

Quantitative risk analyses for RCF: survey and synthesis

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Received 1 May 2003

Abstract

Refractory ceramic fiber (RCF) is a high-temperature insulating fiber used principally in industrial applications. Epidemiological studies on occupationally exposed cohorts have not indicated that exposure leads to fibrosis, increased lung cancer, or mesothelioma. However, inhalation bioassays with rats and hamsters have shown that these animals can develop each of these endpoints when exposed to high levels of RCF-particle mixtures. This work summarizes relevant quantitative risk analyses based upon analysis of the rat bioassay studies, which lead to predicted unit risks that range nearly three orders of magnitude. Additionally, we identify key assumptions that affect the risk estimates and provide additional estimates using the benchmark dose methodology favored by the U.S. EPA in cases where mechanistic models are inadequate or not available. We show that a key determinant of risk is how lung burdens are normalized (e.g., in terms of the number of fibers per square centimeter of lung surface or the number of fibers per milligram dry lung) for species conversion. Plausible values of unit potency/risk range from 1.4×10^{-4} to 7.2×10^{-4} , neglecting any allowance for the effects of particulate material in the RCF tested in the bioassay experiments.

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1. Background

RCF (Chemical abstract service [CAS] No. 142844-00-6) is an amorphous fiber that belongs to a class of materials termed synthetic vitreous fibers (SVFs). Other SVFs include glass wool fibers, rock wool fibers, slag wool fibers, and special-purpose glass fibers. RCF is a useful high-temperature insulating refractory used chiefly in industrial applications. The history, chemical and physical properties, production methods, and commercial applications have been extensively studied and documented (e.g., ECA, 1996; IARC, 1988, 2002; Mast et al., 2000a,b; Maxim et al., 1994, 1997, 2000b).

When RCF is subject to normal handling, fibers and fragments of varying diameters and lengths result; some of which fall into the respirable range (Mast et al., 2000a). Moreover, RCF is relatively biopersistent (Maxim et al., 1999; Zoitos et al., 1997). These two properties suggest that workplace exposure to RCF

might pose risks for exposed cohorts. The RCF industry has developed a comprehensive worldwide product stewardship program (PSP) to identify, control, and reduce possible risks. The research component of this PSP include short-term animal inhalation studies (Bellmann et al., 2001; Creutzenberg et al., 1997), long-term animal inhalation bioassays (Mast et al., 1995a,b, 2000a,b; Rossiter and Chase, 1995), development of dosimetry (lung deposition and clearance) models in rats and humans (Yu et al., 1995, 1997; Zoitos et al., 1997), mortality and morbidity studies of worker cohorts in the United States (LeMasters et al., 1994, 2003; Lockey et al., 1996, 2002; Walker et al., 2002) and Europe (Cowie et al., 2001), studies of workplace exposure in the United States (Maxim et al., 1994, 1997, 1998b, 2000a,b; Rice et al., 1997) and Europe (Maxim et al., 1998a), and quantitative risk analyses (Moolgavkar et al., 1999, 2000; Sciences International Incorporated (SII), 1998).

1.1. Key bioassay results

Nose-only animal inhalation studies conducted at the Research and Consulting Company (RCC) indicated

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Table 1
Results of the RCC experiments

Exposure (mg/m ³)	Total f/ml	WHO f/ml	Fibers >20 μm long/ml	Number of animals at risk ^a	Number of tumors				
					Adenomas	Carcinomas	Adenomas and carcinomas	Mesothelioma	All tumors
0	0	0	0	256	3	0	3	0	3
3	36	26	12.5	123	2	0	2	0	2
9	91	75	36	127	4	1	5	1	6
16	162	120	58	124	1	1	2	0	2
30	234	187	101	121	8	8	16	2	18

^a Data taken from Yu and Oberdörster (2000) and SII (1998). Minor differences exist between the data and assumptions used in these references.

that rats exposed to high levels of RCF developed fibrosis and tumors (adenomas, carcinomas, and mesotheliomas) [Mast et al., 1995a,b]. Table 1 shows the RCF exposure concentrations (in milligrams per cubic meter [mg/m³], and total and World Health Organization [WHO] fibers per milliliter [f/ml]) and the resulting incidence of various tumors in the RCC rat studies.

The RCC studies on RCF (and other SVFs) were intended to provide a definitive body of data on which to base future classification decisions and risk assessments. These studies were carefully designed and referred to at the time as the “gold standard.” Subsequent analysis, however, revealed (among other things) flaws in the sample preparation method for RCF, which lowered—and may have compromised—their value. Specifically, the specially prepared RCF (referred to as RCF 1) administered to the rats had a particle-to-fiber ratio significantly greater than that found in the workplace (Mast et al., 2000a,b; Maxim et al., 1997) or those of the other SVFs tested (Hesterberg et al., 1993, 1995) in parallel RCC experiments. The RCF tested in the RCC experiments was not representative of that found in workplace air samples, nor comparable in particle-to-fiber ratio to those for other SVFs. A growing body of evidence indicates that these particles resulted in overload at the putative maximum tolerated dose (MTD) experiments (Mast et al., 2000a,b; Yu and Oberdörster, 2000) and account for an unknown component of the observed toxicity. It is well known that poorly soluble (but otherwise nontoxic) particles can contribute to overload and toxicity (ILSI, 2000; Yu and Oberdörster, 2000). Subsequently, it has been shown that an RCF (termed *RCF 1a*) prepared by the same method used in the RCC studies for other SVFs (and having a comparable particle-to-fiber ratio) barely retarded alveolar clearance of radio labeled ⁴⁶Sc₂O₃ particles (Bellmann et al., 2001; Creutzenberg et al., 1997). Unfortunately, no long-term bioassay study has been conducted with RCF 1a.

1.2. Key epidemiological results

Morbidity studies indicated that occupational exposure to RCF is associated with the development of pleural

plaques and statistically significant but clinically insignificant changes in certain measures of lung function. An ongoing mortality study of an occupational cohort in the United States indicates (LeMasters et al., 2003; Walker et al., 2002) that the standard mortality ratio (SMR) for malignancies of the respiratory system was not elevated (SMR = 78.8; 95% confidence interval 36.0 – 149.7).

1.3. Regulatory interest

Results from these health effects studies—particularly the animal bioassay results—attracted the interest of regulatory and advisory bodies. From the perspective of carcinogen classification, EPA has reviewed the available health effects research and placed RCF into Group B2 (probable human carcinogen based upon sufficient evidence of carcinogenicity in animals, but inadequate or no data from epidemiological studies). A second example, the International Agency for Research on Cancer (IARC) reviewed RCF in 1988 (IARC, 1988) and placed it in Group 2B (possible human carcinogen). More recently IARC (2002) again examined the available evidence and reaffirmed its original classification for RCF.

There is continuing interest in the possible human health risks posed by exposure (almost exclusively workplace exposure) to RCF. For example, EPA is in the process of updating the data contained in the Integrated Risk Information System (IRIS). IRIS is a centralized repository for information on more than 500 specific materials. One section of IRIS contains quantitative estimates of carcinogenic risk; for inhalation risks this is expressed as the exposure concentrations estimated to result in incremental lifetime cancer risks of 10⁻⁶, 10⁻⁵, and 10⁻⁴ (EPA, 2002). The results reported in this analysis may prove useful to EPA in updating the IRIS entries for RCF.

2. Quantitative risk analyses for RCF

This section summarizes results of the quantitative risk analyses (QRAs) of occupational exposure to RCF. In principle, the use of human data is preferred for

estimating occupational risks. Although the mortality study of the U.S. worker cohort (LeMasters et al., 2003) has not found any mesothelioma or any excess of lung cancer, this study has limited statistical power because of the limited size of the cohort and duration of exposures. Walker et al. (2002) showed that, notwithstanding these limits, it is possible to derive bounds on possible lung cancer risks. Specifically, Walker et al. (2002) showed that the observed mortality data are inconsistent with the hypothesis that RCF is as potent as amphibole asbestos with respect to lung cancer. The data do not yet enable RCF to be distinguished from chrysotile asbestos based upon the most recent reanalysis of epidemiological studies on asbestos (Hodgson and Darnton, 2000).

Because of the limited epidemiological data, nearly all QRAs for RCF have been based upon analysis of the RCC data given in Table 1 and, in one study (see Moolgavkar et al., 2000), of similar data from companion studies of other SVFs. QRAs for occupational exposure to RCF have been prepared by the Dutch Expert Committee on Occupational Standards (DECOS) (Fayerweather et al., 1997; DECOS, 1995; Moolgavkar et al., 1999, 2000; SII, 1998; Yu and Oberdörster, 2000). Table 2 shows these estimates, together with others made in this analysis, and some of the assumptions that underlie the results. The risk estimates are expressed in terms of the maximum likelihood estimate (MLE) of the incremental cancer risk associated with a working lifetime exposure to 1 f/ml RCF, also termed the *unit*

potency or *unit risk*. Additional details relevant to each of these estimates are provided below, but it is interesting to note that these estimates vary by a factor of nearly 1000, from approximately 4.1×10^{-6} to 3.4×10^{-3} . With the exception of Moolgavkar et al. (2000), which uses data from RCC studies on RCF and other SVFs, each of these risk estimates are based on analysis of the same bioassay data given in Table 1.

To those familiar with risk estimates for other materials, the nearly 1000-fold range in workplace risks shown in Table 2 may not be surprising. For example (Health Effects Institute-Asbestos Research [HEI-AR], 1991), the reported range in the percentage increase in lung cancer per fiber-year per milliliter ($100 \times K_L$ in the usual notation) occupational asbestos exposure for various cohorts also varies by a factor of nearly 1000 from 0.01 to 9.1. Other examples of chemicals and risk ranges reported in the literature include benzene (Occupational Safety and Health Administration [OSHA], 1987), factor of 10; methylene chloride (OSHA, 1997), factor of 26; 1,3 butadiene (OSHA, 1996), factor of 64; trichloroethylene (RIAP, 1994), factor of 288; ethylene dibromide (OSHA, 1983), factor of 1950; and vinyl chloride (Barr, 1984), factor of 10^{+8} .

The reported range of RCF workplace risks may not be unusual. Nonetheless, this range is quite broad and may have material consequences for the development of risk-based exposure guidelines or standards. It is desirable to identify reasons for differences in these

Table 2

Summary of MLE unit potency values (lifetime incremental workplace risk associated with 1 f/ml RCF) based upon several models fitted to RCC data vary by factor of nearly 1000

Source	MLE unit potency	Remarks/Assumptions
SII (1998)	4.10×10^{-6}	MVK quadratic potency model, Yu et al., dosimetry model, ACS cohort, RCF only
SII (1998)	1.40×10^{-5}	MVK quadratic potency model, Yu et al., dosimetry model, steel worker cohort, RCF only
Moolgavkar et al. (2000)	1.50×10^{-5}	MVK potency model, Yu et al., dosimetry model, ACS cohort, high dose deleted, all MMVFs
Moolgavkar et al. (2000)	2.80×10^{-5}	MVK potency model, Yu et al., dosimetry model, ACS cohort, high dose deleted, RCF only
SII (1998)	3.70×10^{-5}	MVK exponential potency model, Yu et al., dosimetry model, ACS cohort, RCF only
Fayerweather et al. (1997)	3.80×10^{-5}	Linearized multistage model, installer exposure, fibers/kg/day scaling
Moolgavkar et al. (2000)	4.60×10^{-5}	MVK potency model, Yu et al., dosimetry model, steel worker cohort, high dose deleted, all MMVFs
Moolgavkar et al. (2000)	8.80×10^{-5}	MVK potency model, Yu et al., dosimetry model, steel worker cohort, high dose deleted, RCF only
BMD	1.23×10^{-4}	Weibull, Yu et al., dosimetry model, fibers/lung weight normalization, RCF only, in vitro K_{dis}
SII (1998)	1.50×10^{-4}	MVK exponential potency model, Yu et al., dosimetry model, steel worker cohort, RCF only
SII (1998)	2.70×10^{-4}	MVK linear potency model, Yu et al., dosimetry model, ACS cohort, RCF only
BMD	4.59×10^{-4}	Weibull, Yu et al., dosimetry model, fibers/lung weight normalization, RCF only
DECOS (1995)	7.00×10^{-4}	Unspecified
Yu and Oberdörster (2000)	7.20×10^{-4}	Linearized multistage, Yu et al., dosimetry model, fibers/lung area normalization, RCF only
SII (1998)	1.10×10^{-3}	MVK linear potency model, Yu et al., dosimetry model, steel worker cohort, RCF only
BMD	3.38×10^{-3}	Weibull, Yu et al., dosimetry model, fibers/lung area normalization, RCF only

Note. All except BMD previously published, BMD results included in this analysis.

estimates and, if possible, to narrow the reported range by deleting less plausible alternatives. At a minimum, it is appropriate to identify the critical assumptions that determine this risk so that informed decisions can be made. Although a large number of (potentially uncertain) factors enter into the risk calculation, this analysis shows that only a few are critical to the end result.

In what follows, the various risk analyses are reviewed in chronological order.

2.1. DECOS

DECOS published a series of health-based recommended occupational exposure limits (OELs) for RCF and other SVFs (Health Council of the Netherlands, DECOS, 1995). Based on the RCC results reported in Table 1, DECOS concluded that RCF may pose a carcinogenic risk for humans. DECOS could not decide whether or not the carcinogenic effect was induced by a genotoxic mechanism. Accordingly, DECOS made replicate calculations based upon two assumptions. Assuming first that a nongenotoxic mechanism was operative, DECOS derived an OEL from the established no-observed-adverse-effect-level (NOAEL) of 25 f/ml. Using a safety factor of 25, DECOS estimated an OEL of 1 f/ml for RCF. Assuming alternatively that a genotoxic mechanism accounted for the observed RCC results, DECOS fitted a linear model (not otherwise specified) to these data, concluding that occupational exposure to 1 f/ml would result in an incremental working lifetime lung cancer risk of 7×10^{-4} .

Unfortunately, few details of the calculation procedure used by DECOS for RCF are available and, therefore, it is difficult to evaluate what confidence should be placed in this estimate. Therefore, it is not considered further.

2.2. Fayerweather et al. (1997)

Fayerweather et al. (1997) published a risk analysis of several SVFs, including RCF. This analysis applied (among others) the linearized multistage (LMS) model—a variant of the Armitage and Doll (1954) model of carcinogenesis that postulates cancer induction to result from a series of mutational changes in cell lines once used as the policy default (EPA, 1986)—to the data (adenomas and carcinomas) given in Table 1. Fayerweather et al. (1997) did not address the possible confounding effects of particles and/or overload in their analysis of the RCC data.

The Fayerweather et al. (1997) analysis did not develop a complete dosimetry model—assuming instead that RCF and other SVFs would have similar deposition fractions—but did consider the relative rates of dissolution of these SVFs for estimating toxicological equiva-

lence. The dissolution rate constant, K_{dis} , assumed for RCF, 3 nanograms per square centimeter per hour (ng/cm²/h) in the Fayerweather et al. (1997) analysis differs from other in vivo and in vitro estimates of this parameter given below, but was used for extrapolating from RCF to other SVFs, so this discrepancy is not material to an analysis of RCF risks.

Fayerweather et al. (1997) scaled from the rat to the human by equating the fiber intake for rats and humans in terms of fibers per day per kilogram of body weight (f/day/kg body weight) and employed an exposure scenario consisting of 4 hours per day (h/day) (representative of insulation workers), 5 days/week, 50 weeks/year, over a 40-year working lifetime. The MLE of the incremental risk of developing lung cancer over a working lifetime was 3.8×10^{-5} , for insulation workers exposed to 1 f/ml RCF.

Fayerweather et al. (1997) offered numerous arguments in favor of *interspecies scaling* (also referred to as “lung burden normalization”) in terms of f/day/kg body weight in preference to (body weight)^{2/3} [recommended by EPA] or (body weight)^{3/4} [an EPA/Food and Drug Administration (FDA)/Consumer Product Safety Commission (CPSC) joint proposal] then recommended as default scaling assumptions. In particular Fayerweather et al. (1997) remarked:

The EPA/FDA/CPSC joint proposal recognizes that an exception to the (body weight)^{3/4} scaling occurs when a material's removal rate hinges on physicochemical properties of the material and its milieu. Under these conditions, material removal rate from the body becomes species independent, and areas under the concentration-over-time curve tend to be equalized when doses are scaled to bodyweight.

At the time (see, e.g., RIAP, 1994) interspecies scaling factors in use included body mass equivalence (BME) [i.e., equal effects in different species when normalized on a body weight basis], “equal proportions” (i.e., materials in equal concentrations [e.g., parts per million (ppm) or f/ml] have similar effects in all species), body surface area equivalence (SAE) [then favored by EPA], and (body weight)^{3/4} [a joint proposal by EPA, the FDA, and the CPSC]. Current thinking is that it is preferable to relate doses to the target organ (lung in this instance) rather than body weights. Therefore, lung weight, volume, or area, are now favored for scaling/normalization. Table 3 shows a comparison of anatomical and physiological parameters between rats and humans. As can be seen, there are substantial differences in human/rat ratios among the various possible bases for normalization.

The Fayerweather et al. (1997) analysis was significant and novel in many ways—and may be entirely correct—but the (then recommended) models on which it was based have evolved. Therefore, this is not discussed further.

Table 3
Comparisons of anatomical and physiological parameters between rats and humans

Parameter	Human	Rat	Ratio human/rat	Remarks
Body weight [BW] (kg) ^a	70	0.3	233	Body mass equivalence (BME) for scaling
BW ^{3/4}	24.2	0.405	59.8	EPA/FDA/CPSC joint proposal
BW ^{2/3}	17.0	0.448	37.9	Body surface are equivalence (SAE) once recommended by EPA
Lung weight (g) ^a	1000	1.48	676	
Airway volume (cm ³) ^a	3.2 × 10 ³	6.18	518	
Airway surface area (cm ²) ^a	6.27 × 10 ⁵	5.5 × 10 ³	114	
Diameter of alveolar macrophage [AM] (μm) ^a	16.82	10.68	1.57	
Number of AM ^a	7 × 10 ⁹	2.6 × 10 ⁷	269	

^a Yu and Oberdörster, 2000.

2.3. Sciences international incorporated (1998)

SII (1998), sponsored by the Refractory Ceramic Fibers Coalition (RCFC), developed an integrated, biologically based, dosimetry-potency model that is more consistent with current (EPA, 2003) guidelines. The 1998 SII report was published in abridged form by Moolgavkar et al. (1999). The SII (1998) analysis did not address the possible toxic effects of the particulate contamination in the RCC RCF experiments discussed above, but included (implicitly) the effects of these particles on fiber clearance rates.

The SII (1998) analysis included two linked sub-models shown schematically in Fig. 1: (i) an exposure-dose submodel to determine the time-dependent lung burden (expressed as fibers/milligram (mg) dry lung) as a function of workplace exposure and (ii) a dose-response submodel that estimates the incremental risk of developing lung cancer as a function of the time-dependent lung burden. For potency determination, the combined number of adenomas and carcinomas (shown in Table 1) was employed as the relevant endpoint.

The dosimetry submodel extended the work of Yu et al. (1995, 1997). The worker inhalation (minute ventilation) rate used in the SII analysis was 13.5 liters/minute (L/min). The rate constant for fiber dissolution, K_{dis} , was derived from in vivo estimates developed by C.P. Yu, numerically equal to 0.73 ng/cm²/h, lower than that (3 ng/cm²/h) used by Fayerweather et al. (1997) or that (8 ng/cm²/h) estimated from in vitro experiments (Maxim et al., 1999; Zoitos et al., 1997).

The exposure scenario used by SII (1998) [and also by Moolgavkar et al., 1999, 2000, see below] assumed that a worker would be exposed to RCF starting at age 20, for 8 h/day, 5 days/week, 52 weeks/year, until the worker reached the age of 50, followed by a post-exposure period of 20 years. SII (1998) also showed that the estimated risks are essentially the same for an exposure scenario of 8 h/day, 5 days/week, 50 weeks/year, for a 40-year period, which matches more closely the workplace exposure assumptions used by OSHA.

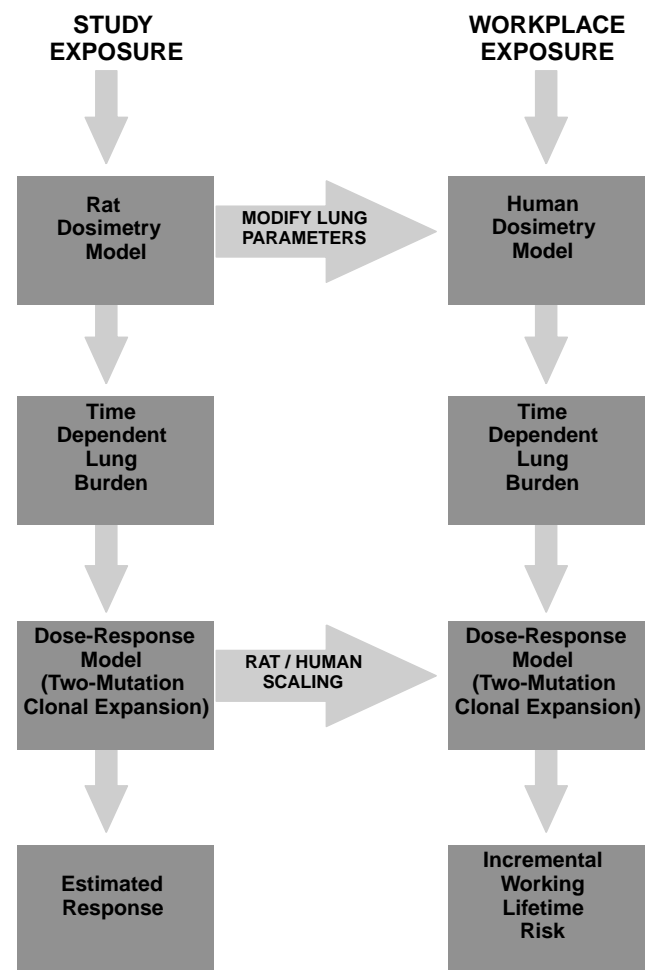


Fig. 1. Overview of SII risk analysis methodology.

The dose-response submodel was the two-mutation clonal expansion model developed by Moolgavkar and co-workers known as the Moolgavkar-Venzon-Knudson (MVK) model. This considers cell division and death explicitly and provides a mathematical framework that incorporates tumor initiation and promotion. The MVK model was selected in preference to the LMS

model because the LMS model does not explicitly consider cell division and apoptosis. The MVK model (a generalization of Knudson's recessive oncogenesis model for retinoblastoma) considers cell division and death explicitly, and utilizes a data-based framework for incorporating initiation and promotion and progression.

As noted above, the potency analysis considered both initiation and promotion models (the initiation model was favored statistically) and three alternative functional forms (linear, quadratic, and exponential) of the MVK model. The exponential model provided the best fit to the data, followed by the quadratic and linear models.

Risk estimates were developed for two populations; a population of nonsmokers (the American Cancer Society [ACS] cohort) and a population more likely to be typical of a cohort of industrial workers (a cohort of steel industry workers not exposed to coke oven emissions). The SII (1998) analysis estimated human risks from scaled lung burdens and, additionally, assumed that the proportionate increase (over background rates) in initiation rates in response to a given fiber burden is the same in rats and humans.

Risk estimates developed by SII (1998) are summarized in Table 2. Among these, the exponential initiation rate submodel provided a better fit to the data and the steel industry cohort is believed to be more representative of the RCF-exposed workforce.¹ Therefore, the MLE (unit potency) of 1.4×10^{-4} is retained in favor of the other estimates developed by SII that are shown in Table 2. The 95% upper confidence limit (UCL) on this unit risk estimated by SII was 1.8×10^{-4} .

2.4. Moolgavkar et al. (2000)

Moolgavkar et al. (2000) extended the SII analysis, using many of the same assumptions. The novel feature of this work was an analysis of the hypothesis that (in terms of carcinogenic potency) "a fiber is a fiber." The "fiber is a fiber" hypothesis assumes that cancer risk (at least for SVFs) is determined entirely by the temporal profile of fiber lung burden. If so, the expected health effect from SVF exposure is determined entirely by the relative dosimetry of these fibers and hence the temporal profile of lung burdens. Because many SVFs have similar diameter-length distributions (at least with respect to those that remain airborne in the workplace), the deposition fractions of these fibers are similar and dosimetry differences are largely accounted for by differences in biopersistence. Although the specific risk estimates developed by Moolgavkar et al. (2000) differ

from those developed by SII (1998) (by virtue of pooling data from other SVFs and deletion of possible outliers), the structure of this model is the same as that used by SII. Therefore, it is not explored further in this comparison.

2.5. Yu and Oberdörster (2000)

Yu and Oberdörster (2000) also performed a QRA on RCF in an unpublished report prepared for EPA. This analysis integrated the LMS potency submodel with a dosimetry submodel developed originally by Yu et al. (1995, 1997) and also used in the SII (1998) and Moolgavkar et al. (1999, 2000) analyses. Yu and Oberdörster (2000) acknowledged the confounding effects of the particles in the RCF tested in the RCC experiments, but included these only to the extent that these influenced the clearance rate for RCF. Unlike the analyses discussed above, Yu and Oberdörster (2000) included adenomas, carcinomas, and mesotheliomas as the relevant endpoint. The Yu and Oberdörster (2000) analysis considered only the RCF data shown in Table 1.

Regarding dosimetry, Yu and Oberdörster (2000) used the same model employed in the SII (1998) and Moolgavkar et al. (1999, 2000) analyses. However, certain inputs differed. The human tidal volume (1290 cm^3) and breathing frequency (15.5 min^{-1}) used by Yu and Oberdörster (2000) correspond to an inhalation (minute ventilation) rate of 20 L/min, somewhat higher than that used in the SII (1998) and Moolgavkar et al. (1999, 2000) analyses.² The equivalent dissolution rate constant, K_{dis} , for RCF used in this analysis was $0.73 \text{ ng/cm}^2/\text{h}$, estimated by C.P. Yu based on the analysis of in vivo data. The human workplace exposure scenario corresponded to 8 h/day, 5 days/week, and 50 weeks/year, for 40 years. Perhaps most important, Yu and Oberdörster (2000) assumed that the appropriate dose metric (for interspecies scaling or lung burden normalization) is the number of fibers present at the epithelial surface of the lung. Thus, fibers (WHO)/ cm^2 pulmonary surface was used, rather than fibers/mg dry lung. Based upon the relative ratios of lung weight (676) compared to airway surface (114) shown in Table 3, the Yu and Oberdörster (2000) analysis would be expected to yield a higher human risk estimate than one based upon fibers per milligram dry lung equivalence.

The Yu and Oberdörster (2000) analysis used the above dosimetry and exposure scenario assumptions to

¹ The major RCF producers do not permit smoking in the workplace and have smoking cessation programs. In the long run predictions based upon a nonsmoking cohort may be more appropriate.

² OSHA (OSHA, 1997) uses $9.6 \text{ m}^3/\text{workday} = 20 \text{ L/min}$ in its analyses. The most recent edition of the EPA Exposure Factors Handbook (1997) [Tables 5–23] recommends an inhalation rate of $1 \text{ m}^3/\text{h}$ (16.67 L/min) for adults engaged in light activities, intermediate in value between the SII and Yu and Oberdörster assumptions. As shown following, estimated risks are not sensitive to which of these assumptions is more nearly correct.

determine the ratio of the fiber concentration used in the rat experiments to a human equivalent concentration (HEC) to produce the same lung burden (measured in terms of WHO fibers per square centimeter surface area) in humans. The actual ratio of rat/HEC estimated by Yu and Oberdörster (2000) varied slightly with fiber concentration, but averaged 36:5.2. That is, exposure to 36 f/ml (total fibers) in the rat RCC experiments was determined to produce the same lung burden as exposure to 5.2 f/ml in humans (based upon the human workplace exposure scenario). The rat/HEC conversion adjusts for the effects of interspecies scaling and the difference in exposure conditions between the RCC experiments and the human workplace exposure scenario. The HECs were used by Yu and Oberdörster (2000) as inputs to the LMS model.

Based upon these assumptions the MLE and 95% UCL of unit risks determined by Yu and Oberdörster (2000) were 7.2×10^{-4} (see Table 2) and 2.36×10^{-3} , respectively.³ These are higher than corresponding estimates derived by SII (1998) [MLE = 1.5×10^{-4} and UCL = 1.8×10^{-4}] by factors of approximately 5 and 13, respectively. Several factors account for these differences but, as is shown below, probably the most important factor is the different basis for normalization of lung burdens in rats and humans.

Before discussing the above estimates, it is useful to develop additional estimates based upon the use of benchmark dose methodology.

2.6. BMD analysis

EPA's (2003) guidance for carcinogen risk assessment indicates a preference for use of biologically based extrapolation models, such as those developed by SII (1998) and Moolgavkar et al. (1999, 2000), when information is available on the mechanism of carcinogenesis. In cases where such models are not available, the most recent EPA guidance recommends straight-line extrapolation based upon a benchmark dose (BMD) model. This section develops risk estimates for RCF based upon the BMD procedure.

In practice, the BMD procedure amounts to fitting one or more of a series (e.g., Weibull, gamma multi-hit, probit, logistic, quantal, or multistage) of exposure–

dose–response models to the bioassay data. (EPA has developed and published software for this purpose [EPA, 2000].) In the case of rat inhalation bioassay data with fibers, it is ultimately necessary to convert fiber concentrations inhaled by rats to HECs, which entails using a dosimetry model as discussed above.

Next, a benchmark response (BMR) is defined, normally set at a 0.1 increase in the fraction responding,⁴ and either the MLE or lower confidence limit (LCL) [typically a 95% lower confidence bound] of the fiber concentration (denoted the BMD or BMDL) used for risk estimation. The unit potency [here the lifetime incremental cancer risk associated with workplace exposure to 1 f/ml] is estimated as the slope of the extrapolated line from the BMR to the background response—i.e., BMR/BMD or BMR/BMDL for the MLE or UCL⁵ estimate of unit risk, respectively. (For BMD models included in the EPA BMD software this linear extrapolation from the BMD or BMDL results in a risk estimate at 1 f/ml that is greater than the estimated response [using the model prediction] at this concentration. This extrapolation is conservative.)

For the data considered here, the benchmark dose procedure involves the following six steps:

- Assemble the appropriate bioassay data, including the definition of the tumors to be included and the specification of which fiber (e.g., all, WHO, fibers >20 μm in length) concentrations are to be modeled.
- Develop a rat/HEC scaling factor using a dosimetry model and assumed basis for lung burden normalization.
- Select a BMD model that provides an adequate fit to the observed exposure–response data. The EPA software (used in this analysis) calculates a *p*-value for each model and recommends that the model selected have a *p*-value of at least 0.10. EPA (2000) guidance for model selection recommends, “If the BMDL estimates from these remaining models [i.e., those with *p*-value >0.1] are within a factor of 3 they are considered indistinguishable, and the model with the lowest AIC can be selected to provide the BMDL.” The criterion recommended for selection is Akaike's information criterion (AIC), defined as $-2L + 2p$, where *L* is the log-likelihood at the MLE estimates for the parameters and *p* is the number of degrees of freedom. The AIC statistic is calculated by the BMD software.

³ The ratio of the 95% UCL to the MLE unit risk for the Yu and Oberdörster (2000), 3.2, is greater than that estimated in the SII (1998), Moolgavkar et al. (2000), or the BMD analysis (presented below). Thus, the apparent discrepancy between the risk estimates depends upon which estimates (MLE or UCL) are being compared. One possible reason for this difference is that Yu and Oberdörster (2000) included adenomas, carcinomas, and mesotheliomas in their analysis. Model fits including mesotheliomas are worse than those based on adenomas and carcinomas, so it is possible that (for the LMS model) the UCLs vary to a greater extent than the MLEs.

⁴ According to EPA (2000), “For quantal data, an excess risk of 10% is the default BMR, since the 10% response is at or near the limit of sensitivity in most cancer bioassays...”

⁵ The UCL risk estimate corresponds to use of the LCL on the BMD or BMDL.

- Specify a BMR (default = 0.1), confidence limit (default = 95%), basis for handling background risk (“extra risk” versus “added risk”),⁶
- Calculate the unit potency (MLE or UCL) based upon linear extrapolation of the BMD (for MLE) or BMDL (for UCL risk estimates).
- Document the results of the BMD analysis in accord with recommendations provided by EPA (2000).

2.7. BMD Analysis Based upon Yu and Oberdörster (2000) Dosimetry Assumptions

This procedure is first illustrated based upon dosimetry assumptions identical to those used by Yu and Oberdörster (2000). In terms of the above steps, Yu and Oberdörster (2000) included adenomas, carcinomas, and mesotheliomas as the response variable, chose (among others) total fibers for measurement of exposure, calculated the rat/HEC ratio for each of the five (four plus control) dose levels based upon an occupational exposure scenario, and normalized lung burdens based upon the number of retained WHO fibers per square centimeter of lung surface area. The actual ratio of rat/HEC estimated by Yu and Oberdörster (2000) varied slightly with fiber concentration, but averaged approximately 36:5.2.

Fig. 2 shows a Weibull model fitted to the bioassay data. (Among the various models included in EPA’s BMD software, the Weibull model consistently provided good fits to the data.) This model includes adenomas and carcinomas, uses an “extra risk” formulation, a BMR of 0.1, and a 95% BMDL for calculation of UCL risks. EPA’s (2000) guidance indicates that “it is preferable to have studies with one or more doses near the level of the BMR to give a better estimate of the BMD, and thus, a shorter confidence interval.” The RCC data with a BMR of 0.10 fulfill this EPA criterion.

The estimated p -value for this model is approximately 0.27 (an acceptable fit in terms of EPA guidance),

⁶ In the “extra risk” model,

$$\text{BMR} = [p(\text{BMD}; \gamma, \alpha, \beta, \dots) - p(0; \gamma, \alpha, \beta, \dots)] / (1 - p(0; \gamma, \alpha, \beta, \dots)),$$

where p = probability of response and $\gamma, \alpha, \beta, \dots$ are parameters of the BMD model. Alternatively, in the “added risk” model,

$$\text{BMR} = p(\text{BMD}; \gamma, \alpha, \beta, \dots) - p(0; \gamma, \alpha, \beta, \dots).$$

Added risk is the additional proportion of total animals that respond at a particular dose level, or the predicted probability of response at this dose minus the predicted probability of response in the absence of exposure. Extra risk is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure. Extra and additional risk are equal when the background rate is zero. Extra risk is the default option in the EPA BMD software and, except where noted, is used in this work. As a practical matter, for these data, the estimated risks are insensitive to the type of risk estimate used.

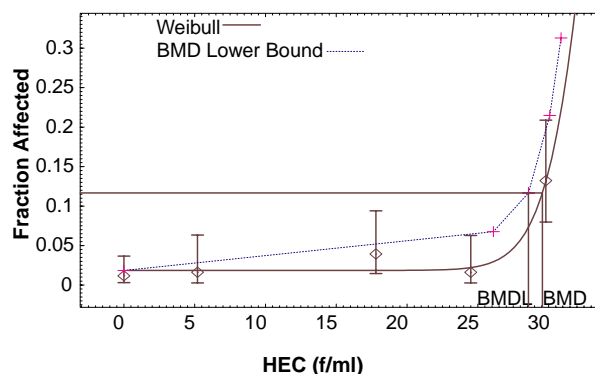


Fig. 2. Estimated exposure–response curve and fitted Weibull model (extra risk) assuming rat/HEC ratios reported in Yu and Oberdörster (2000) and BMR = 0.10. Estimates of BMD and BMDL (95% confidence) are 29.56 and 28.57 f/ml, respectively. The p -value is approximately 0.27.

AIC = 217.54,⁷ and the BMD and BMDL (in HEC units) values are approximately 29.6 and 28.6 f/ml, respectively. The MLE and UCL unit risks corresponding to this set of assumptions are approximately 3.4×10^{-3} and 3.5×10^{-3} , respectively. These estimates depend upon choices made at each of the steps defined above.

Table 4 provides some idea of the sensitivity of the estimated incremental workplace lifetime risks to choices made for the model (including Weibull, gamma multi-hit, logistic, multistage, probit, quantal-quadratic, and quantal-linear) and tumors included (either adenomas and carcinomas alone or together with mesotheliomas). Among these choices:

- Models based upon adenomas and carcinomas typically provide better fits to the data than those including mesotheliomas. This is because the incidence of mesotheliomas is relatively low and the dose–response less clear cut.
- The log-probit, Weibull, log-logistic, and gamma multi-hit models provide acceptable fits when adenomas and carcinomas are included. Indeed, among all models (including those with p -value < 0.1) the range of BMD and BMDL values is so small that (using EPA’s criterion) these are “considered indistinguishable.”
- The estimated BMDs and BMDLs are not greatly sensitive to either the choice of model or to which tumors are included. Additionally, the results are not sensitive to whether the “extra risk” or “added risk” formulations are employed. This lack of sensitivity is an attractive result, because it minimizes the consequences of choices among these alternatives. The resulting risk estimates are robust.

⁷ In contrast, the AIC for the MVK model is considerably lower, 212.1, indicating that (in statistical terms) the BMD model is less favored.

Table 4
Risk estimates based upon BMD/BMDL and Yu and Oberdörster (2000) dosimetry model assumptions

Exposure scenario	Occupational		Surface area 36:5.2 (actual ratio varies with concentration)		Total							
	Adenoma and carcinoma only model output	BMD (f/cc)	BMDL (f/cc)	MLE unit potency ^b (f/cc) ⁻¹	UCL unit potency (f/cc) ⁻¹	Including mesotheliomas model output	p-Value	BMD (f/cc)	BMDL (f/cc)	MLE unit potency (f/cc) ⁻¹	UCL unit potency (f/cc) ⁻¹	% Difference in MLE unit potency
Log-logistic	0.269	29.55	28.54	3.38E-003	3.50E-003	0.107	29.32	28.31	3.41E-003	3.53E-003	0.89	0.86
Weibull	0.271	29.56	28.57	3.38E-003	3.50E-003	0.108	29.34	28.36	3.41E-003	3.53E-003	0.73	0.76
Log-probit	0.302	29.66	28.46	3.37E-003	3.51E-003	0.127	29.54	28.25	3.39E-003	3.54E-003	0.60	0.85
Gamma multi-hit	0.125	29.80	28.00	3.36E-003	3.57E-003	0.040	29.29	27.52	3.41E-003	3.63E-003	1.73	1.73
Logistic	0.073	31.68	27.26	3.16E-003	3.67E-003	0.043	29.92	26.17	3.34E-003	3.82E-003	5.70	4.08
Multistage ^c	0.051	34.15	28.06	2.93E-003	3.56E-003	0.027	31.74	26.45	3.15E-003	3.78E-003	7.61	6.11
Probit	0.055	32.89	27.46	3.04E-003	3.64E-003	0.031	30.72	26.14	3.26E-003	3.83E-003	7.24	5.22
Quantal quadratic	0.051	34.15	28.06	2.93E-003	3.56E-003	0.027	31.74	26.45	3.15E-003	3.78E-003	7.61	6.18
Quantal linear	0.011	46.87	31.97	2.13E-003	3.13E-003	0.005	40.61	28.51	2.46E-003	3.51E-003	15.39	12.14

^a All above models sum with “extra risk” as risk type. Use of “added risk” rather than “extra risk” results in only minor changes. For example, BMD and BMDL for Weibull model fitted to adenomas and carcinomas are 29.59 and 28.62 f/ml, respectively if an “added risk” model is used in place of an “extra risk” model.

^b Based upon linear extrapolation with BMR = 0.10 (actual value could be smaller).

^c Multi-stage model run as a second degree polynomial.

- Among models with p -value >0.1 , the average MLE unit potency is approximately 3.4×10^{-3} , slightly higher than that estimated by Yu and Oberdörster (2000) using the LMS model.

2.8. BMD analysis with alternative dosimetry assumptions

This section provides alternative estimates of workplace risks, based upon revised inputs to the dosimetry model and the basis for normalization of lung burdens. Although the results are not greatly sensitive to the choice of tumors included, most of the results in the section are based upon adenomas and carcinomas alone because these models offer improved fits to the bioassay data. Table 5 shows replicate computations for various dosimetry assumptions in terms of tidal volume, breathing frequency (hence minute ventilation rate), K_{dis} , and the basis for lung burden normalization (e.g., fibers per milligram dry lung or fibers per square centimeter lung area). The same dosimetry model used by Yu and Oberdörster (2000) is employed. For each set of assumptions, the ratio rat/HEC corresponding to 36 total f/ml (rat concentration) is calculated and this common ratio is used to scale all other HECs based upon the measured rat exposure concentrations.

Cases A (adenomas and carcinomas) and A1 (also including mesotheliomas) in Table 5 correspond to the Yu and Oberdörster (2000) dosimetry assumptions. Cases B and B1 retain the Yu and Oberdörster (2000) assumptions regarding K_{dis} and basis for lung burden normalization, but change the inhalation rate from 20 to 13.5 L/min (used by SII, 1998; Moolgavkar et al., 1999, 2000). Comparing these two sets of cases, the estimated ratio rat/HEC changes only slightly from 36:5.2 (Yu and Oberdörster, 2000) to 36:5.7—almost a negligible difference if an inhalation rate of 13.5 L/min is assumed rather than 20 L/min. Other factors held constant, a lower inhalation rate would be expected to reduce fiber deposition in the human and, therefore, lower the rat/HEC ratio in direct proportion. However, the deposition efficiency is also a function of the breathing frequency—lower frequencies imply greater residence times in the lung and therefore, greater deposition efficiencies. These two factors are almost self-canceling—the rat/HEC ratio is insensitive to inhalation rates. Cases C (adenomas and carcinomas) and C1 (also including mesotheliomas) in Table 5 retain the same dosimetry assumptions as shown in Cases B and B1, except that the basis for lung burden normalization is changed from fibers per square centimeter surface area (used by Yu and Oberdörster, 2000) to fibers per milligram dry lung (used by Moolgavkar et al., 1999, 2000; SII, 1998). This changes the rat/HEC ratio from 36:5.7 to 36:33.8, a substantial adjustment, as might be expected from the data presented in Table 3. In turn,

this shift in rat/HEC changes the BMDs, BMDLs, MLE, and UCL risks.

Cases D, D1, E, and E1 are identical to corresponding cases B, B1, C, and C1, except that the value for K_{dis} is changed from 0.73 ng/cm²/h estimated by C.P. Yu based upon the analysis of in vivo data to 8.0 ng/cm²/h, based upon in vitro estimates of K_{dis} (Maxim et al., 1999; Zoitos et al., 1997). Results shown in Table 5 confirm the sensitivity of the results to the basis for normalization of lung burdens, but also show that the results are quite sensitive to the value estimated for K_{dis} . If lung burdens are normalized in terms of fibers per milligram dry lung and the K_{dis} is equal to 8 ng/cm²/h, the ratio of rat/HEC becomes 36:127.1.

Thus, in addition to lung burden normalization, K_{dis} is an influential parameter. Fig. 3 shows the RCF rat lung burden (10^5 f/mg dry lung) data gathered in the RCC study (means and SDs) as a function of time for each of the dose levels tested. The solid and dashed curved lines corresponds to estimated lung burdens from the fitted dosimetry model for $K_{\text{dis}} = 0.73$ and 8 ng/cm²/h, respectively. A value of 0.73 ng/cm²/h offers an improved fit and, therefore, is recommended for use in the dosimetry model.

The calculations shown in Table 5 confirm that the results are insensitive to whether or not mesotheliomas are included (although fits are improved if these are not included), demonstrate that the inhalation rate is not a major determinant of risk, highlight the importance of lung burden normalization, and (in concert with the results shown in Fig. 3) support the choice of a value of 0.73 ng/cm²/h for K_{dis} . Lung burden normalization is addressed in Section 3. Before summarizing these results, it is useful to address the sensitivity of BMD-based risk estimates on other factors. For this purpose, case C of Table 5 is used as a base case.

Fig. 4 shows experimental data and the fitted Weibull model corresponding to the dosimetry assumptions given in case “C” in Table 5, which results in a ratio of rat/HEC of 36:33.8 or approximately 1.07. For these data, the Weibull model consistently offers the best fit. The p -value, AIC, BMD, BMDL, MLE, and UCL risks are approximately 0.30 (slightly better than based upon the Yu and Oberdörster (2000) assumptions), 217.36, 217.9, and 203.5 f/ml, 4.6×10^{-4} , and 4.9×10^{-4} , respectively. Risks estimated using these assumptions are lower than those estimated by Yu and Oberdörster (2000)—chiefly because of the differences in the assumed basis for normalization of lung burdens. The 36:33.8 rat/HEC ratio results if the basis for lung burden normalization is fibers per milligram dry lung.

Several additional computations have been made to understand the sensitivity of the risk estimates to the underlying assumptions of BMD-based risk estimates for RCF.

Fig. 5 shows the sensitivity of the estimated lifetime incremental occupational risk associated with exposure

Table 5
BMD cancer model runs based upon alternative dosimetry assumptions

Run	A	AI	B	BI	C	CI	D	DI	E	EI
Exposure scenario	Workplace	Workplace	Workplace	Workplace	Workplace	Workplace	Workplace	Workplace	Workplace	Workplace
Tidal volume (cm ³)	1290	1290	1060	1060	1060	1060	1290	1290	1060	1060
Breathing frequency (min ⁻¹)	15.50	15.50	12.74	12.74	12.74	12.74	15.50	15.50	12.74	12.74
Minute ventilation (L/min)	20	20	13.5	13.5	13.5	13.5	20	20	13.5	13.5
K_{dis} (ng/cm ² /h)	0.73	0.73	0.73	0.73	0.73	0.73	8	8	8	8
Lung normalization	Fibers per lung area	Fibers per lung area	Fibers per lung area	Fibers per lung area	Fibers per milligram lung	Fibers per milligram lung	Fibers per lung area	Fibers per lung area	Fibers per milligram lung	Fibers per milligram lung
HEC corresponding to 36 f/cc rat	5.2	5.2	5.7	5.7	33.8	33.8	21.3	21.3	127.1	127.1
Model	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull
Mesotheliomas included?	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
<i>p</i> -value	0.27	0.11	0.30	0.13	0.30	0.13	0.30	0.13	0.30	0.13
BMD	29.56	29.34	36.74	36.47	217.86	216.24	137.29	136.27	819.23	813.15
BMDL	28.57	28.36	34.34	33.89	203.54	200.98	128.26	126.65	765.37	755.75
Unit potency-MLE	3.38E-003	3.41E-003	2.72E-003	2.74E-003	4.59E-004	4.62E-004	7.28E-004	7.34E-004	1.22E-004	1.23E-004
Unit potency-UCL	3.50E-003	3.53E-003	2.91E-003	2.95E-003	4.91E-004	4.98E-004	7.80E-004	7.90E-004	1.31E-004	1.32E-004

Note. A/AI, B/BI, etc., are duplicate runs for which the only difference is whether or not mesotheliomas are included.

Original Yu and Oberdörster runs are closest (except for BMD analysis) to A1.

C/CI represents our best estimate of lung parameters and uses fibers per milligram dry lung as basis for normalization.

E/EI is identical to C/CI except that K_{dis} is set equal to that measured in vitro.

RCF1

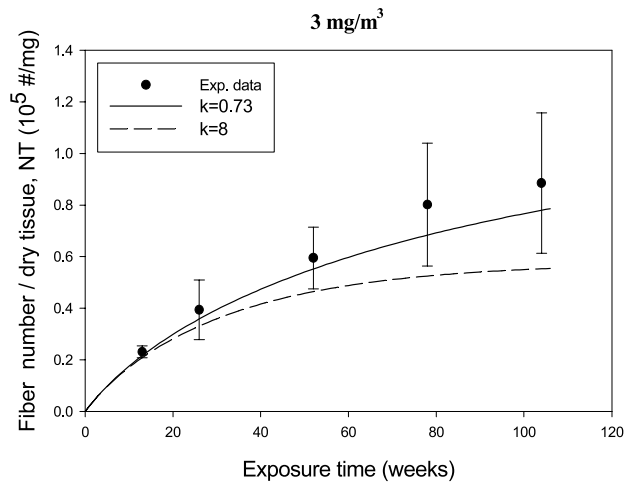
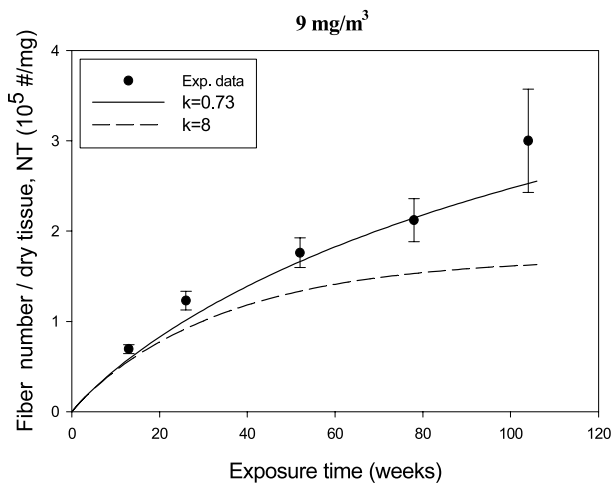
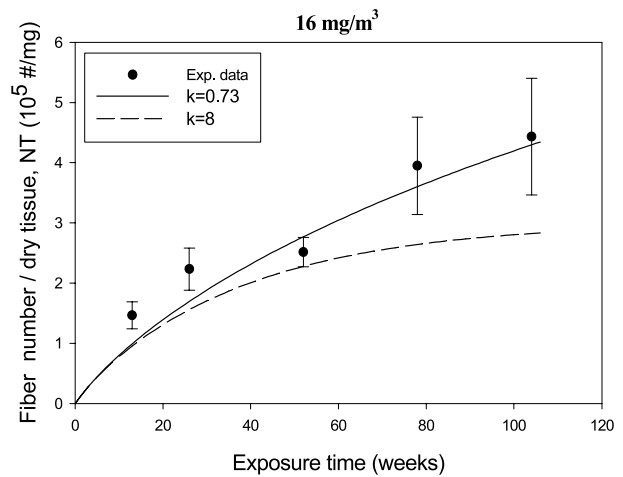
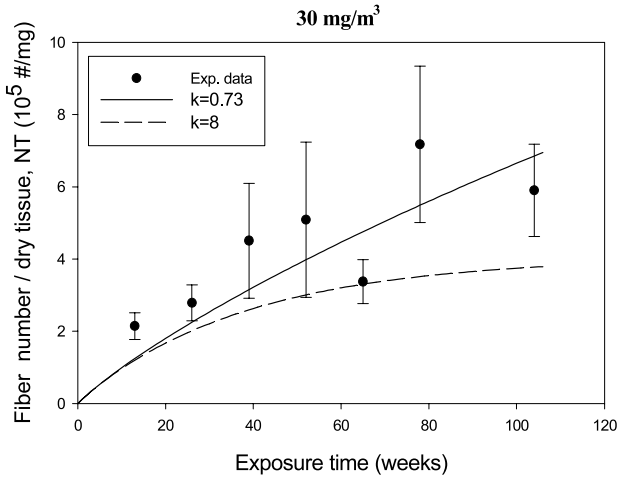


Fig. 3. Number of fibers/mg dry lung versus time as measured in RCC study and predicted using Yu/Oberdörster models for two values of K_{dis} .

to 1 f/ml (unit potency) to the BMR chosen as a point of departure (POD) in the benchmark analysis. The dosimetry assumptions correspond to case “C” in Table 5.

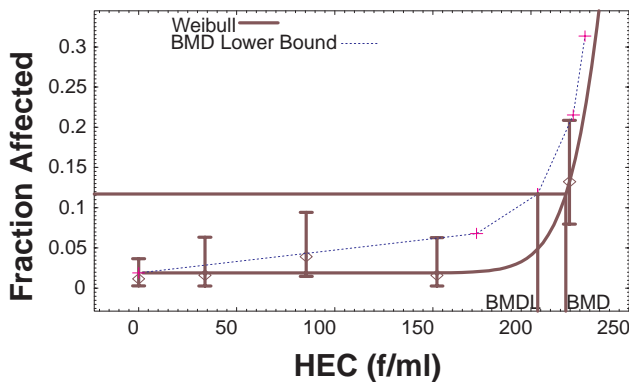


Fig. 4. Estimated exposure–response curve and fitted Weibull model (extra risk) assuming $rat/HEC = 36:33.8$ and $BMR = 0.10$. Estimates of BMD and BMDL (95% confidence) are 217.86 and 203.54 f/ml, respectively.

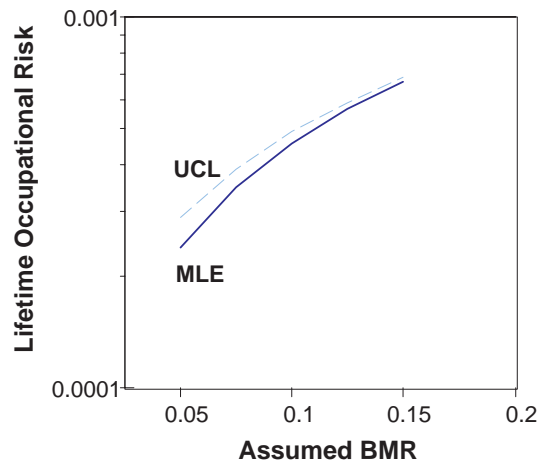


Fig. 5. Relation between MLE and 95% UCL estimate of working lifetime occupational risk when exposed to 1 f/ml RCF for BMD (Weibull model) and assumed BMR for rat/HEC of 36:33.8.

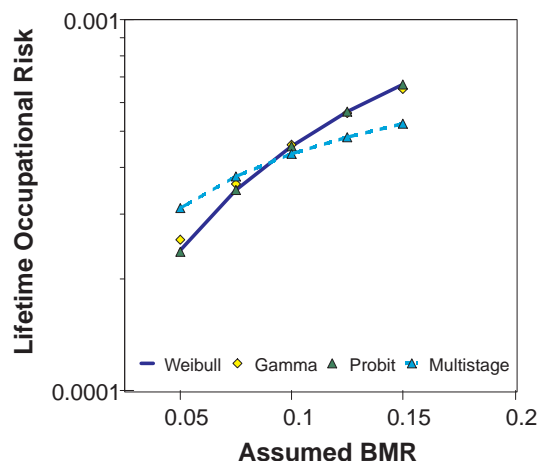


Fig. 6. Relation between MLE estimate of working lifetime occupational risk when exposed to 1 f/ml RCF as a function of assumed BMR for various good-fit models for rat/HEC of 36:33.8.

Over a range of BMRs from 0.05 to 0.15, the resulting MLE risks (based upon linear extrapolation)⁸ range by a factor of 2.8 from approximately 2.4×10^{-4} to 6.7×10^{-4} . As noted above, EPA guidance recommends a value of 0.10 for the BMR. The sensitivity of the extrapolated unit potency depends upon the curvature of the fitted model in the vicinity of the BMR.

Fig. 6 shows how the MLE unit potency varies with the assumed BMR for all models with *p*-values exceeding 0.1, including the Weibull, probit (log dose), gamma multi-hit, and multistage. The first three of these models exhibit similar sensitivity, whereas the multistage risk estimates are less sensitive to the choice of BMR. Table 6 shows the sensitivity of MLE and UCL unit potency to the choice of model, BMR, and confidence level. (As indicated above, results are insensitive to whether or not mesotheliomas are included and the risk type used.)

A key dosimetry parameter is the ratio of rat/HEC—and, derivatively, the assumed basis for normalization of lung burdens. Fig. 7 shows how the UCL and MLE unit potencies vary with the ratio of rat/HEC. Results are quite sensitive to the estimated value of this ratio.

Although the BMD approach for risk estimation is not favored when a biologically based model is available, the use of this model facilitates an understanding of the importance of various inputs to the risk analysis. Specifically the results of this section demonstrate the relative unimportance of assumptions regarding inhalation rates and which tumors are included and the relative importance of the basis for lung burden normalization and fiber clearance rate (K_{dis}).

With respect to BMD-based risk estimates specifically, the following parameters are relatively unimportant: (i) choice of model and (ii) confidence level. The

choice of BMR is of intermediate importance. The choice of the basis for lung burden normalization is more important.

3. Discussion

At the outset, it is appropriate to note that none of the QRAs performed for RCF explicitly take into account the possible confounding of effects of exposure to particles and fibers. Because even low-toxicity particles are known to be capable of causing fibrosis and tumors in rats under overload conditions, it is likely that these contribute to some degree to the observed biological responses. Because of this, all risk estimates presented in this paper should be regarded as conservative—albeit to an unknown degree.

All the QRAs reviewed above assume that the same retained lung burden (when appropriately normalized) will cause the same biological effect in both the rat and human. That is, it is assumed that humans and rats are equally sensitive. Yu and Oberdörster (2000) examined the evidence for and against the assumption of equal sensitivity and concluded, “Thus, there is no convincing evidence that the rat is less sensitive than humans for developing lung tumors after chronic inhalation. Using the result of the chronic rat inhalation study with RCF in combination with our dosimetric extrapolation model, therefore, appears to be justified for human cancer risk estimates from exposures to RCF, and there is no need to include factors for lower sensitivity of the rat model.” Maxim and McConnell (2001) also concluded on a weight of the evidence basis that there seems little reason to believe that humans and rats have greatly different sensitivities with respect to the development of pulmonary fibrosis or lung cancer.

Based upon the material presented above, it is possible to delete certain of the unit risk estimates shown in Table 2 from further consideration. Bases for deletion include lack of documentation (e.g., DECOS), use of less favored models (e.g., Fayerweather et al., 1997), or estimates based on parameters or models that are less favored statistically (e.g., deletion of results based upon linear or quadratic initiation models in the MVK analyses). The Moolgavkar et al. (2000) analysis was deleted because the overall model was similar to that used by SII (1998) and thus addressed in comments on the SII (1998) analysis. Moolgavkar et al. (2000) estimated different risks for RCF, in part because data from other SVFs were pooled with RCF and in part because assumed outliers were deleted—practices that deserve additional exploration.

These deletions leave a smaller set of estimates shown in Table 7 for further consideration.

Current EPA guidance favors use of biologically based risk models, such as those proposed by SII (1998)

⁸ Risks estimated from the BMD model are typically very much smaller than those developed using this linear extrapolation.

Table 6
Sensitivity of unit potency estimates

Model: Weibull Risk: Extra rat/HEC 36:33.8		Tumors: adenoma and carcinoma Confidence: 0.95				
Assumed BMR	BMD (f/ml)	BMDL (f/ml)	Unit potency		Remarks	
			MLE	UCL		
<i>Effect of varying BMR at 95% confidence level</i>						
0.050	209.32	172.30	2.39E-004	2.90E-004	Default value	
0.075	214.24	191.60	3.50E-004	3.91E-004		
0.100	217.86	203.54	4.59E-004	4.91E-004		
0.125	220.75	211.30	5.66E-004	5.92E-004		
0.150	223.17	216.60	6.72E-004	6.93E-004		
Assumed confidence level	BMDL (f/ml)	UCL unit potency	Remarks			
<i>Effect of varying confidence level at BMR=0.10</i>						
75.0%	213.05	4.69E-004	Default value			
90.0%	207.45	4.82E-004				
95.0%	203.54	4.91E-004				
97.5%	199.48	5.01E-004				
99.0%	192.47	5.20E-004				
Model	p-value	BMD (f/ml)	BMDL (f/ml)	Unit potency		Remarks
				MLE	UCL	
<i>Effect of varying model at BMR=0.1 and 95% confidence interval</i>						
Weibull	0.300	217.86	203.54	4.59E-004	4.91E-004	Best-fit model Identical to Weibull
Log-logistic	0.300	217.86	203.54	4.59E-004	4.91E-004	
Gamma multi-hit	0.253	215.63	201.06	4.64E-004	4.97E-004	Identical to multistage
Probit (log dose)	0.161	218.08	201.47	4.59E-004	4.96E-004	
Probit	0.145	223.31	186.58	4.48E-004	5.36E-004	
Multistage	0.124	229.23	187.17	4.36E-004	5.34E-004	
Quantal-quadratic	0.124	229.23	187.17	4.36E-004	5.34E-004	
Quantal-linear	0.040	294.61	201.50	3.39E-004	4.96E-004	

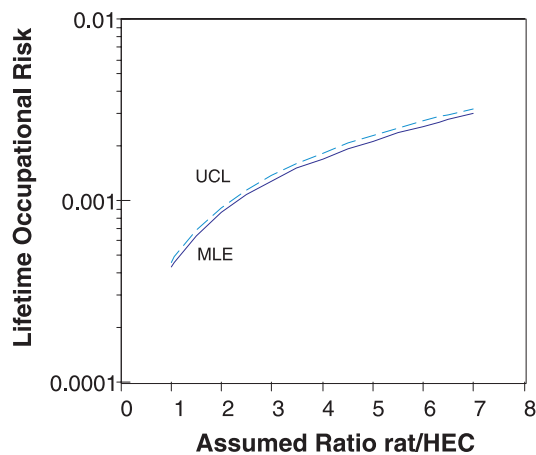


Fig. 7. Relation between MLE and 95% UCL estimate of lifetime occupational risk when exposed to 1f/ml RCF for BMD (Weibull model) and ratio rat/HEC.

and Moolgavkar et al. (1999, 2000) in preference to more empirical constructs such as the LMS (Yu and Oberdörster, 2000) or BMD models. The MVK approach simulates the initiation and promotion activities that are believed to underlie cancer induction, rests upon a plausible theory of chemical carcinogenesis, and considers explicitly both the time-to-tumor and temporal pattern of lung burdens—all features that are attractive in principle. (Mechanisms of fiber carcinogenesis are not fully understood, however.)

The BMD models also have lower AIC values in comparison to the MVK models, indicating poorer fits. Additionally, the BMD risk estimates are sensitive to the assumed BMR. Although EPA offers guidance on BMR selection, this is based more on policy and the need for uniformity, rather than scientifically observed. Thus, there are both statistical and normative reasons for deleting the BMD-based risk estimates in Table 7—which narrows the resulting risk range to a factor of approximately 5 (SII, 1998; Yu and Oberdörster,

Table 7

Reduced set based upon documentation and fit still shows estimates varying by factor of approximately 22

Source	MLE unit potency	Upper 95% confidence limit	Remarks/Assumptions
SII (1998)	1.50×10^{-4}	1.8×10^{-4}	MVK exponential potency model, Yu et al., dosimetry model, steel worker cohort, RCF only
BMD	4.59×10^{-4}	4.9×10^{-4}	Weibull, Yu et al., dosimetry model, fibers/lung weight normalization, RCF only
Yu and Oberdörster (2000)	7.20×10^{-4}	2.4×10^{-3}	Linearized multistage, Yu et al., dosimetry model, fibers/lung area normalization, RCF only
BMD	3.38×10^{-3}	3.5×10^{-3}	Weibull, Yu et al. dosimetry model, fibers/lung area normalization, RCF only

2000)—a considerable reduction in the range of values presented in Table 2.

This said, the LMS and BMD analyses summarized above are relevant because these highlight the importance of the method used for normalization of lung burdens. For the same model and plausible values of other dosimetry parameters, risks calculated on the assumption that the proper basis for normalization of lung burdens is fibers per milligram dry lung are lower by a factor of approximately 6 compared to those based on the assumption that equal biological responses result in the rat and the human if lung burden is measured as fibers per square centimeter lung surface. The SII (1998) and Yu and Oberdörster (2000) MLEs of unit risks differ by approximately a factor of 5, which suggests that the combined net effect of all other assumptions (e.g., MVK compared to LMS, differences in inhalation rates, and whether or not mesotheliomas are included) is negligible for the RCF data. This simplifies the task of discriminating among risk estimates, because it enables us to focus upon the key determinants of estimated risk.

As noted above, lung burden normalization is an important determinant of estimated risks for the Yu and Oberdörster (2000) and BMD analyses. Risks extrapolated from rats to humans using these models are greater by a factor of approximately 6 if dose equivalence is determined based upon epithelial surface area, rather than lung weight.

Regulatory agencies have favored different bases for the determination of species equivalence. OSHA, for example, normalized doses based upon body weight (rather than $BW^{2/3}$ or $BW^{3/4}$ in estimating human risks (see, e.g., risk analyses for ethylene oxide [OSHA, 1983], 1,3-butadiene [OSHA, 1996], and methylene chloride [OSHA, 1997]). With respect to health effects of fibers, many authors have chosen to normalize lung burdens on the basis of lung weight.

In their most recent work, Yu and Oberdörster (2000) normalized on the basis of lung area claiming, "For the endpoint cancer of the respiratory system in rodent assays, target cells are the epithelial surface of the lower respiratory tract and of the pleural surface." They noted that, "Instead of using pulmonary surface area for normalizing lung dose between rats and humans, other possibilities could have been lung weight, lung volume,

or specific target cells. However, we feel that the use of lung epithelial surface area is appropriate since inflammatory mediators released by activated cells upon fiber exposure interact with epithelial cells to induce either proliferative effects, or have to cross epithelial cells to cause other effects."

Although the most appropriate basis for normalizing lung burden remains uncertain, the concept of normalizing to specific target cells presents an attractive mechanistic strategy. Thus, for epithelial lung tumors, such as squamous cell carcinomas arising from chronic injured bronchial epithelium, or adenocarcinomas originating from bronchial glands or peripheral mucosa, normalization to surface area seems reasonable from a mechanistic perspective. However, if the stimulus for epithelial activation and cell proliferation arises from interstitial cells which are critically targeted by fibers, normalization based on lung weight may be appropriate. Indeed, a newly emerging hypothesis is that interstitial fibroblasts activated by substances released during tissue injury or by environmental factors (e.g., fibers) are vital for initiating inflammation (Smith et al., 1997). Using the model of colon carcinoma and extending it to lung inflammation and cancer, the fibroblast gets activated and produces mediators such as reactive oxygen species, Cox-2 or prostaglandins that can damage and activate epithelial cells that predispose to malignancy (Coussens and Werb, 2002; Zhang et al., 1998). Thus the initial stimulus for the lung tumor may be the interstitial fibroblast; in such circumstances, it is reasonable to consider normalizing to some other index, such as lung weight. This would also be the case for a small number of adenocarcinomas which arise from parenchymal fibrotic "scar" tissue (Filderman and Matthay, 1996). Therefore, the most accurate basis for normalization depends on the location of cells initially interacting with fibers resulting in tumor formation. If additional data confirm the fibroblast hypothesis of fiber-induced lung tumors, then both bases for normalization, lung weight and lung epithelial surface area, should be considered.

The SII (1998) and Yu and Oberdörster (2000) (and the BMD calculations given here) use basically the same dosimetry model developed by Yu and colleagues. The parameters in the dosimetry model have been calibrated

based upon data from rats and extrapolated to humans using the best information available on relative physiological characteristics (e.g., the number and volume of alveolar macrophages) of each species. Only limited data on human lung burdens are available (see Yu et al., 1997), which has precluded direct estimation of the parameters of the human dosimetry model. Nonetheless, the available human data are consistent with the model predictions and there is no known reason why the dosimetry model would either under- or over-predict lung burdens. Thus, the human dosimetry estimates are uncertain to a degree, but are not believed to be biased. Moreover, the QRAs summarized in Table 7 use essentially the same dosimetry model, so possible limitations of this model do not affect the choice among risk predictions.

The key uncertainties in risk estimation for RCF are the basis for lung burden normalization and the possible confounding effects of particles in the RCC experiments. The quantitative significance of the choice of either an epithelial area or lung weight basis for lung burden normalization is understood. In contrast to this important parameter, the choice of potency models has only a minor effect on the results. Directionally, the effect of a greater ratio of particles to fibers in the RCC experiment would be to overstate the actual workplace risk for airborne fiber, but we lack data to estimate the magnitude of this possible confounder—a fruitful area for additional research.

Acknowledgments

This work was supported by the Refractory Ceramic Fibers Coalition. The views and conclusions expressed herein are solely those of the authors and do not necessarily represent those of RCFC or its member companies. The efforts of Ron Niebo, Everest Consulting Associates, in performing some of the BMD analyses and checking other computations are gratefully acknowledged. Finally, we appreciate the helpful comments of the reviewers.

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