- carcinogenic fibers. *Am J Respir Cell Mol Biol* 11(5): 522-530. (Supported by NIEHS, the National Heart, Lung and Blood Institute, and the U.S. EPA. Authors affiliated with University of Vermont College of Medicine, VT; University of Limburg, Netherlands.)
159. Johnson DL, Healey JJ, Ayer HE, Lynch JR. 1969. Exposure to fibers in the manufacture of fibrous glass. *Am Ind Hyg Assoc J* 30: 545-550. (Support not reported. Authors affiliated with U.S. Department of Health.)
160. Johnson NF, Jaramillo RJ. 1997. p53, Cip1, and Gadd153 expression following treatment of A549 cells with natural and man-made vitreous fibers. *Environ Health Perspect* 105(Suppl 5): 1143-1145. (Supported by the U.S. Department of Energy and NIH. Authors affiliated with Lovelace Respiratory Research Institute, NM.)
161. Kane AB. 1996a. Mechanisms of mineral fibre carcinogenesis. In *Mechanisms of Fibre Carcinogenesis*, IARC Scientific Publications No. 140. Kane AB, Boffetta P, Saracci R, Wilbourn JD, eds. Lyon, France: International Agency for Cancer Research. p. 11-34. (Supported by NIEHS and the American Cancer Society. Authors affiliated with Brown University, RI.)
162. Kane AB, Boffetta P, Saracci R, Wilbourn JD, eds. 1996b. *Mechanisms of Fibre Carcinogenesis*. IARC Scientific Publications No. 140. Lyon, France: International Agency for Research on Cancer.
163. Kilburn KH, Warshaw RH. 1991. Difficulties of attribution of effect in workers exposed to fiberglass and asbestos. *Am J Ind Med* 20(6): 745-751. (Support not reported. Authors affiliated with University of Southern California School of Medicine, CA; Workers Disease Detection Service, Inc., CA.)
164. Kilburn KH, Powers D, Warshaw RH. 1992. Pulmonary effects of exposure to fine fibreglass: irregular opacities and small airways obstruction. *Br J Ind Med* 49(10): 714-720. (Supported by the Sheet Metal Occupational Health Institute, Inc. Authors affiliated with USC School of Medicine, CA; Workers Disease Detection Services, Inc., CA.)
165. Kjuus H, Skjaerven R, Langård S, Lien JT, Aamodt T. 1986. A case-referant study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. *Scand J Work Environ Health* 12: 193-202. (Supported by the Norwegian Cancer Society and the Norwegian Society for Fighting Cancer. Authors affiliated with Telemark County Hospital, Norway; University of Bergen, Norway; Vestfold County Hospital, Norway.)
166. Koshi K, Kohyama N, Myojo T, Fukuda K. 1991. Cell toxicity, hemolytic action and clastogenic activity of asbestos and its substitutes. *Ind Health* 29(2):

- 37-56. (Support not reported. Authors affiliated with National Institute of Industrial Health, Japan; Central Motor Co., Ltd., Japan.)
167. Kovacikova Z, Petrovska H, Tatrai E, Dusinska M. 2004. The effect of fibrous dusts on lung cells. In vitro study. *Cent Eur J Public Health* 12 Suppl: S44-S48. (Supported by research grants FIBRETOX EC QLK4CT-1999-01629, OTKA T 033007/1999 and NFKP 1/008/2001. Authors affiliated with Slovak Medical University, Slovak Republic; NIOH, Hungary.)
168. Krantz S. 1988. Exposure to man-made mineral fibers at ten production plants in Sweden. *Scand J Work Environ Health* 14(Suppl 1): 49-51. (Support not reported. Author affiliated with National Institute of Occupational Health, Sweden.)
169. Kuschner M, Wright GW. 1976. The effects of intratracheal instillation of glass fiber of varying size in guinea pigs. In *Occupational Exposure to Fibrous Glass. Proceedings of a Symposium Presented by the Center of Adult Education, University of Maryland, College Park, Maryland, June 26-27, 1974*. Rockville, MD: U.S. Department of Health, Education and Welfare. p. 151-168. (Support not reported. Authors affiliated with State University of New York, NY.)
170. Lambré C, Schorsch F, Blanchard O, Richard J, Boivin JC, Hanton D, Grimm H, Morscheidt C. 1998. An evaluation of the carcinogenic potential of five man-made vitreous fibers using the intraperitoneal test. *Inhalation Toxicology* 10(11): 995-1021. (Support not reported. Authors affiliated with INERIS, France; Centre International de Toxicologie, France; Domaine de Bois La Croix, France; ISOVER-St. Gobain, France; St. Gobain Branche Isolatione, France.)
171. Landrigan PJ, Lioy PJ, Thurston G, Berkowitz G, Chen LC, Chillrud SN, Gavett SH, Georgopoulos PG, Geyh AS, Levin S, Perera F, Rappaport SM, Small C, Becker M, Breyse PN, Cohen B, Costa M, Efstathiou C, Eisenreich S, Foley G, Frank R, McGee JK, Groopman JD, Herbert R, Herbstman J, Jayjock E, Kendall M, Lederman SA, Lim HJ, Lippman M, Maciejczyk P, Millette J, Miretzky A, Ng SP, Offenber JH, Å-zkaynak HA, Pleil JD, Pozzi F, Quan C, Reibman J, Ross J, Samet JM, Santella RM, Schwab M, Shade P, Sobo M, Stenchikov G, Sun Q, Symons JM, Turpin B, Vyas V, Wang SW, Weisel CP, Williams DL, Wolff MS, Yiin LM, Zhong M, Gallo MA. 2004. Health and environmental consequences of the World Trade Center disaster. *Environ Health Perspect* 112(6): 731-739. (Supported by NIEHS, the Centers for Environmental Health Science, U.S. EPA, the New York Community Trust and United Way of New York City. Authors affiliated with Mount Sinai School of Medicine, NY; Environmental and Occupational Health Science Institute, NJ; New York University School of Medicine, NY; Columbia University, NY; U.S. EPA; Johns Hopkins University Bloomberg, MD; University of North Carolina, NC.)

172. Lasky JA, Coin PG, Lindroos PM, Ostrowski LE, Brody AR, Bonner JC. 1995. Chrysotile asbestos stimulates platelet-derived growth factor-AA production by rat lung fibroblasts in vitro: evidence for an autocrine loop. *Am J Respir Cell Mol Biol* 12(2): 162-170. (Supported by NIH and the ALA of North Carolina. Authors affiliated with NIEHS; Duke University Medical Center, NC; Tulane University Medical Center, LA.)
173. Le Bouffant L, Henin JP, Martin JC, Normand C, Tichoux G, Trolard F. 1984. Distribution of inhaled MMMF in the rat lung - long term effects. In *Biological Effects of Man-Made Mineral Fibres: Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA, Copenhagen, 2-22 April, 1982*, vol. 2. Copenhagen: World Health Organization. p. 143-167. (Supported by the Joint European Medical Research Board. Author affiliations not reported.)
174. Leanderson P, Söderkvist P, Tagesson C, Axelson O. 1988. Formation of DNA adduct 8-hydroxy-2'-deoxyguanosine induced by man-made mineral fibres. In *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention*, IARC Scientific Publications No. 89. Bartsch H, Hemminiki K, O'Neal IK, eds. Lyon: International Agency for Research on Cancer. p. 422-424. (Support not reported. Authors affiliated with Faculty of Health Sciences, Sweden.)
175. Leanderson P, Söderkvist P, Tagesson C. 1989. Hydroxyl radical mediated DNA base modification by manmade mineral fibres. *Br J Ind Med* 46(7): 435-438. (Supported by the Swedish Work Environment Fund. Authors affiliated with University Hospital, Sweden; Karolinska Institute, Sweden.)
176. Leanderson P, Tagesson C. 1989. Cigarette smoke potentiates the DNA-damaging effect of manmade mineral fibers. *Am J Ind Med* 16(6): 697-706. (Supported by the Swedish Work Environment Fund and the County Council of Ostergotland Research Fund. Authors affiliated with Faculty of Health Sciences, Sweden.)
177. Leanderson P, Tagesson C. 1992. Hydrogen peroxide release and hydroxyl radical formation in mixtures containing mineral fibres and human neutrophils. *Br J Ind Med* 49(11): 745-749. (Supported by the Swedish Work Environment Fund. Authors affiliated with Faculty of Health Sciences, Sweden.)
178. Lee IM, Hennekens CH, Trichopoulos D, Buring JE. 1995. Man-made vitreous fibers and risk of respiratory system cancer: a review of the epidemiologic evidence. *J Occup Environ Med* 37(6): 725-738. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with Brigham and Women's Hospital, MA; Harvard University, MA.)
179. Lee KP, Barras CE, Griffith FD, Waritz RS, Lapin CA. 1981. Comparative pulmonary responses to inhaled inorganic fibers with asbestos and fiberglass.

- Environ Res* 24(1): 167-191. (Support not reported. Authors affiliated with E.I. Du Pont de Nemours and Company, Inc., DE; Hercules Inc., DE; 3M Co., MN.)
180. Lees PSJ, Breyse PN, McArthur BR, Miller ME, Rooney BC, Robbins CA, Corn M. 1993. End user exposures to man-made vitreous fibers: I. Installation of residential insulation products. *Appl Occup Environ Hyg* 8(12): 1022-1030. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Johns Hopkins University School of Hygiene and Public Health, MD.)
181. Levin JL, McLarty JW, Hurst GA, Smith AN, Frank AL. 1998. Tyler asbestos workers: mortality experience in a cohort exposed to amosite. *Occup Environ Med* 55(3): 155-160. (Support not reported. Authors affiliated with University of Texas, TX.)
182. Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenber J, Buckley B, Turpin B, Zhong M, Cohen MD, Prophete C, Yang I, Stiles R, Chee G, Johnson W, Porcja R, Alimokhtari S, Hale RC, Weschler C, Chen LC. 2002. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. *Environ Health Perspect* 110(7): 703-714. (Support not reported. Authors affiliated with UMDNJ-Robert Wood Johnson Medical School and Rutgers University, NJ; MVA, GA; U.S. EPA; NYU School of Medicine, NY; College of William and Mary, VA.)
183. Luoto K, Holopainen M, Karppinen K, Perander M, Savolainen K. 1994. Dissolution of man-made vitreous fibers in rat alveolar macrophage culture and Gamble's saline solution: influence of different media and chemical composition of the fibers. *Environ Health Perspect* 102 Suppl 5: 103-107. (Support not reported. Authors affiliated with National Public Health Institute, Finland; Paroc Oy Ab, Finland.)
184. Luoto K, Holopainen M, Savolainen H. 1995a. Durability of man-made vitreous fibres as assessed by dissolution of silicon, iron and aluminum in rat alveolar macrophages. *Ann Occup Hyg* 39(6): 855-867. (Supported by Paroc Oy Ab. Authors affiliated with National Public Health Institute, Finland.)
185. Luoto K, Holopainen M, Kangas J, Kalliokoski P, Savolainen K. 1995b. The effect of fiber length on the dissolution by macrophages of rockwool and glasswool fibers. *Environ Res* 70(1): 51-61. (Supported by the Finnish Work Environment Fund and Paroc Oy Ab. Authors affiliated with National Public Health Institute, Finland; Kuopio Regional Institute of Occupational Health, Finland; University of Kuopio, Finland.)
186. Luoto K, Holopainen M, Sarataho M, Savolainen K. 1997. Comparison of cytotoxicity of man-made vitreous fibres. *Ann Occup Hyg* 41(1): 37-50.

(Supported by Partek Insulations Oy Ab. Authors affiliated with National Public Health Institute, Finland; University of Kuopio, Finland.)

187. Maples KR, Johnson NF. 1992. Fiber-induced hydroxyl radical formation: correlation with mesothelioma induction in rats and humans. *Carcinogenesis* 13(11): 2035-2039. (Supported by the U.S. Department of Energy. Authors affiliated with Inhalation Toxicology Research Institute, NM.)
188. Marchand JL, Luce D, Leclerc A, Goldberg P, Orlowski E, Bugel I, Brugère J. 2000. Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: results of a case-control study. *Am J Ind Med* 37(6): 581-589. (Supported by the Ministère du Travail. Authors affiliated with INSERM, France; Institut Curie, France.)
189. Marchant G, Bullock C, Carter C, Connelly R, Crane A, Fayerweather W, Johnson K, Reynolds J. 2009. Applications and findings of an occupational exposure database for synthetic vitreous fibers. *J Occup Environ Hyg* 6(3): 143-150. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with Arizona State University, AZ; Rock Wool Manufacturing Company, AL; Johns Manville, CO; North American Insulation Manufacturer's Association, VA; Owens-Corning, OH; CertainTeed Corporation, PA.)
190. Marsh GM, Enterline PE, Stone RA, Henderson VL. 1990. Mortality among a cohort of US man-made mineral fiber workers: 1985 follow-up. *J Occup Med* 32(7): 594-604. (Supported by the U.S. Thermal Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA.)
191. Marsh GM, Youk AO, Stone RA, Buchanich JM, Gula MJ, Smith TJ, Quinn MM. 2001a. Historical cohort study of US man-made vitreous fiber production workers: I. 1992 fiberglass cohort follow-up: initial findings. *J Occup Environ Med* 43(9): 741-756. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA; Harvard School of Public Health, MA; University of Massachusetts Lowell, MA.)
192. Marsh GM, Gula MJ, Youk AO, Buchanich JM, Churg A, Colby TV. 2001b. Historical cohort study of US man-made vitreous fiber production workers: II. Mortality from mesothelioma. *J Occup Environ Med* 43(9): 757-766. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA; University of British Columbia; Mayo Clinic.)
193. Marsh GM, Buchanich JM, Youk AO. 2001c. Historical cohort study of US man-made vitreous fiber production workers: VI. Respiratory system cancer standardized mortality ratios adjusted for the confounding effect of cigarette smoking. *J Occup Environ Med* 43(9): 803-808. (Supported by the North

American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA.)

194. Martin JC, Imbernon E, Goldberg M, Chevalier A, Bonenfant S. 2000. Occupational risk factors for lung cancer in the French electricity and gas industry: a case-control survey nested in a cohort of active employees. *Am J Epidemiol* 151(9): 902-912. (Support not reported. Authors affiliated with INSERM, France; Electricite de France, France.)

195. Mast RW, McConnell EE, Andersen R, Chevalier J, Kotin P, Bernstein DM, Thevenaz P, Glass LR, Miiller WC, Hesterberg TW. 1995a. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. *Inhal Toxicol* 7: 425-467. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Dow Corning Corporation, MI; Carborundum Company, NY; Schuller International, Inc., CO; Experimental Pathology Services AG, Switzerland; Research and Consulting Company, Switzerland.)

196. Mast RW, McConnell EE, Hesterberg TW, Chevalier J, Kotin P, Thevenaz P, Bernstein DM, Glass LR, Miiller W, Andersen A. 1995b. Multiple-dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. *Inhal Toxicol* 7: 469-502. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Dow Corning Corporation, MI; Carborundum Company, NY; Schuller International, Inc., CO; Experimental Pathology Services AG, Switzerland; Research and Consulting Company, Switzerland.)

197. Maxim LD, McConnell EE. 2001. Interspecies comparisons of the toxicity of asbestos and synthetic vitreous fibers: a weight-of-the-evidence approach. *Regul Toxicol Pharmacol* 33(3): 319-342. (Supported by the Refractory Ceramic Fibers Coalition. Authors affiliated with Everest Consulting Associates, NJ; ToxPath, Inc., NC.)

198. Maxim LD, Boymel P, Chase GR, Bernstein DM. 2002. Indices of fiber biopersistence and carcinogen classification for synthetic vitreous fibers (SVFs). *Regul Toxicol Pharmacol* 35(3): 357-378. (Supported by the Unifrax Corporation. Authors affiliated with Everest Consulting Associates, NJ; Unifrax Corporation, NY.)

199. Maxim LD, Eastes W, Hadley JG, Carter CM, Reynolds JW, Niebo R. 2003. Fiber glass and rock/slag wool exposure of professional and do-it-yourself installers. *Regul Toxicol Pharmacol* 37(1): 28-44. (Support not reported. Authors affiliated with Everest Consulting Associates, NJ; Owens Corning Science and Technology Center, OH; Johns Manville, CO; CertainTeed Corporation, PA.)

200. Maxim LD, Hadley JG, Potter RM, Niebo R. 2006. The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology. *Regul Toxicol Pharmacol* 46(1): 42-62. (Supported by the Owens-Corning Corporation. Authors affiliated with Everest Consulting Associates, NJ; Owens-Corning Science and Technology Center, OH.)
201. McConnell EE, Wagner JC, Skidmore JW, Moore JA. 1984. A comparative study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and glass microfibre (JM 100). In *Biological Effects of Man-Made Mineral Fibres: Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA, Copenhagen, 2-22 April, 1982*, vol. 2. Copenhagen: World Health Organization. p. 234-252. (Support and author affiliations not reported.)
202. McConnell EE. 1994. Synthetic vitreous fibers--inhalation studies. *Regul Toxicol Pharmacol* 20(3 Pt 2): S22-34. (Support and author affiliation not reported.)
203. McConnell EE, Kamstrup O, Musselman R, Hesterberg TW, Chevalier J, Miiller WC, Thevenaz P. 1994. Chronic inhalation study of size-separated rock slag and slag wool insulation fibers in Fischer 344/N rats. *Inhal Toxicol* 6: 571-614. (Support not reported. Authors affiliated with Rockwool International, Denmark; USG Interiors, IL; Schuller International, CO; Experimental Pathology Services, Switzerland; Research and Consulting Company, Switzerland.)
204. McConnell EE, Axten C, Hesterberg TW, Chevalier J, Miiller WC, Everitt J, Oberdörster G, Chase GR, Thevenaz P, Kotin P. 1999. Studies on the inhalation toxicology of two fibreglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure. *Inhal Toxicol* 11(9): 785-835. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with ToxPath, Inc., NC; North American Insulation Manufacturer's Association, VA; Johns Manville Corp., CO; Experimental Pathology Services, Switzerland; Chemical Industry Institute of Toxicology, NC; University of Rochester, NY; Research and Consulting Company, Switzerland.)
205. McDonald JC, Case BW, Enterline PE, Henderson V, McDonald AD, Plourde M, Sebastien P. 1990. Lung dust analysis in the assessment of past exposure of man-made mineral fibre workers. *Ann Occup Hyg* 34(5): 427-441. (Supported by the National Cancer Institute of Canada, NHRDP and the U.S. EPA. Authors affiliated with McGill University, Canada; University of Pittsburgh, PA; Centre d'Etudes et Recherches de Charbonages de France, France.)
206. Miller BG, Jones AD, Searl A, Buchanan D, Cullen RT, Soutar CA, Davis JMG, Donaldson K. 1999a. Influence of characteristics of inhaled fibres on development of tumours in the rat lung. *Annals of Occupational Hygiene* 43(3): 167-179. (Supported by the Colt Foundation, the UK Health and Safety

- Executive, EURISOL, ECFIA, Cape plc and BBA plc. Authors affiliated with Institute of Occupational Medicine, UK; Napier University, UK.)
207. Miller BG, Searl A, Davis JM, Donaldson K, Cullen RT, Bolton RE, Buchanan D, Soutar CA. 1999b. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. *Ann Occup Hyg* 43(3): 155-166. (Supported by the Colt Foundation, UK Health and Safety Executive, EURISOL, ECFIA, Cape plc and BBA plc. Authors affiliated with Institute of Occupational Health, UK; Napier University, UK.)
208. Miller ME, Lees PSJ, Breysse PN. 1995. A comparison of airborne man-made vitreous fiber concentrations before and after installation of insulation in new construction housing. *Appl Occup Environ Hyg* 10(3): 182-187. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Johns Hopkins University, MD; Zeneca, Inc., DE.)
209. Mitchell RI, Donofrio DJ, Moorman WJ. 1986. Chronic inhalation toxicity of fibrous glass in rats and monkeys. *J Am Coll Toxicol* 5(6): 545-575. (Supported by NIOSH. Authors affiliated with R.I.M. Technical Services, OH; Donofrio Enterprises, OH; NIOSH.)
210. Mohr U, Pott F, Vonnahme FJ. 1984. Morphological aspects of mesotheliomas after intratracheal instillations of fibrous dusts in Syrian golden hamsters. *Exp Pathol* 26(3): 179-183. (Support not reported. Authors affiliated with Medizinische Hochschule Hannover, Germany; Universitat Dusseldorf, Germany.)
211. Monchaux G, Bignon J, Jaurand MC, Lafuma J, Sebastien P, Masse R, Hirsch A, Goni J. 1981. Mesotheliomas in rats following inoculation with acid-leached chrysotile asbestos and other mineral fibres. *Carcinogenesis* 2(3): 229-236. (Supported by Institut National de la Sante et de la Recherche Medical. Authors affiliated with DDASS, France; Universite Paris-Val de Marne, France; IPSN, France; BRGM, France.)
212. Moore MA, Boymel PM, Maxim LD, Turim J. 2002. Categorization and nomenclature of vitreous silicate wools. *Regul Toxicol Pharmacol* 35(1): 1-13. (Support not reported. Authors affiliated with The Morgan Crucible Company, UK; Unifrax Corporation, NY; Everest Consulting Associates, NJ; Sciences International, Inc., VA.)
213. Moorman WJ, Mitchell RT, Mosberg AT, Donofrio DJ. 1988. Chronic inhalation toxicology of fibrous glass in rats and monkeys. *Ann Occup Hyg* 32(Suppl 1): 757-767. (Support not reported. Authors affiliated with NIOSH; Battelle Columbus Laboratories, OH.)
214. Morgan A. 1980. Effect of length on the clearance of fibres from the lung and on body formation. *IARC Sci Publ*(30): 329-335. (Supported by the Asbestosis

- Research Council and the EEC Environmental Research Programme. Author affiliated with Inhalation Toxicology and Radionuclide Analysis Group, UK.)
215. Morgan RW, Kaplan SD, Bratsberg JA. 1981. Mortality study of fibrous glass production workers. *Arch Environ Health* 36(4): 179-183. (Supported by Owens-Corning Fiberglas. Authors affiliated with Environmental Health Associates, CA; SRI International, CA.)
 216. Mossman BT, Sesko AM. 1990. In vitro assays to predict the pathogenicity of mineral fibers. *Toxicology* 60(1-2): 53-61. (Supported by NCI, NIEHS and NHLBI. Authors affiliated with University of Vermont College of Medicine, VT.)
 217. Moulin JJ, Mur JM, Wild P, Perreaux JP, Pham QT. 1986. Oral cavity and laryngeal cancers among man-made mineral fiber production workers. *Scand J Work Environ Health* 12(1): 27-31. (Support not reported. Authors affiliated with National Institute for Research in Safety and Occupational Health, France; National Institute for Health and Medical Research, France.)
 218. Moulin JJ, Pham QT, Mur JM, Meyer-Bisch C, Caillard JF, Massin N, Wild P, Teculescu D, Delepine P, Hunzinger E, Perreaux JP, Muller J. 1987. Epidemiological study in two factories producing artificial mineral fibers: II. Respiratory symptoms. *Arch Mal Prof* 48: 7-16. (as cited in IARC 2002).
 219. Moulin JJ, Wild P, Mur JM, Caillard JF, Massin N, Meyer-Bisch C, Toamain JP, Hanser P, Liet S, Du Roscoat MN, Segala A. 1988a. Respiratory health assessment by questionnaire of 2024 workers involved in man-made mineral fiber production. *Int Arch Occup Environ Health* 61(3): 171-178. (Support not reported. Authors affiliated with Institut National de Recherche et du Securite Service d'epidemiologie, France; Institut de Medecine du Travail de Haute Normandie, France.)
 220. Muhle H, Pott F, Bellmann B, Takenaka S, Ziem U. 1987. Inhalation and injection experiments in rats to test the carcinogenicity of MMMF. *Ann Occup Hyg* 31(4B): 755-764. (Supported by the Umweltbundesamt and the Commission of the European Communities. Authors affiliated with Fraunhofer Institut fur Toxikologie und Aerosolforschung, Germany; Universitat Dusseldorf, Germany.)
 221. Muhle H, Bellmann B, Creutzenberg O, Fuhst R, Koch W, Mohr U, Takenaka S, Morrow P, Kilpper R, MacKenzie J, Mermelstein R. 1990. Subchronic inhalation study of toner in rats. *Inhal Toxicol* 2: 341-360. (Support not reported. Authors affiliated with Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Germany; University of Rochester, NY; Xerox Corporation, NY.)
 222. Muhle H, Pott F. 2000. Asbestos as reference material for fibre-induced cancer. *Int Arch Occup Environ Health* 73 Suppl: S53-S59. (Support not

- reported. Authors affiliated with Fraunhofer Institute of Toxicology and Aerosol Research, Germany.)
223. Murata-Kamiya N, Tsutsui T, Fujino A, Kasai H, Kaji H. 1997. Determination of carcinogenic potential of mineral fibers by 8-hydroxydeoxyguanosine as a marker of oxidative DNA damage in mammalian cells. *Int Arch Occup Environ Health* 70(5): 321-326. (Supported by the Ministry of Education, Science, Sports and Culture, Japan. Authors affiliated with University of Occupational and Environmental Health, Japan.)
224. Nasr AN, Ditchek T, Scholtens PA. 1971. The prevalence of radiographic abnormalities in the chests of fiber glass workers. *J Occup Med* 13(8): 371-376 (as cited in IARC 1988).
225. Newhouse ML, Berry G. 1979. Patterns of mortality in asbestos factory workers in London. *Ann N Y Acad Sci* 330: 53-60. (Supported by the Medical Research Council. Authors affiliated with London School of Hygiene and Tropical Medicine, UK; Llandough Hospital, UK.)
226. Nguea H, Rihn B, Mahon D, Bernard JL, De Reydellet A, Le Faou A. 2005. Effects of various man-made mineral fibers on cell apoptosis and viability. *Arch Toxicol* 79(9): 487-492. (Support not reported. Authors affiliated with Unite Mixte de Recherche CNRS-UHP, France; INSERM, France; St. Gobain Isover, France.)
227. Nguea HD, de Reydellet A, Le Faou A, Zaiou M, Rihn B. 2008. Macrophage culture as a suitable paradigm for evaluation of synthetic vitreous fibers. *Crit Rev Toxicol* 38(8): 675-695. (Support not reported. Authors affiliated with Nancy University, France; St. Gobain Insulation, France.)
228. NIOSH. 1994. Asbestos and Other Fibers by PCM. Method 7400. In *NIOSH Manual of Analytical Methods*. 4th ed. National Institute for Occupational Safety and Health.
229. Nishiike T, Nishimura Y, Wada Y, Iguchi H. 2005. Production of nitric oxide elevates nitrosothiol formation resulting in decreased glutathione in macrophages exposed to asbestos or asbestos substitutes. *Arch Toxicol* 79(2): 83-89. (Supported by the Scientific Research Fund of Education, Science and Culture of the government of Japan. Authors affiliated with Hyogo College of Medicine, Japan.)
230. NTP. 1994. *Report on Carcinogens* 7th ed., Research Triangle Park: National Toxicology Program.
231. Oberdörster G. 1996. Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. *Inhal Toxicol* 8 Suppl: 73-89. (Supported by NIH. Author affiliated with University of Rochester, NY.)

232. Oberdörster G. 2002. Toxicokinetics and effects of fibrous and nonfibrous particles. *Inhalation Toxicology* 14(1): 29-56. (Supported by NIEHS. Author affiliated with University of Rochester, NY.)
233. Oberdörster G. 2000. Determinants of the pathogenicity of man-made vitreous fibers (MMVF). *Int Arch Occup Environ Health* 73(Suppl): S60-68. (Support not reported. Authors affiliated with University of Rochester Medical Center, NY.)
234. Oehlert GW. 1991. A reanalysis of the Stanton et al. pleural sarcoma data. *Environ Res* 54(2): 194-205. (Support not reported. Author affiliated with University of Minnesota, MN.)
235. Ohyama M, Otake T, Morinaga K. 2000. The chemiluminescent response from human monocyte-derived macrophages exposed to various mineral fibers of different sizes. *Ind Health* 38(3): 289-293. (Support not reported. Authors affiliated with Osaka Prefectural Institute of Public Health, Japan; Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.)
236. Ohyama M, Otake T, Morinaga K. 2001. Effect of size of man-made and natural mineral fibers on chemiluminescent response in human monocyte-derived macrophages. *Environ Health Perspect* 109(10): 1033-1038. (Support not reported. Authors affiliated with Osaka Prefectural Institute of Public Health, Japan; Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.)
237. Okada F. 2007. Beyond foreign-body-induced carcinogenesis: impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progression. *Int J Cancer* 121(11): 2364-2372. (Supported by the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Japanese Ministry of Health and Welfare. Author affiliated with Yamagata University, Japan.)
238. Ong T, Liu Y, Zhong BZ, Jones WG, Whong WZ. 1997. Induction of micronucleated and multinucleated cells by man-made fibers in vitro in mammalian cells. *J Toxicol Environ Health* 50(4): 409-414. (Support not reported. Authors affiliated with NIOSH.)
239. Ottery J, Cherrie JW, Dodgson J, Harrison GE. 1984. A Summary Report on Environmental Conditions at 13 MMMF Plants. In *Biological Effects of Man-Made Mineral Fibres. Proceedings of an IARC/WHO Conference, Copenhagen, 20-22 April, 1982* vol. 1, Introduction and Session I - V. Copenhagen: World Health Organization. p. 83-117. (Supported by the Joint European Medical Research Board. Author affiliations not reported.)
240. Paananen H, Holopainen M, Kalliokoski P, Kangas J, Kotilainen M, Pennanen S, Savolainen H, Tossavainen A, Luoto K. 2004. Evaluation of exposure to man-made vitreous fibers by nasal lavage. *J Occup Environ Hyg* 1(2): 82-87.

(Supported by the Finnish Work Environment Fund. Authors affiliated with Kuopio Regional Institute of Occupational Health, Finland; Finnish Institute of Occupational Health, Finland; University of Kuopio, Finland; Ministry of Social Affairs and Health, Finland.)

241. Pache JC, Janssen YM, Walsh ES, Quinlan TR, Zanella CL, Low RB, Taatjes DJ, Mossman BT. 1998. Increased epidermal growth factor-receptor protein in a human mesothelial cell line in response to long asbestos fibers. *Am J Pathol* 152(2): 333-340. (Supported by NIH. Authors affiliated with University of Vermont College of Medicine, VT.)
242. Pelin K, Kivipensas P, Linnainmaa K. 1995. Effects of asbestos and man-made vitreous fibers on cell division in cultured human mesothelial cells in comparison to rodent cells. *Environ Mol Mutagen* 25(2): 118-125. (Supported by the Academy of Finland. Authors affiliated with Finnish Institute of Occupational Health, Finland.)
243. Perrault G, Dion C, Cloutier Y. 1992. Sampling and analysis of mineral fibers on construction sites. *Appl Occup Environ Hyg* 7: 323-326. (Support not reported. Authors affiliated with Institut de Recherche en Sante et en Securite du Travail, Canada.)
244. Pintos J, Parent ME, Rousseau MC, Case BW, Siemiatycki J. 2008. Occupational exposure to asbestos and man-made vitreous fibers, and risk of lung cancer: evidence from two case-control studies in Montreal, Canada. *J Occup Environ Med* 50(11): 1273-1281. (Supported by Health Canada, the Institut de recherche en sante et securite au Travail du Quebec, FRSQ, Medical Research Council of Canada, CIHR, NCIC, the Fondation J. Louis Levesque and the Fondation Armand Frappier. Authors affiliated with INRS, Canada; University of Montreal, Canada.)
245. Plato N, Krantz S, Andersson L, Gustavsson P, Lundgren L. 1995a. Characterization of current exposure to man-made vitreous fibres (MMVF) in the prefabricated house industry in Sweden. *Ann Occup Hyg* 39(2): 167-179. (Supported by the Swedish Work Environment Fund. Authors affiliated with Karolinska Hospital, Sweden; National Institute of Occupational Health, Sweden; University Hospital, Sweden.)
246. Plato N, Westerholm P, Gustavsson P, Hemmingsson T, Hogstedt C, Krantz S. 1995b. Cancer incidence, mortality and exposure-response among Swedish man-made vitreous fiber production workers. *Scand J Work Environ Health* 21(5): 353-361. (Supported by the Swedish Work Environment Fund. Authors affiliated with Karolinska Hospital, Sweden; National Institute of Occupational Health, Sweden.)
247. Plato N, Gustavsson P, Krantz S. 1997. Assessment of past exposure to man-made vitreous fibers in the Swedish prefabricated house industry. *Am J Ind*

- Med* 32(4): 349-354. (Supported by the Swedish Work Environment Fund. Authors affiliated with Karolinska Hospital, Sweden; Institute of Occupational Health, Sweden; National Institute of Occupational Health, Sweden.)
248. Pohlabein H, Jöckel KH, Brüske-Hohlfeld I, Möhner M, Ahrens W, Bolm-Audorff U, Arhelger R, Römer W, Kreienbrock L, Kreuzer M, Jahn I, Wichmann HE. 2000. Lung cancer and exposure to man-made vitreous fibers: results from a pooled case-control study in Germany. *Am J Ind Med* 37(5): 469-477. (Supported by the Federal Ministry of Education, Science, Research, and Technology. Authors affiliated with Bremen Institute for Prevention Research and Social Medicine, Germany; University Clinics of Essen, Germany; GSF - Institute of Epidemiology, Germany; Federal Institute for Occupational Safety and Health, Germany; Ludwig-Maximilians University, Germany; Labour Inspection, Germany; Justus-Liebig University, Germany.)
249. Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A, Stone V, Brown S, Macnee W, Donaldson K. 2008. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol* 3(7): 423-428. (Supported by the Colt Foundation, the Engineering and Physical Sciences Research Council and the Royal Academy of Engineering. Authors affiliated with MRC/University of Edinburgh, UK; University of Manchester, UK; Woodrow Wilson International Center for Scholars, Washington, D.C.; Institute of Occupational Medicine, UK; Napier University, UK.)
250. Pott F, Huth F, Friedrichs KH. 1974. Tumorigenic effect of fibrous dusts in experimental animals. *Environ Health Perspect* 9: 313-315. (Support not reported. Authors affiliated with University of Dusseldorf, Germany.)
251. Pott F, Friedrichs KH, Huth F. 1976a. [Results of animal experiments concerning the carcinogenic effect of fibrous dusts and their interpretation with regard to the carcinogenesis in humans (author's transl)]. *Zentralbl Bakteriol [Orig B]* 162(5-6): 467-505. (Support unknown due to foreign language. Authors affiliated with University of Dusseldorf, Germany.)
252. Pott F, Schlipkötter HW, Ziem U, Spurny K, Huth F. 1984a. New results from implantation experiments with mineral fibres. In *Biological Effects of Man-Made Mineral Fibres*, vol. 2. Copenhagen: World Health Organization. p. 286-302. (Support and author affiliations not reported.)
253. Pott F, Ziem U, Mohr U (1984b). Lung carcinomas and mesotheliomas following intratracheal instillation of glass fibres and asbestos, Sixth International Pneumoconiosis Conference, Bochum, Federal Republic of Germany, September 20-23, 1983, International Labour Office.p. 746-756. (Support not reported. Authors affiliated with University of Dusseldorf, Germany; Institut für Experimentelle Pathologie, Germany.)

254. Pott F. 1987. Problems in defining carcinogenic fibres. *Ann Occup Hyg* 31(4B): 799-802. (Support not reported. Authors affiliated with University of Dusseldorf, Germany.)
255. Pott F, Ziem U, Reiffer FJ, Huth F, Ernst H, Mohr U. 1987. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Exp Pathol* 32(3): 129-152. (Support not reported. Authors affiliated with Universitat Dusseldorf, Germany; Städtisches Krankenhaus, Germany; Institut für Experimentelle Pathologie, Germany.)
256. Pott F. 1989. Carcinogenicity of fibres in experimental animals - data and evaluation. In *Assessment of Inhalation Hazards*, ILSI Monographs. Bates DV, Dungworth DL, Lee PN, McClellan RO, Roe FJC, eds. New York, NY: Springer-Verlag. p. 243-253. (Support not reported. Author affiliated with University of Dusseldorf, Germany.)
257. Pott F, Roller M, Ziem U, Reiffer FJ, Bellmann B, Rosenbruch M, Huth F. 1989. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. In *Non-Occupational Exposure to Mineral Fibres*, IARC Scientific Publications No. 90. Bignon J, Peto J, Saracci R, eds. Lyon: International Agency for Research on Cancer. p. 173-179. (Supported by the Bundesanstalt für Arbeitsschutz. Authors affiliated with University of Dusseldorf, Germany; Fraunhofer Institute of Toxicology and Aerosol Research, Germany; Municipal Hospital, Germany.)
258. Pott F, Roller M, Rippe RM, Germann P-G, Bellmann B. 1991. Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibres. In *Mechanisms in Fibre Carcinogenesis*, NATO ASI Series 223. Brown RC, Hoskins JA, Johnson NF, eds. New York: Plenum Press. p. 547-565. (Support not reported. Authors affiliated with University of Dusseldorf, Germany; Fraunhofer Institute of Toxicology and Aerosol Research, Germany.)
259. Quinn MM, Smith TJ, Youk AO, Marsh GM, Stone RA, Buchanich JM, Gula MJ. 2001. Historical cohort study of US man-made vitreous fiber production workers: VIII. Exposure-specific job analysis. *J Occup Environ Med* 43(9): 824-834. (Supported by the North American Insulation Manufacturer's Association, University of Pittsburgh and the University of Massachusetts. Authors affiliated with University of Massachusetts Lowell, MA; University of Pittsburgh, PA.)
260. Rihn B, Coulais C, Kauffer E, Bottin MC, Martin P, Yvon F, Vigneron JC, Binet S, Monhoven N, Steiblen G, Keith G. 2000. Inhaled crocidolite mutagenicity in lung DNA. *Environ Health Perspect* 108(4): 341-346. (Supported by the Fondation pour la Recherche Medicale. Authors affiliated with Institut National de Recherche et de Securite, France; Laboratoire de Biologie Moleculaire de l'Hopital Central de Nancy, France; CNRS, France.)

261. Rivera Z, Strianese O, Bertino P, Yang H, Pass H, Carbone M. 2008. The relationship between simian virus 40 and mesothelioma. *Curr Opin Pulm Med* 14(4): 316-321. (Supported by NCI, the Riviera Country Club of Illinois and the Mark Butitta Mesothelioma Foundation. Authors affiliated with University of Hawaii, HI; University of Genoa, Italy; University of Piemonte Orientale 'A. Avogadro,' Italy; New York University School of Medicine, NY.)
262. Rödelsperger K, Jöckel KH, Pohlabein H, Römer W, Voitowitz HJ. 2001. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. *Am J Ind Med* 39(3): 262-275. (Supported by the Federal Ministry of Research and Technology. Authors affiliated with North German Research Center for Public Health and Bremen Institute for Prevention Research and Social Medicine, Germany; University of Giessen, Germany; University Clinics of Essen, Germany.)
263. Rödelsperger K. 2004. Extrapolation of the carcinogenic potency of fibers from rats to humans. *Inhal Toxicol* 16: 801-807. (Support not reported. Authors affiliated with Justus Liebig Universität Gießen, Germany.)
264. Roller M, Pott F, Kamino K, Althoff GH, Bellmann B. 1996. Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. *Exp Toxicol Pathol* 48(1): 3-12. (Support not reported. Authors affiliated with Heinrich Heine University, Germany; Hannover Medical School, Germany; Fraunhofer Institute of Toxicology and Aerosol Research, Germany.)
265. Roller M, Pott F, Kamino K, Althoff GH, Bellmann B. 1997. Dose-response relationship of fibrous dusts in intraperitoneal studies. *Environ Health Perspect* 105(Suppl 5): 1253-1256. (Support not reported. Authors affiliated with Heinrich Heine University, Germany; Hannover Medical School, Germany; Fraunhofer Institute of Toxicology and Aerosol Research, Germany.)
266. Roller M, Pott F. 1998. Carcinogenicity of man-made fibres in experimental animals and its relevance for classification of insulation wools. *Eur J Oncol* 3(3): 231-239. (Support not reported. Authors affiliated with Heinrich Heine University, Germany.)
267. Rossiter CE, Chase JR. 1995. Statistical analysis of results of carcinogenicity studies of synthetic vitreous fibres at Research and Consulting Company, Geneva. *Ann Occup Hyg* 39(5): 759-769. (Support not reported. Authors affiliated with Joint European Medical Research Board, UK; Schuller International, Inc., CO.)
268. Rowe JN, Springer JA. 1986. Asbestos lung cancer risks: comparison of animal and human extrapolations. *Risk Anal* 6(2): 171-180 (as cited in Maxim and McConnell 2001).

269. Ruotsalainen M, Hirvonen MR, Luoto K, Savolainen KM. 1999. Production of reactive oxygen species by man-made vitreous fibres in human polymorphonuclear leukocytes. *Hum Exp Toxicol* 18(6): 354-362. (Supported by the Finnish Work Environment Fund. Authors affiliated with National Public Health Institute, Finland; University of Kuopio, Finland; Finnish Institute of Occupational Health, Finland.)
270. Sali D, Boffetta P, Andersen A, Cherrie JW, Claude JC, Hansen J, Olsen JH, Pesatori AC, Plato N, Teppo L, Westerholm P, Winter P, Saracci R. 1999. Non-neoplastic mortality of European workers who produce man made vitreous fibres. *Occup Environ Med* 56(9): 612-617. (Supported by the Joint European Medical Research Board. Authors affiliated with IARC; University of Pavia, Italy; Norwegian Cancer Registry, Norway; University of Aberdeen and Institute of Occupational Medicine, UK; German Center for Cancer Research, Germany; Danish Cancer Society, Denmark; University of Milan, Italy; Karolinska Hospital, Sweden; Finnish Cancer Registry, Finland; National Institute of Occupational Health, Sweden; MRC Environmental Epidemiology Unit, UK; National Research Council, Italy.)
271. Saracci R, Simonato L, Acheson ED, Andersen A, Bertazzi PA, Claude J, Charnay N, Esteve J, Frentzel-Beyme RR, Gardner MJ, Jensen OM, Maasing R, Olsen JH, Teppo L, Westerholm P, Zocchetti C. 1984. Mortality and incidence of cancer of workers in the man made vitreous fibres producing industry: an international investigation at 13 European plants. *Br J Ind Med* 41(4): 425-436. (Supported by the Joint European Medical Research Board. Authors affiliated with IARC; MRC Environmental Epidemiology Unit, UK; Norwegian Cancer Registry, Norway; University of Milan, Italy; German Cancer Research Center, Germany; Danish Cancer Registry, Denmark; Kabi AB Drug Corporation, Sweden; Finnish Cancer Registry, Finland; Swedish Trade Union Confederation, Sweden.)
272. Schepers GW, Delahant AB. 1955. An experimental study of the effects of glass wool on animal lungs. *AMA Arch Ind Health* 12(3): 276-279. (Support not reported. Authors affiliated with Saranac Laboratory.)
273. Schepers GW. 1974. The comparative pathogenicity of inhaled fibrous glass dust. In *Occupational Exposure to Fibrous Glass. Proceedings of a Symposium Presented by the Center of Adult Education, University of Maryland, College Park, Maryland, June 26-27, 1974*. Rockville, MD: U.S. Department of Health, Education and Welfare. p. 265-341. (Support not reported. Authors affiliated with State University Medical School, PA.)
274. Schins RPF, Donaldson K. 2000. Nuclear factor kappa-beta activation by particles and fibers. *Inhal Toxicol* 12(Suppl 3): 317-326. (Supported by the Colt Foundation. Authors affiliated with Napier University, UK; Heinrich-Heine-University, Germany.)

275. Schürkes C, Brock W, Abel J, Unfried K. 2004. Induction of 8-hydroxydeoxyguanosine by man made vitreous fibres and crocidolite asbestos administered intraperitoneally in rats. *Mutat Res* 553(1-2): 59-65. (Supported by the Deutsche Forschungsgemeinschaft. Authors affiliated with Heinrich-Heine-Universität, Germany.)
276. Selikoff IJ, Seidman H. 1992. Use of death certificates in epidemiological studies, including occupational hazards: variations in discordance of different asbestos-associated diseases on best evidence ascertainment. *Am J Ind Med* 22(4): 481-492. (Support not reported. Authors affiliated with Mount Sinai School of Medicine, NY; American Cancer Society.)
277. Shannon H, Muir A, Haines T, Verma D. 2005. Mortality and cancer incidence in Ontario glass fiber workers. *Occup Med (Lond)* 55(7): 528-534. (Supported by the Workplace Safety and Insurance Board of Ontario. Authors affiliated with McMaster University, Canada; Institute for Work and Health, Canada.)
278. Shannon HS, Hayes M, Julian JA, Muir DC. 1984. Mortality experience of glass fibre workers. *Br J Ind Med* 41(1): 35-38. (Supported by Fiberglass Canada. Authors affiliated with McMaster University Health Sciences Center, Canada.)
279. Shannon HS, Jamieson E, Julian JA, Muir DC, Walsh C. 1987. Mortality experience of Ontario glass fibre workers--extended follow-up. *Ann Occup Hyg* 31(4B): 657-662. (Supported by Fiberglass Canada, Inc. and the Ontario Ministry of Labor. Authors affiliated with McMaster University, Canada.)
280. Siemiatycki J. 1991. *Risk Factors for Cancer in the Workplace*, Boca Raton, FL: CRC Press. 325 pp. (Support not reported. Author affiliated with University of Quebec, Canada.)
281. Simonato L, Fletcher AC, Cherrie J, Andersen A, Bertazzi PA, Charnay N, Claude J, Dodgson J, Estève J, Frentzel-Beyme R, Gardner MJ, Jensen OM, Olsen J, Saracci R, Teppo L, Winkelmann R, Westerholm P, Winter P, Zocchetti C. 1986. The man-made mineral fiber European historical cohort study. Extension of the follow-up. *Scand J Work Environ Health* 12(Suppl 1): 34-47. (Support not reported. Authors affiliated with IARC; Institute of Occupational Medicine, UK; Norwegian Cancer Registry, Norway; University of Milan, Italy; German Cancer Research Center, Germany; MRC Environmental Epidemiology Unit, UK; Danish Cancer Registry, Denmark; Finnish Cancer Registry, Finland; Swedish Trade Union Confederation, Sweden.)
282. Sincock AM, Delhanty JD, Casey G. 1982. A comparison of the cytogenetic response to asbestos and glass fibre in Chinese hamster and human cell lines. Demonstration of growth inhibition in primary human fibroblasts. *Mutat Res* 101(3): 257-268. (Supported by the Health and Safety Executive. Authors

affiliated with University College London, UK; Fund for the Replacement of Animals in Medical Experiments, UK; Royal Marsden Hospital, UK.)

283. Sixt R, Bake B, Abrahamsson G, Thiringer G. 1983. Lung function of sheet metal workers exposed to fiber glass. *Scand J Work Environ Health* 9(1): 9-14 (as cited in IARC 1988).
284. Smith DM, Ortiz LW, Archuleta RF, Johnson NF. 1987. Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. *Ann Occup Hyg* 31(4B): 731-754. (Supported by the Thermal Insulation Manufacturer's Association. Authors affiliated with Los Alamos National Laboratory, NM.)
285. Smith TJ, Quinn MM, Marsh GM, Youk AO, Stone RA, Buchanich JM, Gula MJ. 2001. Historical cohort study of US man-made vitreous fiber production workers: VII. Overview of the exposure assessment. *J Occup Environ Med* 43(9): 809-823. (Supported by the North American Thermal Insulation Manufacturer's Association, the Harvard Environmental Health Center and NIEHS. Authors affiliated with Harvard School of Public Health, MA; University of Massachusetts, MA; University of Pittsburgh, PA.)
286. Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, Harlow BL, Benichou J. 1994. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 51(12): 804-811. (Support not reported. Authors affiliated with NCI; University of Southern California, CA; National Academy of Sciences, Washington, D.C.; New York State Department of Health; Westat, Inc., MD; Brigham and Women's Hospital, MA.)
287. Stanton MF, Wrench C. 1972. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst* 48(3): 797-821. (Support not reported. Authors affiliated with NCI.)
288. Stanton MF, Laynard M, Tegeris A, Miller E, May M, Kent E. 1977. Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. *J Natl Cancer Inst* 58(3): 587-603. (Support not reported. Authors affiliated with NCI; Pharmacopathics Research Laboratories, Inc., MD.)
289. Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J Natl Cancer Inst* 67(5): 965-975. (Support not reported. Authors affiliated with NCI; Veterans Administration Medical Center, CA; Pharmacopathics Research Laboratories, Inc., MD; Triangle Resource Industries, MD.)
290. Steenland K, Stayner L. 1997. Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control* 8(3): 491-503. (Support not reported. Authors affiliated with NIOSH.)

291. Stone RA, Marsh GM, Youk AO, Smith TJ, Quinn MM. 1996. Statistical estimation of exposure to fibers in jobs for which no direct measurements are available. *Occup Hyg* 3: 91-101. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA; Harvard University, MA; University of Massachusetts at Lowell, MA.)
292. Stone RA, Youk AO, Marsh GM, Buchanich JM, McHenry MB, Smith TJ. 2001. Historical cohort study of US man-made vitreous fiber production workers: IV. Quantitative exposure-response analysis of the nested case-control study of respiratory system cancer. *J Occup Environ Med* 43(9): 779-792. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA; Harvard School of Public Health, MA.)
293. Stone RA, Youk AO, Marsh GM, Buchanich JM, Smith TJ. 2004. Historical cohort study of U.S. man-made vitreous fiber production workers IX: summary of 1992 mortality follow up and analysis of respiratory system cancer among female workers. *J Occup Environ Med* 46(1): 55-67. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA; Harvard School of Public Health, MA.)
294. Switala ED, Harlan RC, Schlaudecker DG, Bender JR. 1994. Measurement of respirable glass and total fiber concentrations in the ambient air around a fiberglass wool manufacturing facility and a rural area. *Regul Toxicol Pharmacol* 20(3 Pt 2): S76-88. (Support not reported. Authors affiliated with Owens-Corning Fiberglas Corporation, OH.)
295. Teppo L, Kojonen E. 1986. Mortality and cancer risk among workers exposed to man-made mineral fibers in Finland. *Scand J Work Environ Health* 12(Suppl 1): 61-64. (Support not reported. Authors affiliated with Finnish Cancer Registry.)
296. Topinka J, Loli P, Hurbánková M, Kováčiková Z, Volkovová K, Wolff T, Oesterle D, Kyrtopoulos SA, Georgiadis P. 2006a. Benzo[a]pyrene-enhanced mutagenesis by man-made mineral fibres in the lung of *lambda-lacI* transgenic rats. *Mutat Res* 595: 167-173. (Supported by E.U. Authors affiliated with GSF-National Research Center for Environment and Health, Germany; Institute of Experimental Medicine AS CR; Czech Republic; National Hellenic Research Foundation, Greece; Institute of Preventive and Clinical Medicine, Slovak Republic.)
297. Topinka J, Loli P, Dušinská M, Hurbánková M, Kováčiková Z, Volkovová K, Kažimirová A, Barancoková M, Tatrai E, Wolff T, Oesterle D, Kyrtopoulos SA, Georgiadis P. 2006b. Mutagenesis by man-made mineral fibres in the lung of rats. *Mutat Res* 595: 174-183. (Supported by an E.U. grant, the Hungarian Scientific Research Fund and the Hungarian Research and Development Project. Authors affiliated with GSF-National Research Center for

Environment and Health, Germany; Institute of Experimental Medicine, Czech Republic; National Hellenic Research Foundation, Greece; Institute of Preventive and Clinical Medicine, Slovak Republic; Fodor Jozsef National Center of Public Health, Hungary.)

298. Tsou JA, Galler JS, Wali A, Ye W, Siegmund KD, Groshen S, Laird PW, Turla S, Koss MN, Pass HI, Laird-Offringa IA. 2007. DNA methylation profile of 28 potential marker loci in malignant mesothelioma. *Lung Cancer* 58(2): 220-230. (Supported by the Mesothelioma Applied Research Foundation and NCI. Authors affiliated with University of Southern California, CA; Wayne State University, MI.)
299. USCB. 2005. *Mineral Wool Manufacturing: 2002*. U.S. Census Bureau. <http://www.census.gov/epcd/ec97/industry/E327993.HTM>. Last accessed: 1/28/05.
300. USITC. 2009a. *U.S. Imports for Consumption: Glass Fibers (including Glass Wool) and Articles Thereof, Including Yarn and Woven Fabrics* U.S. International Trade Commission. <http://www.usitc.gov/>.
301. USITC. 2009b. *U.S. Domestic Exports: Glass Fibers (Including Glass Wool) and Articles Thereof, Including Yarn and Woven Fabrics*. U.S. International Trade Commission. <http://www.usitc.gov>.
302. Valentin H, Bost H-P, Essing H-G. 1977. Are glass fibre dusts of concern for health? *Berufsgenossenschaft* February: 60-64 (as cited in IARC 1988).
303. Vasama-Neuvonen K, Pukkala E, Paakkulainen H, Mutanen P, Weiderpass E, Boffetta P, Shen N, Kauppinen T, Vainio H, Partanen T. 1999. Ovarian cancer and occupational exposures in Finland. *Am J Ind Med* 36(1): 83-89. (Supported by the Finnish Work Environment Fund. Authors affiliated with Finnish Institute of Occupational Health, Finland; Finnish Cancer Registry, Finland; Karolinska Institute, Sweden; IARC; McGill University, Canada.)
304. Vorwald AJ, Durkan TM, Pratt PC. 1951. Experimental studies of asbestosis. *A M A Arch Ind Hyg Occup Med* 3(1): 1-43. (Supported by the asbestos industry. Authors affiliated with the Saranac Laboratory of the Edward L. Trudeau Foundation.)
305. Wagner JC, Berry G, Timbrell V. 1973. Mesotheliomata in rats after inoculation with asbestos and other materials. *Br J Cancer* 28(2): 173-185. (Support not reported. Authors affiliated with Llandough Hospital, UK.)
306. Wagner JC, Berry G, Skidmore JW, Timbrell V. 1974. The effects of the inhalation of asbestos in rats. *Br J Cancer* 29(3): 252-269. (Support not reported. Authors affiliated with Llandough Hospital, UK.)

307. Wagner JC, Berry G, Skidmore JW. 1976. Studies of the carcinogenic effects of fiber glass of different diameters following intrapleural inoculation in experimental animals. In *Occupational Exposure to Fibrous Glass: Proceedings of a Symposium Presented by the Center of Adult Education, University of Maryland, College Park, Maryland, June 26-27, 1974*. LeVee WN, Schulte PA, eds. Rockville, MD: U.S. Department of Health, Education and Welfare. p. 193-204. (Support not reported. Authors affiliated with Medical Research Council, UK.)
308. Wagner JC, Berry G, Hill RJ, Munday DE, Skidmore JW. 1984a. Animal experiments with MMM(V)F - Effects of inhalation and intrapleural inoculation in rats. In *Biological Effects of Man-Made Mineral Fibres: Proceedings of a WHO/IARC Conference in Association with JEMRB and TIMA, Copenhagen, 2-22 April 1982*, vol. 2. Copenhagen: World Health Organization. p. 209-233. (Support and author affiliations not reported.)
309. Wagner JC, Griffiths DM, Hill RJ. 1984b. The effect of fibre size on the *in vivo* activity of UICC crocidolite. *Br J Cancer* 49(4): 453-458. (Support not reported. Authors affiliated with Llandough Hospital, UK.)
310. Wagner JC, Skidmore JW, Hill RJ, Griffiths DM. 1985. Erionite exposure and mesotheliomas in rats. *Br J Cancer* 51(5): 727-730. (Support not reported. Authors affiliated with Llandough Hospital, UK.)
311. Wallenberger FT, Watson JC, Li H. 2001. Glass Fibers. In *ASM Handbook*, vol. 21: Composites. Materials Park, OH: ASM International. (Support not reported. Authors affiliated with PPG Industries, Inc.)
312. Walton WH. 1982. The nature, hazards and assessment of occupational exposure to airborne asbestos dust: a review. *Ann Occup Hyg* 25(2): 117-247. (Support and author affiliations not reported.)
313. Wang QE, Han CH, Yang YP, Wang HB, Wu WD, Liu SJ, Kohyama N. 1999a. Biological effects of man-made mineral fibers (II)--their genetic damages examined by *in vitro* assay. *Ind Health* 37(3): 342-347. (Supported by Japan-China Medical Association. Authors affiliated with Beijing Medical University, China; Beijing Teacher's College of Physical Education, China; National Institute of Industrial Health, Japan.)
314. Wang QE, Han CH, Wu WD, Wang HB, Liu SJ, Kohyama N. 1999b. Biological effects of man-made mineral fibers (I)--Reactive oxygen species production and calcium homeostasis in alveolar macrophages. *Ind Health* 37(1): 62-67. (Supported by the Japan-China Medical Association. Authors affiliated with Beijing Medical University, China; Beijing Teacher's College of Physical Education, China; National Institute of Industrial Health, Japan.)
315. Wang Y, Faux SP, Hallden G, Kirn DH, Houghton CE, Lemoine NR, Patrick G. 2004. Interleukin-1beta and tumour necrosis factor-alpha promote the

- transformation of human immortalised mesothelial cells by erionite. *International journal of oncology* 25(1): 173-178. (Support not reported. Authors affiliated with Imperial College London Hammersmith Hospital, UK; Henan Medical University, China; Leicester University, UK.)
316. Wardenbach P, Rödelsperger K, Roller M, Muhle H. 2005. Classification of man-made vitreous fibers: Comments on the revaluation by an IARC working group. *Regul Toxicol Pharmacol* 43(2): 181-193. (Support not reported. Authors affiliated with Federal Institute for Occupational Safety and Health, Germany; Institute and Outpatient Clinic for Occupational and Social Medicine of the Justice Liebig University, Germany; Advisory Office for Risk Assessment, Germany; Fraunhofer Institute of Toxicology and Experimental Medicine, Germany.)
317. Weiderpass E, Pukkala E, Kauppinen T, Mutanen P, Paakkulainen H, Vasama-Neuvonen K, Boffetta P, Partanen T. 1999. Breast cancer and occupational exposures in women in Finland. *Am J Ind Med* 36(1): 48-53. (Supported by the Finnish Work Environment Fund. Authors affiliated with Karolinska Institute, Sweden; Finnish Institute of Occupational Health, Finland; Finnish Cancer Registry, Finland; IARC.)
318. Weiderpass E, Vainio H, Kauppinen T, Vasama-Neuvonen K, Partanen T, Pukkala E. 2003. Occupational exposures and gastrointestinal cancers among Finnish women. *J Occup Environ Med* 45(3): 305-315. (Supported by the Swedish Work Environment Fund and the Foundation for the Finnish Cancer Institute. Authors affiliated with IARC; Karolinska Institute, Sweden; Finnish Institute of Occupational Health, Finland; University of Tampere, Finland; Universidad Nacional, Costa Rica; Finnish Cancer Registry, Finland.)
319. WHO. 1988. *Environmental Health Criteria 77: Man-made mineral fibres*. World Health Organization.
320. WHO. 2000. *Air Quality Guidelines*. World Health Organizations.
321. Whong WZ, Gao HG, Zhou G, Ong T. 1999. Genetic alterations of cancer-related genes in glass fiber-induced transformed cells. *J Toxicol Environ Health A* 56(6): 397-404. (Support not reported. Authors affiliated with NIOSH.)
322. Wilson MS, Wynn TA. 2009. Pulmonary fibrosis: pathogenesis, etiology and regulation. *Mucosal Immunol* 2(2): 103-121. (Supported by the State of New York and the Insulation Contractor's Association of American. Authors affiliated with Harvard University, MA; Brooklyn College, NY.)
323. Wilson R, Langer AM, Nolan RP. 1999. A risk assessment for exposure to glass wool. *Regul Toxicol Pharmacol* 30(2 Pt 1): 96-109. (Supported by the State of New York and the Insulations Contractor's Association of America. Authors affiliated with Harvard University, MA; Brooklyn College, NY.)

324. Wright GW. 1968. Airborne fibrous glass particles. Chest roentgenograms of persons with prolonged exposure. *Arch Environ Health* 16(2): 175-181 (as cited in IARC 1988).
325. Wright GW, Kuschner M. 1977. The influence of varying lengths of glass and asbestos fibres on tissue response in guinea pigs. In *Inhaled Particles. IV. Proceedings of an International Symposium Organized by the British Occupational Hygiene Society, Edinburgh, 22-26, September 1975*. Walton WH, ed. Oxford: Pergamon Press. p. 455-474. (Support not reported. Authors affiliated with Saint Luke's Hospital, OH; State University of New York at Stony Brook, NY.)
326. Wylie AG, Virta RL, Segreti JM. 1987. Characterization of mineral population by index particle: implication for the Stanton hypothesis. *Environ Res* 43(2): 427-439. (Support not reported. Authors affiliated with University of Maryland, MD; U.S. Department of the Interior, MD.)
327. Xie C, Reusse A, Dai J, Zay K, Harnett J, Churg A. 2000. TNF-alpha increases tracheal epithelial asbestos and fiberglass binding via a NF-kappaB-dependent mechanism. *Am J Physiol Lung Cell Mol Physiol* 279(3): L608-L614. (Supported by the Medical Research Council of Canada. Authors affiliated with University of British Columbia, Canada.)
328. Ye J, Shi X, Jones W, Rojanasakul Y, Cheng N, Schwegler-Berry D, Baron P, Deye GJ, Li C, Castranova V. 1999. Critical role of glass fiber length in TNF-alpha production and transcription factor activation in macrophages. *Am J Physiol* 276(3 Pt 1): L426-L434. (Support not reported. Authors affiliated with NIOSH; West Virginia University, WV.)
329. Ye J, Zeidler P, Young SH, Martinez A, Robinson VA, Jones W, Baron P, Shi X, Castranova V. 2001. Activation of mitogen-activated protein kinase p38 and extracellular signal-regulated kinase is involved in glass fiber-induced tumor necrosis factor-alpha production in macrophages. *J Biol Chem* 276(7): 5360-7. (Support not reported. Authors affiliated with NIOSH.)
330. Yegles M, Janson X, Dong HY, Renier A, Jaurand MC. 1995. Role of fibre characteristics on cytotoxicity and induction of anaphase/telophase aberrations in rat pleural mesothelial cells *in vitro*: Correlations with *in vivo* animal findings. *Carcinogenesis* 16(11): 2751-2758. (Support not reported. Authors affiliated with INSERM, France.)
331. Yeung P, Rogers A. 1996. A comparison of synthetic mineral fibres exposures pre- and post- the NOHSC national exposure standard and code of practice. *J Occup Health Safety - Aus & NZ* 12(3): 279-288. (Supported by the Insulation Wools Research Advisory Board and Worksafe Australia. Authors affiliated with Worksafe Australia, Australia.)

332. Youk AO, Marsh GM, Stone RA, Buchanich JM, Smith TJ. 2001. Historical cohort study of US man-made vitreous fiber production workers: III. Analysis of exposure-weighted measures of respirable fibers and formaldehyde in the nested case-control study of respiratory system cancer. *J Occup Environ Med* 43(9): 767-778. (Supported by the North American Insulation Manufacturer's Association. Authors affiliated with University of Pittsburgh, PA; Harvard School of Public Health, MA.)
333. Yu CP, Dai YT, Boymel PM, Zoitos BK, Oberdörster G, Utell MJ. 1998. A clearance model of man-made vitreous fibers (MMVFs) in the rat lung. *Inhal Toxicol* 10: 253-274. (Supported by Unifrax Corporation. Authors affiliated with State University of New York at Buffalo, NY; Unifrax Corporation, NY; University of Rochester, NY.)
334. Zeidler-Erdely PC, Calhoun WJ, Ameredes BT, Clark MP, Deye GJ, Baron P, Jones W, Blake T, Castranova V. 2006. In vitro cytotoxicity of Manville Code 100 glass fibers: effect of fiber length on human alveolar macrophages. *Part Fibre Toxicol* 3: 5. (Support not reported. Authors affiliated with NIOSH; University of Pittsburgh, PA.)
335. Zguris G, Windisch J, Svoboda P, Vulfson Y (2005). Glass Compositions. U.S. Patent and Trademark Office. United States of America, KVG Technologies, Inc.
336. Zhong BZ, Ong T, Whong WZ. 1997a. Studies on the relationship between treatment condition and micronucleus induction in V79 cells exposed to silica and glass fibers. *Mutat Res* 391(1-2): 111-116. (Support not reported. Authors affiliated with NIOSH.)
337. Zhong BZ, Whong WZ, Ong TM. 1997b. Detection of mineral-dust-induced DNA damage in two mammalian cell lines using the alkaline single cell gel/comet assay. *Mutation Research* 393(3): 181-187. (Support not reported. Authors affiliated with NIOSH.)
338. Zoitos BK, De Moringo A, Rouyer E, Thelohan S, Bauer J, Law B, Boymel PM, Olson JR, Christensen VR, Guldborg M, Koenig AR, Parender M. 1997. In vitro measurement of fiber dissolution rate relevant to biopersistence at neutral pH: An interlaboratory round robin. *Inhal Toxicol* 9: 525-540. (Support not reported. Authors affiliated with Unifrax Corporation, NY; Saint-Gobain Recherche, France; Johns Manville Corporation, CO; Rockwool International, Denmark; Center for Applied Engineering, FL; Paroc Oy Ab, Finland.)
339. Zoller T, Zeller WJ. 2000. Production of reactive oxygen species by phagocytic cells after exposure to glass wool and stone wool fibres - effect of fibre preincubation in aqueous solution. *Toxicol Lett* 114(1-3): 1-9. (Support not reported. Authors affiliated with German Cancer Research Center, Germany.)

Glossary of Terms

Acute: The clinical term is used for a disease having a short and relatively severe course. In rodent testing, usually pertains to administration of an agent in a single dose.

Adduct: A complex that forms when a chemical binds to a biological molecule such as DNA or a protein.

Adenocarcinomas: A cancerous tissue of epithelial origin.

Adenoma: An ordinarily benign neoplasm of epithelial tissue in which the neoplastic cells form glands or gland-like structures in the stroma.

Aerodynamic diameter: A physical property of a particle or fiber in a viscous fluid such as air. In general, particles have irregular shapes with actual geometric diameters that are difficult to measure. The equivalent aerodynamic diameter is defined as the diameter of a spherical particle of unit density which has the same terminal settling velocity in still air as the particle or fiber in question.

Allele: Any one of a series of two or more different genes that occupy the same position (locus) on a chromosome.

Alveolar/bronchiolar: Pertaining to the alveoli or bronchi of the lungs.

Ambient air: Outdoor air to which the general public is exposed.

Aneuploidy: One or a few chromosomes above or below the normal chromosome number.

Apoptosis: Cell deletion by fragmentation into membrane-bound particles which are phagocytosed by other cells.

Aromatic hydrocarbon: An organic chemical compound formed primarily from carbon and hydrogen atoms with a structure based on benzene rings and resembling benzene in chemical behavior; substituents on the rings(s) may contain atoms other than carbon or hydrogen.

Aspect ratio: The ratio of a fiber's length to its diameter.

Assay: A procedure whereby a property or concentration of an analyte is measured.

Batt: Precut panels of insulation available in a variety of widths, lengths, and R-values.

Benign tumor: An abnormal mass of tissue that does not spread and that is not life-threatening.

Bioaccumulation: The process by which a material in an organism's environment progressively concentrates within the organism.

Biodegradation: Biotransformation; the conversion within an organism of molecules from one form to another. A change often associated with change in pharmacologic activity.

Biodurability: The rate of removal of a fiber from the lungs by dissolution or disintegration.

Biopersistence: The ability of a fiber to remain in the lung. Biopersistence is a function of the fiber solubility and the biological ability of the lung to clear the fiber.

Bronchiolization: A process of migrating bronchiolar cells progressively colonizing alveolar spaces.

Bronchioloalveolar: Derived from epithelium of terminal bronchioles.

Bronchoalveolar lavage: A technique used to obtain a sample of the cells, fluids, and other materials present in the very small airways and alveoli of the lung by instilling saline into the airway via a bronchoscope.

Carcinoma: A malignant neoplasm of the epithelium.

Chromosomal aberrations: Any abnormality of a chromosome's number or structure.

Chronic: Continuing for a long period time. In rodent testing, pertains to dosing schedules of greater than 3 months.

Clastogen: Any substance which causes chromosomal breaks.

Clearance rate: The rate at which deposited particles are removed by various processes from the respiratory tract. Both the fiber's physical and chemical characteristics affect the clearance rate.

Confounding: A relationship between the effects of two or more causal factors observed in a set of data such that it is not logically possible to separate the contribution of any single causal factor to the observed effects.

Continuous glass filament: An extruded filament usually having a relatively large diameter (greater than 6 μm) and a very narrow range of diameter distribution.

Dehydrogenation: The removal of one or more hydrogen ions or protons from a molecule.

Density: The density for solids and liquids is expressed in grams per cubic centimeter (g/cm^3) and is generally assumed to refer to temperatures near room temperature unless otherwise stated. Values for gases are generally the calculated ideal gas densities in grams per liter at 25°C and 101.325 kPa.

Diffusion: One of four mechanisms of fiber deposition in the respiratory tract (see also impaction, sedimentation, and interception). Deposition by diffusion is especially important for smaller particles. As particles decrease in size, thermodynamic properties prevail over aerodynamic properties, and for particles $< 0.5 \mu\text{m}$, deposition and is governed mainly by the diffusional movement induced by Brownian motion of gas molecules.

Diffusion coefficient: The rate at which a substance moves from an area of high concentration to an area of low concentration.

Dissolution: The act or process of dissolving.

Durability: The ability to exist for a long time without significant deterioration.

Endogenous: Originating within an organism.

Epidemiology: A science concerned with the occurrence and distribution of disease in populations.

Epithelial: Relating to or consisting of epithelium.

Ferruginous body: A mineral particle to which pulmonary macrophages have added an iron protein coat. Ferruginous bodies are used as an indicator of exposure to specific dusts or fibers.

Fiber: A particle with a length to width ratio of at least 3:1

Flux: Another term used for a modifier in the glass wool manufacturing process. Typically, oxides such as magnesium oxide (magnesia, MgO), lithium oxide (Lithia, Li_2O), barium oxide (baria, BaO), calcium oxide (calcia, CaO), sodium oxide (soda, Na_2O) and potassium oxide (K_2O) are used as fluxes.

Fibroblasts: Connective tissue cells.

Genotoxicity: The amount of damage caused to a DNA molecule.

Glass fiber: General term that may be used to refer to reinforcing glass filament, glass wool, or superfine glass fiber.

Glass wool: A fibrous product formed by blowing or spinning molten glass. The resultant fibers are collected as a tangled mat of fibrous product.

Hematopoietic: Pertaining to the formation of blood or blood cells.

Half-life: The time required for a substance to be reduced to one-half its present value through degradation or through elimination from an organism.

Hodgkin's disease: A form of malignant lymphoma characterized by painless progressive enlargement of the lymph nodes, spleen, and general lymphoid tissue.

Homozygotes: An organism that has the same alleles at a particular gene locus on homologous chromosomes.

Hydrolysis: The chemical breakdown of a compound due to reaction with water.

Hydroxyl radicals: A particularly reactive, damaging type of free radical that is formed when superoxide radicals react with hydrogen peroxide.

ICD: The International Classification of Diseases. Published by World Health Organization, ICD codes are specific three-character codes used to describe a patient's health care condition.

Impaction: One of four mechanisms of fiber deposition in the respiratory tract (see also sedimentation, diffusion, and interception). Deposition by impaction occurs when the airflow encounters rapid changes in direction and the momentum of the fiber carries it along in a straight line to deposit on the airway wall. The larger the aerodynamic diameter, the greater the deposition efficiency due to impaction. This mechanism is most effective for aerodynamic diameters 0.5–1.0 μm .

***In vitro*:** Biological process taking place in a test tube, culture dish, or elsewhere outside a living organism.

***In vivo*:** Biological processes taking place in a living organism.

Interception: One of four mechanisms of fiber deposition in the respiratory tract (see also impaction, diffusion, and sedimentation). Deposition by interception occurs when an airborne fibre in the airway gets close enough to the airway wall to allow one end to touch the wall. For an elongated object such as a fibre, this occurs more readily than for a spherical particle, and thus, interception is a particularly important mechanism for fibre deposition, especially for longer fibers.

Intraperitoneal [i.p.] injection: Injection within the peritoneal cavity, i.e., the area that contains the abdominal organs.

Intrapleural injection: Injection within the serous membrane (pleura) investing the lungs.

Intrathoracic injection: Injection within the thoracic cavity, i.e., the area that contains the heart and lungs.

Intratracheal instillation: Instillation within the trachea.

k_{dis} : The dissolution rate (k) of a fiber is typically determined by elemental analysis of the flow-through solution to measure the mass of material leached from the fibers over a given time (ng/cm^2 per hour).

Leukemia: A cancer of the blood-forming tissues that is characterized by a marked increase in the number of abnormal white blood cells (leukocytes).

Lymphatic: A small sac or node in which lymph is stored; or pertaining to the lymph, lymph nodes, or vascular channels that transport lymph to the lymph nodes.

Lymphohaematopoietic: Of, relating to, or involved in the production of lymphocytes and cells of blood, bone marrow, spleen, lymph nodes, and thymus.

Lymphoma: A neoplasm of the lymphatic tissue.

Lymphosarcoma: Any of various malignant neoplastic disorders of lymphoid tissue; excluding Hodgkin's disease.

Macrophage: A large cell that is present in blood, lymph, and connective tissues, removing waste products, harmful microorganisms, and foreign material from the bloodstream.

Malignant: Tending to become progressively worse; life-threatening.

Mesothelioma: Cancer of the mesothelium a lining covering most internal organs.

Metabolism: The whole range of biochemical processes that occur within living organisms, consisting both of anabolism and catabolism (the buildup and breakdown of substances, respectively).

Metabolite: A substance produced by metabolism.

Micronuclei: Nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

Mineral wool: May refer to either slag wool or rock wool depending on the raw material from which it is produced.

Multiple myeloma: A malignant neoplasm derived from plasma cells and found at several locations in the body.

Necropsy: The examination of the dead body of an animal by dissection so as to detail the effects of the disease.

Necrosis: The pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage.

Neoplasm: An abnormal mass of cells.

Non-Hodgkin's lymphoma: A heterogeneous group of malignant lymphomas; the only common feature being an absence of the giant Reed-Sternberg cells characteristic of Hodgkin's disease.

Odds ratio: The odds ratio is a way of comparing whether the probability of a certain event is the same for two groups. It is often used as a statistical measure of the likelihood of developing a disease if a certain factor – such as exposure to an agent.

Parenchyma: The distinguishing or specific cells of a gland or organ, contained in and supported by the connective tissue, framework, or stroma.

Pledget: A small plug.

Resin: Any of numerous physically similar polymerized synthetics or chemically modified natural resins.

Respirability: The relative amount of airborne particles or fibers reaching the alveolar region of the lung.

Respirable fiber: These fibers can reach the deepest part of the lung. For humans, respirable fibers are defined as particles with a diameter less than 3 μm and length greater than 5 μm and with an aspect ratio of greater than 3:1. These fibers can reach the deepest part of the lung.

Respirable fraction: That portion of dust or fibers that can reach the lower, or gas exchange, part of the respiratory system.

Sarcoma: Cancer of connective tissue; can also refer to tumors in soft tissue.

Sedimentation: One of four mechanisms of fiber deposition in the respiratory tract (see also impaction, diffusion, and interception). Sedimentation refers to the settling of fibers due to gravitational forces, which eventually results in the fibers touching the airway wall and depositing on the epithelium. This mechanism operates mainly on fibers with aerodynamic diameters of 0.5–1.0 μm .

Sister chromatid exchange (SCE): The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

Slag wool: a fibrous product manufactured by blowing or spinning of a molten mass of metallurgical furnace slag.

Standardized Incidence Ratio (SIR): The ratio of observed to expected new incidences of a specific health outcome (e.g., cancer). The figure for expected incidence reflects the number of incidences for the larger population from which the study sample has been taken e.g., national level incidences.

Standardized Mortality Ratio (SMR): The ratio of observed to expected deaths to a specific health outcome (e.g., cancer). The figure for expected deaths reflects the number of deaths for the larger population from which the study sample has been taken e.g., national level of mortality attributed to a particular health outcome.

Stanton fibers: Fibers with length $> 8 \mu\text{m}$ and diameter $\leq 0.25 \mu\text{m}$.

Subacute: Between acute and chronic; denoting the course of a disease of moderate duration or severity. In rodent testing, usually pertains to a dosing schedule of less than one month.

Subchronic: In rodent testing, generally refers to a dosing schedule lasting from one to three months.

Subcutaneous injection: Injection beneath the skin.

Threshold limit value (TLV): The maximum permissible concentration of a material, generally expressed in parts per million in air for some defined period of time.

Time-weighted average (TWA): The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

Volatile: Quality of a solid or liquid allowing it to pass into the vapor state.

Xenobiotic: A pharmacologically, endocrinologically, or toxicologically active substance not endogenously produced and therefore foreign to an organism.

Z-score: The sum of the percent composition of alkali and alkaline earth oxides ($\text{Na}_2\text{O} + \text{K}_2\text{O} + \text{CaO} + \text{MgO} + \text{BaO}$).

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