REVIEW ARTICLE

Perspectives on refractory ceramic fiber (RCF) carcinogenicity: comparisons with other fibers*

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Abstract

In 2011, SCOEL classified RCF as a secondary genotoxic carcinogen and supported a practical threshold. Inflammation was considered the predominant manifestation of RCF toxicity. Intrapleural and intraperitoneal implantation induced mesotheliomas and sarcomas in laboratory animals. Chronic nose-only inhalation bioassays indicated that RCF exposure in rats increased the incidence of lung cancer and similar exposures resulted in mesothelioma in hamsters, but these studies may have been compromised by overload. Epidemiological studies in the US and Europe showed an association between exposure and prevalence of respiratory symptoms and pleural plaques, but no interstitial fibrosis, mesotheliomas, or increased numbers of lung tumors were observed. As the latency of asbestos induced mesotheliomas can be up to 50 years, the relationship between RCF exposure and respiratory malignances has not been fully determined. Nonetheless, it is possible to offer useful perspectives. RCF and rock wool have similar airborne fiber dimensions and biopersistence. Therefore, it is likely that these fibers have similar toxicology. Traditional rock wool has been the subject of numerous cohort and case control studies. For rock wool, IARC (2002) concluded that the epidemiological studies did not provide evidence of carcinogenicity. Based on analogies with rock wool (read across), it is reasonable to believe that increases in lung cancer or any mesotheliomas are unlikely to be found in the RCF-exposed cohort. RCF producers have developed a product stewardship program to measure and control fiber concentrations and to further understand the health status of their workers.

Introduction

This article offers some fresh perspectives on the possible carcinogenicity of refractory ceramic fiber (RCF) with relevance to setting occupational exposure limits (OELs). It builds upon earlier work (Brown et al., 2005; Mast et al., 2000a; Utell & Maxim, 2010) seeking to understand the relevant toxicological and epidemiological data on this fiber. Briefly, we conclude that there are many similarities between RCF and traditional rock wool.[1] These fibers have similar

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[1]When administered in various animal tests this traditional rock wool was referred to as MMVF21. In the early 2000s, Rockwool International developed a less biopersistent fiber called HT wool (Kamstrup et al., 2002). Lower biopersistence rock wool has replaced traditional rock wool in Europe and Japan and is displacing traditional rock wool elsewhere. Rock/stone wool (included under CAS # 65997-17-3) also included under mineral wool is produced/sold in the United States according to various extant safety data sheets that specifically reference this CAS # and is also produced elsewhere in the world (e.g. China, Colombia and Pakistan) according to manufacturers' literature. HT-stone wool, the more soluble product has a different chemical abstracts service number (CAS # 287922-11-6).

dimensions (when airborne in the workplace), similar breakage mechanisms, and similar biopersistence. The results of intraperitoneal (IP) injection studies are similar for both fibers and a nose-only inhalation bioassay resulted in fibrosis and tumors for RCF and fibrosis, but no tumors for rock wool. Both fibers are included in epidemiological studies; to date the ongoing RCF study has not resulted in interstitial fibrosis, incremental lung cancer, or any mesothelioma. The RCF study is limited in terms of the size and exposure duration of the cohort, although the duration (and, therefore, ability to detect effects with greater latency) will increase in the future. However, the rock wool studies are much more powerful statistically and do not reveal any elevated SMRs for lung cancer or mesothelioma.

Background

RCFs (CAS no. 142844-00-6), also termed aluminosilicate wools (ASW) are amorphous fibers that belong to a class of materials termed synthetic vitreous fibers (SVFs), which also includes glass wool, rock (stone) wool, slag wool and special purpose glass fibers. Details on RCF composition and production methods are available in several sources (e.g. AFSSET, 2007; ATSDR, 2004; IARC 2002; National Research Council, 2000; NIOSH, 2006; SCOEL, 2011).

RCFs have several desirable properties as high-temperature insulating materials, including low thermal conductivity, low heat storage (low volumetric heat capacity), excellent thermal shock resistance, light weight, good corrosion resistance and ease of installation (ERM, 1995). Depending upon the formulation, the maximum use temperature can be as high as 1430 °C (ERM, 1995; NIOSH 2006; TIMA, 1993). For this reason, RCFs (and certain other fibers) are also termed high temperature insulating wools (HTIWs).

As produced or processed some RCF is respirable and RCF is relatively biopersistent compared to many other SVFs (but very much less biopersistent than amphibole asbestos). The combination of respirability and biopersistence raises concern over possible adverse health effects (including carcinogenicity) resulting from inhalation of RCF.

Carcinogen classification

In 1988, an IARC Working Group reviewed the available evidence for RCF and placed RCF in Group 2B (possibly carcinogenic to humans). This classification was reaffirmed by a subsequent Working Group meeting in 2001 (IARC, 2002), which concluded that there was *sufficient evidence* in experimental animals but *inadequate evidence* in humans for the carcinogenicity of refractory ceramic fibers.

In Europe, the 1997 Dangerous Substances Directive, RCF was listed as a Category 2 carcinogen based only on animal studies. The Dangerous Substances Directive is being phased out in favor of the new globally harmonized system. The phase-out process began with EC Regulation No. 1272/2008 of the European Parliament and the Council of 16 December 2008 on classification, labeling and packaging (CLP) of substances and mixtures. As part of the transition to the new CLP regulation, substance category labels under the Dangerous Substance Directive were "translated" into the CLP globally harmonized system, a new but equivalent scheme for classification and labeling in 2009. As a result, the old Category 2 Carcinogens are now automatically classified as Category 1B carcinogens which are substances "presumed to have carcinogenic potential for humans, classification is largely based on animal evidence".

The Scientific Committee on Occupational Exposure Limits (SCOEL, 2011) classified refractory ceramic fibers as a secondary genotoxic carcinogen and supported a practical threshold. Inflammation was considered the predominant manifestation of RCF toxicity.

Potential health effects associated with RCF exposure have been assessed using both experiments on laboratory animals and epidemiological studies (morbidity and mortality) of cohorts occupationally exposed to RCF. Other relevant information includes studies on the dimensions of airborne fibers in the workplace and *in vitro* and *in vivo* studies on dissolution/biopersistence.

Results of the animal studies are widely regarded as evidence of RCF carcinogenicity. Utell & Maxim (2010) provide a short history of the results of the animal studies conducted from the late 1950s until the present. Perhaps of greatest potential relevance to carcinogen classification for RCF are the results of chronic nose-only inhalation bioassays on rats and hamsters conducted by RCC in Geneva

(Mast et al., 1995a,b; McConnell et al., 1995), which indicated RCF-exposed rats and hamsters developed fibrosis and tumors. As noted above, an IARC Working Group has reviewed the available evidence and concluded on two occasions that, on balance, there was sufficient evidence of carcinogenicity in experimental animals. Nonetheless, interpretation of the available animal studies is not straightforward. The RCC studies were believed to be the "state of the art" at the time. However, subsequent analysis of these studies concluded that overload was likely (Mast et al., 2000a,b) – chiefly due to a high and non-representative amount of particles in the exposure aerosol (Maxim et al., 1997) – and it was not possible to assess the relative contribution of these particles to the observed response (Brown et al., 2005, references therein). The IARC Working Group acknowledged possible confounding (IARC, 2002, p. 233):

> "The Working Group noted that the greater particulate fraction of RCF 1 could have influenced the development of inflammation and subsequent carcinogenic response in the chronic inhalation studies of RCF 1. The extent of this influence is difficult to assess quantitatively".

As noted above, several epidemiological studies of occupational exposure to RCF have been conducted in both Europe (at the Institute of Occupational Medicine [IOM]) and the United States (at the University of Cincinnati) as part of a comprehensive product stewardship program [PSP] (Maxim et al., 2008 for details) designed to detect, measure and control risks associated with occupational exposure to RCF. These morbidity and mortality studies have been extensively reported in the peer-reviewed literature (Burge et al., 1995; Cowie et al., 2001; LeMasters et al., 1998, 2003; Lockey et al., 1996, 1998, 2002; McKay et al., 2010; Trethowan et al., 1995; Utell & Maxim, 2010; Walker et al., 2002, 2012a,b). Collectively, these studies indicate that occupational exposure to RCF results in:

- Respiratory symptoms (LeMasters et al., 1998) similar to those reported in other dust-exposed populations,
- A statistically, but not clinically, significant decrease in certain measures of respiratory function in one cross-sectional study (LeMasters et al., 1998) for certain subgroups (e.g. male current or former smokers). A further longitudinal study (Lockey et al., 1998) revealed no excessive decline in lung function.
- A statistically significant increase in the prevalence of pleural plaques (Lockey et al., 1996, 2002), but no evidence of parenchymal disease and
- No evidence of increased deaths from lung cancer or any cases of mesothelioma (LeMasters et al., 2003).

In sum, the available epidemiological data indicate that symptoms are similar to other dust-exposed populations; there is some evidence for decreases in certain measures of lung function, a dose-related increase in pleural plaques, but no interstitial fibrosis, no elevated lung cancer rates and no mesotheliomas.

When IARC reviewed the available epidemiological data on RCF in 2002, they concluded that these data were "inadequate", in part based on the limited size and (at the

time) relatively short exposure duration of the cohort in the mortality study. The number of persons in the cohort places limits on the statistical power of the results and the exposure duration needs to be considered in terms of the latency for various lung diseases (see below). The mortality study is ongoing, however, and will become more powerful in the future.

SCOEL (2011) addressed the question of whether or not RCF was genotoxic to assess whether or not it might have a threshold. This Committee concluded that genotoxic effects noted in some studies were secondary and used some of the epidemiology data (lung function data) to derive a no observed adverse effects level based on cumulative exposure over a 45-year working lifetime. Based on these calculations, SCOEL recommended an OEL of 0.3 f/ml. The Health Council of the Netherlands (DECOS, 2011) also reviewed the available data on RCF and concluded:

> "Overall, the Committee considers the induction of chronic inflammation as the most plausible mechanism of carcinogenic action of RCFs. This would imply a threshold mechanism of action. In addition, it is unlikely that RCFs possess stochastic genotoxic properties via direct production or reactive oxygen species, due to the very low iron content. However, the Committee emphasizes that the relevance of genotoxicity testing for fibers is limited due to a lack of *in vitro* assays suitable for fibres''.

Although the epidemiological data on RCF are limited, other SVFs have been the subject of much more powerful studies. In particular, rock wool has been extensively studied and these studies (see discussion below) are properly viewed as negative, so it is of interest to make some comparisons between RCF and rock wool.

Other relevant fiber properties

Most scientists subscribe to the so-called 3Ds (dose-durability-dimension) theory of fiber toxicity (Dement, 1990; Donaldson & Tran, 2004; Maxim et al., 2006; Oberdörster, 2000; Oberdörster et al., 2005). The importance of dose is obvious. Fiber dimensions are relevant for two reasons:

- Fiber *diameters* are relevant because diameters affect the *respirability of fibers*. Broadly, fibers with diameters greater than 3 microns (µm) do not penetrate the deep lung. What is relevant here is the distribution of fiber diameters as found in or near the breaching zone of those exposed, not the diameters of the bulk fibers.
- Fiber *lengths* are potentially relevant because there is evidence that longer fibers (at least those longer than approximately 20 µm)[2] *are potentially more toxic because these are too large to be fully engulfed by macrophages*. As noted by ATSDR (2004):

> "Fibers with diameters greater than about 3 µm are not inhaled into the deepest regions of the lungs. Fibers with lengths greater than about 15–20 µm are not engulfed by macrophages, and are more likely to lead to lung injury

than shorter fibers that are more readily removed by macrophages''.

There is a substantial body of literature from both animal experiments and epidemiological studies with asbestos and other fibers that supports the idea that longer fibers are likely to be more toxic than shorter fibers (Berman & Crump, 2008; Berman et al., 1995; Bernstein, 2007; Bernstein et al., 2001a,b; Bolton et al., 1982, 1984; Davis & Jones, 1988; Davis et al., 1986; Dodson et al., 2003; Heintz et al., 2010; Lippmann, 1990; Miller et al., 1999; Pott et al., 1974; Schinwald et al., 2012; Stanton et al., 1977; Stayner et al., 2007; and references therein). There may or may not be a unique "bright line" separating more from less toxic fibers, but the evidence suggests that longer than around 10–20 µm (Schinwald et al., 2012, estimate a shorter critical length) are more toxic if they are also respirable and biopersistent.

The ability of the fiber to remain in the lung, termed durability if measured in *in vitro* studies, or biopersistence if measured in *in vivo* studies has also been found to be a key determinant of fiber toxicity (ATSDR, 2004; Bernstein et al., 2001a,b; Eastes & Hadley, 1994; Eastes et al., 1996; Hesterberg et al., 1994, 1998; ILSI Working Group, 2005; McConnell, 2000; Maxim et al., 2006; Moolgavkar et al., 2000, 2001a,b,c; Oberdörster, 2000).

- Dissolution rates are measured in *in vitro* studies in simulated lung fluid. These rates are quantified by a kinetic constant for dissolution, K_{dis}, typically measured in units of nanograms per square centimeter per hour ($ng/cm^2/h$).
- Biopersistence is measured *in vivo* in studies of laboratory animals. The recommended standardized *in vivo* protocol uses short term (5-day, 6 h/day) inhalation exposures of Fischer 344 rats to a well characterized (length and diameter distribution) fiber aerosol with at least 100 fibers per milliliter (100 f/ml) greater than 20 microns (µm) long, followed by a post-exposure period during which animals are sacrificed at intervals of (at least) 1 day, 2 or 3 days, 14 days, 4 weeks and 3 months and fiber lung burdens determined. Alternatively, repeated intra-tracheal applications of small doses can be used. The weighted halftime ($WT_{1/2}$) for fibers $\geqq 20$ µm long (calculated from one- or two-compartment models) is taken as the relevant measure of biopersistence. Studies show (Maxim et al., 2006, references therein) that there is very good correlation between K_{dis} and $WT_{1/2}$ for various synthetic vitreous fibers (SVFs) and, as or more important, excellent correlation between either of these measures and the results of chronic animal bioassays.

Fiber chemistry is also relevant, particularly as chemistry affects biopersistence. Based on the 3D model, it is likely that fibers with similar airborne fiber dimensions and similar biopersistence are likely to have similar toxicological properties. The next sections compare dimensions and biopersistence of RCF with rock wool fibers.

Fiber dimensions

Critical fiber dimensions are fiber diameter and length. As part of the product stewardship program for RCF,

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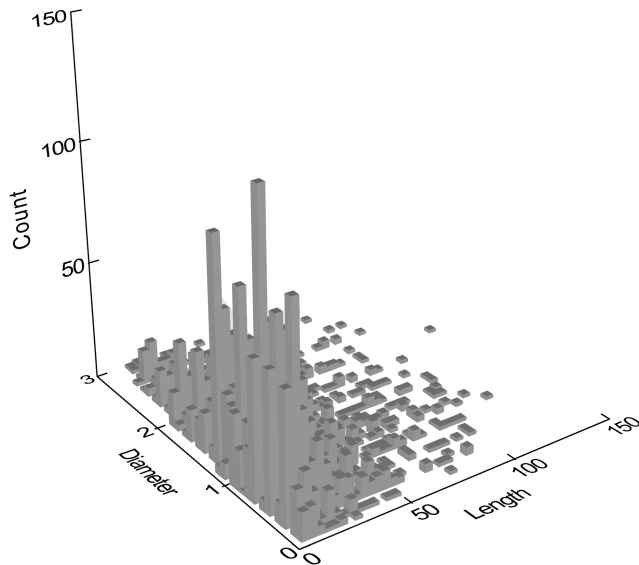[2]Krombach et al. (1997) estimate the average size of a human macrophage is approximately 21.2 ± 0.3 µm.

Figure 1. Diameter and length distribution of 4031 airborne respirable RCF fibers from workplace samples.

Table 1. RCF fiber diameter and length data.

Number of fibers	4031 Diameters (µm)	4031 Lengths (µm)
Minimum	0.070	5.000
Maximum	3.000	138.000
Range	2.930	133.000
Geometric mean	0.911	17.406
Median	1.000	16.670
Arithmetic Mean	1.091	22.428
Std. Error	0.010	0.285
Standard Dev	0.616	18.088
Variance	0.379	327.189
Coefficient of variation (CV)	0.565	0.807
Skewness (G1)	0.755	2.071
SE Skewness	0.039	0.039
Kurtosis (G2)	0.011	5.131
SE Kurtosis	0.077	0.077

manufacturers collect fiber concentrations at plants that produce RCF and facilities operated by their customers. Most of these are analyzed using phase contrast optical microscopy (PCOM) and concentrations determined using either NIOSH 7400 B or WHO counting rules. For various research purposes these personal monitoring samples are analyzed using transmission electron microscopy (TEM) and the fiber lengths and diameters are measured. Figure 1 shows a histogram of the joint distribution of lengths and diameters of 4031 airborne respirable RCF fibers using NIOSH 7400 B counting rules.[3] As can be seen, the combination of the fiberization process and subsequent dispersion (settling) of fibers in the workplace leads to a very broad distribution of airborne respirable fiber diameters and lengths.

Measured airborne respirable RCF fiber diameters range from 0.07 to 3.0 microns (µm) and lengths that range from 5.0 (the threshold length requirement for both NIOSH 7400 B and WHO counting rules) to 138 µm.

Table 1 provides summary statistics on airborne respirable RCF fiber lengths and diameters. Note that the respirable fiber diameters are ≤3 µm, the limit of respirability, and lengths all ≧5 µm in accordance with NIOSH 7400 B counting rules.

The statistics shown in Figure 1 and Table 1 are airborne (from personal monitoring samplers) respirable fibers, not bulk fibers. Airborne fibers are relevant in terms of human exposure. Size distributions of bulk and airborne fibers differ. Diameters of airborne fibers are typically smaller than the bulk fiber (Schneider et al., 1983) due to the effects of settling and ventilation. As noted by Schneider et al. (1983):

"When the fibers are dispersed into the air during handling, cutting, etc. only thin fibers will remain airborne.

It is a general experience that the measured median diameter in an air-sample is consistently and substantially smaller than the nominal diameter of the product''.

Christensen et al. (1993) reported the diameters of bulk RCF ranged from 2.4 to 3.8 µm (as measured by scanning electron microscopy), depending upon product (higher for spun than blown blanket). However, once airborne the structures with greater diameters settle out preferentially, leaving the size distribution of the airborne structures shifted downwards towards fibers with smaller diameters as shown in Table 1. The diameter distribution data shown here are for a mixture of RCF products as produced and used in the workplace and include both blown and spun fibers. The sections provided below provide comparable data for rock wool fibers.

Fiber diameter comparisons

Comparisons of airborne respirable RCF and rock wool fiber dimensions as reported in several studies are given below. Generally speaking, the diameters of *bulk* RSW (rock/slag wool) products are greater than those for RCF (IARC, 2002), but as noted above, the relevant comparison is between *airborne* fiber dimensions.

Corn et al. (1976) measured fiber concentrations in two rock wool plants using the spinning process. They did not report the mean or median diameters of the airborne fibers, but from the data presented on the percentage of fibers with diameters <1 µm and <3 µm, it is clear that this interval included the median diameters. The true median diameters of the respirable fibers are likely to be significantly less than 3 µm as the samples included fibers with diameters of as much as 7 µm, which would not be respirable.

Esman et al. (1979) measured fiber concentrations and dimensions in 16 facilities producing manmade mineral fibers. Among these plants 2, 5, 7, 11 and 13 produced RSW with nominal diameters ranging from 5 to 8 µm. The median diameters of the airborne fibers were less than the nominal diameters and ranged from ~0.5 to ~1.5 µm, a range that brackets that for RCF shown in Table 1.

Robinson et al. (1982) conducted an epidemiological and environmental study of rock and slag mineral wool production workers was undertaken at a plant that has been in operation since the early 1900s (using the spinning process).

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[3]These rules count all structures with length ≥5 microns, diameter ≤3 microns and aspect ratio (ratio of length to diameter) ≥5:1 as respirable fibers. WHO conventions use an aspect ratio cutoff of 3:1.

Table 2. Parameters of the size distribution of rock wool reported by Schneider et al. (1985).

Site	Number of samples	Geometric mean diameter (μm)	Geometric standard deviation	Geometric mean length (μm)	Geometric standard deviation
Rock wool Plant A	6	0.95	3.1	13	3.4
Rock wool Plant B	38	0.99	3.3	14	3.6
Use of Rock wool	21	1.20	2.7	22	4.0

Table 3. Comparison of fiber diameters (microns) for RCF and rock wool from different sources.

Fiber	Geometric mean diameter	Median diameter	Arithmetic mean diameter	Source	Comments
RCF	0.91	1.00	1.09	Table 1	
Rock/Slag wool		<3		Corn et al. (1976)	Median overstated because non-respirable fibers counted.
		0.5–1.5		Esmen et al. (1979)	Median values vary with nominal diameter of bulk fibers.
		2.2		Robinson et al. (1982)	Single plant using spinning process measured by PCOM.
	0.95–1.2			Schneider et al. (1985)	Reported values vary with plant and process.
		1.2–2		Cherrie et al. (1986)	Median diameters varied with plant.
			1.0	Krantz (1988)	Mean diameters ranged from 0.57 to 1.77 μm among ten plants.
	0.3–1.9			IARC (2002)	Range from various studies cited in this publication.
		1.12	1.27	Campopiano et al. (2012)	SEM measurements on workers installing ceiling panels.

These investigators measured fiber diameters and lengths using PCOM. (Because the practical limit of detection for PCOM is ∼ 0.2 μm, this will tend to overstate diameters.) The reported median diameter was 2.2 μm. Although this is larger than that shown above for RCF, the discrepancy is partially accounted for by the fact that the rock wool was spun (not blown) and PCOM was used.

Schneider et al. (1985) measured respirable airborne fiber dimensions of rock and glass wool. Table 2 shows the relevant diameter measurements for rock wool.

These diameters (and lengths) are generally comparable to those for RCF (Table 1). For example, the geometric mean diameter and length from the RCF data set are 0.91 and 17 μm, respectively.

Cherrie et al. (1986) reported results of fiber monitoring at European glass and rock wool plants. Among other things, this article presents data relevant to the distribution of fiber diameters and lengths. Median diameters of rock wool samples (p 21) ranged from 1.2 to 2.0 μm.

In a 1988 study sponsored by the Swedish Work Environmental Fund, Krantz provided exposure measurements of manmade mineral fibers (both glass wool and rock wool) from ten production plants in Sweden. In addition to fiber concentration measurements, Krantz (1988) used scanning electron microscopy (SEM) data on the lengths and diameters of glass and rock wool fibers. With respect to fiber diameters, Krantz (1988) reported the mean diameter of airborne respirable rock wool insulation fibers to be 1.0 μm, with a range from 0.57 to 1.77 μm. Note from Table 1 that the median and arithmetic mean diameters for RCF are 1.0 and 1.09 μm, respectively, which closely matches the Krantz (1988) measurements for rock wool. In accordance with expectation, the arithmetic mean and median diameters for airborne respirable rock wool fibers were substantially smaller than the nominal diameter (5–7 μm) of the bulk rock wool fibers.

The IARC (2002) Working Group that reviewed various mineral fibers summarized data on the dimensions of airborne respirable rock wool fibers from several papers. Geometric mean diameters for rock wool varied among the papers cited from 0.3 to 1.9 μm, depending upon the study.

Kauffer et al. (2003) reported on a study of various instrumental techniques for measuring airborne fiber concentrations. They used a dust-generating device to generate clouds of various types of fibers, including rock wool. The measured geometric diameter of the rock wool fiber in this study was 0.34 μm, which is considerable smaller than that for RCF. This study is of limited utility for comparative purposes because the fiber clouds were artificially generated and are not necessarily representative of those in the workplace.

More recently, Campopiano et al. (2012) studied personal monitoring samples of airborne fiber concentrations of pressed mineral panels employed as false ceilings. Four workers were investigated for eight working days. As part of this study, SEM was used to measure the diameters and lengths of these fibers. Airborne respirable mineral wool fiber diameters measured in this study ranged from 0.1 to 2.7 μm, with reported (sample size not specified) arithmetic mean and median diameters of 1.27 and 1.12 μm, respectively. These diameters are not materially different from those given above for RCF.

Table 3 summarizes the studies reported above in terms of RCF and rock wool diameters. Collectively, these indicate that, notwithstanding differences in the diameters of bulk RCF and rock wool, the airborne diameters are quite similar. For comparison, fiber diameters of various types of asbestos are very much smaller (typically very much thinner than

Table 4. Comparison of fiber lengths for RCF and rock wool from different sources.

Fiber	Geometric mean length	Median length	Arithmetic mean length	Source	Comments
RCF	17.4	16.7	22.4	This study	See Table 1.
Rock/Slag wool		~20		Corn et al. (1976)	Values shown are approximate.
		12–30		Esmen et al. (1979)	Median values are approximate as read from graph.
		16		Robinson et al. (1982)	Single plant using spinning process measured by PCOM.
	13–22			Schneider et al. (1985)	Reported values vary with plant and process.
		10–20		Cherrie et al. (1986)	Median lengths varied with plant.
		10–30		Krantz (1988)	Range is approximate as read from graph.
	7–22			IARC (2002)	Range from various studies cited in this publication.
	27.77	28.05	37.52	Campopiano et al. (2012)	SEM measurements on workers installing ceiling panels.

0.5 μm; ATSDR, 2001; Cheng, 1986; Gibbs & Hwang, 1980; Hwang, 1983; Rood & Streeter, 1984; Verma & Clark, 1995).

Fiber length comparisons

Lengths of airborne respirable rock wool fibers have also been measured by several investigators. Table 4 provides a summary in similar format to Table 3. As can be seen, RCF fiber lengths are broadly similar to those reported for RSW. Rock wool fiber lengths reported by Campopiano et al. (2012) are longer than those measured for RCF, but this difference may not be material because fiber potency may not increase materially beyond a certain length. If this conjecture is not correct, then the possible potency of might be greater than that for RCF based on length.

Fiber concentrations

Workplace fiber concentrations vary *inter alia* with the fiber type, plant, type of work being done, the engineering (e.g. general and local exhaust ventilation) and workplace controls in use, and whether or not respirators are worn and, if so, the assigned protection factor). Several authors have reported on fiber concentrations at plants producing rock or slag wool (Cherrie et al., 1986; Corn et al., 1976; Esman et al., 1979, 1982). For the most part, fiber concentrations at MMVF plants were reportedly <0.5 f/ml (Esman et al., 1979) and more recently (Cherrie et al., 1986) perhaps <0.1 f/ml. Fiber concentrations at RCF plants have been systematically monitored at both manufacturing plants and customer locations as part of a product stewardship program for more than 20 years (Maxim et al., 2008). Weighted average (by number of workers in each functional job category) fiber concentrations at manufacturing facilities in recent years are approximately 0.2 f/ml (0.3 f/ml at customer facilities).

Biopersistence

As noted above, biopersistence is a key determinant of fiber toxicology. Deposited fibers are cleared from the deep lung by dissolution, breakage, and clearance by macrophages. *In vitro* studies measure rates of dissolution, whereas *in vivo* measurements capture all three ways that fibers are removed. Although studies show that *in vitro* and *in vivo* measurements are correlated, *in vivo* measurements (particularly those taken using standard protocols, such as short-term inhalation studies on rats) are preferred. The most relevant measure of biopersistence is the weighted half time, $WT_{1/2}$ of fibers

$\geqq 20$ μm in length as calculated from a one compartment or two compartment model. Measured values of $WT_{1/2}$ range from just a few days for very low biopersistence fibers, such as wollastonite and certain glass wools, to 1000 or more days for some forms of amphibole asbestos.

The measured *in vitro* durability (K_{dis}) constant for rock wool is larger than that measured for RCF and also that there is good correlation between *in vitro* and *in vivo* measures. For example, data provided in Guldberg et al., 1998, report values for K_{dis} of 47 and 24 ng/cm^2 h for MMVF21 and RCF, respectively, at a pH of 4.5 and 23 and 8 ng/cm^2 h for MMVF21 and RCF, respectively, at a pH of 7.4. These data alone would argue that RCF is more durable than MMVF21, although the difference in K_{dis} values is relatively small when compared to the likely error of the measurement.

However, where available, *in vivo* measures of biopersistence ($WT_{1/2}$ values) are preferable as these more closely mimic the various processes by which fibers are removed (removal by macrophages, dissolution and breakage). Therefore, for example, the EU Directive 97/69/EC, dated 5 December 1997, provides a system, through Nota Q, for demonstrating that mineral wool fibers can be exonerated from carcinogenicity and not be classified as a hazardous substance. Nota Q allows for exoneration by any one of four methods. The four methods are: short-term biopersistence test by inhalation, short-term biopersistance test by intra-tracheal instillation, an appropriate intra-peritoneal test or a long term inhalation test. These criteria are all based on *in vivo*, rather than *in vitro* data. Because we have extensive data on $WT_{1/2}$ values for both fibers, we have used these for comparison.

Rock wool

Traditional rock wool (referred to as MMVF21 or in one study, "fiber L") $WT_{1/2}$ values have been measured in several studies (see, e.g. results reported in Bernstein et al., 1996, 2001a,b; Hesterberg et al., 1996, 1998; HVGB, 1998; Kudo & Aizawa, 2008; Musselman et al., 1994). Measured $WT_{1/2}$ values vary among the studies, with an arithmetic mean value of approximately 59 days. [This is slightly lower than the value cited in Maxim et al. (2006) 62.5 days, because additional and more recent measurements are included.]

The specific chemical composition of MMVF21 is given in Hesterberg et al. (1998); the five largest components in terms of weight percent are SiO_2, 45.9%; CaO, 17%; Al_2O_3, 13.75%; MgO, 9.5%; and Fe_2O_3, 6.9%. The corresponding percentages for the similar fiber L are given in

Bernstein et al. (1996) as SiO_2, 46.3%; CaO, 10.04%; Al_2O_3, 13.5%; MgO, 9.1%; and Fe_2O_3, 13.2%.

RCF

RCF $WT_{1/2}$ values have also been measured in several studies (see reported results in Bernstein, 1997a,b; Bernstein et al., 1997, 2001a,b; Hesterberg et al., 1998; HVGB, 1998). These $WT_{1/2}$ values range from 41 to 64 days with an arithmetic mean of approximately 50 days.

Similarities in fiber dimension and biopersistence

The difference between the $WT_{1/2}$ values of 50 and 59 days for RCF and traditional rock wool is neither statistically significant nor material. Therefore, for practical purposes, rock wool and RCF can be regarded as having similar biopersistence. And, although both fibers have half times greater than several other SVFs, both fibers are very much less biopersistent than various types of amphibole asbestos including amosite ($WT_{1/2} = 418$ days, Hesterberg et al., 1998), crocidolite ($WT_{1/2} = 817$ days, Hesterberg et al., 1998) or tremolite ($WT_{1/2} \cong \infty$; Bernstein & Hoskins, 2006; Bernstein et al., 2003). In addition, as noted above, breathing zone samples of these two fibers have similar dimensions. These comparisons suggest that RCF and rock wool are likely to have similar toxicological properties as well.

Fiber breakage mechanism similarities

As noted above, fibers undergo various changes when deposited in the lower regions of the lung, including breakage, dissolution and removal by macrophages. The mechanism of fiber breakage is a potentially relevant property because some fibers, such as chrysotile asbestos break along the longitudinal axis, creating additional fibers of smaller diameter. However, because they are amorphous (i.e. non-crystalline), neither rock wool nor RCF have cleavage planes that cause them to split lengthwise into fibers with smaller diameters. Rather, these break transversely (across the fiber), resulting in fibers which are of the same diameter as the original fiber but shorter (thus more easily removed by macrophages), together with a small amount of dust (Assuncao & Corn, 1975; IARC, 2002; NIOSH, 2006).

Animal studies

Both RCF and rock wool have been included in several animal (intraperitoneal injection and inhalation) studies. Similarities and differences are reviewed below.

Similarities in animal studies

Animal tests results also indicate that effects of exposure to RCF and rock wool are similar. Although intraperitoneal (IP) injection studies have been criticized because they are not a normal physiological route of exposure, IP studies are sometimes used to provide an indication of potential hazard. IP injection studies on rats and hamsters indicated that RCF was capable of inducing tumors (Davis et al., 1984; Miller et al., 1999; Pott et al., 1987; Smith et al., 1987). Similarly, IP studies of various rock wool fibers, including MMVF21,

have produced tumors in experimental animals (Pott et al., 1987; Roller et al., 1996). The Roller et al. (1996) study estimated the dose (in 10^9 fibers of l/d > 5 and d < 2 μm) necessary to produce a 25% tumor risk as 0.032×10^9 fibers and, on the basis of this measure, concluded that MMVF21 was intermediate in toxicity between crocidolite (0.012×10^9 fibers) and tremolite (0.064×10^9 fibers) asbestos – a result inconsistent with available epidemiological evidence on rock wool. Roller et al. (1996) did not estimate a corresponding value for RCF.

Rödelsperger (2004) used a model devised by Berry (1999) to explain how results might differ between animals and humans. Specifically, Rödelsperger (2004) noted:

> ''The carcinogenic potency of crocidolite and ceramic fibers from inhalation and intraperitoneal injection in rats is similar. However, it cannot be predicted, that this similarity likewise exists for humans, despite of differences in fiber size and bio-persistency. Rather the consequences of the dissolution rates may be quite different for humans and rats''.

Differences in animal studies

Well-designed chronic inhalation studies are thought preferable to other animal studies for risk assessment and both RCF and MMVF21 have been evaluated in these studies. The RCF studies (Mast et al., 1995a,b) resulted in the development of both fibrosis and tumors, whereas the MMVF21 study (McConnell et al., 1994) resulted in fibrosis, but no tumors – a potentially relevant difference. The RCF and MMVF21 rat studies were conducted using a similar protocol and at the same laboratory (Research and Consulting Company then of Geneva, Switzerland) and used similar experimental conditions.[4] For example, similar gravimetric doses were used (nominal values of 0 through 30 mg/m^3) and similar aerosol fiber concentrations (ranging from 0 to approximately 200 f/cc of WHO fibers[5]). After 24 months exposure, lung burdens (in fibers per milligram of dry lung) at the high dose (30 mg/m^3) were approximately 242×10^3, 177×10^3 and 275×10^3 for rock wool, slag wool and RCF, respectively.

However (Brown et al., 2005) the RCF study may have been compromised by overload resulting from use of a test substance that was not representative of that found in the workplace.

RCF was also the subject of a chronic inhalation study in Syrian golden hamsters (McConnell et al., 1995). This chronic, single-dose, nose-only inhalation study resulted in a significant incidence (41%) of pleural mesotheliomas in hamsters exposed to 30 mg/m^3 (215 WHO f/ml) RCF for 18 months. No similar inhalation study on hamsters has been reported for MMVF21, however, so there is no basis for comparison with RCF. Moreover (Morrow et al., 1996; Warheit & Hartsky, 1994) the relevance of the hamster

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[4]A different positive control was used in these studies. The RCF study used chrysotile asbestos as a positive control, whereas the MMVF21 study used crocidolite asbestos.

[5]At the high dose, WHO aerosol concentrations were 243, 213 and 187 f/cc for rock wool, stone wool and RCF, respectively.

model for assessments of mesothelioma in humans has been questioned.

Epidemiological studies

As noted above, both RCF and rock wool have been the subjects of epidemiological studies. Similarities and differences are highlighted below. For epidemiological studies in the United States, the rock wool cohorts were (and are) chiefly exposed to traditional rock wool. For studies in Europe, workers were exposed to traditional rock wool through approximately the year 2002 and afterwards to a newly developed (and less biopersistent) material. As the effects of interest have relatively long latency periods, it is appropriate to regard both cohorts as consisting of traditional rock wool.

Mortality studies (RCF)

The RCF mortality study (LeMasters et al., 2003) followed current and former male workers employed in two manufacturing plants between 1952 and 2000 to investigate any possible excess mortality. This ongoing study found no excess mortality related to all deaths, all cancers, malignancies or diseases of the respiratory system, including mesothelioma. The study also employed Cox's proportional hazards model (adjusted for age and race), which did not show elevated total risk with cumulative RCF exposure. The study found an unexpected, but statistically significant association with cancers of the urinary organs, which will continue to be investigated. Although negative with respect to lung disease, the study is limited by sample size (942 workers) and by the limited time since first exposure (mean latency period of 21 years at time of publication). The study had sufficient time since first exposure to address lung cancer (most studies conclude that lung cancer has a latency $\sim$20 or more years).

However, as shown in Table A1 (at end of the report due to its length), reported mesothelioma latencies range from a minimum of approximately 6 years (McDonald & McDonald, 1979) to as much as 75 years (Bianchi & Bianchi, 2007), with a median in the range of 20–50 years. The most recent study (Frost, 2013) from the Great Britain asbestos survey offers the following conclusions:

> "After excluding missing data, there were 614 workers who died with mesothelioma between 1978 and 2005. Total follow-up time was 9280 person-years, with a median latency of 22.8 years (95% confidence interval (CI) 16.0–27.2 years). In the fully adjusted model, latency was around 29% longer for females compared with males (TR (time ratio) = 1.29, 95% CI = 1.18–1.42), and 5% shorter for those who died with asbestosis compared with those who did not (TR = 0.95, 95% CI = 0.91–0.99)''.

In reviewing Table A1, note that the estimated/measured mesothelioma latency is not constant even for a specific cohort; *latency is a random variable*. Although 20–50 years may be a reasonable range for the *median* latency, the observed range of reported latencies in any sample of mesotheliomas cases is very broad. Thus, among those persons who have developed mesothelioma, some will

develop it in a much shorter or much longer time period than the estimated mean or median latency.

The RCF mortality study, therefore, has limited power to address mesothelioma. Nonetheless, as mesothelioma, latency is a random variable if there was any appreciable incidence of mesothelioma in the RCF-exposed cohort, then we might have expected to have seen some cases with latencies less than the mean/median latency. The fact that none have been seen to date is beginning to be relevant. As these cohort ages, the strength of the strength of the evidence will increase if no mesotheliomas are observed subsequently.

Mortality studies (rock wool)

IARC conducted a careful review of various SVFs (including rock wool) in 2001 (IARC, 2002). The IARC Working Group reviewed all the available evidence – particularly the available epidemiological evidence, including all the studies then published by Marsh and others at the University of Pittsburgh. Based on this comprehensive review, IARC changed the carcinogen classification for rock wool (and fiberglass) from Group 2B (possible human carcinogen) to group 3 (not classifiable as to its carcinogenicity to humans). Table A2 (first part, shown at the end because of its length) summarizes the studies cited in the IARC Monograph.

In summarizing the results of human studies, IARC (2002) concluded:

> "The present evaluation relies mainly on cohort and nested case–control studies, in which exposure to rock (stone) wool and exposure to slag wool were not considered separately. The extended follow-up of the rock (stone)/slag wool cohort from the USA indicated an overall elevated risk of respiratory cancer when either national or local comparison rates were used. However, no association was found with duration of exposure or with time since first exposure. Standardized mortality ratios were no longer elevated when indirect adjustment for smoking was made. The nested case–control study showed no association between respiratory cancer and estimated cumulative exposure to respirable fibers, with or without adjustment for possible confounding by smoking and other sources of occupational exposure. Another nested case–control study partially overlapping with the study in the USA showed no increased risk for respiratory cancer in association with exposure to slag wool. The extended follow-up of the European cohort study indicated an overall elevated risk for lung cancer when national comparison rates were used. This study showed an increasing risk with years since first exposure. The highest standardized mortality ratio was found among workers with the longest time since first employment and among those first employed in the 'early technological phase', i.e. before the introduction of oil and binders and use of the batch-processing method. However, in a case–control study that included detailed information on exposure to fibers, individual smoking habits and potential occupational confounders, no increased risk of lung cancer with increasing fiber exposure was reported. *The results from these studies provide no evidence of an*

increased risk for pleural mesotheliomas or any other tumours''. [Emphasis added]

The available evidence that exposures to rock or slag wool did not lead to significant increases in lung cancer or mesothelioma was substantial as of 2002. Since the 2002 IARC Monograph was published, additional studies have appeared in the literature covering both fiberglass and rock wool that are broadly consistent with IARC's 2002 decision. These additional studies are also summarized in Table A2.

With respect to rock wool, for example, Kjaerheim et al. (2002)[6] analyzed data on rock and slag wool (RSW) workers in plants in Denmark, Germany, Norway and Sweden and found:

> ''For cumulative exposure to RSW assessed with a 15-year lag, the smoking-adjusted odds ratios in the second, third, and fourth quartiles of exposure were 1.3 (95% confidence interval [CI] = 0.7–2.3), 1.0 (CI = 0.5–1.9) and 0.7 (CI = 0.3–1.3). Similar results were obtained when we included only those workers employed for more than 1 year, when we included other indicators of RSW exposure, and after control for co-exposures''.

The authors concluded:

> ''This study provides no evidence of a carcinogenic effect on the lung of rock and slag wool under exposure circumstances in the production industry during the last 4–5 decades''.

Baccarelli et al. (2006) conducted a study to examine the risk of lung cancer from exposure to dusts and fibers (including MMVF) in Leningrad Province, Russia. The study is not fully informative because fiberglass and rock/slag (mineral) wool exposures were pooled in the analysis. To investigate lung cancer risk in relation to exposure to various dusts and fibers, the authors identified 540 pathologically diagnosed lung cancer cases and 582 controls from the 1993–1998 autopsy records of the 88 hospitals of Leningrad Province, Russia. Lifetime job-specific exposure measurements were available for 15 organic, 15 manmade and 28 natural-inorganic agents. Results of this study were described by the authors as follows:

> ''In male workers, increased risks were found for linen dust (OR = 3.68, 95% CI 1.00–13.6, adjusted for age, smoking and residence), and unspecified DFs (OR = 1.44, 95% CI 1.07–1.94). Small non-significant excess risks were observed for quartz dust (OR = 1.27; 95% CI 0.83–1.93) and manmade vitreous fibers (MMVFs; OR = 1.82, 95% CI 0.88–3.75). In female subjects, risks were non-significantly associated with paper dust (OR = 1.77, 95% CI 0.74–4.20), and unspecified DFs (OR = 1.52, 95% CI 0.77–3.03)''.

Carel et al. (2007) performed a multicenter case-control study of exposure to asbestos and manmade vitreous fibers and risk of lung cancer in Europe and concluded that the odds ratio (OR) for exposure to MMVF was elevated (1.23) but not significantly so (95% CI = 0.88–1.71). These investigators did not distinguish between fiberglass and mineral wool; these were lumped into a general category of exposure to MMVFs.

Pintos et al. (2008) performed two case-control studies on cohorts from Montreal, Canada. They found increased risks of lung cancer for substantial exposure to asbestos, but a non-significant odds ratio (1.1, 95% CI = 0.37–3.22) for exposure to manmade vitreous fibers. The authors grouped fiberglass and mineral wool together because they were not able to distinguish between exposures to the two fiber types from interviews. Pintos et al. (2009) performed a similar analysis for mesothelioma and computed the mesothelioma OR for exposure to any asbestos type as 3.7 (95% CI = 1.7–7.8), but were not able to disentangle the effects of MMVF.

Lipworth et al. (2009) performed a meta-analysis of 16 studies relative to rock wool specifically and reported:

> ''Sixteen estimates of lung cancer risk yielded a summary relative risk (RR) of 1.21 (95% CI = 1.11–1.32, based on 1662 exposed cases). Corresponding RRs were 1.26 (95% CI = 1.10–1.44) in studies of production workers (with similar risk for RW and GW workers), 1.06 (95% CI = 0.77–1.48) in studies of end users and 1.18 (95% CI = 0.98–1.42) in community-based studies. The summary RR for [lung and head and neck] HN cancer was 1.36 (95% CI = 1.13–1.63, 414 exposed cases). With a few exceptions, all studies that assessed the risk of lung or HN cancer according to various indices of MMVF exposure failed to detect a dose-risk relation. There was limited evidence of a confounding effect of tobacco smoking. No clear excess of pleural mesothelioma has been reported in MMVF-exposed workers''. [Material in square brackets added for clarity.]

Lipworth et al. (2009) concluded:

> ''Despite a small elevation in RR [relative risk] for lung cancer among MMVF [man made vitreous fibers] production workers, the lack of excess risk among end users, the absence of any dose-risk relation, the likelihood of detection bias, and the potential for residual confounding by smoking and asbestos exposure argue against a carcinogenic effect of MMVF, RW [rock wool], or GW [glass wool] at this time. Similar conclusions apply to HN cancer risk among workers exposed to MMVF''. [Material in square brackets added for clarity.]

Marsh et al. (2011) reexamined the available evidence on the relation between respiratory system cancer risk and MMVF exposure. This article was focused on exposure to fiberglass, but covered other MMVFs as well. Specifically Marsh et al. (2011) cites work of Pintos et al. (2008) from two population-based case-control studies in Montreal, Canada. Exposures to MMVF (fiberglass and RSW combined) were categorized as non-exposed, non-substantial and substantial. Neither study revealed a statistically significant elevated risk of lung cancer

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[6]This study was actually published after the IARC Working Group meeting, but was available to the authors of the IARC Monograph and was included in the 2002 Monograph.

Table 5. Occurrence of pleural plaques among males exposed to mineral wool.

Age group (years)	Workers	Exposed to mineral wool		Referents	Not exposed	
		Workers with plaques	Frequency (%)		Referents with plaques	Frequency (%)
20–29	202	0	0.00	159	0	0.00
30–39	215	1	0.47	136	0	0.00
40–49	138	2	1.45	107	0	0.00
50–59	122	6	4.92	86	2	2.33
60–69	77	3	3.90	53	1	1.89
All	754	12	1.59	541	3	0.55

Summary of data from Järvholm et al. (1995).

among those exposed to MMVF. Marsh et al. (2011) also cited a review and meta-analysis by Lipworth et al. (2009) and concluded:

> ''...despite a small elevation in the risk for lung cancer in the industry and community-based studies, the absence of consistent evidence of an exposure–response relationship, the likelihood of detection bias, and the potential for residual confounding by smoking and asbestos exposure argue against a carcinogenic effect of MMVF, GW, or RSW at this time''.

SCOEL (2012) examined the available evidence for carcinogenicity of rock and glass wool fibers and concluded:

> ''The life time studies in rats on rock wool and slag wool as well as insulation fiber glass (and of TISMO[7]) did not reveal carcinogenic effects. Recent evaluations of the epidemiological studies of workers exposed to respirable rock wool and glass wool fibers (Lipworth et al., 2010) and glass wool fibers (NTP, 2010) support these data''.[8]

Lacourt et al. (2013) reported results of a French pooled case–control study of persons occupationally co-exposed to asbestos, mineral wool and silica. The authors claim that a significant association between mesothelioma and mineral wool exposure was observed after adjustment for occupational asbestos exposure. Bonde (2013) criticized this study because the selection of the control group was inappropriate and that exposures to asbestos, mineral wool and silica were highly correlated.

Pleural plaques

As noted above, the epidemiology studies on RCF have shown a dose-related increase in the prevalence of pleural plaques (Lockey et al., 1996, 2002, 2012). Pleural plaques are usually taken as a measure of fiber (particularly asbestos) exposure, but do not cause impairment of lung function, are not precursors of lung cancer or mesothelioma, and are not an independent risk factor in the development of cancer (ACC Review, 2004; ATSDR, 2000; Ameille, 2012; Ameille et al., 2011; Banks & Dedhia, 2011; British Lung Foundation, 2011;

Crapo, 2005; Downer et al., 2013; Edelman, 1988; Federal Register, 2005; Gevenois & de Vuyst, 2006; Harber et al., 1987; Hillerdal, 1997, 2001; IIAC, 2008; Jones et al., 1996; Letourneux, 1999; Newman & Rose, 1989; Partanen et al., 1992; Reid et al., 2005; Reinhartz, 2004; Robinson & Lake, 2005; Rubin, 1986; Smith, 1994).

Much less has been published regarding the relationship between rock wool exposure and pleural plaques in exposed populations. Table 5 summarizes results from a study by Järvholm et al. (1995) of workers in a factory producing rock wool as compared to the occurrence of pleural plaques in non-exposed referents. These data are subdivided by age group because of the likelihood that the appearance of plaques is correlated with age. Although a higher proportion of the exposed group (1.59%) than referents (0.55%) were found to have plaques, the association fails to reach statistical significance ($p = 0.09$ computed by the authors).

Interstitial fibrosis

Lockey et al. (2012) studied the relationship between RCF exposure and possible interstitial fibrosis. They used three possible measures of RCF exposure, production duration, production latency and cumulative RCF exposure. They concluded:

> ''There was no association between any exposure metric and interstitial radiographic changes for either profusion > 1/0 or > 0/1 group''.

A comprehensive review on the relationship between occupational exposure to rock wool and the development of interstitial fibrosis was conducted by de Vuyst et al. (1995). These investigators concluded:

> ''There is no firm evidence that exposure to glass-, rock- and slag-wool is associated with lung fibrosis, pleural lesions or non-specific respiratory disease in humans''.

There have been isolated case reports of interstitial fibrosis among those exposed to rock or glass wool (Guber et al., 2006; Yamaya et al., 2000), however.

Similarities and differences between RCF and rock wool based on epidemiological studies

The RCF studies have shown that exposed workers have a significantly greater likelihood of developing pleural plaques than non-exposed referents. Moreover, the frequency of

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[7]These are potassium octatitanate fibres.
[8]The inclusion of ''Lipworth et al., 2010'' is thought to be in error in the original cited text; SCOEL (2012) does not include a reference for Lipworth et al., (2010). The reference should be to ''Lipworth et al., 2009''.

Table 6. Similarities and differences between RCF and rock wool.

		Comparison
Physical properties	Biopersistence	RCF and rock wool have nearly identical biopersistence as measured by $WT_{1/2}$ values from short term inhalation exposures with rats.
	Airborne fiber dimensions	Though bulk fiber diameters differ, diameters of airborne fibers from personal monitoring samples are quite similar.
		Fiber lengths of RCF and rock wool are similar.
	Breakage mechanism	Both RCF and rock wool break transversely rather than longitudinally. Thus, any breakage results in fibers that are more easily removed by macrophages.
Animal studies	IP studies	IP studies of rats show that exposure to both RCF and rock wool result in the development of tumors.
	Inhalation studies	A well-done chronic bioassay of rats exposed (nose-only) to rock wool (MMVF21) resulted in mild fibrosis, but no tumors.
		A similar study on RCF resulted in both fibrosis and tumors, although the result may have been undermined by overload resulting from exposure to a test article with a non-representative ratio of particles to fibers.
Epidemiological studies	Pleural plaques	Exposure to RCF results in a dose-dependent statistically significant increase in the frequency of pleural plaques.
		Limited data on rock wool exposure resulted in an increase in the frequency of pleural plaques in exposed workers that was not statistically significant.
	Interstitial Fibrosis	No interstitial fibrosis seen in cohorts exposed to either rock wool or RCF.
	Increased lung cancer or mesothelioma	Mortality studies fail to indicate any increase in either lung cancer or mesothelioma among cohorts exposed to either RCF or mesothelioma. The statistical power of the rock wool studies is much larger, however.

pleural plaques increases with dose. Rock wool has been less well studied in this regard. The limited available data suggest that rock wool exposure might be associated with the development of pleural plaques, but in the only study available the differences in frequency of plaques among exposed and non-exposed populations was not statistically significant.

There is no evidence that occupational exposure to RCF results in the development of interstitial fibrosis. Epidemiological studies on rock wool lead to a similar conclusion.

Mortality studies on both RCF and rock wool fail to demonstrate any statistically significant increase in lung cancer or mesothelioma in fiber-exposed populations. For rock wool, there is a very large database of studies that support this conclusion. The ongoing RCF studies have less statistical power and shorter exposure duration. Over time, the ability to detect differences in disease frequency for effects with greater latency will increase.

Overall summary

Table 6 summarizes the key similarities and differences between RCF and rock wool in terms of relevant studies.

Conclusions

This analysis summarizes some key similarities between rock wool, which is appropriately regarded as non-carcinogenic, and RCF, which is classified as a potential human carcinogen. Key physical similarities include comparable fiber dimensions, fiber breakage mechanism and biopersistence. Animal IP studies have similar outcomes. A chronic nose-only inhalation bioassay resulted in fibrosis, but no tumors, in laboratory animals exposed to rock wool. A similar study on RCF resulted in both fibrosis and tumors, although interpretation of this study is not straightforward as the test substance used was not representative of that found in the workplace and

overload may have resulted. Epidemiological studies with cohorts occupationally exposed to RCF and rock wool show that neither substance has resulted in interstitial fibrosis, increased rates of lung cancer, or any mesotheliomas. Exposure to RCF results in a statistically significant dose-related increase in pleural plaques. Limited data on rock wool suggests that there might be a similar increase, but this result is not statistically significant. As a class, the epidemiological studies on rock wool are substantially more powerful because the sizes of the exposed cohorts are much larger and the exposure duration longer, which permits improved assessment of effects with long latencies, such as mesothelioma. For RCF, the mortality study continues and the duration of exposure of members of the cohort will increase, permitting more robust conclusions to be drawn in the future.

These similarities suggest that possible risks associated with occupational exposure to RCF have been overstated. Our study further supports the assumption that mesothelioma is specifically related to asbestos and erionite exposure:

- DECOS (2010): ''It is likely that in the Netherlands almost all mesotheliomas are attributable to asbestos'', especially amphiboles.
- Murphy et al. (2011): ''Mesothelioma is almost exclusively found after asbestos exposure and is a particle response unique to fibrous particles''.
- Lacourt et al. (2013): ''Except asbestos, only erionite fibers are recognized as an etiologic factor for pleural mesothelioma''.
- Boffetta et al. (2014): ''The combined evidence from epidemiology and toxicology provide little evidence that exposure to SVF increases the risk of mesothelioma''.

However, risks of exposure to any respirable and relatively durable fiber need to be managed. Manufacturers of both RCF and rock wool have developed product stewardship programs, which seek to assess and control possible risks.

Based on analogies with rock wool (read across), it is reasonable to believe that increases in lung cancer or any

mesotheliomas are unlikely to be found in the RCF-exposed cohort. However, despite several attempts to find predictors with reasonable sensitivity, specificity, positive prediction value, and ''lead'' time, there are no published studies reporting success. For example, Sandén & Järvholm (1991) examined a cohort study of 3893 shipyard workers exposed to asbestos and assessed the value of medical monitoring, asbestos exposure, pleural plaques and respiratory symptoms, and found that all were of low value as predictors of risk of mesothelioma. Nor have various biomarkers proven useful in predicting mesothelioma (Filiberti et al., 2014; Gube et al., 2011; Imperatori et al., 2013), although some may have promise (Hirohashi et al., 2014). Robinson & Lake (2005) discuss various indicators with diagnostic relevance but these present no useful lead time as a predictor. Given the present state of the art, therefore, it will be necessary to continue the ongoing RCF mortality study to provide definitive evidence regarding the development of mesothelioma.

Acknowledgements

Declaration of interest

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Appendix

Table A1. Mesothelioma latency as reported in various studies and review articles listed in chronological order.

Mean (Years)	Median (Years)	Range	Cohort	Source
NR	NR	NR	Article claims that latency period is approximately 35 years.	Selikoff et al. (1965, as cited in Banaei et al., 2000)
		24–36	Canadian gas mask assembly workers. Study reports ranges from other studies as 20–35 years and 6–44 years.	McDonald & McDonald (1979)
32.3		14–57	144 workers with mesothelioma in UK factories using asbestos in manufacturing and insulation.	Browne & Smither (1983)
	37	19–68	Cancer registry of Norway.	Mowé et al. (1984)
	35–40		Study of mesothelioma in Great Britain in 1968–1983 concludes that the median latency is 35–40 years.	Jones et al. (1988)
	32	11 to >50	1105 workers in 24 cohorts summarized in this review; latency exceed 20 years in 96% of all cases.	Lanphear & Buncher (1992); see also Weill et al. (2004)
33		24–43	Shipyard workers in Sweden	Sandén et al. (1992)
48.1			Cohort from Uppsala, Sweden	Hillerdal (1994)
		30–40	Inhabitants of the Metsovo area, north-west Greece	Sakellariou et al. (1996)
41.4	<30	15–67	168 mesothelioma cases in south east England	Yates et al. (1997)
NR	NR	NR	Review article, claims that ''extensive research revealed a latency period of 30–45 years in most cases''.	Baas et al. (1998)
37.4		4–66	Different groups in Australia	Yeung et al. (1999)
39.7	42	17–60	Three cases in UK	Attanoos et al. (2000)
48.8	51.0	14–75	380 cases of malignant pleural mesothelioma in the Trieste–Monfalcone area, 1968–2000.	Bianchi et al. (2001)
>40			Mean latency times greater than 40 years among subjects occupationally exposed to asbestos were reported by the French Mesothelioma Registry.	Desoubeaux (2001, as cited in Marinaccio et al., 2005)
			Latency reported to be 40–50 years for asbestos related mesothelioma in Japan.	Morinaga et al. (2001)

(continued)

Mean (Years)	Median (Years)	Range	Cohort	Source
NR	43.0	20–49	Review article covers two small occupationally exposed Japanese cohorts.	Morinaga et al. (2001)
37.6	NR	NR		
37.8		11–68	821 cases from German mesothelioma register.	Neumann et al. (2001)
	~39	11 to >50	800 among 1517 cases of mesothelioma from various cohorts.	Suzuki (2001)
44.9			Workers in South African mines	Carbone et al. (2002)
51.0			Crocidolite miners	
12.3			Amosite miners	
			Miners exposed to both crocidolite and amosite	
56 both sexes			Turkish cohort living in a rural area.	Metintas et al. (2002)
48.5			301 cases of mesothelioma between 1979 and 1999 in workers from the Devonport Naval Dockyard; the mean was lower (42 years) among more heavily exposed trades.	Hilliard et al. (2003)
46 SD 11 years			22 mesothelioma cases in Hong Kong.	Chang et al. (2006)
			10 cases of mesothelioma among patients <40 years old	Kane et al. (2006)
	19		Review article covers several cohorts	Bianchi & Bianchi (2007, and references therein)
48.8	51	14–75	400 pleural mesotheliomas in Italy	
29.6	29	28–32	Insulation workers in Italian cohort	
52.6	53.0	32–64	215 cases of malignant pleural mesothelioma were diagnosed at the Hospital of Monfalcone, Italy.	Bianchi et al. (2007)
43.7 men			1941 cases of mesothelioma (pleural and peritoneal) in New South Wales, Australia.	Hyland et al. (2007)
42.8 women				
	44.6		Italian register	Marinaccio et al. (2007)
			801 pleural mesotheliomas diagnosed in hospitals in the Trieste and Monfalcone districts of Italy. Latency estimates varied with cohort as shown below:	Bianchi & Bianchi (2009)
34.8	33.0	27–49	Insulation	
48.7	51.0	13–73	Shipbuilding	
55.3	56.0	35–71	Maritime trades	
37.1	33.0	25–60	Port activities	
46.0	47.5	28–69	Other industries	
50.8	55.0	27–62	Domestic exposure	
44.9	46.0	25–64	Other	
8.5	8.5		Case report of single bystander exposed to a site at which asbestos-containing materials were being dismantled	Bitchatchi et al. (2010)
	36.9	<10 to >60	679 cases from GB Asbestosis and Mesothelioma Registers	Harding & Darnton (2010)
36.8			Former workers and residents exposed to crocidolite at Wittenoom, Western Australia.	Aboagye-Sarfo et al. (2011)
48.5		18–70	238 cases of malignant mesothelioma for which latency was estimated for 191 cases.	Haber & Haber (2011)
36.9			Estimates given for various cohorts:	Olsen et al. (2011)
39.8			Wittenoom workers 95% CI (31.4–42.3)	
43.7			Other asbestos workers 95% CI (34.3–45.2)	
39.7			Wittenoom residents 95% CI (38.0–49.5)	
33.1			Other non-occupational 95% CI (33.9–45.6)	
			Home renovators 95% CI (27.5–38.8)	
48.3		25–68	Shipyard workers in Monfalcone	Bianchi & Bianchi (2012)
NR	43	13–81	929 clinically confirmed deaths due to mesothelioma	Gemba et al. (2012)
NR	22.8	NR	614 mesotheliomas deaths (between 1978 and 2005) among asbestos workers in the UK; latency approximately 29% longer for females compared to males. Median latencies vary among other groups from 8.2 to 34 years	Frost (2013)

NR = not reported.

Table A2. Studies of cancer in workers exposed to rock (stone) and wool and slag wool.

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
As reported in IARC (2002). USA (University of Pittsburgh) *Cohort studies*						
Marsh et al. (1990) 6 plants	1846 male workers[a] employed 1945–1963, follow-up 1946–1985	73 deaths from respiratory cancer	Time since first employment		SMR 1.36 [1.06–1.71]	Local rates
			<10 years	2	0.89	
			10–19 years	13	1.56	
			20–29 years	24	1.37	
			≥30 years	34	1.32	
			Duration of employment			
			<10 years	38	1.43 [1.01–1.96]	Local rates
			10–19 years	15	1.46	
			20–29 years	11	1.18	
			≥30 years	9	1.18	
Marsh et al. (1996) 5 plants	*N-cohort* (cohort participating in the new program): 3035 male and female workers[a] employed 1945–1978	71 deaths from respiratory cancer (68 in men)	Time since first employment *N-cohort (men only)*		SMR	Local rates
			<10 years	2	0.58	
			10–19 years	13	1.22	
			20–29 years	23	1.35	
			≥30 years	30	1.06	
1 plant	*O-cohort* (cohort from the original plant): 443 male workers[a] employed 1945–1963	32 deaths from respiratory cancer	*O-cohort*			
			<20 years	3	0.95 [0.20–2.78]	Asbestos exposure
			20–29 years	8	1.41 [0.61–2.78]	
			≥30 years	21	1.71 [1.06–2.61]	
Marsh et al. (1996) 1 plant	Follow-up until 1989		Duration of employment *N-cohort (men only)*		SMR	
			<10 years	39	1.14	
			10–19 years	15	1.34	
			20–29 years	8	1.07	
			≥30 years	6	0.89	
			O-cohort			
			<10 years	15	1.32	
			10–19 years	7	2.02	
			≥20 years	10	1.61	
Nested case–control study Marsh et al. (1996) 5 plants	*N-cohort* 54 deaths[a] from respiratory cancer (men)	107 male controls	Cumulative exposure to respiratory fibers		Odds ratio	Unadjusted for smoking
			<3 fibers/cm³-months		1.0	
			3–14 fibers/cm³-months		0.70	
			15–39 fibers/cm³-months		0.59	
		101 male controls	≥40 fibers/cm³-months		0.71	*p* for linear trend = 0.76

USA
Nested case–control study

Reference / plant	Description	Exposure category	No.	Risk estimate	Comments
1 plant	54 deaths from respiratory cancer (men)	<3 fibers/cm³-months		1.0	Adjusted for smoking
		3–14 fibers/cm³-months		0.64	
		15–39 fibers/cm³-months		0.55	
		≥40 fibers/cm³-months		0.58	*p* for linear trend = 0.64
	O-cohort 24 deaths[a] from respiratory cancer (men) 1970–1989		47 controls	**Odds ratio**	
		Duration of employment			
		<2 years		1.0	Smokers only
		2–4 years		1.62	
		5–19 years		0.23	
		≥20 years		0.85	*p* for linear trend = 0.21
	18 deaths from respiratory cancer 1970–1989		31 controls		
		<2 years		1.0	Smokers only
		2–4 years		1.82	
		5–19 years		0.33	
		≥20 years		0.73	*p* for linear trend = 0.47
Wong et al. (1991) 9 plants slag wool workers (4 plants also in Marsh et al., 1990, 1996)	55 men who died from lung cancer[a] 1970–1989		98 male controls who had died from other causes	**Odds ratio**	NIOSH exposure classification
		Exposed/unexposed	50	0.90 (0.23–3.49)	Unadjusted for smoking
				0.94 (0.23–3.78)	Adjusted for smoking
		Exposed ≥7 fibers/cm³-months	27	0.86 (0.42–1.79)	Unadjusted for smoking
		Exposed <7 fibers/cm³-months		0.98 (0.47–2.04)	Adjusted for smoking

European study
Cohort study

Reference / plant	Description	Exposure category	No.	Risk estimate	Comments
Plato et al. (1995) Sweden 2 plants (included in Boffetta et al., 1997)	1569 male and female workers employed[a] before 1978, follow-up 1952–1990 for mortality	13 deaths from lung cancer		**SMR**	
				[1.57 (0.83–2.68)]	Local rates
				[1.02 (0.55–1.75)]	National rates
		Duration of employment with 20-year lag:			
		<2 years	1	1.10 (0.28–6.12)	Local rates
		2–9 years	5	2.69 (0.87–6.27)	
		10–19 years	1	0.87 (0.02–4.89)	
		≥20 years	2	1.43 (0.17–5.16)	
		Plant-specific cumulative fiber exposure (fibers/cm³-years):		**SMR**	
		<1	7	2.01 (0.81–4.13)	
		1–2	4	2.45 (0.67–6.21)	
		>2	2	0.62 (0.08–2.24)	
Plato et al. (1995) Sweden 2 plants (included in Boffetta et al., 1997)	Follow-up 1958–1989 for incidence	13 cases of lung cancer		**SIR**	
		Duration of employment:			
		<2 years	1	0.69 (0.02–3.84)	Local rates
		2–9 years	7	2.12 (0.85–4.37)	
		10–19 years	3	1.63 (0.34–4.76)	
		≥20 years	2	1.61 (0.20–5.83)	
		13 cases of stomach cancer		**SIR**	
				1.71 (0.91–2.93)	Local rates

Table A2. Continued

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Boffetta et al. (1997) 7 plants Denmark, Germany, Norway and Sweden Mortality study	4912 male and female workers[a] employed 1933–1977, follow-up until 1990–1991	97 deaths from lung cancer			SMR 1.34 (1.08–1.63)	National rates Adjusted for age, calendar year, country, technological phase and duration of employment.
			Time since first employment:		Relative risk[b]	
			≤9 years	10	1.0	
			10–19 years	26	1.3 (0.6–3.0)	
			20–29 years	29	1.2 (0.5–3.1)	
			≥30 years	32	1.4 (0.4–4.6)	
						p for linear trend = 0.67
			Duration of employment			Adjusted for age, calendar year, country, technological phase and time since first employment.
			1–4 years	31	1.0	
			5–9 years	21	1.4 (0.8–2.4)	
			10–19 years	21	1.0 (0.5–1.8)	
			≥20 years	24	1.6 (0.8–3.1)	
						p for linear trend = 0.27
			Technological phase			Adjusted for age, calendar year, country, duration of employment and time since first employment.
			Late	76	1.0	
			Intermediate	12	1.0 (0.5–2.3)	
			Early	9	1.1 (0.4–2.8)	
Boffetta et al. (1997) 7 plants Denmark, Germany, Norway and Sweden Mortality study		8 deaths from oral cancer +cancer of the pharynx; 6 deaths from cancer of the larynx; 8 deaths from cancer of the oesophagu			SMR 1.33 (0.57–2.61) 1.96 (0.72–4.27) 1.25 (0.54–2.46)	National rates
Consonni et al. (1998) Denmark, Germany, Norway and Sweden 7 plants	9603 male workers employed until 1977 follow-up until 1990–1991	159 deaths from lung cancer	Cumulative exposure		Relative risk[b]	Adjusted for age, calendar period, country, time since first employment and employment status.
			≤0.007 fiber/cm³-years	39	1.0	
			0.008–0.136 fiber/cm³-years	40	1.3 (0.8–2.4)	
			0.137–1.367 fiber/cm³-years	40	1.2 (0.7–2.1)	
			>1.368 fibers/cm³-years	40	1.5 (0.7–3.0)	
						p for linear trend = 0.4
		97 deaths from lung cancer in workers with ≥1 year of employment	≤0.139 fiber/cm³-years	25	1.0	
			0.140–0.729 fiber/cm³-years	24	0.9 (0.4–2.0)	
			0.730–2.622 fibers/cm³-years	24	0.8 (0.3–1.9)	
			>2.622 fibers/cm³-years	24	1.0 (0.4–2.7)	p for linear trend = 1.0
Boffetta et al. (1999)	3685 male and female workers[a] employed 1933–1977 follow-up 1994–1995	73 cases of lung cancer			SIR 1.08 (0.85–1.36)	National rates
			Time since first employment:		Relative risk[b]	Adjusted for ages, gender, country and technological phase
			≤9 years	7	1.0	
			10–19 years	21	1.8 (0.7–4.7)	
			20–29 years	25	2.4 (0.9–6.8)	
			≥30 years	20	3.0 (0.8–10.5)	
						p for linear trend = 0.1
			Duration of employment (15-year lag)			Adjusted for age, gender, country, technological phase and time since first employment
			1–4 years	33	1.0	
			5–9 years	11	1.0 (0.5–2.1)	

Study	Study description	Exposure category	N	Estimate (95% CI)	Notes
		10–19 years	10	1.2 (0.5–2.6)	
		≥20 years	5	2.0 (0.7–6.2)	Adjusted for age, gender, country and time since first employment
					p for linear trend = 0.4
		Technological phase			
		Late	50	1.0	
		Intermediate	14	0.8 (0.4–1.7)	
		Early	9	0.8 (0.3–2.0)	*p* for linear trend = 0.5
	31 cases of cancer of the oral cavity, pharynx or larynx			SIR	
				1.46 (0.99–2.07)	National rates
Post-IARC (2002).					
Case–control study					
Kjaerheim et al. (2002) 7 plants	133 cases of lung cancer, rock (stone) wool/slag wool male workers employed 1937–1976, follow-up 1971–1996				Although after the IARC meeting, this was included in the IARC Monograph.
	513 male controls				
		Cumulative fiber exposure in quartiles		Odds ratio	
		All workers			
		quartile 1	33	1.0	
		quartile 2	32	0.86 (0.47–1.56)	Adjusted for age, country and tobacco smoking.
		quartile 3	33	0.91 (0.51–1.63)	
		quartile 4	34	0.51 (0.28–0.93)	*p* for linear trend = 0.04
		Workers employed >1 year			
		quartile 1	12	1.0	
		quartile 2	3	2.08 (0.36–11.91)	
		quartile 3	26	0.85 (0.34–2.15)	
		quartile 4	34	0.52 (0.21–1.30)	*p* for linear trend = 0.11
		Cumulative fiber exposure, in quartiles, lagged 15 years			
		All workers			
		quartile 1	36	1.0	
		quartile 2	36	1.25 (0.66–2.34)	
		quartile 3	30	1.02 (0.54–1.93)	
		quartile 4	30	0.67 (0.35–1.27)	*p* for linear trend = 0.17
		Workers employed >1 year			
		quartile 1	23	1.0	
		quartile 2	5	2.00 (0.41–9.83)	
		quartile 3	18	0.76 (0.27–2.17)\	
		quartile 4	29	0.63 (0.28–1.42)	*p* for linear trend = 0.19
Kjaerheim et al. (2002)		Duration of exposure in rock (stone)/slag wool industry		Odds ratio	
		All workers			
		Unexposed	7	1.0	
		1 year	58	1.24 (0.47–3.26)	
		2–6 years	32	0.86 (0.32–2.31)	
		7–40 years	35	0.85 (0.32–2.26)	*p* for linear trend = 0.23
		Workers employed >1 year			
		Unexposed	6	1.0	
		1 year	2	0.51 (0.05–5.50)	
		2–6 years	32	0.60 (0.17–2.08)	
		7–40 years	35	0.65 (0.20–2.12)	*p* for linear trend = 0.63
		Duration of exposure in rock (stone)/slag wool industry, lagged 15 years			

Table A2. Continued

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
			All workers			
			Unexposed	28	1.0	
			1 year	51	1.57 (0.82–2.99)	
			2–5 years	28	1.20 (0.61–2.34)	
			6–39 years	25	0.97 (0.48–2.00)	*p* for linear trend = 0.15
			Workers employed >1year			
			Unexpected	18	1.0	
			1 year	4	1.06 (0.21–5.30)	
			2–5 years	28	1.01 (0.44–2.34)	
			6–39 years	25	0.98 (0.39–2.47)	*p* for linear trend = 0.96
Baccarelli et al. (2006)	Lifetime job-specific exposure measurements were available for 15 organic, 15 man-made and 28 natural-inorganic agents	540 lung cancer cases and 582 controls from the 1993–1998 autopsy records.	Various exposure categories including those exposed to MMVFs		1.82 (0.88–3.75)	All MMVFs pooled, RSW not included as specific category.
Carel et al. (2007)	Multi-center case-control study of lung cancer and exposure to asbestos and MMVFs	16 centers in six Central and Eastern European countries and the UK during the period 1998–2002, 115 cases and 89 controls exposed to MMVF	Low exposure intensity	73	1.23 (0.82–1.84)	All MMVFs pooled.
			Medium	34	1.28 (0.70–2.34)	
			High	8	1.02 (0.31–3.33)	
			Year of first exposure ~1960	45	1.36 (0.80–2.31)	
			1961–1970	30	1.09 (0.60–1.97)	
			1971–1980	25	1.05 (0.54–2.03)	
			1981–1990	11	1.64 (0.54–4.96)	
			1991–	4	1.57 (0.25–9.88)	
			Overall		1.23 (0.88–1.71)	
Pintos et al. (2008)	Two case control studies in Montreal, Canada studying effects of exposure on lung cancer	1144 controls/922 cases in cohort 1; 978 controls/809 cases in study 2	Non-exposed	1425	1.00	All MMVFs pooled. Figures at left refer to both cohorts pooled.
			Any exposure	153	1.05 (0.80–1.40)	
			Non-substantial level	129	1.10 (0.81–1.49)	
			Substantial level	24	0.86 (0.45–1.63)	
Lacourt et al. (2013)	Cases came from hospital-based case-control study performed between 1987 and 1996 or identified through the French National Mesothelioma Surveillance Program.	Cases and controls varied with type of exposure studied; table at right is one of several related to MMVF exposure	Not exposed	474	1.00	Study considered exposure to asbestos, MMVF and silica. Exposure to all MMVFs pooled. See critical comments by Bonde (2013).
			Exposed	725	1.8 (1.5–2.3)	
			Exposure duration (years)			
			0–7	144	1.6 (1.2–2.1)	
			7–18	173	1.8 (1.3–2.4)	
			18–32	164	1.3 (1.0–1.9)	
			>32	244	3.5 (2.5–4.9)	

SMR, standardized mortality ratio; SIR, standardized incidence ratio; respiratory cancer, ICD-8, 160–163.
[a]Employed for ≥ 1 year.
[b]Poisson regression analysis.