5 Effects of Exposure

5.1 Health Effects in Animals (In Vivo Studies)

The health effects of RCF exposures have been evaluated in animal studies using intrapleural, intraperitoneal, intratracheal, and inhalation routes of exposure. All of these routes have demonstrated the carcinogenic potential of RCFs. Chronic inhalation studies provide information that is most relevant to the occupational route of exposure and human risk assessment. Mechanistic information about fiber toxicity may also be derived from other types of studies. Studies investigating the cellular effects of RCFs in vitro are reviewed in Section 5.2 and Appendix C.

When comparing the effects of a fiber dose in animal studies, it is possible to compare fibers on a gravimetric basis (effect per unit weight) or a fiber basis (effect per number of fibers). The same gravimetric dose of different fiber types may contain vastly different numbers of fibers because of differences in their dimensions. RCF1 is a relatively thick fiber compared with many types of asbestos, such as chrysotile, a fiber commonly used as a positive control in pulmonary carcinogenesis experiments in animals (see Table 2–2 for descriptions of RCF1, RCF2, RCF3, and RCF4). A gravimetric dose of RCF1 usually contains far fewer fibers than the same gravimetric dose of chrysotile asbestos fibers, making a direct comparison of their effects difficult when the number of fibers per unit weight is not reported. Comparison on a per-fiber basis rather than a weight basis provides information most applicable to occupational risk assessment.

Animal studies report the concentration(s) to which the animals were exposed. The distinction between administered exposure concentration and received dose is important when analyzing these studies. The dose affecting the target tissues is known only when the amount of fiber present in the lung is measured and reported. To analyze the results of RCF studies, the number of fibers per exposure, their dimensions, durabilities, and the delivered dose should be considered for making comparisons and conclusions regarding potential and relative toxicity.

5.1.1 Intrapleural, Intraperitoneal, and Intratracheal Studies

Instillation and implantation studies deliver fibers directly to the trachea, pleural cavity, or peritoneal cavity, bypassing some of the defense and clearance mechanisms that act on inhaled fibers. Implantation of fibers into either the pleural or abdominal cavities delivers fibers directly to the pleural or abdominal mesothelium, bypassing some or all of the normal defense and clearance mechanisms of the respiratory tract. Intratracheal instillation delivers fibers directly to the trachea, bypassing the upper respiratory tract. These exposure methods do not mimic an occupational inhalation exposure of several hours per day for several days per week over an extended period. However, one advantage of these studies is that they allow the administration of a precise dose of fibers that can be replicated between animals. They also permit the administration of higher doses than may be obtainable by inhalation exposure.

Although the results of implantation and instillation studies may not be directly applicable to occupational exposure and human health effects, they provide important information about the potential toxicity of RCFs. Experiments that control fiber dimensions and other variables provide information about the physiological characteristics relevant to fiber toxicity. They provide a less expensive, quicker means to screen the potential toxicity of a fiber than inhalation studies.

Many of the implantation and instillation studies reviewed here report the administered fiber dose on a gravimetric basis rather than on a per-fiber basis. Some studies assess the toxicity of both RCFs and asbestos independently, which allows for the comparison of these fibers on a gravimetric basis but not on a per-fiber basis.

5.1.1.1 Intraperitoneal Implantation Studies

In intraperitoneal studies, fibers are implanted directly into the abdominal cavity, bypassing the respiratory system defense and clearance mechanisms that act on inhaled fibers. Although the implanted fibers act on some of the same target cell types as the fibers of an inhalation exposure (such as the mesothelium), the effects elicited in the abdominal mesothelium cannot be assumed to be identical to the response of the pleural mesothelium. Table 5–1 summarizes the results of three RCF intraperitoneal implantation studies [Davis et al. 1984; Smith et al. 1987; Pott et al. 1987]. A brief description of these studies follows.

Davis et al. [1987] dosed Wistar rats with 25 mg ceramic aluminum silicate dust by intraperitoneal injection. Tumors were induced in 3 of 32 rats: 2 fibrosarcomas and 1 mesothelioma. Smith et al. [1987] dosed Osborne Mendel (OM) rats and Syrian hamsters with 25 mg RCFs by intraperitoneal injection. Abdominal mesothelioma induction rates were 83% (19/23) in OM rats and 13% (2/15) and 24% (5/21) in two groups of male hamsters. Crocidolite asbestos at 25 mg induced abdominal mesotheliomas in 80% (20/25) of OM rats and 32% (8/25) of hamsters. The difference in tumor incidence reported by Davis et al. [1984] and Smith et al. [1987] may be explained in part by differences in fiber length. Eighty-three percent of RCF fibers used by Smith et al. [1987] had a length >10 μm; 86% had a diameter <2.0 μm. Ninety percent of the ceramic aluminum silicate material used by Davis et al. [1984] had a length <3 μm and a diameter <0.3 μm.

Pott et al. [1987] dosed female Wistar rats by intraperitoneal injection with 9 or 15 mg/week for 5 weeks with 2 ceramic (aluminum silicate) wool fibers, Fibrefrax (RCFs), and MAN (Manville RCFs); total doses of 45 and 75 mg were administered, respectively. Fifty percent of Fibrefrax fibers had a length <8.3 μm and diameter <0.91 μm. Exposure to Fibrefrax fibers induced abdominal tumors (sarcomas, mesotheliomas, or carcinomas) in 68% of the rats. Fifty percent of MAN fibers had a length <6.9 μm and diameter <1.1 μm. The number of fibers in different length categories was not reported. Exposure to MAN fibers induced abdominal tumors in 22% of the rats. Chrysotile (UICC/B) injected intraperitoneally at a single dose of 0.05, 0.25, or 1.00 mg induced abdominal tumors in 19%, 62%, or 86% of rats, respectively. Fifty percent of chrysotile fibers had a length <0.9 μm and diameter <0.11 μm. The number of fibers per dose was not reported for the ceramic fibers and asbestos. Saline induced tumors in 2% of rats.

5.1.1.2 Intrapleural Implantation Studies

Intrapleural implantation studies permit the investigation of the effect of RCFs directly on the pleural mesothelium while controlling variables such as inhalation kinetics and translocation.

Table 5–1. Intraperitoneal implantation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Davis et al. [1984]	Wistar rats	32, sex unspecified	25 mg ceramic fibers (aluminum silicate glass)	L=90% <3 D=90% <0.3	1 mesothelioma 2 fibrosarcomas First tumor occurred 850 days postinjection.
Pott et al. [1987]	Wistar rats	47, female	9 mg (×5)=45 mg RCFs (Fibrefrax)	L=50% <8.3 D=50% <0.91	32 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
		54, female	15 mg (×5)=75 mg Manville RCFs (MAN)	L=50% <6.9 D=50% <1.1	12 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
		36, female	1 mg UICC/B chrysotile	L=50% <0.9 D=50% <0.11	31 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
		102, female	2 ml saline (×5)=10 ml	NA	2 mesotheliomas, sarcomas, or adenomas of the abdominal cavity
Smith et al. [1987]	Osborne Mendel rats	23, female	25 mg RCFs (Fibrefrax)	GM_L=25.0 L=83% >10 GM_D=0.9 D=80% <2	20 abdominal mesotheliomas

See footnotes at end of table.

(Continued)

Table 5–1 (Continued). Intraperitoneal implantation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Smith et al. [1987] (continued)		25, female	25 mg UICC crocidolite	Mean L=3.1 (SD, 10.2)	20 abdominal mesotheliomas
		25, female	0.5 ml physiological saline	L=95% ≤5 NA	0 abdominal mesotheliomas
		125, female	Cage controls	NA	0 abdominal mesotheliomas
	Syrian golden hamsters	15, male	25 mg RCF (Fibrefrax)	L=83% >10 GM_L=25.0 D=80% <2 GM_D= 0.9	2 abdominal mesotheliomas
		21,male	25 mg RCFs	GM_L=25.0 L=83% >10 GM_D=0.9 D=80% <2	5 abdominal mesotheliomas
		25, male	25 mg UICC crocidolite	Mean L=3.1 (SD, 10.2) L=95% ≤5	8 abdominal mesotheliomas
		25, male	0.5 ml physiological saline	NA	0 abdominal mesotheliomas
		112, male	Cage controls	NA	0 abdominal mesotheliomas

*Abbreviations: D=diameter; GM_D=geometric mean diameter; GM_L=geometric mean length; L=length; NA=not applicable; RCFs=refractory ceramic fibers; SD=standard deviation; UICC=Union Internationale Contre le Cancer; UICC/B=Union Internationale Contre le Cancer/Type B.

Table 5–2 summarizes the results of the intrapleural study of Wagner et al. [1973]. Intrapleural injection of 20 mg of ceramic fiber (unspecified type) or 20 mg for each of two samples of chrysotile produced mesotheliomas in 10% (3/31), 64% (23/36), and 66% (21/32) of Wistar rats, respectively. The mean ceramic fiber diameter was 0.5 to 1.0 μm. The lengths of the chrysotile fibers were mostly <6 μm. The chrysotile fiber diameter, RCF fiber length, and number of fibers per dose were not reported, making a direct comparison of the samples difficult.

5.1.1.3 Intratracheal Instillation Studies

The technique of intratracheal instillation has the advantage of affecting the same target tissues (other than the upper respiratory tract) as an inhalation exposure. Other advantages, compared with inhalation exposure, include a simpler technique, lower cost, accurate dosing, and the ability to deliver materials (such as long fibers) that may not be respirable to rodents [Driscoll et al. 2000]. The faster dose rate and bolus delivery of tracheal instillation may affect the response of the lung defense mechanisms, resulting in differences in clearance and biopersistence relative to an inhalation exposure. Intratracheal instillation may also produce a clumping of fibers with a resulting effect on fiber distribution and clearance [Davis et al. 1996; Driscoll et al. 2000]. Intratracheal instillation results in a heavier, more centralized distribution pattern; inhalation exposure results in a more evenly and widely distributed pattern [Brain et al. 1976]. Table 5–3 summarizes the results of two RCF intratracheal instillation studies [Smith et al. 1987; Manville 1991]. A brief description of these studies follows.

In the study by Smith et al. [1987], Syrian golden hamsters and OM rats were dosed with 2 mg of RCFs suspended in saline (Fibrefrax) by intratracheal instillation once a week for 5 weeks (10 mg total). The animals were maintained for the rest of their lives. Approximately 50% of the RCFs were <20 μm long with a mean fiber diameter of 1.8 μm. No primary lung tumors developed in RCF-exposed animals. These animals did not have an increased incidence of pulmonary fibrosis or tumor production compared with controls; however, the rats had a statistically significant increase in bronchoalveolar metaplasia. The median lifespan was 479 days for hamsters and 736 days for rats. Hamsters (median lifespan 657 days) and rats (median lifespan 663 days) exposed to the same dosing schedule with 2 mg crocidolite asbestos had a statistically significant increase in bronchoalveolar lung tumors in 20 of 27 (74%) and 2 of 25 (8%) animals, respectively. The fiber numbers per dose were not reported.

Manville [1991] reported a statistically significant increase in lung tumors in Fischer rats exposed intratracheally to 2 mg of RCF1, RCF2, RCF3, and RCF4 in saline [Manville 1991]. Animals were terminally sacrificed at 128 weeks with interim sacrifices at 13, 26, 52, 78, and 104 weeks. RCF1, RCF2, RCF3, and RCF4 exposure resulted in adenomas or adenocarcinomas in 6 of 109 (5.5%), 4 of 107 (3.7%), 4 of 109 (3.7%), and 7 of 108 (6.5%) rats, respectively. One mesothelioma was identified in a rat exposed to RCF2. Exposure to 0.66 mg chrysotile asbestos resulted in 8 primary lung tumors in 8 of 55 rats (14.5%). The fiber dimensions and numbers per dose were not reported.

5.1.2 Chronic Inhalation Studies

In animal bioassays, administering RCFs by chronic inhalation most closely mimics the occupational route of exposure. Exposure to RCFs over a time period that approximates the lifespan of the animal provides the most accurate prediction of the potential pathogenicity and carcinogenicity of these fibers in animals.

Table 5–2. Intrapleural study of RCFs* in animals

Reference	Species	Number per group†	Fiber dose	Fiber dimensions (µm)	Tumor incidence
Wagner et al. [1973]	Wistar rats	31	20 mg ceramic fibers (aluminum silicate)	D=0.5–1.0	3 mesotheliomas
		35	20 mg aluminum oxide	Area D=<10	1 mesothelioma
		35	20 mg fiberglass	L=60%>20 D=55% 2.5–7	0 mesotheliomas
		35	20 mg glass powder	Area D=<8	1 mesothelioma
		36	20 mg Canadian chrysotile	L=92% <6	23 mesotheliomas
		32	20 mg Canadian chrysotile	L=92% <6	21 mesotheliomas

*Abbreviations: D=diameter; L=length; RCFs=refractory ceramic fibers.
†The sex ratio for all groups was approximately 2 male rats to 1 female rat.

Table 5–3. Intratracheal studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Manville [1991]	Fischer 344 rats	109, male	2 mg RCF1 (0.2 ml of a 10-mg/ml suspension)	NR	6 lung adenomas
		107, male	2 mg RCF2 (0.2 ml of a 10-mg/ml suspension)	NR	4 lung tumors: 3 adenomas 1 carcinoma 1 mesothelioma
		109, male	2 mg RCF3 (0.2 ml of a 10-mg/ml suspension)	NR	4 lung tumors: 2 adenomas 2 carcinomas
		108, male	2 mg RCF4 (0.2 ml of a 10-mg/ml suspension)	NR	7 lung adenomas
		55, male	0.66 mg Canadian chrysotile (0.2 ml of a 3.3-g/ml suspension)	NR	8 lung tumors: 4 adenomas 4 carcinomas
		118, male	0.2 ml (vehicle not specified)	NR	0 lung tumors

(Continued)

See footnotes at end of table.

Table 5–3 (Continued). Intratracheal studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
Smith et al. [1987]	Osborne Mendel rats	22, female	10 mg RCFs (Fibrefrax) (2 mg/week × 5=10 mg)	GM_L=25.0 GM_D=0.9 L=3% >10 D=80% <2	0 lung tumors
		25, female	10 mg UICC* crocidolite (2 mg/week × 5=10 mg)	L=95% ≤5 mean L=3.1 (SD, 10.2)	2 bronchoalveolar tumors
		25, female	Saline controls	NA	0 lung tumors
		125, female	Cage controls	NA	0 lung tumors
	Syrian golden hamsters	25, male	10 mg RCFs (Fibrefrax) (2 mg/week × 5=10 mg)	GM_L=25.0 GM_D =0.9 L=83% >10 D=80% < 2	0 lung tumors
		27, male	10 mg UICC crocidolite (2 mg/week × 5=10 mg)	mean L=3.1 (SD, 10.2) L=95% ≤ 5	20 bronchoalveolar tumors
		24, male	Saline controls	NA	0 lung tumors
		112, male	Cage controls	NA	0 lung tumors

*Abbreviations: D=diameter; GM_D=geometric mean diameter; GM_L=geometric mean length; L=length; NA=not applicable; NR=not reported; RCFs=refractory ceramic fibers; SD=standard deviation; UICC=Union Internationale Contre le Cancer.

The effects seen in animals may be used to predict the effects of these fibers in humans, although interspecies differences exist in respiratory anatomy, physiology, and tissue sensitivity. Chronic inhalation studies provide the best means to predict the critical disease endpoints of cancer induction and nonmalignant respiratory disease that may occur in humans because of fiber exposure [McConnell 1995; Vu et al. 1996].

Five chronic RCF inhalation studies have been conducted on rats or hamsters [Davis et al. 1984; Smith et al. 1987; Mast et al. 1995a,b; McConnell et al. 1995]. These studies are summarized in Tables 5–4 and 5–5 and are described below.

Davis et al. [1984] exposed Wistar rats by whole-body inhalation to 10 mg/m^3 (95 f/cm^3) ceramic (aluminum silicate glass) dust for 7 hr/day, 5 days/week for 12 months. Ninety percent of the exposure fibers were short (<3 μm) and thin (<0.3 μm). The particle ratio of nonfibrous particulate to fibers was 4:1. Eight of 48 exposed rats (17%) developed pulmonary neoplasms: 1 adenoma, 3 bronchial carcinomas, and 4 histiocytomas. Interstitial fibrosis was observed. No pulmonary tumors were observed in control animals.

Smith et al. [1987] exposed OM rats and Syrian golden hamsters by nose-only inhalation to 10.8±3.4 mg/m^3 (200 f/cm^3) ceramic fiber (Fibrefrax) for 6 hr/day, 5 days/week for 24 months. The ratio of nonfibrous particulate to fibers was 33:1. Exposure to RCFs did not induce pulmonary tumors in rats. One RCF-exposed rat and one chamber control rat developed primary lung tumors. Rats exposed to RCFs had more severe pulmonary lesions than hamsters, and a greater percentage of rats had fibrosis than hamsters (22% versus 1%, respectively). Under similar conditions, exposure to 7 mg/cm^3 (3,000 f/cm^3) crocidolite asbestos produced pulmonary tumors in 3 of 57 rats, including 1 mesothelioma and 2 bronchoalveolar tumors. No pulmonary tumors were observed in crocidolite-exposed hamsters. Exposure to slag wool at 10 mg/m^3 (200 f/cm^3) and several fibrous glasses at similar gravimetric concentrations did not result in pulmonary neoplasms (not shown in Table 5–4).

Mast et al. [1995a] exposed Fischer 344 rats by nose-only inhalation to 30 mg/m^3 (187±53 WHO f/cm^3 RCF1, 220±52 WHO f/cm^3 RCF2, 182±66 WHO f/cm^3 RCF3, 153±49 WHO f/cm^3 RCF4) of one of four types of RCFs for 6 hr/day, 5 days/week for 24 months and held until sacrifice at 30 months. Groups of 3 to 6 animals were sacrificed at 3, 6, 9, 12, 15, 18, and 24 months to examine lesions and determine fiber lung burdens. Other animals were removed from exposure at the same time points and held until sacrifice at 24 months. Positive control rats were exposed to 10 mg/m^3 (1.06±1.14×10^4 WHO f/cm^3) chrysotile under similar exposure conditions. RCF fibers with a mean diameter of 1 μm and mean length of 20 to 30 μm were selected. A particle ratio of nonfibrous particulate to fiber of 1.02–1.88:1 was reported. Interstitial fibrosis was first observed at 6 months with RCF1, RCF2, and RCF3 and at 12 months with RCF4 exposure. Pleural fibrosis was first observed at 9 months with RCF1, RCF2, and RCF3 and at 12 months with RCF4 exposure. A progression in the severity of pleural fibrosis was seen in animals exposed to 30 mg/m^3 for 24 months and examined at 6 months post exposure. The incidence of total lung tumors was significantly increased from controls after exposure to RCF1, RCF2, and RCF3 but not RCF4. Neoplastic disease, including adenomas and carcinomas, was observed in all treatment groups: with RCF1, in 16 of 123 rats (13%); RCF2, 9 of 121 (7.4%); RCF3, 19 of 121(15.7%); RCF4, 4 of 118 (3.4%); and chrysotile, 13 of 69 (18.5%). Mesotheliomas were induced in some rats in all treatment groups: 2 with RCF1; 3 with RCF2; 2 with RCF3; 1 with

Table 5–4. Chronic inhalation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (µm)	Tumor incidence
Davis et al. [1984]	Wistar rats	48, sex unspecified	10 mg/m^3 ceramic fibers (aluminum silicate glass) 95 fibers/cm^3	L~90%<3 D~90%<0.3	8 pulmonary tumors: 1 adenoma 3 bronchoalveolar carcinomas 4 histiocytomas 16 nonpulmonary tumors: 8 benign 8 malignant 1 peritoneal mesothelioma
		40, sex unspecified	Control	NA	No pulmonary tumors Nonpulmonary tumors: 11 benign 9 malignant
Mast et al. [1995a]	Fischer 344 rats	123, male	29.1 (SD, 5.2) mg/m^3 RCF1 234 (SD, 35) total f/cm^3 187 (SD, 53) WHO† f/cm^3	mean L=22.3 (SD, 17.0) mean D=0.98 (SD, 0.61)	16 lung tumors: 8 adenomas 8 carcinomas 2 pleural mesotheliomas
		121, male	28.9 (SD, 4.5) mg/m^3 RCF2 268 (SD, 45) total f/cm^3 220 (SD, 52) WHO f/cm^3	mean L=18.7 (SD, 15.5) mean D=1.07 (SD, 0.69)	9 lung tumors: 4 adenomas 5 carcinomas 3 pleural mesotheliomas

See footnotes at end of table.

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Table 5–4 (Continued). Chronic inhalation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (µm)	Tumor incidence
		121, male	29.2 (SD, 7.0) mg/m^3 RCF3 213 (SD, 44) total f/cm^3 182 (SD, 66) WHO f/cm^3	mean L=24.2 (SD, 17.9) mean D=1.05 (SD, 0.7)	19 lung tumors: 10 adenomas 9 carcinomas 2 pleural mesotheliomas
		118, male	30.1 (SD, 7.8) mg/m^3 RCF4 206 (SD, 48) total f/cm^3 153 (SD, 49) WHO f/cm^3	mean L=12.7 (SD, 9.9) mean D=1.38 (SD, 0.7)	4 lung tumors: 2 adenomas 2 carcinomas 1 pleural mesothelioma
		130, male	Air only	NA	2 lung adenomas
Mast et al. [1995b]	Fischer 344 rats	131, male	3.0 (SD, 0.4) mg/m^3 RCF1 36 (SD, 17) f/cm^3 26 (SD, 12) WHO f/cm^3	mean L=19.88 (SD, 17.93) mean D=1.03 (SD, 0.73)	2 lung adenomas
		134, male	8.8 (SD, 0.7) mg/m^3 91 (SD, 34) f/cm^3 75 (SD, 35) WHO f/cm^3	mean L=20.54 (SD, 17.08) mean D=1.04 (SD, 0.72)	5 lung tumors: 4 adenoma 1 carcinoma 1 mesothelioma
		132, male	16.5 (SD, 1.1) mg/m^3 RCF 162 (SD, 37) f/cm^3 120 (SD, 35) WHO f/cm^{3†}	mean L=20.11 (SD, 16.87) mean D=1.06 (SD, 0.72)	2 lung tumors: 1 adenoma 1 carcinoma
		132, male	Air only	NA	1 lung adenoma

See footnotes at end of table.

(Continued)

Table 5–4 (Continued). Chronic inhalation studies of RCFs* in animals

Reference	Species	Number and sex per group	Fiber dose	Fiber dimensions (μm)	Tumor incidence
McConnell et al. [1995]	Syrian golden hamsters	102, male	30 mg/m^3 RCF1 256 (SD, 58) f/cm^3 215 (SD, 56) WHO f/cm^3	mean L=22.12 (SD, 6.7) mean D=0.94 (SD, 0.63)	42 pleural mesotheliomas
		49, male	10 mg/m^3 chrysotile, Canadian 8.4 (SD, 9.0)×10^4 f/cm^3 3.0 (SD, 1.4)×10^3 WHO f/cm^3	mean L=1.68 (SD, 2.71) mean D=0.09 (SD, 0.06)	None
		106, male	Negative controls	NA	None
Smith et al. [1987]	Osborne-Mendel rats	55, female	10.8 mg/m^3 RCFs (Fibrefrax), 200 f/cm^3	GM_L=25 GM_D=0.9	None
		57, female	7 mg/m^3 UICC crocidolite, 3,000 f/cm^3	L=95% ≤5	1 mesothelioma 2 bronchoalveolar tumors
		59, female	Chamber controls	NA	None
		125, female	Room controls	NA	None
	Syrian golden hamsters	70, male	10.8 mg/m^3 RCFs (Fibrefrax), 200 f/cm^3	GM_L=25 GM_D=0.9	1 mesothelioma
		58, male	7 mg/m^3 UICC crocidolite, 3,000 f/cm^3	L=91%≤5	None
		58, male	Chamber controls	NA	1 bronchoalveolar tumor
		112, male	Room controls	NA	None

*Abbreviations: D=diameter; GM_D=geometric mean diameter; GM_L=geometric mean length; L=length; NA=not applicable, RCFs=refractory ceramic fibers; UICC=Union Internationale Contre le Cancer; WHO=World Health Organization.

†WHO fibers have diameters <3μm, lengths >5μm, and aspect ratios >3:1 [WHO 1985].

Table 5–5. Nontumor lung effects in animals exposed to RCFs* by inhalation

Reference	Species	Fibrosis	Lung changes	Lung fiber burden
Davis et al. [1984]	Wistar rats	Minimal peribronchiolar fibrosis Interstitial fibrosis at final sacrifice Mean % of lung area (n=6 rats)=5.0% Range=0.2%–14.5%	Large areas of alveolar proteinosis Foamy and aggregated macrophages	Mean=4,130 µg n=4 rats Range=2,800–6,800 µg
Mast et al. [1995a]	Fischer 344 rats	Interstitial fibrosis seen at 3 months (RCFs) 6 months (RCF2, RCF3) 12 months (RCF4) Pleural fibrosis seen at 9 months (RCF1, RCF2, RCF3) 12 months (RCF4)	Alveolar bronchiolization, microgranulomas, collagen deposition, and alveolar macrophage deposition were seen at 6 months (RCF1) 9 months (RCF2, RCF3) 12 months (RCF4)	3.70×10^5 RCF1 fibers/mg dry lung 9.58×10^5 RCF2 fibers/mg dry lung 2.57×10^5 RCF3 fibers/mg dry lung 5.95×10^5 RCF4 fibers/mg dry lung

See footnote at end of table.

(Continued)

Table 5–5 (Continued). Nontumor lung effects in animals exposed to RCFs* by inhalation

Reference	Species	Fibrosis	Lung changes	Lung fiber burden
Mast et al. [1995b]	Fischer 344 rats	Reversible interstitial fibrosis seen at 12 months in 16-mg/m^3 group Pleural fibrosis was minimal Interstitial fibrosis progressed in 16-mg/m^3 group such that it was irreversible Pleural and interstitial fibrosis were irreversible at final sacrifice.	Microgranulomas in 16-mg/m^3 dose group at 3 months Similar but less severe in other dose groups Progression in all 3 groups at 6 months Alveolar bronchiolization in 16-mg/m^3 group	Dose- and time-dependent increases occurred in lung and lung/body weights. RCFs were cleared quickly from lungs of animals with long recovery periods.
McConnell et al. [1995]	Syrian golden hamsters	Pleural fibrosis plateaued after 12 months as diffused thickening to raised nodules. Fibrosis seen between 12 and 18 months showed increased severity.	Alveolar bronchiolization, microgranulomas, and collagen deposition; alveolar macrophage aggregation	RCF burdens leveled off between 9 and 12 months. Recovery animals showed decreased RCF burdens with decreasing lengths and widths.
Smith et al. [1987]	Osborne-Mendel rats	12/55=22%	Bronchoalveolar metaplasia, 1/55=2%	2.18±0.99×10^4 fibers
	Syrian golden hamsters	1/70=1%	Bronchoalveolar metaplasia, 2/69=3%	0.86±0.45×10^4 fibers

*Abbreviation: RCFs=refractory ceramic fibers.

RCF4; and 1 in the chrysotile exposure group. All mesotheliomas were detected at or after 24 months of exposure. Most RCF fibers recovered in the lung were 5 to 10 μm long regardless of exposure time and recovery time. An 80% reduction in fiber lung burden was seen in rats allowed to recover for 21 months following 3 months of RCF exposure.

Mast et al. [1995b] exposed Fischer 344 rats by nose-only inhalation to 0 (air), 3, 9, or 16 mg/m^3 (0, 26±12, 75±35, or 120±35 WHO f/cm^3) RCF1 for 6 hr/day, 5 days/week for 24 months and held them until sacrifice at 30 months. Fibers were selected by size as in Mast et al. [1995a]. A particle ratio of nonfibrous particulate to fibers of 0.9–1.5:1 was reported. Groups of 3 to 6 animals were sacrificed at 3, 6, 9, 12, 18, and 24 months to examine lesions and determine fiber lung burdens. Other animals were removed from exposure at the same time points and held until sacrifice at 24 months. Interstitial fibrosis was observed after 12 months of exposure in the 9- and 16-mg/m^3 exposure groups. Pulmonary fibrosis was first observed after 12 months with 16 mg/m^3 exposure and after 18 months with 9 mg/m^3 exposure. The mean Wagner grades of pulmonary cellular change and fibrosis in rats exposed to 0, 3, 9, 16, and 30 mg/m^3 of RCFs for 24 months were 1.0, 3.2, 4.0, 4.2, and 4.0, respectively. Rats exposed at the same range of doses for 24 months and allowed to recover for 6 months had mean Wagner grades of 1.0, 2.9, 3.8, 4.0, and 4.3. The severity of interstitial and pleural fibrosis was similar between those animals sacrificed at 24 months and those allowed 6 months of recovery following the 24 months of exposure. The incidence of pulmonary neoplasms was not statistically different from the controls in all exposure groups. One pleural mesothelioma was observed in the 9-mg/m^3 exposure group. A dose-related increase occurred in fiber lung burden. Fiber lengths of 5 to 10 μm were most prevalent in the lung fibers recovered after 3 months of exposure followed by 21 months of recovery, after 12 months of exposure, and after 24 months of exposure to all doses of RCFs. Animals exposed for 3 or 6 months and then allowed to recover until sacrifice at 24 months had lung burdens reduced by 96% to 97% compared with animals not allowed recovery time.

McConnell et al. [1995] exposed Syrian golden hamsters by nose-only inhalation to 30 mg/m^3 RCF1 (256±58 WHO f/cm^3) for 6 hr/day, 5 days/week for 18 months and held them until sacrifice at 20 months. Positive control animals were exposed to 10 mg/m^3 (8.4±9.0×10^4 WHO f/cm^3) chrysotile asbestos. Groups of 3 to 6 animals were sacrificed at 3, 6, 9, 12, 15, and 18 months to examine lesions and determine fiber lung burdens. Other animals were removed from exposure at the same time points and held until sacrifice at 20 months. Interstitial and pleural fibrosis were first observed after 6 months of exposure in RCF-exposed hamsters. No pulmonary neoplasms developed. Forty-two of 102 (41.2%) RCF-exposed animals developed pleural mesotheliomas. Most mesotheliomas developed after 18 months of exposure. Animals exposed to chrysotile developed a more severe interstitial fibrosis and pleural fibrosis than those exposed to RCFs. No neoplasms were observed in the lungs or pleura of the chrysotile-exposed or air control animals. The greatest percentage of retained fibers had lengths of 5 to 10 μm and diameters <5 μm in the lungs after 6 months of exposure followed by 12 months of recovery.

McConnell et al. [1999] conducted a multidose chronic study of the effects of amosite inhalation in hamsters. The data can be compared with the effects of RCF1. Syrian golden hamsters were exposed to 0.8 (36±23 WHO f/cm^3), 3.7 (165±61 WHO f/cm^3), or 7 mg/m^3 (263±90 WHO f/cm^3) amosite asbestos. Pleural mesothelioma incidences of 3.6%, 25.9%, and 19.5%, respectively, were reported. The aerosol mean

diameter of the amosite asbestos was 0.60 µm ±0.25; its aerosol mean length was 13.4 µm ±16.7. The dimensions of this asbestos fiber were more similar to those of the RCFs used in the chronic inhalation studies of McConnell et al. [1995] than the chrysotile asbestos used as the positive control in that same study.

NIOSH [Dankovic 2001] analyzed the hamster data from the RCF [McConnell et al. 1995] and amosite studies [McConnell et al. 1999]. A dose-response model was developed for amosite and was used to predict the amosite response at the one and only dose at which RCFs were tested in hamsters. The modeled amosite response was compared with the observed RCF response. These results are presented in Figures 5–1 and 5–2. Log-probit, log-logistic, multistage, and unrestricted Weibull models were analyzed. The transformation for the log-probit and log-logistic models was log (fibers/cm^3 +1). The dose metric of the multistage and Weibull models was fibers/cm^3, as they did not require a log-transformation. Results of the log-probit model analysis of these data indicated RCF/amosite relative potency estimates of 1.85 and 1.19, using WHO fibers and fibers >20 µm as the dose metric, respectively. The model fits were poor when the amosite high-dose group and 20 µm-fiber dose were included. Sensitivity analyses in which the high-dose amosite group was dropped suggest that the relative potency of RCFs to amosite could be as low as 0.66 based on the log-probit model. Results using the log-logistic, multistage, and Weibull models were similar to those using the log-probit model, with an overall range of RCF/amosite relative potency estimates from these models using all four amosite dose groups of 1.03 to 1.89. Although no clear toxicologic basis exists for disregarding the high-dose amosite data, sensitivity analyses based on excluding these data suggest that the potency of RCFs relative to amosite could be as low as 0.47, based on the multistage model. These models indicate that the plausible carcinogenic potency estimates for RCFs relative to amosite, based on hamster mesotheliomas, range from about half to nearly twice the carcinogenicity of amosite.

5.1.3 Discussion of RCF Studies in Animals

The intrapleural, intraperitoneal, and intratracheal RCF studies have demonstrated the carcinogenicity of RCFs. Because of the nonphysiologic delivery of fibers by these methods, it is difficult to compare their results with those of an inhalation exposure. Although tracheal instillation may result in different distribution patterns than an inhalation exposure, this route of exposure is useful as a screening test for relative toxicity and to compare the toxicity of new materials with the toxicity of materials for which data already exist [Driscoll et al. 2000]. Tracheal instillation also is useful when testing fibers respirable by humans but not rodents. Chronic inhalation studies provide the data most relevant to occupational exposure to RCFs.

The RCF chronic animal inhalation studies described above allow for the comparison of health effects of exposure to different doses of RCF1, different types of RCFs, and the interspecies susceptibility of the rat and hamster to RCF exposure.

Results of the multidose chronic inhalation testing of RCF1 in rats indicate the pathogenic potential of RCFs at high doses [Mast et al. 1995a,b]. The incidence of total lung tumors was significantly increased from controls after exposure to 30 mg/m^3 RCF1, RCF2, and RCF3 but not RCF4. A dose-response relationship was demonstrated for nonneoplastic pulmonary changes in rats exposed to 3, 9, and 16 mg/m^3 RCFs. The severity of interstitial and pleural fibrosis was similar between those animals sacrificed at 24 months and those allowed 6 months

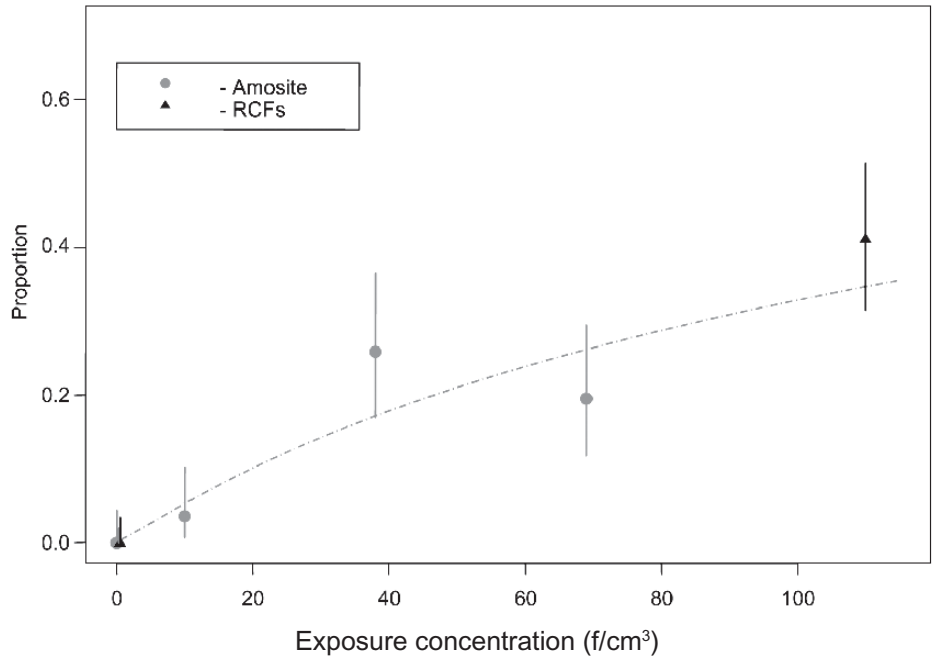

Figure 5–1. Proportion of hamsters with mesotheliomas following exposure to amosite or RCFs. Concentrations are based on fibers >20μm long. The 95% confidence limits are based on assuming a binomial distribution. Dashed lines represent the log-probit model fitted to the amosite data [Dankovic 2001]. (Source: McConnell et al. [1995, 1999].)

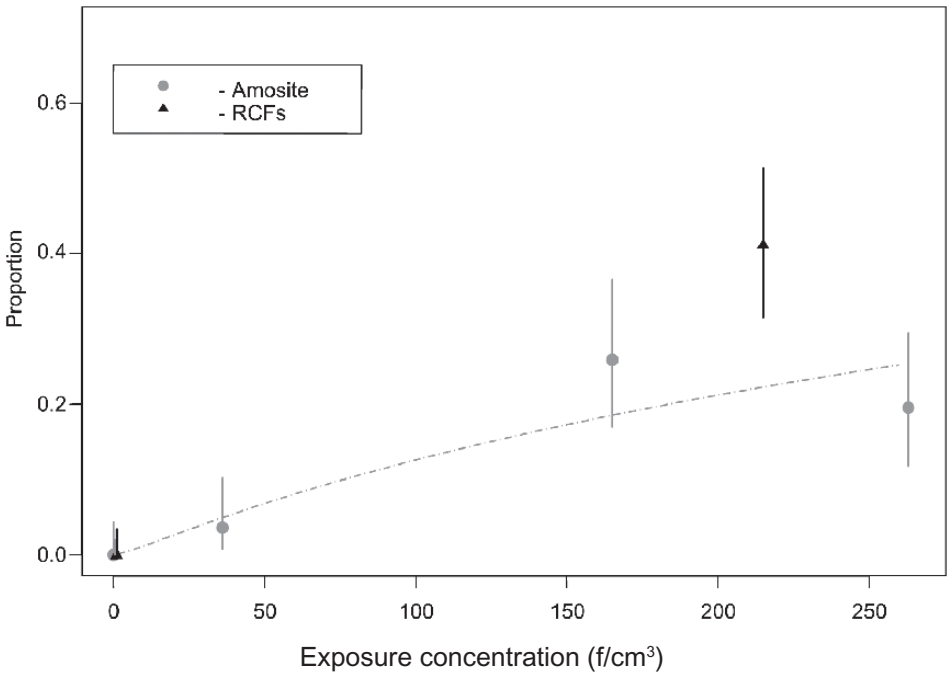

Figure 5–2. Proportion of hamsters with mesotheliomas following exposure to amosite or RCFs. Concentrations are based on WHO fiber dimension criteria. The 95% confidence limits are based on assuming a binomial distribution. Dashed lines represent the log-probit model fitted to the amosite data [Dankovic 2001]. (Source: McConnell et al. [1995, 1999].)

of recovery following the 24-month exposure. Spontaneous primary pulmonary mesotheliomas are rare in rats [Analytical Sciences Incorporated 1999]. Therefore, the presence of any mesothelioma in treated animals is biologically significant and warrants caution.

Comparing the chronic effects of RCF1 with its positive control, chrysotile asbestos, in the hamster is difficult because of the differences in dose, dimensions, and durability of the two fibers tested [McConnell et al. 1995]. More recent dose-response data on amosite asbestos provide a comparison because these amosite fiber dimensions more closely resemble those of RCF1 [McConnell et al. 1999]. The mean lengths of the RCFs and amosite asbestos fibers were 22.1 (±16.7) and 13.4 (±16.7) µm, respectively. Forty-three percent of RCF fibers and ~26% of amosite asbestos fibers were longer than 20 µm. The mean diameters of the RCFs and amosite asbestos fibers were 0.94 (±0.63) and 0.60 (±0.25) µm, respectively. Interstitial and pleural fibrosis were seen much earlier with amosite exposure than with RCF exposure. RCF exposure at 215 (±56) WHO f/cm^3 resulted in mesotheliomas in 42 of 102 (41%) hamsters. Amosite asbestos exposure at 263 (±90) WHO f/cm^3 resulted in mesotheliomas in 17 of 87 (19.5%) hamsters. Modeling of these data indicates that the plausible carcinogenic potency estimates for RCFs relative to amosite, based on hamster mesotheliomas, range from about half to nearly twice the carcinogenicity of amosite [Dankovic 2001]. Differences in the physical characteristics and biopersistence of RCF1 and amosite asbestos must be considered before extrapolating these animal data to human risk.

Hamsters showed a greater susceptibility to mesothelioma induction after RCF1 exposure than did rats under similar exposure conditions [Mast et al. 1995a; McConnell et al. 1995]. Chronic inhalation studies of amosite asbestos in hamsters showed no pulmonary neoplasms, but high incidences of mesothelioma occurred at doses of 125 and 250 f/cm^3 [McConnell et al. 1999]. Many of the mesotheliomas in the more recent hamster studies were identified only on microscopic examination [Mast et al. 1995a; McConnell et al. 1995, 1999]. Previous studies reporting mesotheliomas only by macroscopic identification may have underestimated the mesothelioma incidence. Recent, short-term inhalation studies indicate that hamster mesothelial cells may have a more pronounced inflammatory and proliferative response to RCF1 exposure than those of rats [Everitt 1997; Gelzleichter et al. 1996a,b, 1999]. The reasons for this species difference in response to RCFs have not been explained. The results of these animal studies indicate the need for the inclusion of the hamster as a sensitive test species in those studies in which pleural mesothelioma is an endpoint of concern.

Results from Mast et al. [1995a] indicate that under the conditions studied, exposure to RCF4 may have a less pronounced effect on pulmonary pathology than exposure to RCF1, RCF2, and RCF3. Rats exposed to RCF4 did not have a significant increase in total lung tumors compared with controls; those exposed to RCF1, RCF2, and RCF3 did. Exposure to RCF4 produced a less severe fibrosis than was seen in the other RCF exposure groups. Differences in the dimensions or physical properties of RCF4 may explain its different respiratory effects from RCF1, RCF2, and RCF3. RCF4 was produced by heating RCF1 in a furnace at 2,400 °F for 24 hr. This "after-service" fiber contained approximately 27% free crystalline silica. Silicotic nodules were observed in the RCF4-exposed animals. RCF4 fibers were shorter (~34% between 5 and 10 µm) and thicker (~35% <0.5 µm) than those of RCF1, RCF2, and RCF3.

The particle content of the RCF test material may have been responsible for some of the respiratory pathology observed in these studies.

However, an analysis of the ratio of nonfibrous to fibrous particulates in the reviewed studies does not indicate a correlation between the particulate content and observed effects. Smith et al. [1987] performed testing with the highest particulate to fiber ratio at 33:1 and did not report a high tumor incidence. Comparing studies based on the ratio of nonfibrous particulates to fibers is complicated by differences among the studies in fiber preparation, doses tested, fiber dimensions, and methods of fiber analysis. The techniques used to detect and measure nonfibrous particulates have improved over time so that the comparison of recent and older studies may reflect these inconsistencies.

These chronic RCF inhalation studies indicate the ability of RCFs to induce cancer in two laboratory species—mesotheliomas in hamsters and pulmonary tumors in rats. The late onset of tumors indicates the importance of chronic studies on the effects of RCF exposure. Short-term intraperitoneal, intrapleural, intratracheal, and inhalation studies provide important information about the action of fibers, the fiber characteristics associated with toxicity, and potential toxicity. Currently it is only through lifespan toxicologic testing of animals that the respiratory and other chronic health effects of RCFs can be accurately assessed.

5.1.4 Lung Overload Argument Regarding Inhalation Studies in Animals

Mast et al. [2000] published a review interpreting the results of chronic inhalation studies of RCF1 in rats and hamsters [Mast et al. 1995a,b; McConnell et al. 1995]. In the review, the authors suggest the possibility that the maximum tolerated dose (MTD) may have been exceeded and that lung overload may have compromised the pulmonary clearance mechanisms of test animals. Building on the concept of lung overload (first advanced by Bolton et al. [1983]), Mast et al. [2000] considered particulate coexposure (i.e., nonfibrous particulate or shot) to be a confounding factor that may have had a major effect on the observed chronic adverse effects. The authors propose that the MTD was exceeded at the highest exposure concentration of 30 mg/m^3 for RCF1 in the rat bioassay.

The concept of pulmonary overload in the Fischer 344 rats is based on the recognition that excessive particulate exposures (>1,500 μg/rat, according to Bolton et al. [1983]) eventually reduce the clearance effectiveness of the lungs, causing the normal linear clearance kinetics to follow a nonlinear pattern. On a cellular level, the overload conditions may result in alveolar macrophages becoming engorged with particulate, pulmonary and alveolar inflammation, increased translocation of particles to the interstitium and lymph, granuloma formation, pulmonary fibrosis, and lung tumors, depending on the time and severity of the overload [Mast et al. 2000]. Ambiguity about the definition of MTD for chronic inhalation studies with animals was also a concern expressed by the authors. One reference [Morrow 1986] recognizes the MTD as that which causes "a significant functional impairment of lung clearance." At a National Toxicology Program (NTP) workshop on establishing exposure concentrations for inhalation studies in animals, it was concluded that the highest exposure concentration should produce only minimal changes in lung defense mechanisms as measured by clearance [Lewis et al. 1989]. At a similar workshop convened by the EPA, it was proposed that the MTD for fiber inhalation studies is equivalent to the lung dose produced at the maximum achievable concentration (MAC) [Vu et al. 1996]. The MAC is calculated as the highest fiber concentration based on a 90-day study that results in significant changes in alveolar macrophage clearance rates, lung burden normalized to exposure

concentration, cell proliferation, inflammation, lung weight, and other measures.

The methodology described for the RCF chronic inhalation studies involved procedures (i.e., wet cyclone separation technology) for removing the nonfibrous particulate fraction from the commercial fiber (RCF1) used for the inhalation exposures [Mast et al. 1995a,b 2000; McConnell et al. 1995]. This process resulted in an aerosol with a 9.1:1 particle-to-fiber ratio [Maxim et al. 1997; Mast et al. 2000], compared with a study by Smith et al. [1987], which reported 33 nonfibrous particles per fiber in airborne exposures. Results from Esmen et al. [1979] indicate that despite a poor correlation between mass of total airborne dust and fiber concentration in RCFs measured in manufacturing, fibers generally constitute only a small portion of the total dust. This finding is consistent with other reported measures of occupational exposures to airborne RCFs [Krantz et al. 1994; Trethowan et al. 1995]. However, Maxim et al. [1997] reported an average particle-to-fiber ratio of 0.53:1 (n=10, range not reported), or roughly 1 particle to 2 fibers in RCF manufacturing facilities.

Muhle and Bellmann [1996] conducted a 5-day inhalation study with Fischer 344 rats to measure the biopersistence of RCF1 (with the 9:1 particulate-to-fiber ratio) and RCF1a (RCF1 that is further processed to reduce particulate mass). The study showed a 1.5-fold longer time-weighted half-life for RCF1 ($t_{1/2}$=78 days) compared with RCF1a ($t_{1/2}$=54 days). That study also involved a 3-week inhalation experiment with Fischer 344 rats, in which the clearance of RCF1 ($t_{1/2}$=103 days) was almost twice as long as that of RCF1a ($t_{1/2}$=54 days).

In a follow-up study by Brown et al. [2000], female Wistar rats were exposed to RCF1 and RCF1a by inhalation for 3 weeks and followed for 12 months to evaluate alveolar macrophage clearance and inflammation. The exposure concentrations were 130 fibers/ml >20 μm for RCF1 and 125 fibers/ml >20 μm for RCF1a. The nonfibrous content of RCF1 was approximately 25%, whereas the nonfibrous content of RCF1a was 2%. The mean diameter of the nonfibrous particles was 2 to 3 μm. The aerosol exposure to RCF1 contained twice as many short fibers (<20 μm) as RCF1a and twice the amount of dust (fibers and nonfibrous dust/mg · m^3) as RCF1a (51 versus 25.8 mg/m^3). At the end of the inhalation period, animals exposed to RCF1a had a higher pulmonary concentration of long fibers but lower concentrations of short fibers and nonfibrous particles. The difference in particle content was enhanced in the lungs—15 times more particles were found in the lungs of the RCF1-exposed animals than in those exposed to RCF1a. In the aerosol exposure, only an eightfold difference was found in the number of particles between RCF1 and RCF1a. The RCF1a-exposed animals had a half-time alveolar clearance of 80 days (71–91) compared with 60 days (49–77) for the controls; clearance half-time for exposed RCF1 animals was 1,200 days (573-infinity) compared with 66 (58–88) for the corresponding controls. To evaluate respiratory inflammation, bronchoalveolar lavage (BAL) measurements (lactose dehyrdogenase [LDH], γ-glutamyltransferase [γ –GT], total protein, reduced glutathione [GSH]) were taken at the end of the 3-week study period and at subsequent intervals over the next 12 months. Immediately following the 3-week inhalation study, all BAL measurements were statistically elevated in both RCF1 and RCF1a animals. However, after 91 days of recovery, the BAL measurements for RCF1a animals returned to normal. Indications of inflammation continued for RCF1 through the entire observation period. The greater and more persistent inflammation seen with RCF1 was attributed to the greater mass of material or to increased activity of the nonfibrous particles, although the high concentration of short fibers in RCF1 (twice that of RCF1a) could

have contributed to the observed impedance in alveolar macrophage clearance and inflammation.

Tran et al. [1997] examined how overloading the alveolar macrophage defense system affects the clearance of fibers versus that of nonfibrous particles. Modeling was performed based on data for rats exposed by inhalation to titanium dioxide (TiO_2) at 1, 10, and 50 mg/m^3 or to glass wool (MMVF10) at 3, 16, and 30 mg/m^3. Lung burdens and clearance kinetics during exposure (0 to 100 weeks) were compared with those at 3, 10, and 38 days post-exposure. The models showed that overloading of the lung by fibers or nonfibrous particles are similar when fibers are short (<15 µm). This observation is plausible, as nonfibrous particles and short fibers smaller than the diameter of the alveolar macrophage are most readily engulfed and cleared via the macrophages. When this defense is overwhelmed (lung burden ≥10 mg), these particles are cleared less effectively. For fibers longer than 15 µm, phagocytosis by alveolar macrophage is reduced. As fiber length increases, fibers tend to be cleared by dissolution and disintegration of long fibers into shorter fibers or fragments. Therefore, clearance of long fibers is not affected by the overloading of macrophage-mediated defenses with shorter fibers or nonfibrous particles.

The exposure concentrations for the RCF chronic inhalation bioassays were measured and reported as mass in mg/m^3. Monitoring of exposures as performed by gravimetric analysis does not distinguish fibers from nonfibrous particulate, although fiber concentration and dimensions were also checked by phase contrast and electron microscopy [Mast et al. 1995a,b]. Consequently, the particulate fraction was included in the dose measurements. This fact does complicate efforts to compare the relative toxicity of fibers, nonfibrous particulate, and total combined particulate, especially regarding the lung overload hypothesis. During production of RCFs and RCF products, however, the nonfibrous particulate fraction is associated with the fiber, as shown in Table 2–1 (i.e., 20% to 50% of RCFs by weight is nonfibrous particulate). This suggests that occupational exposures to airborne RCFs necessarily involve coexposures to a fraction of nonfibrous particulate, a suggestion that has been supported by exposure assessment studies [Esmen et al. 1979; Krantz et al. 1994; van den Bergen et al. 1994; Trethowan et al. 1995; Maxim et al. 1997; Mast et al. 2000].

5.2 Cellular and Molecular Effects of RCFs (In Vitro Studies)

The cellular and molecular effects of RCF exposures have been studied with two different objectives. One purpose of these in vitro studies is to provide a quicker, less expensive, and more controlled alternative to animal toxicity testing. These experiments are best interpreted by comparing their results with those of in vivo experiments. The second objective of in vitro studies is to provide data that may help to explain the pathogenesis and mechanisms of action of RCFs at the cellular and molecular levels. These cytotoxicity and genotoxicity studies are best interpreted by comparing the effects of RCFs with those of other SVFs and asbestos fibers. In vitro studies serve as screening tools and provide insights into the molecular mechanisms of fibers. They are an important complement to animal studies. Currently it is not possible to use these data to derive the NIOSH REL for RCFs. For this reason, a discussion of in vitro studies is included here, but the more comprehensive summaries of studies are included in Appendix C.

The toxicity of fibers has been attributed to their dose, dimensions, and durability. Any test

system that is designed to assess the potential toxicity of fibers must address these factors. Durability is difficult to assess using in vitro studies because of their acute time course. However, in vitro studies provide an opportunity to study the effects of varying doses and dimensions of fibers in a quicker, more efficient method than animal testing. They do not currently provide data that can be extrapolated to occupational risk assessment.

The association between fiber dimension and toxicity has been documented and reviewed [Stanton et al. 1977, 1981; Pott et al. 1987; Warheit 1994]. RCFs may have different toxicities, depending on the fiber length relative to macrophage size. Longer fibers are more toxic. Fiber length has been correlated with the cytotoxicity of glass fibers [Blake et al.1998]. Manville code 100 (JM–100) fiber samples with average lengths of 3, 4, 7, 17, and 33 μm were assessed for their effects on LDH activity and rat alveolar macrophage function. The greatest cytotoxicity was reported in the 17- and 33-μm samples, indicating that length is an important factor in the toxicity of this fiber. Multiple macrophages were observed attached along the length of long fibers. Relatively short fibers (<20 μm) were usually phagocytized by one rat alveolar macrophage [Luoto et al. 1994]. Longer fibers were phagocytized by two or more macrophages. Incomplete or frustrated phagocytosis may play a role in the increased toxicity of longer fibers. Long fibers (17 μm average length) were a more potent inducer of tumor necrosis factor (TNF) production and transcription factor activation than shorter fibers (7 μm average length) [Ye et al. 1999]. These studies demonstrate the important role of length in fiber toxicity and suggest that the capacity for macrophage phagocytosis may be a critical factor in determining fiber toxicity.

Several of the in vitro RCF studies (summarized in Appendix C) reported a direct association between a longer fiber length and greater cytotoxicity. Hart et al. [1992] reported the shortest fibers to be the least cytotoxic. Brown et al. [1986] reported an association between length, but not diameter, and cytotoxic activity. Wright et al. [1986] reported that cytotoxicity was correlated with fibers >8 μm long. Yegles et al. [1995] reported that the longest and thickest fibers were the most cytotoxic. The four most cytotoxic fibers had GM lengths ≥13 μm and GM diameters >0.5 μm. The production of abnormal anaphases and telophases was associated with Stanton fibers with a length >8 μm and diameter <0.25 μm. Hart et al. [1994] reported that cytotoxicity increased with increasing average fiber lengths from 1.4 to 22 μm, but did not increase with average lengths from 22 to 31 μm.

Additional studies assessing the cytotoxicity of specific RCF fiber lengths are needed. Such studies will help to describe the association between fiber length and toxicity for RCFs and may allow determination of a threshold length above which toxicity increases significantly. In addition to providing data on the correlation between fiber length and toxicity, in vitro studies have provided data on the relative toxicity of RCFs compared with other fibers, although some uncertainties remain in the interpretation of these studies because of differences in fiber doses, dimensions, and durabilities. RCFs have direct and indirect effects on cells and alter gene function in similar ways. They are capable of inducing enzyme release and cell hemolysis. They may decrease cell viability and inhibit proliferation. RCFs affect the production of TNF and reactive oxygen species (ROS) and affect cell viability and proliferation. They induce necrosis in rat pleural mesothelial cells. They may also induce free radicals, micronuclei, polynuclei, chromosomal breakage, and hyperdiploid cells in vitro.

In vitro studies provide an excellent opportunity for investigating the pathogenesis of RCFs. However, comparisons are difficult to make

between in vitro studies based on differences in fiber doses, dimensions, preparations, and compositions. Important information such as fiber length distribution is not always determined. Even when comparable fibers are studied, the cell line or conditions under which they are tested may vary. Much of the research to date has been done in rodent cell lines and in cells that are not related to the primary target organ. In vitro studies using human pulmonary cell lines should provide pathogenesis data most relevant to human health risk assessment.

Short-term in vitro studies cannot take into account the influence of fiber dissolution and fiber compositional changes that may occur over time. In an in vivo exposure, fibers are continually modified physically, chemically, and structurally by components of the lung environment. This complex set of conditions is difficult to recreate in vitro. Just as it is unlikely that only one factor is an accurate predictor of fiber toxicity, it is unlikely that any one in vitro test is able to predict fiber toxicity.

5.3 Health Effects in Humans

5.3.1 Morbidity and Mortality Studies

Two major research efforts evaluated the morbidity of RCF-exposed workers—one conducted in U.S. plants and one in European plants. Table 5–6 describes the populations analyzed for both studies. The objective of these research efforts was to evaluate the relationship between occupational exposure to RCFs and potential adverse health effects. These studies included standardized respiratory and occupational history questionnaires, chest radiographs, and pulmonary function tests (PFTs) of workers, as well as air sampling to estimate worker exposures. The studies of European plants began in 1986. Study subjects included only current workers at seven RCF manufacturing plants [Rossiter et al. 1994; Trethowan et al. 1995; Burge et al. 1995]. A followup cross-sectional study conducted in 1996 evaluated the same medical endpoints in workers from six of these seven European manufacturing plants (one plant had ceased operation) [Cowie et al. 1999, 2001]. Current and former workers were included as study subjects in the followup study. The studies of U.S. plants began in 1987 and involved evaluations of current workers at five RCF manufacturing plants and former workers at two RCF manufacturing plants [Lemasters et al. 1994, 1998; Lockey et al. 1993, 1996, 1998, 2002].

In the United States, the earliest commercial production of RCFs and RCF products began in 1953; in Europe, RCF production began in 1968. The demographics of the U.S. and European populations were similar at the time they were studied, although the average age of U.S. workers was slightly higher than that of the workforce in the 1986 European studies because of the earlier development of this industry in the United States. The mean age for the European RCF workers was 37.7 in the 1986 study [Trethowan et al. 1995] and 42.0 for males and 39.4 for female workers in the 1996 study [Cowie et al. 1999]. In the U.S. RCF manufacturing industry, the average age is 40 for current workers and 45 for former workers [Lemasters et al. 1994]. The mean duration of employment in the European cohort was 10.2 years (range 7.2 to 13.8 years) in 1986 [Trethowan et al. 1995] and 13.0 years in 1996 [Cowie et al. 1999]. The U.S. study reports the mean duration of employment for 23 workers with pleural plaques as 13.6 years (±9.8); the median is 11.2 years (range 1.4 to 32.7) [Lemasters et al. 1994].

The following text and Table 5–7 summarize findings from the U.S. and European research efforts, organized according to results from radiographic examinations, respiratory symptoms, and PFTs. Discussion of two related

Table 5–6. Cited studies of populations with occupational exposures to RCFs*

Study	Design	Population analyzed				Outcome measures		
		Employment status	Number	% male workers	% female workers	Radiography	PFT	Symptoms
European:								
Burge et al. 1995‡	Cross-sectional	Current§	532	100	0	N	Y	Y
Rossiter et al. 1994‡	Cohort morbidity	Current**	543	100	0	Y	N	N
Trethowanet al. 1995‡	Cross-sectional	Current	628	91	9	Y	Y	Y
Cowie et al. 1999††	Cross-sectional	Current	695	90	10	Y	Y	Y
		Former	79	85	15			
United States:‡‡								
Lemasters et al. 1994	Cross-sectional	Current	627	83	17	Y	N	N
Lemasters et al. 1994	Cross-sectional	Former§§	220	91	9			
Lockey et al. 1993:	Cohort mortality	Current and former	684 (including 46 deceased and 5 lost to followup)***	100	0	N	N	N (Cause of death)
	Cohort morbidity	Current and former	801 (participants; 99% provided respiratory history, 94% provided PFTs, and 90% provided chest X-rays [radiography])	85	15	Y	Y	Y
Lockey et al. 1996	Cohort morbidity	Current	370	NA	NA	Y	N	N
		Former	282†††	NA	NA	NA	NA	NA
	Nested case-control	Both (17 cases with 3 controls each matched on current versus former status)	NA	NA	Y	Y	N	N
Lockey et al. 1998	Cross-sectional and longitudinal	Current	361‡‡‡	100	0	N	Y	N

See footnotes on next page.

*Abbreviations: N=number; NA=not available from published citation; PFT=pulmonary function test; RCFs=refractory ceramic fibers; Y=yes.
†Current versus former (and leaver) worker status at an RCF manufacturing plant as determined at time of survey.
‡Study included current workers at seven ceramic fiber manufacturing plants in three European countries.
§From a possible 708 current workers, 628 eligible participants were identified and 596 had chest X-ray examinations; 51 female workers and 13 unexplained others were excluded from analysis.
**From a possible 708 current workers, 628 eligible participants were identified and 596 had chest X-ray examinations; 2 unreadable films and those of 51 female workers were excluded from the analysis.
††Study included current workers at six ceramic fiber manufacturing plants in three European countries as well as leavers from the first three European studies [Burge et al. 1995; Rossiter et al. 1994; Trethowan et al. 1995] (one of the seven plants included earlier had ceased operation).
‡‡Studies included current and former workers at five RCF manufacturing plants in the United States.
§§From a possible 1,030 eligible current and former workers, 183 were either deceased, not located, or did not agree to chest X-ray examinations.
***From a possible 729 eligible current and former workers at 2 plant sites for whom individual work histories were available, 45 were excluded on the basis of insufficient exposures to fibers or insufficient data regarding fiber exposures.
†††From a possible 868 eligible current and former workers at 2 plant sites, 148 were eliminated for lack of exposure characterization data and loss to followup. Of the remaining 720 workers, 68 did not agree to chest X-ray examinations.
‡‡‡From a possible 963 eligible current workers at five plant sites, 209 female workers were excluded as well as 393 male workers with fewer than 5 PFT sessions.

mortality studies is also presented in Section 5.3.5 [Lockey et al. 1993; Lemasters et al. 2003]. Two HHEs of workplaces involving workers exposed to RCFs are also described in Section 5.3.6 [Kominsky 1978; Lyman 1992].

5.3.2 Radiographic Analyses

In both the European and U.S. studies cited in Table 5–6, the study populations included workers at multiple plants involved in the manufacture of RCFs or RCF products. As part of the investigation of potential effects of exposure to airborne RCFs, chest radiography was performed. In all studies, chest radiographs were read independently by three readers using the International Labour Office (ILO) 1980 *International Classification of the Radiographs of Pneumoconioses* [ILO 1980]. Identifiers on films were masked to ensure a blind review by readers, and quality control measures and tests of agreement were used to check consistency among the readers. For each type of abnormality analyzed, the median of the three readings for each film was used.

5.3.2.1 Pleural abnormalities

In the 1986 study of European RCF workers, results of the chest radiography indicated a prevalence of 2.8% (15/543) for pleural abnormalities among male workers [Rossiter et al. 1994]. Of the 15 cases with pleural abnormalities, 4 had bilateral diffuse thickening (1 with calcification), 1 showed bilateral pleural calcification only, 7 presented with unilateral diffuse thickening, and 3 showed costophrenic angle blunting only. The possibility for confounding effects was recognized because of other exposures: 52% of workers reported previous employment in dusty jobs, including 4.5% with prior asbestos exposures and 7% with prior MMMF exposures. When female workers were included in the same population, Trethowan et al. [1995] reported a prevalence of 2.7% (16/592) for pleural abnormalities. Two cases were known to have previous exposure to asbestos, and the possibility for exposure to other respiratory hazards was acknowledged for other persons with pleural abnormalities. Cowie et al. [1999, 2001] reported pleural abnormalities in 10% (78/774) and

Table 5–7. U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lemasters et al. 1994 (U.S. study)	**Cross-sectional study:** 1,030 current and former workers at five U.S. RCF production facilities employed 10/87–8/89. Male workers: at least 1 year of employment in fiber division. Female workers: at least 1 year of employment in fiber division and ≥4 hr per week in production.	Posteroanterior chest X-ray examinations were performed for 847 workers. Occupational and respiratory health histories were obtained using standardized questionnaire. Standardized measures of pulmonary function (FEV_1, FVC, and $FEF_{25–75}$) were used.	**Radiographic analyses:** ***Pleural changes*** Pleural changes were seen in 3.4% of production workers (23/686) and in 0% of nonproduction workers (0/161); 91.3% of pleural changes were classified as pleural plaques. No irregular opacities were observed.	Multiple logistic regression found a statistically significant association between pleural plaques and time since first RCF production job (>20 years) after adjustment for known asbestos exposure and a statistically significant association between pleural plaques and duration (>20 years) of RCF exposure.

Pleural changes

Item	Prevelance (%)	OR	95% CI
Years of latency:†			
>0–10	1.3	1.0	—
>10–20	3.6	2.9‡,§	0.8, 9.7
>20	11.4	7.7‡,§	2.0, 29.1
Years of RCF exposure:			
>0–10	1.9	1.0	—
>10–20	4.3	2.5**,††	0.9, 7.0
>20	20.7	8.8**,††	2.6, 30.1

(Continued)

*Abbreviations: CI=confidence interval; $FEF_{25–75}$=forced expiratory flow between 25% and 75% of the FVC; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; OR=odds ratio; RCFs=refractory ceramic fibers.
†Latency: time since first RCF exposure.
‡Compared with >0–10 years of latency.
§Adjusted for years of latency and years of asbestos exposure.
**Compared with >0–10 years of RCF exposure.
††Adjusted (confounding variables not described).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lemasters et al. 1998 (U.S. study)	**Cross-sectional study:** 742 of 753 active workers (597 male; 145 female) at five RCF manufacturing sites who participated in occupational history interviews between 1987 and 1989.	**Medical Evaluation:** Modified American Thoracic Society (ATS) questionnaire. Spirometric evaluation (pulmonary function) at time of ATS interview. Measures included FEV_1, FVC, and $FEF_{25\%-75\%}$. **Exposure assessment:** Occupational history interview **Production work:** Defined as spending ≥4 hr/week (10% of work time) in production areas.	**Symptom analysis** **Prevalence (%)** **Symptom** | **Nonproduction workers** | **Production workers** | **OR†** | **95% CI** Male workers | n=80 | n=517 | — | — Dyspnea 1 | 2.5 | 15.7 | 7.3‡ | 1.7, 30.5 Dyspnea 2 | 0.0 | 4.8 | — | *P*=0.03‡ Wheezing | 3.8 | 10.3 | 2.5 | 0.8, 8.5 Asthma | 2.5 | 2.3 | 1.0 | 0.2, 4.7 Chronic cough | 5.0 | 7.4 | 1.0 | 0.3, 3.0 Chronic phlegm | 3.8 | 5.8 | 1.2 | 0.4, 4.6 Pleuritic pain | 0.0 | 1.6 | — | *P*=0.31 One or more symptoms | 11.3 | 29.6 | 2.9‡ | 1.4, 6.2 Female workers | n=59 | n=86 | — | — Dyspnea 1 | 18.6 | 25.6 | 1.3 | 0.6, 3.2 Dyspnea 2 | 0.0 | 10.5 | — | *P*=0.001‡ Wheezing | 1.7 | 7.0 | 3.9 | 0.4, 38.8 Asthma | 0.0 | 3.5 | — | *P*=0.21 Chronic cough | 1.7 | 9.3 | 5.4 | 0.6, 46.9 Chronic phlegm | 1.7 | 9.3 | 3.8 | 0.4, 33.5 Pleuritic pain | 0.0 | 3.5 | — | *P*=0.21 One or more symptoms | 20.3 | 40.7 | 2.4‡ | 1.1, 5.3	Prevalence of respiratory symptoms (except for asthma) was approximately 2- to 5-fold higher in production workers than in nonproduction workers.

(Continued)

*Abbreviations: ATS = American Thoracic Society; CI = confidence interval; $FEF_{25\%-75\%}$ = Forced expiratory flow between 25% and 75% of the FVC; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; n = number; OR = odds ratio; *P* = probability; RCFs = refractory ceramic fibers.

†Adjusted for age, smoking (category and pack years), and years of possible asbestos exposure in a logistic regression model.

‡Statistically significant ($P<0.05$).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods				Results	Comments
Lemasters et al. 1998, continued (U.S. study)	**Multiple regression analysis**† of change in volume (ml) of height-adjusted spirometric measures (95% CI) associated with RCF employment duration. Controlled for smoking status.	**Pulmunary function**				Years of RCF production employment were significantly related to volume decline in (1) FVC for male current and past smokers, (2) FEV_1 in male current smokers, and (3) FVC for female never smokers.	
			Δ volume in (ml)				
		Item	**Current smokers**	**Past smokers**	**Never smokers**		
		Male workers	**n=245**	**n=174**	**n=173**		
		[FVC] years of RCF employment	–165.4‡ (–279.8, –51.0)	–155.5‡(–301.9, –9.1)	–40.6 (–175.1,193.8)		
		[FEV_1] years of RCF employment	–134.9‡ (–231.3, –38.5)	–72.5 (–195.9, 50.9)	–20.4 (–133.7, 92.9)		
		Female workers	**n=56**	**n=20**	**n=68**		
		[FVC] years of RCF employment	–110.8 (–411.5, 190.0)	–330.5 (–872.1, 211.1)	–350.3‡ (–692.0, 8.7)		
		[FEV_1] years of RCF employment	13.9 (–218.7, 246.5)	–321.4 (–740.2, 97.4)	–223.5 (–487.7, 40.7)		

(Continued)

*Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; n=number; O=odds ratio; RCFs=refractory ceramic fibers.
†Variables included in model: smoking category, interaction term for duration of RCF production and smoking category, interaction term for pack-years and smoking category, weight, and plant location.
‡Statistically significant ($P \leq 0.05$).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1996 (U.S. study)	**Cohort study:** 652 workers (a) who were employed between 10/87 and 12/91 or who had ≥1 year of employment in the RCF division at one of two plant sites, *and* (b) who completed an occupational history and provided posterior-anterior and two oblique chest X-rays. **Nested case-control study:** 17 cases of pleural plaque matched to 3 controls by sex and employment status (current or former worker; production or nonproduction)	**Health:** Occupational history interview, information about work/home asbestos exposure; chest X-rays. **Exposure:** Estimated concentrations of fiber exposure for each job using historical plant process, design and engineering controls, and sampling data plus worker interviews [Rice et al. 1994, 1996]. **Exposure:** Controls and cases reinterviewed with additional questions regarding asbestos exposure (application, manipulation, and distance from exposure). Asbestos exposure categorized (rating index = high, medium, low) from interview data.	**Radiographic analyses** **Item** / **Plaque prevalence (%)** / **OR†** / **95% CI** Years since first RCF production job: 0‡ — 0.9 — 1.0 — — >0–10 — 1.7 — 1.4 — 0.2, 10.3 >10–20 — 2.8 — 2.2 — 0.4, 11.2 >20 — 12.5 — 9.5 — 1.9, 48.2 Years of RCF employment: 0 — 0.9 — 1.0 — — >0–10 — 1.4 — 1.1 — 0.2, 6.1 >10–20 — 7.4 — 6.1 — 1.2, 29.7 >20 — 26.3 — 22.3 — 3.6, 137.0 Cumulative fiber-months/cm³: >0–15 — 0.3 — 1.0 — — >15–45 — 5.3 — 15.4 — 1.9, 125.4 >45-135 — 6.4 — 21.3 — 2.6, 176.2 >135 — 7.8 — 24.2 — 2.6, 224.9 Case-controls: Years since first RCF production job — — 1.2 — 1.0, 1.5 Cumulative RCF fiber-months/cm³ (log): Adjusted for years since first asbestos exposure — — 2.8 — 1.3, 5.8 Adjusted for asbestos rating index — — 3.8 — 1.5, 9.9	In the cohort study, 20 cases of pleural plaque were identified in the cohort: 18 production workers and 2 nonproduction workers. In three logistic regression models, pleural plaques were associated ($P<0.001$) with years since first RCF production job, duration of RCF production jobs, and cumulative fiber-months/cm³. 18 of 20 cases were reinterviewed; 17 were included in the case-control study. One was deceased, one refused interview, and one with asbestos exposure was excluded.

*Abbreviations: CI=confidence interval; *P*=probability; OR=odds ratio; RFCs=refractory ceramic fibers.

†All but last entry are adjusted for years since first asbestos exposure. Last entry is adjusted for asbestos rating index, as indicated.

‡Nonproduction workers.

(Continued)

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1998 (U.S. study)	**Cross-sectional and longitudinal study:** Of a possible 754 male workers, the study included 361 who (1) were hired before 6/30/90, (2) were employed ≥1 month at one of five U.S. RCF manufacturing, facilities, and (3) participated in at least five (of a possible seven) PFT sessions between 6/87 and 6/94.	**Medical evaluation:** Yearly spirometric evaluation (pulmonary function) between 1987 and 1994. Measures included FVC and FEV_1. **Exposure assessment:** Period and job-group-specific exposure concentrations; estimated for each of five RCF manufacturing facilities and assigned to each worker based on job history. Cumulative RCF exposure (fiber-months/cm^3) estimated from date of first PFT (1987) through final PFT date. Pre-1987 data on fiber concentrations from two plants permitted calculation of cumulative fiber concentrations from first date of RCF exposure for workers at these plants only.	**Pulmonary function: cross-sectional analysis of initial pulmonary function test for 522 workers** Regression coefficient RCF production years / FVC†,‡ / FEV_1†,‡ ≤7§ / –65.6 (0.44) / –80.6 (0.25) >7§ / –219.4 (<0.01) / –205.2 (<0.01)	193 male workers were excluded from the analysis because they did not participate in at least five PFT sessions. On average, nonparticipants were older, smoked and weighed more, and had lower height-adjusted and percentages of predicted lung function values.

(Continued)

*Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; PFT=pulmonary function test; RCFs=refractory ceramic fibers.
†In milliliters.
‡Height-adjusted; variables included in the analysis were age, categorical RCF production years (0, ≤7 years, >7 years [first test]), smoking category, pack years, weight, and plant location.
§Compared with nonproduction workers.

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1998 (Continued) (U.S. study)			**Pulmonary function: longitudinal analysis**	

Item	Regression coefficient FVC†,‡	Regression coefficient FEV_1 †,‡
Cumulative exposure:		
Initial RCF production category, ≤7 years‡,§	–55.2	–38.9
Initial RCF production category, >7 years‡,§	–168.3**	–99.6
Followup cumulative RCF exposure (fiber-months/cm^3)‡,§	.0.7	+0.5
Production employment duration:		
Initial RCF production years, ≤7 years‡,§	–66.3	–37.6
Initial RCF production years, >7 years‡,§	–171.0**	–100.3
Followup RCF production years§,††	+5.3	+0.2
Cumulative fiber exposure:		
Initial cumulative RCF exposure, >15–60 fiber-months/cm^3,‡‡	–36.2	–100.2
Initial cumulative RCF exposure, >60 fiber-months/cm^3,‡‡	–156.0	–104.7
Followup cumulative RCF exposure, fiber-months/cm^3,‡‡	+0.8**	+0.2

(Continued)

*Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; *P*=probability; RCFs=refractory ceramic fibers.

† In milliliters for male workers tested five to seven times.

‡ Height-adjusted; variables included in the analysis were age, categorical RCF production years to initial test, followup cumulative RCF exposure, pack years at initial test, dichotomized smoking at each test, weight at initial test, weight change and plant location.

§Compared with nonproduction workers.

** $P<0.05$.

††Height-adjusted; variables included in the analysis were age, categorical RCF production years to initial test, followup RCF production years, pack years at initial test, dichotomized smoking at the time of each test, weight at initial test, weight change, plant location.

‡‡ Height-adjusted; variables included in the analysis were age, categorical cumulative RCF exposure to initial test, followup cumulative RCF exposure, pack years at initial test, dichotomized smoking at each test, weight at initial test, weight change, plant location.

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Burge et al. 1995 (European study)	**Cross-sectional study:** From a possible 708 current workers, 628 eligible participants were identified, and 596 of these had chest X-ray examinations. After exclusion of 51 female workers and 13 unexplained others, data were available from pulmonary function tests for 532 male workers in seven European RCF primary production plants.	**Health:** Workers were evaluated by a self-administered expanded respiratory questionnaire that included questions regarding specific symptoms. Pulmonary function testing was also performed. **Exposure:** Whole-shift personal air samples were collected from randomly selected workers from representative job categories in each of seven RCF production plants. Samples were collected and analyzed according to a WHO/EURO [1985] reference method for MMMFs to obtain data on inspirable and total mass and respirable fiber concentration. **Statistical analysis:** Odds ratios (with 95% CI) adjusted for plant, sex, smoking, and age were calculated for symptoms (i.e., dry cough, chronic bronchitis, wheeze, dyspnea≥2, stuffy nose, eye and skin irritation) and current exposure categories using multiple logistic regression. Multiple linear regression coefficients for lung function related to cumulative exposures controlled for the effects of respirable fiber and inspirable mass separately and together.	**Symptom analyses** **Exposure** — **Effect** **Current concentrations of inspirable mass:†** <2.5 mg/m³ — Baseline 2.5 to <3 mg/m³ — Eye irritation [2.25 (1.43, 2.23)]‡ 3 mg/m³ — Dry cough [3.42 (1.41, 8.33)] Dyspnea ≥2 [5.84 (2.25, 15.26)] Stuffy nose [2.01 (1.13, 3.57)] Eye irritation [4.78 (2.66, 8.6)] Skin irritation [3.3 (1.8, 6.05)] **Current concentrations of respirable fibers:†** <0.2 f/cm³ — Baseline 0.2 to <0.6 f/cm³ — Dry cough [2.53 (1.25, 5.11)] Stuffy nose [2.06 (1.25, 3.39)] Eye irritation [2.16 (1.32, 3.54)] Skin irritation [1.25 (0.74, 2.11)] ≥0.6 f/cm³ — Dry cough [2.01 (1.05, 3.84)] Dyspnea 2 [2.66 (1.31, 5.42)] Eye irritation [2.63 (1.7, 4.08)] Skin irritation [3.18 (2.01, 5.03)]	Current exposures to both inspirable dust and respirable fibers were related to dry cough, stuffy nose, eye and skin irritation, and breathlessness. No analysis of cumulative exposures was performed with respect to symptoms. Changes in lung function were more strongly related to cumulative exposure to fibers than to cumulative exposure to inspirable mass. Decrements in lung function were limited to current smokers and former smokers, suggesting that exposure to fibers promotes respiratory effects of smoking.

(Continued)

*Abbreviations: CI=confidence interval; MMMFs=man-made mineral fibers; RCFs=refractory ceramic fibers.
†Separate logistic regression models (adjusted for age, sex, smoking, and plant).
‡Figures in brackets=[OR (95% CI)].

Table 5–7 (Continued). U.S. and European Morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Burge et al. 1995, continued (European study)			**Symptom analyses, continued** **Exposure** — **Effect** **Current concentrations of inspirable mass:**§ 2.5 to <3 mg/m³ — Eye irritation [1.90 (1.15, 3.15)]** ≥3 mg/m³ — Dyspnea ≥2 [4.74 (1.56, 14.4)] Eye irritation [3.31 (1.62, 6.77)] **Current concentrations of respirable fibers:**§ 0.2 to <0.6 f/cm³ — None statistically significant ≥ 0.6 f/cm³ — Skin irritation [2.67 (1.52, 4.70)] **Pulmonary function‡‡** **Cumulative inspirable mass exposure:‡‡** Former smokers — FVC –8.7 ml/mg·m³ per year; FEV_1 –6.4 ml/mg·m³ per year **Cumulative respirable fiber exposure:‡‡** Current smokers — FEV_1 –32 ml/f·cm³ per year; FEF_{25-75} –63 ml/s per f·cm³ per year Former smokers — FEV_1 –37 ml/f·cm³ per year **Cumulative respirable fiber exposure:§§** Current smokers — FEV_1 –36 ml/f·cm³ per year **Exposure** **Mean current inspirable mass:** Primary production — 1.7 to 3.4 mg/m³ Secondary production — 1.8 to 11.2 mg/m³ **Mean current respirable fiber concentration:** Primary production — 0.2 to 0.88 f/cm³ Secondary production — 0.49 to 1.36 f/cm³ **Mean cumulative exposure:** Inspirable mass — 28.24 mg/m³·year Respirable fibers — 3.84 f/cm³·year	(Continued)

§Multiple logistic regression (adjusted for age, sex, smoking, and plant) of symptom prevalence by current respirable fibers and current inspirable mass as independent variables after adjustment for the other.
**Figures in brackets=[OR (95%CI)].
††Only statistically significant associations ($P<0.05$) are shown.
‡‡Linear regression modeling of cumulative exposures to inspirable mass and respirable fibers separately (adjusted for age, height, and smoking).
§§Linear regression modeling with both cumulative exposure variables in the same model (adjusted for age, height, and smoking).

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Rossiter et al. 1994 (European study)	**Cohort morbidity study:** 628 currently working employees in seven European RCF production plants. 543 male workers who had readable chest radiographs were included in the analysis (596 of 628 workers [95%] had chest radiographs; 51 women and 2 unreadable films were excluded).	**Health:** Chest radiographs and questionnaire were administered. Data for 14 descriptive variables were collected for each worker as follows: production plant; age; years since first employment at plant; years since first exposed to RCFs; years of employment in the plant; current respirable fiber exposure; current nonrespirable fiber exposure; current inspirable mass exposure; cumulative respirable fiber exposure; cumulative nonrespirable fiber exposure; cumulative inspirable mass exposure; number of jobs at the plant with asbestos exposure; prior asbestos exposure.	**Radiographic analysis** **Effect** / **Prevalence** Pleural changes: 2.8% (15/543) Large opacities: 0 Small opacities: 7.0% (38/543) Irregular: 5.5% Rounded: 3.5% Mixed: 5.2% **Statistical analysis:** *Prevalence of pleural changes (n=15) associated with age (χ^2 =18.85, P=0.0008).* *Prevalence of cases of small opacity profusion (n=38) related to* production plant (χ^2= 22.10, $P<0.0001$); smoking years since first employment, years of employment, prior asbestos exposure, current nonrespirable fiber exposure (no χ^2 reported, $P\leq0.05$). *Prevalence of cases with mostly rounded opacities (n=23) related to* heavy smoking (χ^2=2.18, P=0.14); asbestos exposure within the RCF plants (χ^2=3.08 with continuity correction, P=0.08); but not age (χ^2=1.25, P=0.87) or production plant (χ^2= 5.13, P=0.53). *Prevalence of cases with mostly irregular opacities (n=15) related to* age (χ^2= 38.9, $P<0.0001$); current nonrespirable fiber levels (χ^2=5.2, P=0.07); years since first RCF employment (χ^2=8.16, P=0.09); years of RCF employment (χ^2=8.70, P=0.07); but not plant (P=0.23).	Pleural changes (n=15) included four cases with bilateral diffuse thickening (one with calcification); one with bilateral pleural calcification only; seven with unilateral diffuse thickening; three with costophrenic angle blunting only. Prevalence of pleural changes was associated with age. Irregular opacities were related to age, current nonrespirable fiber concentrations, and duration and latency of RCF employment. Overall, a slight association was noted for prevalence of small opacities and working in ceramic fiber production (i.e., RCF employment latency and duration). The researchers concluded it was unlikely that fiber exposure was the main cause of radiographic abnormalities. The possibility for confounding effects due to other exposures is recognized: 52% of workers reported previous employment in industries with potential exposure to dusts, including asbestos (5%), stone quarrying (2%), iron/steel foundries (6%), refractory brick work (10%), and man-made mineral fibers (8%).

(Continued)

*Abbreviations. N=number; *P*=probability; RCFs=refractory ceramic fibers.

Table 5–7 (Continued). U.S. and European Morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Trethowan et al. 1995 (European study)	**Cross-sectional respiratory morbidity study:** 628 current workers in seven European RCF manufacturing plants. Mean age = 37.7 years. Mean duration of employment = 10.2 years. 91% were male workers and 9% were female workers. 44% were current smokers.	**Health:** A self-administered questionnaire was used to obtain information about respiratory, nasal, eye, and skin symptoms, plus details of subjects' occupational history. PFT was also performed, and chest X-rays were obtained from 592 subjects. **Exposure assessment:** 140 jobs were identified and classified into seven main groups. Full-shift personal air samples were collected for randomly selected workers in each of the seven main groups. Inspirable dust monitoring was performed according to an ACGIH method. Respirable fiber concentration was measured according to a WHO/EURO [1985] reference method for MMMFs. (Respirable fiber is defined as <5µm long with an aspect ratio >3:1 and a diameter ≤3µm.) **Statistical analysis:** Pulmonary function indices were compared for cumulative exposure groups. Symptoms were investigated by logistic regression, and pulmonary function by linear regression. Models were controlled for effects of age, sex, smoking habits, and previous exposure to respiratory hazards.	**Radiographic analysis** Effect — Prevalence Pleural changes — 2.7% (16/592) Large opacities — 0 Small opacities — 13% Irregular — 5.1% Rounded — 3.2% Mixed — 4.7% **Symptom analyses** Current respirable f/cm³ — Effect — [OR† (95% CI)] <0.2 — Baseline 0.2 to <0.6 — Dry cough — [2.53 (1.25, 5.11)] Stuffy nose — [2.06 (1.25, 3.39)] Eye irritation — [2.16 (1.32, 3.54)] ≥0.6 — Dry cough — [2.01 (1.05, 3.84)] Dyspnea ≥2 — [2.66 (1.31, 5.42)] Eye irritation — [2.63 (1.7, 4.08)] Skin irritation — [3.18 (2.01, 5.03)]	Prevalence of small opacities increased with age, smoking, and previous exposure to asbestos, but not with cumulative exposures to ceramic fibers. No description of this analysis is provided. Symptoms present in the study population were related to exposure to respirable fibers. Statistically significant increases were noted in the prevalence of dyspnea (both grades) with increasing cumulative fiber exposure groups. Lung function tests showed a significant relation between increasing cumulative exposure to respirable fibers and decrements in FEV_1 and FEF_{25-75} in current smokers, and FEV_1 in former smokers. Among never smokers, an increase (not statistically significant) occurred in pulmonary function measures with increasing cumulative fiber exposure. Overall, 19% of the population had worked in dusty occupations outside the production of ceramic fibers. Note: In calculating cumulative exposures, the researchers assume past exposure concentrations were equal to current exposure concentrations.

*Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; CI = confidence interval; MMMFs = man-made mineral fibers; OR = odds ratio; PFT=pulmonary function test; RCFs=refractory ceramic fibers.

†Adjusted for the effects of age, sex, smoking, and previous exposures to respiratory hazards.

(Continued)

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Trethowan et al. 1995, continued (European study)		Logistic regression was used to analyze the trend between symptom prevalence and increasing cumulative respirable fiber exposure. Linear regression was used to analyze the trend between pulmonary function measures and increasing cumulative respirable fiber exposure.	**Symptom Analyses (Continued)** **% workers with various respiratory symptoms by fiber exposure**	

	Cumulative respirable fiber exposure (f/cm³ • year)				
Symptom	<1	1 to <2	2 to <4	4 to <8	>8
Dyspnea ≥2	6	9	13	17	20
Dyspnea ≥3	1	3	5	4	10
Wheeze	15	11	20	20	25
Bronchitis	13	9	12	14	10

Pulmonary function (mean % of predicted values)

	Cumulative respirable fiber exposure (f/cm³ • year)				
Function index	<1	1 to <2	2 to <4	4 to <8	>8
FVC	112.0	110.2	111.5	109.2	110.3
FEV_1†	106.5	105.5	106.0	102.3	102.1
FEF_{25-75}†	89.0	90.1	85.3	79.7	74.4

Pulmonary function (Δml/[f/cm³@ yr]) with cumulative exposure‡

Function index	Never smoker	Former smoker	Current smoker
FVC	+7	-34	-25
FEV_1†	+14	-37†	-32†
FEF_{25-75}†	+28	-51	-63†

Exposures

	Subjects	
Exposure concentrations	Number	%
Current exposure (f/cm³):		
<0.2	294	46.8
0.2 to <0.6	123	19.6
0.6 to <1	200	31.8
≥1	11	1.8
Cumulative exposure§ (f/cm³ • y):		
<1	119	18.9
1 to <2	106	16.9
2 to <4	168	26.8
4 to <8	166	26.4
>8	69	11.0

(Continued)

*Abbreviations: RCFs=refractory ceramic fibers.

†Statistically significant ($P<0.05$).

‡Adjusted for the effects of age, height, sex, smoking, and past exposure to RCFs, asbestos, and refractory work.

§Range=0 to 22.9 f/cm³ · year.

Table 5–7 (Continued). U.S. and European morbidity studies with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Cowie et al. 1999, 2001 (European study) Cowie et al. 1999, 2001 Respiratory health assessment Groat et al. 1999 Exposure assessment	**Cross-sectional study:** **774 workers:** 695 current workers (90% response rate) in six European RCF manufacturing plants 79 former workers (37% response rate) who had been included in the first European survey [Burge et al. 1995, Rossiter et al. 1994, Trethowan et al. 1995] but had since left the industry 89% male workers and 11% female workers **Mean age:** Male workers, 42.0 years Female workers, 39.4 years **Smoking history:** **Male workers:** Nonsmokers 35% Current smokers 38% Ex-smokers 27% **Female workers:** Nonsmokers 57% Current smokers 29% Ex-smokers 13% **Mean time worked at the plants:** 13.0 years	**Health evaluation:** Chest radiographs, n=760 (98%) Lung function: Spirometry Single breath gas transfer Alveolar volume Questionnaires: Respiratory symptoms Modified American Thoracic Society questionnaire Occupational history **Exposure assessment:** 464 shift concentrations were sampled (>4 hr) Measurements included (1) respirable† and nonrespirable fiber concentration (phase contrast optical microscopy), (2) respirable dust and crystalline silica concentrations, (3) fiber concentrations and fiber size (scanning electron microscopy), and (4) mass concentrations of total inhalable dust. **Statistical analyses:** Regression analyses were performed: Radiographic data—logistic regression adjusted for age and smoking Lung function data—linear regression adjusted for age, physique, and smoking Respiratory symptoms—logistic regression adjusted for age, sex, smoking, and country.	**Radiographic analysis:** Pleural changes, 11% Pleural plaques, 5% 51/682 male workers had RCF exposure before 1971: 10/51 had category 1/0+ opacities 8/10 were exposed to asbestos 3 were current smokers, 6 ex-smokers **Symptom analyses:** Recurrent chest illness was associated with estimated cumulative exposure to respirable fibers [OR=1.48, 95% CI=1.11,1.96] and respirable dust [OR=1.32, 95% CI=1.00, 1.75]. **Pulmonary function analysis:** Male workers: FEV_1 and FVC decreased with increasing exposure to RCFs in current smokers only; strongest association was with estimated cumulative exposure to respirable fibers. Female workers: FEV_1 decreased with increasing cumulative exposure to fibers and dust; strongest association was with cumulative exposure to total dust. **Exposure assessment:** Current exposure concentrations: Respirable fibers: Production, 0.09–0.39 f/cm^3 *Conversion/finishing, 0.03–1.25* f/cm^3 Respirable dust, 0.08–0.42 mg/m^3	Only 14 female workers had small opacities of profusion 0/1; radiograph statistical analyses were restricted to male workers. Pleural changes were associated with age and exposure to asbestos; unadjusted for age, there is an association between pleural changes and number of years at the plant. Respiratory symptoms analyzed included chronic bronchitis, breathlessness, recurrent chest illness, and pleuritic chest pain. The average estimated decreased FEV_1 and FVC in male smokers was ~100 ml.

*Abbreviations: RCFs=respirable ceramic fibers; FEV=forced expiratory volume in 1 second; FVC=forced vital capacity.

†Respirable fibers included effectively no asbestos fibers via scanning electron microscopy (SEM) characterization. Asbestos exposure was judged not to warrant specific sampling.

pleural plaques in 5% (40/774) of study participants. In the U.S. study, 23 cases with pleural abnormalities (all production workers) were identified from 847 male and female workers (686 production, 161 nonproduction) [Lemasters et al. 1994]. The prevalence of pleural abnormalities among all workers was 2.7% and for production workers only, 3.4%. Of the cases, 21 were classified as having pleural plaques and 2 as having diffuse pleural thickening. One worker reported having previously diagnosed kaolinosis from prior employment in a kaolin mine. Lockey et al. [1996] conducted a followup report based on review of 652 chest films from current and former workers at two of the U.S. plants. They reported a prevalence of pleural changes of 3.1% (n=20), including 19 pleural plaque cases and 1 with diffuse pleural thickening. Pleural plaques were present in 18 (4.1%) production workers and 2 (0.9%) nonproduction workers. The two nonproduction workers with pleural plaques had worked with RCFs as laboratory technicians. From statistical analyses of pleural abnormalities, Rossiter et al. [1994] reported an association with age [χ^2=18.85, P=0.0008]. However, no attempt was made to assess whether an association existed between pleural abnormalities and RCF exposure. Trethowan et al. [1995] also noted that pleural abnormalities were related to age but not independently to ceramic fiber exposures. Cowie et al. [1999, 2001] reported pleural abnormalities to be associated with age, exposure to asbestos, and body mass index (weight divided by height squared). When the data were unadjusted for age, an association existed between pleural changes and years worked at the plant. Lemasters et al. [1994] found that pleural abnormalities were associated with time since first RCF exposure (RCF latency) after adjusting for duration of asbestos exposure and time since first asbestos exposure (odds ratio [OR]=2.9 [95% CI=0.8–9.7] for >10 to 20 years of RCF latency, and 7.7 [95% CI=2.0–29.1] for >20 years of RCF latency, when compared with workers having <10 years of RCF latency). Pleural abnormalities remained statistically significant (P<0.001) with time since first RCF exposure (latency) after adjustment for the effects of smoking, body weight, and latency and duration of asbestos exposure. The positive association persisted after exclusion of workers exposed to asbestos. In multiple logistic regression analyses, an association between duration of RCF exposure and pleural abnormalities remained significant (χ^2=7.75, P=0.005) after adjustment for asbestos latency, asbestos duration, and age [Lemasters et al. 1994]. In subsequent analyses with adjustment for age, researchers found that associations persisted between pleural plaques and latency and duration of RCF exposure [Lockey et al. 1996]. In three separate analyses, Lockey et al. [1996] found that prevalence of pleural plaques related to the following:

- >20 years of RCF latency (OR=9.5 [95% CI=1.9–48.2])
- >20 years RCF exposure duration in production jobs (OR=22.3 [95% CI=3.6–137.0])
- Cumulative RCF exposure in the highest exposure category (>135 fiber-months/cm^3) (OR=24.2 [95% CI=2.6–224.9])

Results of a nested case-control study of the 20 workers with pleural plaques (matched to 3 controls based on sex, RCF employment status, and production/nonproduction category) support the associations of pleural changes with RCF latency, RCF exposure duration, and cumulative RCF exposure [Lockey et al. 1996]. A latency validity review was also conducted, involving analysis of 205 historical chest radiographs available for workers with pleural changes. The purpose of the review was to confirm that for persons with pleural plaques, a biologically plausible latency period (≥5 years) existed between initial RCF exposure and appearance of a pleural plaque. Of 18 pleural plaque cases for which historical chest

radiographs were available, only 1 had a latency period of <5 years from initial RCF production to recognition of a pleural plaque.

A subsequent analysis by Lockey et al. [2002] included chest radiographs for 625 current workers obtained every 3 years at 5 RCF manufacturing sites and 383 former workers at 2 of the 5 sites. Pleural changes were seen in 27 workers (2.7%), of which 19 were bilateral plaques (70%) and 3 were unilateral plaques (11%). Cumulative RCF exposure (>135 fiber-months/cm^3) was significantly associated with pleural changes (OR = 6.0, 95% CI = 1.4, 31.0). The researchers noted an increasing but nonsignificant trend involving interstitial changes and RCF exposure duration in a production job and cumulative RCF exposure.

5.3.2.2 Parenchymal Opacities

In the 1987 European study, Rossiter et al. [1994] found that 7% (38/543) of the current male workers had small parenchymal opacities with median profusion of 1/0 or more. No large parenchymal opacities were observed. Both predominantly rounded (n=23, or 4.2%) and predominantly irregular (n=15, or 2.8%) small parenchymal opacities were identified. Prevalence of rounded, small opacities was not associated with age (P=0.87) or production plant (P=0.53). However, with prevalence of opacities, stronger associations existed with asbestos exposure in RCF production plants (P=0.08) and heavy smoking (P=0.14) [Rossiter et al. 1994]. Predominantly irregular, small opacities were associated with age (P<0.0001) but not with production plant (P=0.23). After allowing for age, associations with current nonrespirable fiber concentrations, years since first RCF employment, and duration of RCF employment approached statistical significance (P=0.07 to 0.09). In a subsequent analysis of small opacities for both male and female workers, Trethowan et al. [1995] noted that the prevalence of small opacities increased with age, smoking, and previous exposure to asbestos but not with cumulative RCF exposure. No description of the analysis was provided. Cowie et al. [1999] reported that 10 of 51 (19.6%) men with RCF exposure before 1971 had small opacities of category 1/0 or greater. Eight of these 10 had been exposed to asbestos, and 9 were either current or ex-smokers. In the U.S. study, no analyses were performed to assess the relationship between small opacities and RCF exposure because of the small number of cases (n=4) identified by Lemasters et al. [1994, 1996].

5.3.3 Respiratory Conditions and Symptom Analyses

Using respiratory health questionnaires, the U.S. and European studies sought to identify respiratory conditions and symptoms that could be associated with exposure to RCFs. Lockey et al. [1993] administered to 717 subjects a standardized respiratory symptoms questionnaire that included questions about the following symptoms and conditions: chronic cough, chronic phlegm, dyspnea grades 1 and 2 (described in the Definitions section of this document), wheezing, asthma, pleurisy, and pleuritic chest pain. Logistic regression analyses were adjusted for age, sex, smoking (pack years), duration of asbestos exposure, duration of production employment, duration of other hazardous occupational respiratory exposure, and time since last RCF employment. With the exception of asthma, for which self-selection out of production jobs may have occurred, adjusted ORs for respiratory symptoms were significantly elevated in production workers compared with nonproduction workers. Results of a subsequent analysis with 742 RCF workers by Lemasters et al. [1998] indicated that the prevalence of respiratory symptoms and conditions (except for asthma) was approximately twofold to fivefold higher in

production than in nonproduction workers. The most frequently reported symptom for male production workers was dyspnea grade 1 (15.7%, compared with 2.5% for nonproduction), followed by wheezing (10.3%, compared with 3.8% for nonproduction). Prevalence of one or more respiratory symptoms and conditions among female production workers was 40.7%, compared with 20.3% for nonproduction workers.

Trethowan et al. [1995] examined the relationship of dry cough, chronic bronchitis, dyspnea (two grades), wheeze, stuffy nose, eye irritation, and skin irritation to current and cumulative RCF exposure estimates among 628 workers. Current exposures were based on air sampling measurements taken in association with the respiratory health survey. The researchers noted eye and skin irritation were frequent in all plants and increased significantly, as did dyspnea and wheeze, with increasing current exposure concentrations (i.e., 0.2 to 0.6 and ≥0.6 f/cm^3) after controlling for age, sex, and smoking habits. The most frequent symptom, nasal stuffiness (in 55% of the group), showed no clear association with increasing current exposure. Chronic bronchitis, with a prevalence of 12% among all workers, also appeared unaffected by increasing current exposure concentration. Dry cough, eye irritation, and skin irritation all seemed to be associated with increasing exposure, especially at the highest exposure concentration (≥0.6 f/cm^3). Analyses of cumulative exposure to respirable fibers showed statistically significant associations with dyspnea but no apparent association with chronic bronchitis and wheeze. In a separate analysis of the same cohort, Burge et al. [1995] investigated the relative importance of respirable RCF exposure versus inspirable dust exposure in predicting respiratory symptoms and conditions. The study found workers' current exposures to both inspirable dust and respirable fibers were related (P<0.05) to dry cough, stuffy nose, eye and skin irritation, and breathlessness (dyspnea) after adjustment for the effects of smoking, sex, age, and plant. Only skin irritation was significantly associated with current RCF exposure after controlling for exposure to inspirable dust. Burge et al. [1995] did not analyze the relationship between symptoms and cumulative exposure indices. Cowie et al. [1999, 2001] reported that recurrent chest illness was associated with estimated cumulative exposure to respirable fibers but was not significantly associated with recent exposure.

5.3.4 Pulmonary Function Testing

Trethowan et al. [1995] analyzed spirometry test results from 600 of 628 current workers who participated at 7 European RCF production plants. In separate multiple linear regression analyses for male workers in each smoking category (current, former, never), the authors controlled for age, height, and past exposures to various respiratory hazards (including previous employment in other ceramic fiber plants). Results associated cumulative RCFs with statistically significant (P<0.05) decrements in FEV_1 in both current and former smokers and with decreases in FEF_{25-75} in current smokers. In never smokers (n=154), all regression coefficients of cumulative RCF exposure in relation to lung function were small, positive, and not statistically significant.

As with the symptoms data, Burge et al. [1995] further analyzed the spirometry data from the European study to discern whether the observed effects were more highly associated with current respirable RCF exposure than with concurrent inspirable dust exposure. In a multiple linear regression model that excluded cumulative inspirable dust exposure, statistically significant (P<0.05) decreases in FEV_1 and FEF_{25-75} among current smokers and FEV_1 among former smokers were associated with

cumulative exposure to respirable RCFs. In a multiple linear regression model that included variables for cumulative dust and cumulative respirable RCFs, the only statistically significant ($P<0.05$) association for these variables was for the decrease in FEV_1 among current smokers associated with cumulative respirable RCF exposure. No cumulative dust-associated coefficients remained statistically significant after adjusting for the effect of cumulative RCF exposure. Thus, the investigators attributed the adverse pulmonary function effect observed in smokers to the fiber component of occupational dust exposures at RCF manufacturing plants.

Cowie et al. [1999, 2001] observed that RCF-exposed male workers (n=692) showed a decrease in FEV_1 and FVC only for current smokers, the strongest association being with estimated cumulative exposure to respirable fibers. The average estimated decrease in FEV_1 and FVC was mild, approximately 100 ml. Female RCF-exposed workers (n=82) had a decreased FEV_1 with increasing cumulative exposure to respirable fibers and respirable and total dust. Among the female workers, cumulative exposure to total dust was most strongly associated with decreased pulmonary function measurements.

Lemasters et al. [1998] anaylzed PFT data for 736 male and female current workers at five U.S. RCF plants. They reported decreases in the percentage of predicted FVC and FEV_1 with every 10 years of RCF production work. Although the decreases were greatest among current male smokers and former male smokers, they were greater than decreases associated with smoking alone. No significant changes were noted in pulmonary function of RCF production workers who never smoked. A separate study by Lockey et al. [1998] involved longitudinal analysis of data from a cohort of 361 current male RCF workers hired before June 30, 1990, who had participated in at least five PFT sessions between 1987 and 1994. By comparison, nonparticipants who were excluded from the analysis according to the criteria above were on average older, smoked, weighed more, and had lower height-adjusted and percent-predicted lung function values. Cross-sectional analysis of the initial pulmonary function session in a regression model included coefficients for age, ≤7 versus >7 RCF production years, smoking status (pack years, current versus former smoker), weight, and plant location (categorical). The analysis found decreases in FVC and FEV_1 for workers employed >7 years in production compared with nonproduction workers. In longitudinal analyses of followup production years (i.e., from initial PFT to final PFT) and followup cumulative exposure (i.e., from initial PFT to final PFT), neither of these variables had an effect on FVC or FEV_1. These results led the authors to conclude that more recent exposure concentrations during 1980–1994 had no adverse effect on the longitudinal trend of pulmonary function [Lockey et al. 1998]. Decrements in FVC and FEV_1 noted in initial cross-sectional analyses of PFT data were believed to be related to earlier higher exposure concentrations.

5.3.5 Mortality Studies

Table 5–8 presents findings from a cohort mortality study of two U.S. RCF production plants reported by Lockey et al. [1993]. The study is based on a cohort of 684 male workers at two RCF production plants who were employed for at least 1 year between January 1, 1950, and June 1, 1988. Five workers were lost to followup and 46 were deceased. Because this is a relatively new industry (~40 years at the time of the study) that has experienced recent growth of the workforce at the plants studied, person-years at risk were limited at higher latencies (for example, only 126.37 person-years with >30 years since first RCF job). Using standardized mortality ratios (SMRs), the authors found

Table 5–8. Mortality study with RCFs*

Reference	Study design and population	Evaluation methods	Results	Comments
Lockey et al. 1993 (U.S. study)	*Cohort mortality study:* Current and former male workers at two plant sites employed at least l year in the manfacture of RCFs between 10/1/50 and 6/1/88. Of the 684 workers who met the criteria, 633 (92.5%) were alive, 46 (6.7%) were deceased, and 5 (0.7%) were lost to followup.	Cause-specific SMRs were calculated using the total U.S. male population as the reference population. Person-years were stratified by age, race, calendar time, latency, and cumulative duration.	**Demographics:** 624 Caucasions 60 non-Caucasions **Worker distribution** Years since first RCF job / Person-years at risk 1 to 5: 3,390 >5 to 10: 3,155 >10 to 15: 2,512 >15 to 20: 1,197 >20 to 25: 518 >25 to 30: 277 >30: 126 Total: 11,175 Cause of death / SMR (95% CI) All causes: 40 Caucasions: 97 (69–132) 6 non-Caucasions: 126 (46–274) All cancers: 11 Caucasions: 121 (60–216) 2 non-Caucasions: 263 (32–950) 4 lung cancers†: 114 (31–291) 2 cancers of the urinary organs†: 467 (57–1,687) 6 cancers of the digestive organs†: 259 (94–563) 2 pneumoconioses and other respiratory disease†: 205 (25–740)	Statistically significant increase in deaths from the following: (1) pneumoconioses and other respiratory disease for the category of Caucasian male workers with >30 years of RCF latency (n=2, SMR=2,614 [95% CI=246–7,490]); (2) cancers of the digestive organs and peritoneum for non-Caucasian male workers (n=2, SMR=913 [95% CI=110–3,295]); (3) cancers of the urinary organs for male workers with >15–20 years of RCF latency (n=2, SMR=3,306 [95% CI=311–9,471]). The power to detect a significant increase in mortality for any specific cause was low because of the small number of deaths in the cohort.

*Abbreviations: CI=confidence interval; RCFs=refractory ceramic fibers; SMR=standardized mortality ratio.
†Combined race cohort.

the combined-race cohort to have no significant elevations associated with specific causes of death, including cancers of the lung, digestive organs and peritoneum, urinary organs, and pneumoconioses and other respiratory disease. The authors noted that the power to detect a significant increase in mortality for any specific cause was low because of the small number of deaths in the cohort and generally short latencies. However, a statistically significant increase in deaths from pneumoconioses and other respiratory disease occurred in Caucasian males with >30 years RCF latency (n=2, SMR=2,614 [95% CI=246–7,490]). A statistically significant elevation in deaths from cancers of the digestive organs and peritoneum also occurred for non-Caucasian males (n=2, SMR=913 [95% CI=110–3,295]). In addition, a statistically significant elevation occurred in the number of deaths from cancers of the urinary organs for male workers with >15 to 20 years of RCF latency (n=2, SMR=3,306 [95% CI=311–9,471]).

Lemasters et al. [2003] published a subsequent analysis of current and former male workers employed between 1952 and 2000 at the two RCF manufacturing facilities (942 subjects) investigating a possible excess in mortality. The mortality analytic methods included (1) standardized mortality ratios comparing this cohort with the general and State populations and (2) a proportional hazards model that relates risk of death to the lifetime cumulative fiber-months/cm^3 exposure among the RCF cohort, adjusted for age at hire and for race. The analysis found no excess mortality related to all deaths, all cancers, or malignancies or diseases of the respiratory system (including mesothelioma) but found a statistically significant association with cancers of the urinary organs [SMR=344.8 (95% confidence limits of 111.6, 805.4)]. Based on the small size of the cohort, the young average age (51 years), and a mean latency of 21 years, the researchers concluded that the findings warrant continued surveillance of the cohort mortality registry.

Walker et al. [2002] used the same cohort of male RCF production workers described by Lemasters et al. [2003]. Walker et al. performed a risk analysis comparing the lung cancer and mesothelioma in the cohort's accumulated mortality experience to that which would have been expected if RCFs had a carcinogenic potency approximating various forms of asbestos. The authors reported that deaths from lung cancer in the RCF cohort were statistically significantly below that which would be expected if RCFs had the potency of either crocidolite or amosite. The mortality was also lower than would be expected if RCFs had the potency of chrysotile, but the difference is not statistically significant. For mesothelioma, the authors concluded the anticipated numbers of deaths under hypotheses of asbestos-like potency are too small to be rejected by the zero cases seen in the RCF cohorts [Walker et al. 2002]. NIOSH researchers noted that this analysis by Walker et al. was not based on the most current update of the RCF cohort. In addition, the asbestos risk assessment models used by Walker et al. [2002] were fitted to studies with longer followup periods than the cohort of RCF workers. Because these models do not specify length of followup, it is not possible to adjust for these differences. Consequently, it is likely that the RCF cohort has not been followed for a sufficient length of time to demonstrate the risks that were observed in the asbestos cohorts. NIOSH believes the mortality study by Lemasters et al. [2003] and the risk analysis by Walker et al. [2002] have insufficient power for detecting lung cancer risk based on what would be predicted for asbestos.

5.3.6 NIOSH HHEs

As part of its mission as a public health agency, NIOSH performs HHEs at the request of workers, employers, or labor organizations to investigate occupational hazards associated

with a workplace or work-related activity. One such HHE involved evaluating worker exposures to ceramic fibers at a company manufacturing steel forgings [Kominsky 1978]. At the facility, furnaces for heat-treating steel ingots were lined with RCF felt and batting, and this lining required regular maintenance and replacement. Among the workers interviewed were six bricklayers involved in furnace lining maintenance. Four of the bricklayers reported having experienced irritation of exposed skin areas and of the throat during the handling and installation of the RCF-containing insulation. On the basis of the reported symptoms and their consistency with known effects of RCFs, the symptoms of irritation were attributed to RCF exposure. No attempt was made to measure airborne fiber concentrations. Another NIOSH HHE [Lyman 1992] resulted from an OSHA inspection that identified 18 cases of occupational lung disease recorded in 1 year at a plant manufacturing fire bricks, ceramic fiber products, and other thermal insulation components from kaolin. About 600 workers were potentially exposed to respiratory hazards that included not only RCFs but also kaolin dust, crystalline silica dust, and (for maintenance workers) asbestos. A total of 38 workers had been referred to a pulmonary physician for evaluation based on 2 rounds of chest X-ray screening of the workforce in 1980 and 1986. Diagnoses were related to pleural thickening (n=10), pleural plaques (n=3), diffuse pulmonary fibrosis (n=21), mesothelioma (n=1), and other miscellaneous conditions. At least 20 of these cases were classified as work-related by the pulmonologist who evaluated the cases. The nonoccupational classification of some of the remaining 18 cases was questioned by a NIOSH physician who performed a retrospective record review. The 38 cases were reclassified on the basis of job histories into those who were likely to have been exposed to RCFs (n=19, including 4 with pleural abnormalities and 8 with diffuse fibrosis) and those unlikely to have been exposed to RCFs (n=19, including 9 with pleural abnormalities, 13 with fibrosis, and 1 with mesothelioma). However, no attempt was made to analyze further for an association of the cases with exposure to RCFs. The report implied that occupational exposure to kaolin dust and to asbestos caused many or all of the job-related conditions.

5.3.7 Discussion

The radiographic analyses of the U.S. and 1996 European worker groups suggest an association between pleural abnormalities, including pleural plaques, and RCF exposure [Lemasters et al. 1994; Lockey et al. 1996; Cowie et al. 1999]. From Rossiter et al. [1994] it is less apparent whether such an association was investigated. Trethowan et al. [1995] report that pleural abnormalities were not independently related to RCF exposure. Differences between the findings of the U.S. studies and those of the initial European studies may be related to the long latency before pleural abnormalities are detectable, in particular, pleural plaques following RCF exposure. Workers exposed to asbestos developed asbestos-associated pleural plaques after a latency period of more than 15 years after initial exposure [Hillerdal 1994] and in some cases, after 30 to 57 years [Begin et al. 1996]. The European RCF industry developed more than a decade after the U.S. industry. As a result, workers in the U.S. group are slightly older with a longer average employment duration in RCF manufacturing and time since first exposure to RCFs. Historical air sampling data also indicate that airborne fiber concentrations were much higher in early U.S. RCF manufacturing. These factors might explain the finding of RCF-associated pleural abnormalities in the U.S. workers but not in the European workers. A further possible explanation may involve differences in the radiographic surveillance methodologies. Both the U.S. and the European studies used

the 1980 ILO classification systems for pneumonoconioses to review posteroanterior view chest radiographs for study subjects. However, Lockey et al. [2002] began to supplement these views with left and right 45° oblique view films as a standard practice for radiographic surveillance. This methodology, known as a film triad, was evaluated against the posteroanterior-only view to determine reliability, sensitivity, and specificity of each method [Lawson et al. 2001]. The evaluation, involving 652 subjects in the RCF study, showed the film triad had considerably higher interreader reliability (κ=0.59) than the posteroanterior-only method (κ=0.44). The authors concluded that the film triad method provides an optimum approach.

The U.S. and 1986 European studies yielded little evidence of an association between radiographic parenchymal opacities and RCF exposure. In the U.S. study, small opacities were rare [Lockey et al. 1996]. Small opacities of profusion category 1/0 or greater were more frequent in the 1986 European study [Trethowan et al. 1995], but exposures to silica and other dusts were believed to account for many of these cases. The results of statistical analyses did not implicate RCF exposure [Trethowan et al. 1995] or yielded results only slightly suggestive of an RCF exposure effect [Rossiter et al. 1994]. In the 1996 evaluation of the European cohort, small opacities of category 1/0 or greater were positively associated with RCF exposures that occurred before 1971 [Cowie et al. 1999]. Ten of the 51 (19.6%) male workers exposed before 1971 developed category 1/0 or greater opacities—8 had also been exposed to asbestos and 9 were either current or ex-smokers.

Both the U.S. [Lockey et al. 1993; Lemasters et al. 1998] and the European [Trethowan et al. 1995; Burge et al. 1995; Cowie et al. 1999] studies found that occupational exposure to RCFs is associated with various reported respiratory symptoms and conditions, after adjusting for the effects of age, sex, and smoking. Exposure to RCF concentrations in the range of 0.2 to 0.6 f/cm^3 was associated with statistically significant increases in eye irritation (OR=2.16, 95% CI=1.32–3.54), stuffy nose (OR=2.06, 95% CI=1.25–3.39), and dry cough (OR=2.53, 95% CI=1.25–5.11) compared with exposure concentrations lower than 0.2 f/cm^3 [Trethowan et al. 1995]. Increasing ORs were demonstrated for RCF exposure concentrations greater than 0.6 f/cm^3 compared with exposure concentrations <0.2 f/cm^3 for wheeze (P<0.0001), dyspnea (P<0.05), eye irritation (P<0.0001), skin irritation (P<0.0001), and dry cough (P<0.05) but not stuffy nose or chronic bronchitis [Trethowan et al. 1995]. Lockey et al. [1993] found that dyspnea was significantly associated with exposure to >15 fiber-months/cm^3 (that is, >1.25 fiber-years/cm^3) relative to exposure to ≤15 fiber months/cm^3 (dyspnea grade 1—OR=2.1, 95% CI=1.3–3.3; dyspnea grade 2—OR=3.8, 95% CI=1.6–9.4). Lockey et al. [1993] also found statistically significant associations between cumulative RCF exposure and chronic cough (OR=2.0, 95% CI=1.0–4.0) and pleurisy (OR=5.4, 95% CI=1.4–20.2). Lemasters et al. [1998] also noted associations (P<0.05) between employment in an RCF production job and increased prevalence of dyspnea and the presence of at least one respiratory symptom or condition. Recurrent chest illness in the European cohort was associated with cumulative exposure to respirable fibers and was most strongly associated with cumulative exposure to respirable dust [Cowie et al. 1999].

In cross-sectional analyses involving spirometric testing, both the U.S. [Lockey et al. 1998; Lemasters et al. 1998] and 1986 European [Trethowan et al. 1995; Burge et al. 1995] studies found that cumulative RCF exposure was associated with pulmonary function decrements among current and former smokers. The 1996 European study demonstrated

decrements in current smokers only [Cowie et al. 1999]. The observed decreased pulmonary function in the European workers remained significantly associated with cumulative RCF exposure, even after controlling for cumulative exposure to inspirable dust [Burge et al. 1995]. A longitudinal analysis of data from multiple PFTs by Lockey et al. [1998] led the researchers to conclude that exposures to RCFs between 1987 and 1994 were not associated with decreased pulmonary function. The findings from the U.S. and European studies suggest that decrements in pulmonary function observed in current and former smokers result from an interactive effect between smoking and RCF exposure.

5.4 Carcinogenicity Risk Assessment Analyses

The literature contains three significant independent risk analyses of occupational exposure to RCFs and potential health effects. In each of these analyses, health effects data derived from multidose and MTD studies with rats were used with models to extrapolate risks to human populations. The modeling of effects observed in experimental animal studies was necessitated by the lack of adequate data on adverse health effects in humans with occupational exposures to RCFs. The three studies, described in detail below and in Table 5–9, include the following studies: Dutch Expert Committee on Occupational Standards (DECOS) [1995], Fayerweather et al. [1997], and Moolgavkar et al. [1999].

5.4.1 DECOS [1995]

In 1995, DECOS (a workgroup of the Health Council of the Netherlands) published a report evaluating the health effects of occupational exposure to SVFs. The purpose of the report was to establish health-based recommended occupational exposure limits for specific types of SVFs. As one of the criteria for determining the airborne exposure limits for six distinct types of SVFs, risk assessments were performed for each fiber type, including RCFs. The risk analysis for RCFs was based on the assumption that RCFs are a potential human carcinogen as indicated by the positive results of carcinogenicity testing with animals. A health-based recommended occupational exposure limit was determined using the following rationale:

1. If the carcinogenic potential of RCFs is caused by a nongenotoxic mechanism, an occupational exposure limit of 1 respirable f/cm^3 as an 8-hr TWA should be recommended based on an NOAEL of 25 f/cm^3 and a safety factor of 25.

2. If the carcinogenic potential of RCFs is linked to a genotoxic mechanism, a model assuming a linear relationship between dose and the response (cancer) should be used to establish the occupational exposure limit.

The model indicated that an excess cancer risk of 4×10^{-3} is associated with a TWA exposure to 5.6 respirable f/cm^3 based on 40 years of occupational exposure. A cancer risk of 4×10^{-5} is associated with exposure to 0.056 f/cm^3, and a linear extrapolation indicated that occupational exposure to 1 respirable f/cm^3 as an 8-hr TWA for 40 years is associated with a cancer risk of 7×10^{-4}.

The DECOS analysis relied on the data from a long-term multidose study with rats exposed to kaolin ceramic fibers [Bunn et al. 1993; Mast et al. 1995b]. These data showed that exposure by inhalation to 25 f/cm^3 (3 mg/m^3) for 24 months produced a negligible amount of fibrosis (mean Wagner score of 3.2). Consequently, the Dutch committee viewed 25 f/cm^3 as the NOAEL for fibrosis. The report also notes that at the time of publication, no data

Table 5–9. Risk associated with exposure to RCFs* at 1 f/cm³ (TWA) as determined by three independent analyses

Study	Animal data	Extrapolation model	Occupational exposure scenario	Excess lifetime risk of lung cancer–MLE
DECOS 1995	Long-term multidose and MTD rat studies	Linearized multistage model	8 hr/day, 40 years	7×10^{-4}
Fayerweather et al. 1997	Long-term multidose and maximum tolerated dose rat studies (Mast et al. 1995a,b)	Linearized, nonthreshold model	4 hr/day, 5 days/week, 50 weeks/year, 40 years of a 70-year lifespan	3.8×10^{-5}
Moolgavkar et al. 1999	Long-term multidose and maximum tolerated dose rat studies (Mast et al. 1995a,b)	Two-mutation clonal expansion model	8 hr/day, 5 days/week, 52 weeks/year, 30 years (age 20–50) of a 70-year lifespan	**Exponential:** ACS nonsmoking cohort, 3.7×10^{-5} (95% UCL = 0.9×10^{-5}) Steel industry cohort, 1.5×10^{-4} (95% UCL = 1.8×10^{-4}) **Quadratic:** ACS nonsmoking cohort, 4.1×10^{-6} (95% UCL = 1.2×10^{-5}) Steel industry cohort, 1.5×10^{-4} (95% UCL = 1.8×10^{-4}) **Linear:** ACS nonsmoking cohort, 2.7×10^{-4} (95% UCL = 1.5×10^{-3}) Steel industry cohort, 1.1×10^{-3} (95% UCL = 5.8×10^{-3})

*Abbreviations: ACS=American Cancer Society; MLE=maximum likelihood estimate; MTD=maximum tolerated dose; RCFs=refractory ceramic fibers; TWA=time-weighted average; UCL= 95% upper confidence limit.

existed from retrospective cohort mortality or morbidity and case-control studies of persons with occupational exposures to RCFs. The linear modeling approach in this analysis of the exposure-response relationship using the animal data does not take into consideration possible differences in dosimetry and lung burden between rats and humans.

5.4.2 Fayerweather et al. [1997]

Fayerweather et al. [1997] conducted a study primarily focusing on the risk assessment of occupational exposures for glass fiber insulation installers. They performed risk analyses with several other types of SVFs, including RCFs. Only the analysis with RCFs is presented here. This analysis applied an EPA linearized multistage model (representing a linear nonthreshold dose-response) to data from rat multidose and MTD chronic inhalation bioassays [Mast et al. 1995a,b] to determine exposures at which "no significant risk" occurs; i.e., no more than one additional cancer case per 100,000 exposed persons. Nonlinear models were also used for comparison: the Weibull 1.5-hit nonthreshold model (representing the nonlinear, nonthreshold dose-response curve) and Weibull 2-hit threshold model (representing the nonlinear, threshold dose-response curve). Fiber inhalation by rats was equated to humans by determining the fibers/day·kg of body weight for the animals and using an exposure scenario of 4 hr/day (consistent with insulation installation workers' schedules), for 5 days/week and 50 weeks/year over 40 working years of a 70-year lifespan. RCFC interpreted the results of the analysis with the linearized multistage model to represent a risk of 3.8×10^{-5} for developing lung cancer over the working lifetime at an exposure concentration of 1 f/cm^3 [RCFC 1998]. Using the nonlinear models, estimates of nonsignificant exposures (i.e., a working lifetime exposure associated with no more than 1 additional cancer case/100,000 exposed persons) were 2 and 3 orders of magnitude higher. Conversely, the risk estimates for exposure to 1 f/cm^3 for a working lifetime were lower using the Weibull 1.5-hit nonthreshold and Weibull 2-hit threshold models.

5.4.3 Moolgavkar et al. [1999]

This report describes a quantitative assessment of the risk of lung cancer associated with occupational exposure to RCFs [Moolgavkar et al. 1999]. A major premise underlying the risk assessment is that humans are equally susceptible to RCFs as rats, at the tissue level. The risk analysis was performed using data from two chronic inhalation bioassays of RCFs in male Fischer 344 rats [Mast et al. 1995a,b]. Dosimetry in the risk assessment was based on a fiber deposition and clearance model developed by Yu et al. [1996] that was used to estimate the lung burdens of fibers in humans. The dose-response model used for the risk assessment was the two-mutation clonal expansion model, commonly referred to as the Moolgavkar-Venzon-Knudson (MVK) model. The MVK model was fitted to the rat bioassay data to estimate the proportional increase in the rat lung tumor initiation rate in RCF-exposed rats, relative to the background initiation rate in nonexposed rats. An MVK model for human lung cancer was then created by fitting the model to the age-specific lung cancer incidence for either of two human cohorts. Finally, the human lung cancer rate for a given tissue dose was estimated by increasing the tumor initiation rate in the human model by the same proportional amount that an identical tissue dose would increase the initiation rate in the MVK model for rats. The assumption was made that, for any given tissue dose, the proportional increase in the lung tumor initiation rate (relative to the background rate) is the same in humans as in rats. The two human cohorts used for the human modeling were a nonsmoking American

Cancer Society (ACS) cohort [Peto et al. 1992] and a cohort of workers from the steel industry (not exposed to coke oven emissions) believed to be representative of industrial workers. Because of the difference in the baseline lung cancer risk, risk estimates based on the Steel Industry cohort were approximately 4 times higher than those based on the ACS cohort. Both central estimates (maximum likelihood estimates [MLEs]) and 95% upper confidence limits (UCLs) were developed. Three equations were tested to describe the relationship between initiation rate for lung cancer and lung burden:

I=A exp(Bd)	(exponential)
I=A + Bd2	(quadratic)
I=A + Bd	(linear)

where d = lung burden in fibers per milligram of lung (which can vary with time) and A and B are constants (different for each model). With each equation, calculations were made to determine the excess risk for a worker aged 20 to 50 to develop lung cancer by age 70 when exposed to RCFs at a concentration of 1.0 fiber/cm^3 for 8 hr/day, 5 days/week.

Using the exponential model, the excess risk of lung cancer associated with 1.0 f/cm^3 was estimated to be 3.7×10^{-5} (MLE) and 4.9×10^{-5} (95% UCL), based on the ACS cohort. For the same conditions the risk of lung cancer was 1.5×10^{-4} (MLE) and 1.8×10^{-4} (95% UCL) based on the Steel Industry cohort. Using a quadratic equation, the researchers reported slightly lower estimates of excess risk of 4.1×10^{-6} (MLE) and 1.2×10^{-5} (95% UCL) for the ACS cohort, and 1.4×10^{-5} (MLE) and 4.3×10^{-5} (95% UCL) for the Steel Industry cohort. The highest estimates of excess risk resulted with a linear equation: 2.7×10^{-4} (MLE) and 1.5×10^{-3} (95% UCL) for the ACS cohort, and 1.1×10^{-3} (MLE), and 5.8×10^{-3} (95% UCL) for the Steel Industry cohort. Additional risk estimates were calculated according to the conditions described above (i.e., ACS cohort versus Steel Industry cohort; MLE and 95% UCL for exponential, quadratic, and linear models) but with different exposure concentrations. The excess risk was also calculated for exposure concentrations of 0.75 f/cm^3, 0.5 f/cm^3, and 0.25 f/cm^3. These risk estimates are presented in Table 5–10.

As shown in Table 5–10, the highest risk estimates at each of the three exposure concentrations are associated with the linear model, followed by the exponential model. The lowest risk estimates are associated with the quadratic model. At each exposure concentration, more conservative risk estimates are obtained for the ACS cohort than the Steel Industry cohort.

At the recommended exposure guideline established by the RCFC (0.5 f/cm^3), the highest risk estimate (linear model, Steel Industry cohort) is the MLE of 5.3×10^{-4} or 5.3/10,000 (95% UCL=2.9×10^{-3}). At 0.5 f/cm^3, the risk estimates for the steel industry cohort are roughly 1 order of magnitude (factor of 10) lower with the exponential model (MLE=7.3×10^{-5}, 95% UCL= 9.1×10^{-5}), and 2 orders of magnitude lower using the quadratic model (MLE=3.5×10^{-6}, 95% UCL=1.1×10^{-5}). At the lowest exposure concentration (0.25 f/cm^3), the highest risk estimate (Steel Industry cohort, linear model) was the MLE of 2.7×10^{-4} (95% UCL=1.4×10^{-3}). Again, on average, the risk estimates from the 3 models using the steel industry cohort are 3 to 4 times higher than for corresponding model values with the ACS cohort.

The authors concluded that the risk estimates based on the two cohorts "represent bounds on risks likely to be seen in occupational cohorts." However, an occupational cohort is unlikely to share the nonsmoking status of the ACS cohort. Therefore, of the two human populations used for model fitting in the Moolgavkar et al. [1999] risk assessment, the steel industry cohort may be the preferable cohort to use for estimating the risks from occupational exposures to RCFs.

Table 5–10. Estimates (MLE* and 95% UCL) of excess risk of lung cancer at three exposure concentrations using exponential, quadratic, and linear models for an ACS cohort and a steel industry cohort

	ACS cohort			Steel industry cohort		
Exposure	Exponential	Quadratic	Linear	Exponential	Quadratic	Linear
0.75 f/cm^3:						
MLE	2.8×10^{-5}	2.3×10^{-6}	2.0×10^{-4}	1.1×10^{-4}	7.9×10^{-6}	8.0×10^{-4}
95% UCL	3.7×10^{-5}	6.8×10^{-6}	1.1×10^{-3}	1.4×10^{-4}	2.4×10^{-5}	4.3×10^{-3}
0.5 f/cm^3:						
MLE	1.8×10^{-5}	1.0×10^{-6}	1.3×10^{-4}	7.3×10^{-5}	3.5×10^{-6}	5.3×10^{-4}
95% UCL	2.5×10^{-5}	3.0×10^{-6}	7.3×10^{-4}	9.1×10^{-5}	1.1×10^{-5}	2.9×10^{-3}
0.25 f/cm^3:						
MLE	9.2×10^{-6}	2.5×10^{-7}	6.7×10^{-5}	3.6×10^{-5}	8.8×10^{-7}	2.7×10^{-4}
95% UCL	1.2×10^{-5}	7.5×10^{-7}	3.6×10^{-5}	4.6×10^{-5}	2.7×10^{-6}	1.4×10^{-3}

Adapted from Moolgavkar et al.[1999].
*Abbreviations: ACS=American Cancer Society; MLE=maximum likelihood estimate; UCL= 95% upper confidence limit.

The Moolgavkar et al. [1999] report also indicates airborne fiber concentrations estimated to result in excess lifetime risk for cancer of 10^{-4} (1 in 10,000) based on the approaches used by DECOS [1995] and Fayerweather et al. [1997] and using the MVK model for both the ACS cohort and the steel industry cohort. With the DECOS [1995] linearized, nonthreshold model approach, an excess lifetime cancer risk of 10^{-4} was calculated to result from a fiber concentration of 0.14 f/cm^3. Using the linearized, multistage model approach described in Fayerweather et al. [1997], a fiber concentration of 2.6 f/cm^3 was estimated to correspond to the excess lifetime cancer risk of 10^{-4}. With the MVK exponential model, an excess lifetime cancer risk of 10^{-4} was determined for fiber concentrations of 0.7 f/cm^3 for the Steel Industry cohort and 2.7 f/cm^3 for the ACS cohort [Moolgavkar et al. 1999].

5.4.4 Discussion

The estimated lung fiber burden for dosimetry in the analysis by Moolgavkar et al. [1999] is a methodological improvement over the risk assessment for RCFs by Fayerweather et al. [1997], which was based solely on the inhaled fiber concentration. Modeling lung burden dosimetry should, in theory, compensate for the known differences between rats and humans in fiber deposition and clearance. Similarly, using an MVK model for dose-response estimation could compensate for differences in cell mutation and proliferation rates in rats and humans. However, some key parameter values in the MVK and lung dosimetry models are poorly known. For example, the dosimetry model for humans has been validated with only three human tissue samples taken from workers whose exposures to RCFs were not measured [Yu et al. 1997].

A review and comparison of risk modeling approaches for RCFs by Maxim et al. [2003] describes the three models here as well as additional more sophisticated variations of quantitative risk analyses for RCFs. Using approaches such as benchmark dose modeling, Maxim et al. [2003] produced RCF unit potency values ranging from 1.4×10^{-4} to 7.2×10^{-4}.

A common weakness among all three of the risk analyses stems from uncertainty about possible differences in the sensitivity of human lungs to fibers, as compared with rat lungs. The possibility of such a difference is acknowledged in the report by Moolgavkar et al. [1999], but the effect of this uncertainty on the risk estimates is not explored quantitatively. As an example, Pott et al. [1994] estimated that in the case of asbestos fibers, humans are approximately 200-fold more sensitive than rats, on the basis of fiber concentration in air. Pott et al. [1994] further noted that a crocidolite inhalation study that was negative in the rat resulted in a rat lung fiber concentration that was more than 1,000-fold greater than the fiber concentrations in the lungs of asbestos workers with mesotheliomas. In support of this analysis, results of a study by Rödelsperger and Woitowitz [1995] led the authors to conclude that humans are at least 6,000 times more sensitive than rats to a given tissue concentration of amphibole fibers. Although amphibole asbestos fibers have physicochemical characteristics which differ from those of RCFs, these findings raise questions about using experimental animal data for predicting human health effects and assuming that target tissues in humans and rats are equally sensitive to RCF toxicity.

The lung cancer risk estimates for RCFs derived by Moolgavkar et al. [1999] may also be underestimated for occupationally exposed workers because of several basic assumptions made in the lung tissue dosimetry. Tissue dosimetry modeling in the Moolgavkar et al. [1999] risk assessment is based on the assumption that a worker is exposed to RCFs for 8 hr/day, 5 days/week, 52 weeks/year, from age 20 to 50 [Moolgavkar et al. 1999]. An alternative analysis, in which the assumption was changed to 8 hr/day, 5 days/week, 50 weeks/year from age 20 to 60, was also described but not presented in detail. In both cases, the breathing rate for light work was assumed to be 13.5 liters/minute. Additional information might be gained from assuming an exposure period of 8 hr/day, 5 days/week, 50 weeks/year, from age 20 to 65, with a breathing rate matching the International Commission on Radiological Protection "Reference Man" value for light work, which is 20 liters/minute [ICRP 1994]. In addition, the cumulative excess risk of lung cancer was calculated only through age 70 [Moolgavkar et al. 1999]. This practice may underestimate the lifetime risk of lung cancer in the exposed cohort, since a substantial fraction of the cohort may be expected to survive beyond age 70. The excess risk might also be calculated in a competing-risks framework using actuarial methods until most or all of the cohort is presumed to have died because of competing risks (generally 85 years). Finally, risk estimates derived by Moolgavkar et al. [1999] were based solely on data from studies with rats, ignoring data from studies of hamsters [McConnell et al. 1995]. Because 42% of the hamsters in these studies developed mesotheliomas, using this database for the risk assessment would produce higher estimates of risk than the analysis based on the rat data.