Glass Wool Fibers Expert Panel Report

Part B – Recommendation for Listing Status for Glass Wool Fibers and Scientific Justification for the Recommendation

The Report on Carcinogens (RoC) expert panel for glass wool fibers exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, North Carolina on June 9-10, 2009, to peer review the draft background document on glass wool fibers exposures and make a recommendation for listing status in the 12th Edition of the RoC.

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The expert panel's recommendation for listing status and the scientific justification for their recommendation follow.

Overall Evaluation

Following a discussion of the body of knowledge, the expert panel reviewed the RoC listing criteria and made its recommendation. The expert panel recommended by a vote of 8 yes/0 no that glass wool fibers, with the exception of special fibers of concern (characterized physically below), should not be classified either as known to be a human carcinogen or reasonably anticipated to be a human carcinogen.

The expert panel also recommended by a vote of 7 yes/0 no/1 abstention, based on sufficient evidence of carcinogenicity in well-conducted animal inhalation studies, that special-purpose glass fibers with the physical characteristics as follows — longer, thinner, less soluble fibers (for

example, $\geq$ 15 μm length with a k_{dis} of $\leq$ 100 ng/cm^2/h) — are *reasonably anticipated to be a human carcinogen* for the listing status in the RoC.

The major considerations discussed that led the panel to its recommendation include the observations of tumors in multiple species of animals (rats and hamsters). Both inhalation and intraperitoneal routes of exposure produced tumors, although inhalation was considered more relevant for humans.

Section 2. Human Exposure

While it is difficult to rigorously define differences between fiber categories in quantifiable scientific terms, there are two categories of glass wool – that used for thermal insulation and that used for special products – that may have different toxicologic effects. Differences between these categories are evident in terms of fiber diameters, fiber chemistry and resultant durability, production methods, and levels of exposure; although no bright line distinction exists, with the possible exception of the differences in their ultimate use which has historically formed the basis of this distinction.

There is well-documented historic and current exposure information for manufacturing and end-user populations; these populations have been estimated to number from a low of 15,000 to upwards of 200,000 exposed persons in the United States. The overwhelming preponderance of the exposure data is related to the glass wool product category while exposure data for special purpose glass, which is produced at a volume approximately 1% of the glass wool products, are far fewer and more dated. In broad terms, glass wool manufacturing populations have been exposed to fiber concentrations in the range of hundredths to tenths of fibers/cm^3, generally as an 8-hour time weighted average; production of fibers that have been historically referred to as special purpose fibers have typically resulted in exposure levels 2 to 10 times higher. End user populations have been exposed in the range of tenths to single digit fibers/cm^3, generally expressed as a task-length average. Downstream uses of specialty product fibers are mostly limited to fabrication operations incorporating them into products: however, there are no published data on these exposures. The potential for very low-level general population exposure also exists, generally on the order of 10^{-5} to 10^{-3} fibers/cm^3.

Section 3. Human Cancer Studies

Several epidemiologic studies are available to evaluate cancer risks among workers with possible exposure to glass wool. Parts of the cohorts included persons exposed to specialty fibers but the workers were not specifically identified. These studies are all described in the background document. We relied most heavily on results from five cohort studies and one case-control study because they provided information on glass wool exposures (Table 1). Other studies may have included workers exposed to glass wool, but they did not provide direct evaluations of cancer risk among individuals specifically for that exposure. These studies varied in size, information on exposure, adjustments for possible confounders, and comparison populations, but they were all useful in the assessment of cancer and exposure to glass wool. The relevant studies provided considerable information on risk of lung cancer. Some information on other cancers was also available, but, except for mesothelioma, it was not sufficient to contribute to our evaluation and assessment.

Relative risks for lung cancer among workers potentially exposed to glass wool in these studies were 1.18 (95% CI, 1.04-1.34) among men in the U.S. cohort (Marsh *et al*. 2001), 1.02 (95% CI, 0.76-1.34) among women in the U.S. cohort (Stone *et al*., 2004), 1.27 (95% CI, 1.07-1.50) based on national mortality rates and 1.12 (95% CI, 0.95-1.31) based on local mortality rates in the European cohort (Boffetta *et al*. 1997), 1.28 (95% CI, 0.91-1.74) for cancer incidence in the

European cohort (Boffetta *et al*. 1999), 1.63 (95% CI, 1.18-2.21) for mortality and 1.63 (95% CI, 1.18-2.21) for incidence in the Canadian cohort (Shannon *et al*. 2005), and 0.74 (95% CI, 0.24-1.72) in a French cohort (Moulin *et al*. 1986). A case-control study of lung cancer in Russia reported a relative risk of 1.77 (95% CI, 0.57-5.51) among workers possibly exposed to glass wool (Baccarelli *et al*. 2006). A meta-analysis by Berrigan (2002) of respiratory cancer from 10 case-control studies and 10 cohort studies found an overall SMR of 1.23 (95% CI, 1.10-1.38) for glass wool. The meta-analysis included the cohort of Shannon *et al*. (2005), which appears to be an outlier, and included only national rates for the European cohort. Although Marsh *et al*. (2001) was able to perform some adjustment for possible confounding from tobacco use and asbestos exposure and Baccarelli *et al*. (2006) for tobacco use, other studies were unable to make such adjustments.

The small and rather consistent excesses of lung cancer observed in the studies above raise the possibility of a link between exposure to glass wool and development of lung cancer. Several limitations complicate interpretations for this assessment. Most studies could not adjust for possible confounders. The excesses of lung cancer observed in most of these studies are in the range that can easily be explained by confounding. These small excesses were not generally further supported by exposure-response trends, except for the study by Shannon *et al*. (2005), where the data showed increased risk with duration of exposure. Only the Marsh cohort provides quantitative estimates of exposure to glass wool (f/ml). We recognize that quantitative exposure assessment is difficult and prone to misclassification, which would tend to bias estimates of relative risks toward the null in cohort studies.

Mesothelioma is strongly linked to asbestos, and is extremely rare without this exposure. Unlike lung cancer, there is just one major established cause. The largest study in the U.S. showed that 88% of pleural mesothelioma in adult men was attributable to asbestos (Spirtas *et al.* 1994). The consequence of this is that for a subset of workers not known to have occupational exposure to asbestos, the "expected" numbers from the general population are gross overestimates, and the SMR for workers not known to be exposed to asbestos is underestimated. For this reason it is pertinent to identify if there are cases of mesothelioma with exposure to glass wool that were not known to have been exposed to asbestos. There are three studies identifying cases of mesothelioma not known to have been exposed to asbestos.

Marsh *et al.* (2001b) identified ten cases of mesothelioma with the word “mesothelioma” on their death certificates. Three had possible exposure to asbestos at the plants studied (one case 2.46 years, the second 0.38 years, and the third 2.18 fibers/cc months). The results of a questionnaire showed that five additional cases reported potential asbestos exposure at other job locations or within the glass wool industry. This leaves two cases with no known exposure to asbestos (Case 3 and Case 8). The mesothelioma diagnosis for Case 3 was questionable and there was no information concerning exposure to asbestos for the other case. In summary, there were no confirmed cases with a diagnosis of mesothelioma with work history indicating no potential exposure to asbestos.

Rodelsperger *et al.* (2001) studied 125 male cases of malignant mesothelioma in a case-control study in Germany. 114 cases had identified exposure to asbestos in their work histories. 2 cases and controls were exposed MMVF and 2 controls, giving an OR of 15.1 (95% CI = 1.05-218). In view of the difficulty in identifying occupational histories of exposure to asbestos, it remains possible that the 2 cases exposed to MMVF without known asbestos exposure actually had unidentified exposure to asbestos in the past. To place this in context, there were 53 cases with MMVF exposure that were found to have also had asbestos exposure. Engholm *et al.* (1987) studied approximately 135,000 construction workers in Sweden. Twenty-three cases of malignant mesothelioma were identified. Twelve of these cases were not identified as having had asbestos exposure, but there was no evidence that there was an increased risk of mesothelioma in the data presented for exposure to MMVF without asbestos exposure.

It should be noted that exposures in the glass wool cohorts were at least an order of magnitude lower than historical exposures for the asbestos cohorts that noted increases for lung cancer and mesothelioma (Armstrong *et al*. 1988, Levin *et al*. 1998, and Newhouse and Berry, 1985.)

Summary

There is insufficient evidence for the carcinogenicity of glass wool in humans. Despite small excesses of lung cancer in several studies, the less than complete adjustment for possible confounders and little evidence of exposure-response trends led us to conclude that these data do not provide credible support for a causal association. Careful evaluation of information on mesothelioma from these studies provides no evidence of confirmed cases with exposure to glass wool, but without exposure to asbestos.

Summary of findings from human cancer studies evaluating exposure to glass wool and lung or respiratory cancer

Study	Results: lung cancer and glass wool exposure Unadjusted Risk estimate (95% CI); exposed cases or death	Results lung cancer and glass wool exposure Adjusted risk estimate (95% CI); exposed cases or deaths	Comments
Cohort studies			
Marsh *et al.* 2001 (U.S. – males and females)	Mortality – SMR Local rates 1.18 (1.04-1.34); 243	Nested case-control study for lung and larynx in males only, RR adjusted for smoking *Plant type* Filament 1.0 (Ref) GW + F 1.01 (0.69-1.47); 356 GW 1.06 (0.71-1.60); 183 No trends for duration of employment, time or time since first employment	SMR for all SVF using national rates: 1.17 (95% CI = 1.09-1.25)
Stone *et al*. 2004 (U.S. – females)	Mortality – SMR (local rates) Lung 1.02 (0.76-1.34); 52 All causes 0.77 (0.72-0.82); 930	Internal analyses (RR): Multivariate model (model 3) includes formaldehyde exposure, cumulative exposure and duration of employment *Cumulative exposure (f/ml)* 1.0 (0.93- 1.07) *Plant type* Filament 1.0 GW + F 1.42 (0.76-2.65) GW 2.89 (1.07-7.78) *Employment duration* Years RR < 5 1.0; 27 5-9 2.30 (1.21-4.38); 16 10-19 0.80 (0.32-2.02); 6 20 + 0.63 (0.19-2.06); 4 Trend *P* = 0.02	Not adjusted for smoking

Study	Results: lung cancer and glass wool exposure Unadjusted Risk estimate (95% CI); exposed cases or death	Results lung cancer and glass wool exposure Adjusted risk estimate (95% CI); exposed cases or deaths	Comments
Boffetta *et al.* 1997 (European – males and females)	Mortality – SMR National rates 1.27 (1.07-1.50); 140 Local rates 1.12 (0.95-1.31); 140 *Employment duration* Years / SMR 1-4 1.11 (0.82-1.46); 50 5-9 1.18 (0.80-1.68); 30 10-19 1.68 (1.23-2.25); 45 20 + 1.17 (0.66-1.93): 15		Not adjusted for smoking
Boffetta *et al.* 1999 (European – males and females)	Incidence – SIR National rates 1.28 (0.91-1.74); 40	Internal analyses, RR adjusted for gender, age, country and technological phase *Employment duration + 15 year lag* Years / RR < 5 1.0 ref. 23 5-10 0.8 (0.3-2.0); 8 10-19 0.8 (0.3-2.4); 4 20+ 0.7 (0.08-5.3); 1	Not adjusted for smoking
Moulin *et al.* 1986 (French – males)	Incidence – SIR Local rates 0.74 (0.24-1.72); 5		No information on smoking
Shannon *et al.* 2005 (Canadian – males)	Mortality – SMR Local rates 1.63 (1.18-2.21); 42 *Employment duration* Years / SMR; deaths 0 1.50; 13 < 5 1.71; 4 < 10 1.39; 8 < 20 1.89; 17 20+ 1.89, $P < 0.05$ 20 + and > 40 time since first exposure 2.82 (95% CI 1.13-5.82); 7		No information on smoking
Case-control studies[a]			

Study	Results: lung cancer and glass wool exposure Unadjusted Risk estimate (95% CI); exposed cases or death	Results lung cancer and glass wool exposure Adjusted risk estimate (95% CI); exposed cases or deaths	Comments
Baccarelli *et al.* 2006 (Russian - males)		OR adjusted for smoking, age, residence and asbestos All (GW) 1.56 (0.49-5.02) OR adjusted for smoking, age, and residence All (GW) 1.77 (0.57-5.51); 10 *Average intensity* MAC OR (95% CI) < 75% 0.83 (0.16-4.18) ≥ 75% 3.61 (0.64-20.4) *Cumulative exposure* Score[b] OR (95% CI) < 5 1.79 (0.16-20.2) > 5 1.77 (0.49-6.36)	

Abbreviations: F=filaments, GW=glass wool, SVF=synthetic vitreous fibers, MAC= maximum allowable concentration, OR=odds ratio, RR=relative risk, SIR=standardized incidence ratio, SMR = standardized mortality ratio

[a] Only studies specific for GW are included; large case control studies by Pintos *et al.*, Bruske-Holfeld *et al.*, and Carel *et al.* are not included because they are based on all SVF, without discriminating for GW.

[b] Calculated as the product of average intensity score (ranging from 0.25 to 2.25) per total duration

Section 4. Animal Cancer Studies

Based on evaluation of long-term inhalation studies with glass wool fibers, the commercial use as designated in each study (insulation glass wool vs. special purpose fibers) was related to the carcinogenicity by this route of administration.

However, it is difficult to definitively separate these fibers into subcategories based on the criteria below.

1. Special Purpose Fibers vs. Insulation Glass Wool Fibers
According to the definition of special purpose fibers (SPF) provided in the Draft Background Document and in the Public comments, SPF contain specific elements such as Ba, Zn or Zr. This is not reported for several SPF fibers used in the animal experiments. SPF fibers are also supposedly more durable than a typical insulation glass wool. Moreover, there are some uncertainties. [For instance, Bayer B-1, B-2 are considered as SPF on page 6; classified as glass wool (GW) on page 196 (Table 5-1E). According to Table 1-4, on page 8, and Pott *et al*. 1991, they do not contain Ba, Zn or Zr. These elements are also not present in E-glass (E glass microfiber and JM104E), and JM753].

2. Physico-chemical subcategories
Criteria for separation of glass wool fiber into categories of insulation vs. special purpose fibers, especially concerning quantification of "durability" are not consistent. Physico-chemical properties related to carcinogenicity include surface properties, solubility and biopersistence. Surface properties were poorly investigated. Solubility, as assessed by Z-score does not discriminate carcinogenic and non-carcinogenic fibers. The significance of *in vitro* dissolution rate to the *in vivo* situation is difficult to extrapolate. Moreover, fibers prepared for animal experiments are treated to be respirable and may result in changes in their surface and physico-chemical properties.

3. Commercial subcategories
It is difficult to consider categories according to commercial labeled uses. While SPF and GW are commercialized for different purposes, there is a large diversity of chemical compositions, and those may vary with time, and diameters decrease as well. A commercial product may have different compositions. Subcategories according to uses may contain both glass wool and rock wool.

4. Mechanisms of carcinogenicity
Investigations of the mechanism of fiber carcinogenicity strongly suggest that physico-chemical properties are not sufficient to account for the carcinogenicity. Other variables including fiber dimensions, exposure dose and cumulative dose, contributed to the biopersistence.

Studies that are considered most informative for assessment of carcinogenic potential of insulation glass wool and special purpose glass wool fibers are those conducted by the inhalation route of exposure and are listed below. Studies conducted by other routes for insulation glass wool and special purpose fibers are also listed but results of those studies are of limited usefulness for predicting human risk for inhalation of fibers.

Glass wool fibers (insulation)
Inhalation studies

- There is evidence for carcinogenicity in rats based on an inhalation study by Mitchell *et al.* (1986) and Moorman *et al.* (1988) that showed an increased incidence of mononuclear-cell leukemia (MCL) in F344 rats exposed to Owens-Corning glass wool

fibers. However, there was no evidence of pulmonary or mesothelial carcinogenicity associated with inhaled fibrous glass.

- Subsequent studies (several citations, including: Bunn, *et al*. 1993; McConnell, *et al*. 1994; Hesterberg, *et al.* 1993, 1995, 1997, 1999) using the same F344 rat strain exposed to MMVF10 and MMVF11 fibers by the inhalation route did not report an effect on the incidence MCL and did not cause an increase in lung tumors/mesothelioma.
- Hamsters exposed to MMVF10a (McConnell *et al.* 1999 and Hesterberg, *et al*. 1997) by the inhalation route showed no increases in lung tumors/mesothelioma.
- A number of earlier studies (Schepers and Delahant, 1955; Schepers, 1974; Gross *et al*. 1970) conducted by the inhalation route in several species did not result in an increase in lung tumors/mesothelioma. However, because of the design, they were of limited value for assessment of carcinogenic potential of glass wool insulation fibers.

Other routes

- An intraperitoneal injection study (Grimm, *et al*. 2002) in female Wistar rats resulted in increased incidence of mesothelioma with experimental biosoluble glass wool fibers B, P, and V.
- Intraperitoneal injection studies (Miller *et al.* 1999 and Roller *et al*. 1996, 1997) in Wistar rats resulted in increased incidence of mesothelioma with MMVF10 and MMVF11.
- Intrathoracic injection of Osborne Mendel rats administered insulation glass wool fibers (Glass 15 and Glass 12) resulted in one mesothelioma in each group (Stanton, *et al*. 1977,1981).

Glass wool fibers (special purpose)

Inhalation studies

- Sufficient evidence for carcinogenicity in animals is based on increase in lung tumors and mesothelioma in Wistar rats with inhalation exposure to 104E (Cullen *et al.* 2000); and mesothelial hyperplasia and mesothelioma in hamsters exposed to MMVF33 (McConnell *et al.* 1999 and Hesterberg, *et al.* 1997).
- There is evidence for carcinogenicity in rats, based on an inhalation study by Mitchell *et al.* (1986) and Moorman *et al.* (1988), which showed an increased incidence of MCL in F344 rats exposed to Tempstran 100/475. However, there were no increases in lung tumors/mesothelioma in that study.

Other routes

- A carcinogenic effect (primarily mesothelioma) occurred in several studies in rats or hamsters administered special purpose glass fibers (475 glass, E glass, 753 glass, experimental fibers) by the intraperitoneal, intratracheal or intrapleural routes (Roller, *et al.*, 1996, 1997; Miller *et al*., 1999; Muhle, *et al.* 1987; Monchaux, *et al*.1981; Wagner *et al*. 1976, 1984; Pott *et al.* 1984, 1987; Stanton *et al.* 1977, 1981).

Summary of carcinogenicity studies of glass wool fibers in experimental animals (from Table 4-10 in Background Document)

Fiber type/source	Species	Exposure route				
		Inhalation	Intraperitoneal	Intratracheal	Intrathoracic	Intrapleural
Insulation wool						
	Rat (not specified)			–		
	Wistar		+			
	Sprague-Dawley					–
	Osborne-Mendel				±	
	F344	±[a]	–			
	Syrian golden hamster	–		–		
	Guinea pigs			–		
	BALB/c mice					–
	Rabbits			–		
SPF						
475 glass	Wistar	–	+	+		±
	Sprague-Dawley		+			+
	Osborne-Mendel		+	–		
	F344	+[a]	–			
	Syrian golden hamster	+[b]		±		
E glass	Wistar	+	+			
753 glass	Wistar		+			
Experimental fibers	Wistar		±			

– = negative studies; + = positive studies (unless otherwise noted, considered as a treatment-related effect for lung tumors, mesothelioma/sarcoma by study authors); ± = both positive and negative studies.

[a] These studies reported an increase in mononuclear cell leukemia, but no respiratory or mesothelial tumors. In one study (insulation glass wool), there was a trend for an increase in total lung tumors (P=0.047).

[b] The positive study reported mesothelial hyperplasia and one mesothelioma.

Comments on Table:

Glass wool fibers (insulation)

Inhalation studies

- F344 rats: Increased incidence of MCL with exposure to Owens-Corning glass wool fibers in males and females from two dose groups of different diameter/fiber length.
- F344 rats: No neoplastic effects with exposure to MMVF11 and MMVF10 fibers.
- Syrian golden hamster: No neoplastic effect with exposure to MMVF10a fibers

Other routes

- Wistar rats: A positive carcinogenic response in rats administered insulation glass fibers (B glass) by intraperitoneal injection.
- Osborne-Mendel: A weak positive response in rats administered insulation glass wools by intrathoracic injection.

Glass wool fibers (special purpose)

Inhalation studies

- Wistar rats: increased incidence of lung tumors and mesothelioma with exposure to 104E.
- Hamster: Increased incidence of mesothelial hyperplasia and mesothelioma with exposure to MMVF33.
- F344 rats: Increased incidence of MCL with exposure to Tempstran 100/475 (two dose groups of different fiber length but no apparent difference in incidence between groups)

Other routes

- Rats (F344, Sprague-Dawley, Osborne Mendel) and hamsters had increased incidence of mesothelioma when administered special purpose glass fibers (475 glass, E glass, 753 glass, experimental fibers) by the intraperitoneal, intratracheal or intrapleural routes.

Other issues to consider:

Study design (route of exposure) and the relevance to assessment of a carcinogenic effect with exposure to glass wool fibers (ability to establish/assess an MTD).

Specific criteria for separation of glass wool fibers into categories of insulation glass wool vs. special purpose fibers are not always consistent, especially concerning quantification of "durability".

Size and amount of fibers deposited in the lung should be taken into consideration in interpretation of the data, with the same attention as "durability".

Recommend limited evidence of carcinogenicity in animals for <u>insulation glass wool fibers</u> based on an increase in MCL in one strain of rats (F344) from a single study. In addition, there was a positive carcinogenic response in one strain (Wistar) of rats administered insulation glass wool by intraperitoneal injection and a weak positive response in one strain (Osborne-Mendel) of rats by intrathoracic injection. These additional studies were considered to represent non-physiological routes of exposure but provided informative results as screening tests for hazard assessment. Low tumor yield with insulation glass wool by the intracavitary routes was generally not associated with an increase in lung tumors if tested by the inhalation route.

Recommend sufficient evidence for carcinogenicity in animals administered special purpose glass fibers based on positive studies in rats and hamsters by the inhalation route. In addition, a carcinogenic response occurred in several strains of rats injected with special purpose fibers by the intraperitoneal, intrapleural and intratracheal routes. Positive responses also occurred in rats injected by the intrathoracic route and hamsters injected by the intratracheal route, but were considered to have limitations related to route of administration.

Section 5. Other Relevant Data

1. Glass fiber characteristics

Glass fibers may be physically (not by use) divided broadly into: 1) glass wools with relatively large diameters, high biosolubilities, and low biopersistence; and 2) special purpose fibers that are generally characterized by relatively smaller diameters, lower biosolubilities, and higher biopersistence.

The chemical compositions of these fibers (i.e., various metal oxides dissolved within the glass) contribute to the variability in biopersistence and biosolubility of the fibers. Relatively long fibers (approximately >15 μm) are important because macrophages have difficulty clearing fibers that are longer than the macrophage diameter and may result in death of the macrophage and release of inflammatory mediators. In order to provide some guidance to distinguish these two types of fibers, our review of the literature suggests that fibers with a k_{dis} of ≥ 100 ng/cm^2/h and lengths <15 μm are unlikely to be of particular concern.

2. Fiber deposition and retention

The deposition of fibers is determined primarily by their aerodynamic diameters with enhancement of deposition of fibers with lengths greater than 10 μm due to interception at the airway wall. Clearance and retention of deposited fibers are influenced by fiber length as discussed above. Retention is also influenced by fiber dissolution. Low biopersistent fibers would result in a net lower level of total accumulation in the lung, even with continued exposure, while more biopersistent fibers would result in continual accumulation in the lung with continued exposure. The ultimate steady-state number of fibers would increase as biopersistence increases.

3. Genotoxicity

The data indicate that fibers have the potential to cause genetic damage *in vitro*. However, extrapolation from these data to carcinogenicity is problematic.

4. Mechanistic data

Although the available data are not sufficient to define the exact mechanism(s), the data suggest that an underlying chronic inflammatory response is required. Experimental data indicate that long, biodurable fibers are likely to be accompanied by a chronic inflammatory response. There are no data to suggest that the proposed mechanisms are not relevant to humans.

[Redacted]

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Karl Kelsey, M.D., M.O.H., Chair Date

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