APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Refractory Ceramic Fibers
CAS Number: None
Date: July 13, 2004
Profile Status: Final Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 78
Species: Fischer 344 Rats

Minimal Risk Level: 0.03 [ ] mg/kg/day [ ] ppm [X] WHO fiber/cc

References:

Mast RW, McConnell EE, Anderson R, et al. 1995a. Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7:425-467.

Mast RW, McConnell EE, Hesterberg TW, et al. 1995b. Multiple dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7(4):469-502.

Bernstein DW, Sintes JMR, Ersboell BK, et al. 2001b. Biopersistence of synthetic mineral fibers as a predictor of chronic inhalation toxicity in rats. Inhal Toxicol 13:823-849.

Maxim LD, Yu CP, Oberdörster G, et al. 2003. Quantitative risk analyses for RCF: survey and synthesis. Regul Toxicol Pharmacol 38:400-416.

Experimental design and effects noted:

In the multiple-exposure level study (Mast et al. 1995b), four groups of about 140 male F344 rats were exposed via nose-only inhalation to 0 (filtered air controls), 3, 9, or 16 mg/m^3 of a refractory ceramic fiber called RCF1, 6 hours/day, 5 days/week for up to 24 months. The companion study (Mast et al. 1995a) exposed two groups of about 140 male F344 rats to 0 or 30 mg/m^3 RCF1 (from the same lot as the multiple-exposure level study) via the same protocol.

The RCF1 test material was prepared from a bulk sample of kaolin-based refractory ceramic fiber obtained from Carborundum Company, Niagara Falls, New York. The bulk material was separated (before aerosol generation) to concentrate the numbers of fibers with a targeted nominal arithmetic mean diameter of 1 µm and length of 20–30 µm. These dimensions were chosen based on results of an unpublished simulated workplace exposure study showing airborne fibers to be principally of this size range. The generated aerosols had the characteristics listed in Table A-1. In addition to fibers (i.e., particles with length:diameter ≥3:1), the aerosols contained nonfibrous particles, often referred to as "shot". In the experimental aerosols, the ratios of nonfibrous particles (with diameters <3 µm) to total fibers or to WHO fibers were reported by Mast et al. (1995b) to range from 0.9 to 1.5 or from 1.3 to 1.96, respectively (Table A-1).

Table A-1. RCF1 Aerosol Characteristics in the 2-Year Inhalation Bioassays with F344 Rats (Mast et al. 1995a, 1995b)

Character (mean [± standard deviation])	3 mg/m^3	9 mg/m^3	16 mg/m^3	30 mg/m^3
Gravimetric concentration (mg/m^3)	3.0±0.4	8.8 ±0.7	16.5±1.1	29.1±5.2
Total fibers/cc (L:D≥3)	36±17	91±34	162±37	234±35
WHO fibers/cc (L>5 µm; D<3 µm; L:D≥3)	26±12	75±35	120±35	187±53
Diameter (D) range (µm)	0.08–5.32	0.08–5.37	0.07–4.83	0.12–4.53
Length (L) range (µm)	0.77–93.93	1.09–98.25	1.24–97.88	1.30–76.6
Arithmetic mean D (µm)	1.02±0.73	1.02±0.71	1.02±1.70	0.98±0.61
Geometric mean D (µm)	0.80±2.06	0.80±2.03	0.82±1.99	0.82±1.89
Arithmetic mean L (µm)	20.2±18.10	20.3±17.1	19.6±16.5	22.3±17.0
Geometric mean L (µm)	13.5±2.60	13.9±2.50	13.8±2.4	15.9±2.4
Nonfibrous particle counts				
≤1 µm/cc	28.3±19.3	85.7± 63.2	88.0±52.4	17±154
1–3 µm/cc	23.0±11.8	54.8±38.4	68.4±24.2	135±45
3 µm/cc	17.1±8.4	43.6±25.2	58.6±27.1	81±29
Ratio nonfibrous particles (<3 µm):total fibers	1.41	1.54	0.97	1.31
Ratio nonfibrous particles (<3 µm):WHO fibers	1.96	1.87	1.30	1.63

Groups of 3–6 rats from each exposure group were killed at 3, 6, 12, 18, and 24 months of exposure. Additional groups of 3–6 rats were removed from exposure at 3, 6, 12, and 18 months and exposed to filtered air until they were sacrificed at 24 months. Remaining rats exposed for 24 months (15–32 rats per group) were held without further exposure until 30 months when survivors were killed. All rats were necropsied. Lung tissues were removed, and weighed, and the left lung was prepared for routine histopathology that included staining for collagen deposition. Other tissues processed for histopathology included the nasal cavity, larynx, trachea, bronchi, mediastinal and mesenteric lymph nodes, liver, spleen, kidneys, heart, and all tissues with grossly visible lesions. The concentration and size distributions of fibers in lung tissue were determined after ashing of accessory lung lobes. All fibers detected in lungs had diameters <3 µm. Concentrations were expressed as total fibers per mg dry lung (length:diameter >3) or WHO fibers per mg dry lung (length >5 µm, diameter <3 µm, and length:diameter ≥3).

Observed nonneoplastic lung lesions were classified with two different grading scales. One scale (the Wagner scale) contained eight grades ranging from a normal grade of 1 (with no lesions observed), through "cellular change" grades 2 and 3 (few to conspicuous macrophages in terminal bronchioles and alveoli and no collagen deposition at the bronchiolo-alveolar junction), to five "fibrosis" grades. The fibrosis grades increased in severity as follows: grade 4 (minimal), minimal collagen deposition at the bronchoalveolar junction, increased bronchiolization, and associated mucoid debris; grade 5 (mild), interlobular linking of collagen deposition; grade 6 (moderate), early consolidation and decrease in parenchyma tissue; grade 7 (severe), marked fibrosis and consolidation; and grade 8, complete obstruction of most airways. The other scale contained five grades (0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe) and was applied to specific histopathological findings (macrophage aggregation, bronchiolization, granuloma presence, interstitial [i.e., pulmonary] fibrosis, and pleural fibrosis).

Survival was not statistically significantly affected in any of the exposed groups compared with controls. Body weights and body weight gains were not affected in the two lowest exposure groups (3 and

9 mg/m^3). At sporadic intervals of exposure, rats exposed to 16 or 30 mg/m^3 displayed statistically significant decreases in body weight, compared with controls. The decreases were not >10% of control values, and are not considered an adverse effect. In 16- and 30-mg/m^3 rats, absolute and relative lung weights were significantly greater than in control rats, as early as after 3 months of exposure. After 24 months of exposure, mean absolute lung weights in these groups were respectively increased by 32 and 65%, compared with controls. The lung weight changes are considered to be an indicator of pulmonary inflammation from repeated exposure to RCF1.

Lung fiber concentrations increased with increasing exposure duration and concentration. At 24 months, mean values of WHO fibers/mg lung were 4.29×10^4, 15.60×10^4, 22.10×10^4, and 27.50×10^4 for the 3-, 9-, 16-, and 30-mg/m^3 groups, respectively. Mean values for total fibers/mg lung were 5.55±1.71, 18.80±3.59, 27.80±6.06, and 37.00±8.01, respectively.

Exposure-related nonneoplastic histopathological lesions were restricted to the lung or pleura. Signs of pulmonary inflammation (macrophage aggregation, bronchiolization, and granuloma presence) were observed in all exposed groups after 3 months of exposure, whereas these lesions did not occur in the control rats at any interval (see Table A-2). At 24 months, mean scores (on the five-grade scale) in the 3- and 30-mg/m^3 groups ranged from 2 to 3.2 for macrophage aggregation, from 1.2 to 2.7 for bronchiolization, and from 1.5 to 2 for granuloma presence (Table A-2). The mean scores reflect progression of the severity of the inflammatory lesions with increasing exposure concentration (Table A-2). There is also some evidence of progression of the severity of the inflammatory lesions with increasing duration of exposure, most notably between 3 and 12 months (Table A-2).

Signs of interstitial (i.e., pulmonary) fibrosis and pleural fibrosis appeared in rats exposed to concentrations ≥9 mg/m^3 (Table A-2). The five-grade scores for interstitial fibrosis and pleural fibrosis (see note about these scores below) showed some progression in severity with exposure duration and concentrations, but the average severity scores for the exposed groups did not progress beyond a score of 3 (moderate) for pulmonary fibrosis or a score of 2 (mild) for pleural fibrosis (Table A-2). Signs of fibrosis did not appear until 12 months of exposure. Using the eight-grade Wagner scale to classify the pulmonary cellular changes and fibrosis, the mean scores at 24 months were 1.0 (normal), 3.2, 4.0, 4.2, and 4.0 for the control, 3-, 9-, 16-, and 30-mg/m^3 groups, respectively. In rats exposed for 24 months and allowed to live without exposure to 30 months, respective mean scores were 1.0, 2.9, 3.8, 4.0, and 4.3 (Table A-2). These scores indicate that the pulmonary lesions produced by 24 months of exposure showed only minor, if any, regression and that, on average, the most severe nonneoplastic lesions formed were classified as minimal to mild fibrosis. It was reported that the principal difference between 24-month exposed rats killed at 24 and 30 months was a reduction in the number of pulmonary macrophages and granulomas in the 30-month rats; pulmonary or pleural fibrosis showed no signs of regression.

In a later published report, Bernstein et al. (2001b) reported that the pathologist, who originally scored the histological slides from the RCF1 2-year bioassay, had provided scores for collagen deposition at the bronchoalveolar junction. This lesion was scored in each rat on a five-scale system as follows:

> 0=normal;
> 1=minimal–very few (1 or 2 foci) and very small foci of collagen deposition of insufficient severity to score as Grade 4 in the eight-grade Wagner scale;
> 2=mild–slight, but easily detected, few, small foci of collagen deposition, minimally sufficient to classify in Grade 4 of the Wagner scale;
> 3=moderate–easily detected foci of collagen deposition in considerably enlarged areas, corresponding to Grade 4 of the Wagner scale;

4=marked–marked, obvious, or extensive foci of collagen deposition extending into the interstitium, and corresponding to Grade 4 of the Wagner scale;
5=severe–widespread collagen deposition with consolidation at the bronchoalveolar junction, sometimes with interlobular linking, corresponding to Grade 4 to 5 of the Wagner scale.

In accordance with this scale, collagen deposition at the bronchoalveolar junction is taken as an early response at the site where fibrosis can develop. The lesion is not classified as pulmonary fibrosis at a minimal score of 1, but is classified as minimal to mild fibrosis at scores of 2–5. The mean scores (±standard deviations) for the collagen deposition scores reported by Bernstein et al. (2001b) for the six rats in each of the groups sacrificed at 24 months were: control (n=12), 0 (normal); 3 mg/m^3, 0.67±0.8; 9 mg/m^3, 2.0±0; 16 mg/m^3, 2.83±0.4; and 30 mg/m^3, 2.17±0.4. These mean scores for collagen deposition are identical to the mean scores for the lesion named "pulmonary fibrosis" in the Mast et al. (1995a, 1995b) report and shown in Table A-2. Thus, the scores for "pulmonary fibrosis" shown in Table A-2 are actually for collagen deposition as per the original pathology reports.

Neoplastic lesions (lung adenomas, lung carcinomas, and mesotheliomas) were found most prominently in rats exposed to 30 mg/m^3. The tumors appeared predominately late in life. The first adenoma occurred in rats sacrificed at 18 months; carcinomas and mesotheliomas were detected only in the 30-month-sacrifice animals. Incidences for rats (that survived to 12 months) with bronchoalveolar hyperplasia were 8/129, 10/123, 16/127, 13/124, and 17/123 for the control through high-exposure groups. Combined incidences for lung adenomas or carcinoma were 1/129, 2/123, 5/127, 2/124, and 16/123. Incidences for mesothelioma were 0/129, 0/123, 1/127, 0/124, and 2/123. Incidences for mesothelial proliferation were 1/129, 0/123, 1/127, 1/124, and 9/123.

Table A-2. Mean Severity Scores for Pulmonary Lesions in F344 Rats Exposed to RCF1 (Mast et al. 1995a, 1995b)[a]

Exposure level/ sacrifice month	Number of rats	Macrophage Aggregation (0–5 scale)	Bronchio-lization (0–5 scale)	Granuloma (0–5 scale)	Pulmonary fibrosis (0–5 scale)	Pleural fibrosis (0–5 scale)	8-Grade Wagner scale score
Control							
3	3	0	0	0	0	0	1.0
6	3	0	0	0	0	0	1.0
12	6	0	0	0	0	0.3	1.0
18	6	0	0	0	0	0	1.0
24	6	0	0	0	0	0	1.0
30[b]	32	0.1	0.1	0	0	0	1.0
3 mg/m^3							
3	3	1.7	0	0.7	0	0	2.0
6	3	1.7	0	1	0	0	2.0
12	6	2	1	1.3	0.2	0	3.0
18	6	2	1.2	1.7	0.7	0.7	3.2
24	6	2	1.2	1.5	0.7	0.5	3.2
30[b]	23	2.4	1.7	1.5	0.8	0.5	2.9
9 mg/m^3							
3	3	2	0.3	1.3	0	0	2.3
6	3	2	0.7	2	0	0.3	2.7
12	6	2.3	1.2	2.2	1.7	0.2	4.0

Table A-2. Mean Severity Scores for Pulmonary Lesions in F344 Rats Exposed to RCF1 (Mast et al. 1995a, 1995b)[a]

Exposure level/ sacrifice month	Number of rats	Macrophage Aggregation (0–5 scale)	Bronchio-lization (0–5 scale)	Granuloma (0–5 scale)	Pulmonary fibrosis (0–5 scale)	Pleural fibrosis (0–5 scale)	8-Grade Wagner scale score
18	6	2.3	1.8	2.2	1.8	0.7	4.0
24	6	2.5	1.8	2.2	2	0	4.0
30[b]	25	2.7	1.7	1.7	1.7	0.5	3.8
16 mg/m^3							
3	3	2	1	2	0	0	3.0
6	3	2.3	1.3	2	0	0	3.0
12	6	3	1.8	2.8	2.8	0.7	4.0
18	6	3	2.7	2.7	2.2	1.2	4.0
24	6	3	2.7	2.7	2.8	1.5	4.2
30[b]	20	3	2.5	2.1	2	1	4.0
30 mg/m^3							
3	3	2	1	2	2	0	3.3
6	3	2.7	2	2	2	0	4.0
12	6	3	2.3	2.5	2.5	1.5	4.0
18	3	3	2	2.3	2.3	1	4.3
24	6	3.2	2.7	2	2	0.5	4.0
30[b]	15	2.8	2.9	1.9	1.9	1.3	4.3

[a]0–5 Scale for different types of lesions: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked: 5=severe. 8-Grade Wagner Scale for pulmonary cellular change and fibrosis: 1=normal; 2 or 3=cellular change consistent with inflammation; 4=minimal fibrosis with collagen deposition, bronchiolization, and mucoid debris; 5=mild fibrosis with some interlobular linking of collagen; 6=moderate fibrosis with consolidation and parenchymal decrease; 7=severe fibrosis and consolidation; 8=complete obstruction of airways.
[b]Exposed for 24 months and sacrificed at 30 months.
[c]Bernstein et al. (2001b) reported that the original pathologist's score for this lesion was for collagen deposition at the bronchoalveolar junction, not for pulmonary fibrosis; in the five-grade scale used for collagen deposition, a minimal score of 1 is of insufficient severity to be classified as minimal fibrosis (Grade 4 on the Wagner scale).

Dose and end point used for MRL derivation:

Benchmark concentration analysis was conducted for lung weights (absolute weight expressed as percent of control), macrophage aggregation scores, bronchiolization scores, and scores for collagen deposition at the bronchoalveolar junction. Changes in the first three variables are taken as signs of pulmonary inflammation induced by refractory ceramic fibers deposited in the lung. ATSDR policy considers pulmonary fibrosis to be a serious adverse effect that is inappropriate for MRL derivation. Scores for collagen deposition at the bronchoalveolar junction were included in the analysis, because a score of 1 for this lesion is not of sufficient severity to be considered fibrosis; only scores $\geq$2 were classified as pulmonary fibrosis.

Continuous-variable models available in the EPA Benchmark Dose Software were fit to the lung weight, macrophage, bronchiolization, and bronchoalveolar collagen deposition data shown in Table A-3. Each of these end points was increasingly affected with increasing exposure level and increasing concentrations of fibers in the lungs at 24 months (Table A-3). Group means and standard deviations of the lung weight, macrophage aggregation scores, and bronchiolization scores were obtained from a report of an analysis of

the Mast et al. (1995a, 1995b) 24-month-sacrifice data by Yu and Oberdörster (2000). The mean scores and standard deviations for collagen deposition at the bronchoalveolar junction were obtained from data in the report by Bernstein et al. (2001b). The published report by Mast et al. (1995a, 1995b) only cited mean values and did not cite standard deviations. Dr. Yu's analysis did not include scores (and standard deviations) for granuloma presence.

The benchmark response level for lung weight was set at 10% increase in weight. Percentage change below this value is assumed to be nonadverse. Benchmark response levels for scores for macrophage aggregation, bronchiolization, and bronchoalveolar collagen deposition were set at 1.0 (minimal rating on the 0–5 scale, where 0=normal).

Table A-3. Non-neoplastic Lung Responses in F344 Rats Exposed for 24 Months to RCF1 (Mast et al. 1995a, 1995b)

Exposure level	Fiber concentrations in lungs at 24 months	Lung weight	Mean score±standard deviation (0–5 Scale)		
(total fibers/cc)	(mean total fibers per mg lung x10^4)	(Percent of control)	Macrophage aggregation	Bronchio-lization	Collagen deposition at the bronchoalveolar junction
0 (n=12)	NR	100.0±14.0	0±0	0±0	0±0
36 (n=6)	5.55±1.71	116.8±12.3	2.0±0	1.2±0.4	0.7±0.82
91 (n=6)	18.80±3.59	110.9±8.1	2.5±0.6	1.8±0.4	2±0
162 (n=6)	27.80±6.06	131.8±15.3	3.0±0	2.7±0.5	2.8±0.4
234 (n=6)	37.00±8.01	164.7±44.2	3.2±0.4	2.7±0.5	2.2±0.4

0–5 Scale: 0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe; NR= not reported

[ ] NOAEL [ ] LOAEL [X] Benchmark Concentration: Lower 95% confidence limits on benchmark concentrations (BMCLs = lower 95% confidence limit on the estimated concentrations associated with a mean score of 1.0 for macrophage aggregation, bronchiolization, or collagen deposition, or 10% increase in lung weight) were considered for selection of the point of departure for the MRL. The rat exposure-response data for these four end points were first fit to continuous-variable models. The best-fitting models were then used to calculate rat BMCLs for each of the end points. The point of departure for the MRL was selected from the rat BMCLs. The selected rat BMCL was then converted to a $BMCL_{HEC}$ using a cross-species scaling factor derived from the lung deposition and clearance models developed for RCF1 in rats and humans (Maxim et al. 2003b; Yu and Oberdörster 2000; Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b).

Benchmark Concentration Modeling Results. Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models; BMDS version) were fit to the data shown in Table A-3.

Lung Weight. Adequate fits to the data (as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS) were obtained with the linear, polynomial, power, and Hill models with constant variance assumed. Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard deviations listed in Table A-3). Models with non-homogeneous variance (i.e., variance as a power function of dose) generally provided improved fits to the data as assessed with Aikake's Information Criteria, AIC (Table A-4). Comparing across models, a better fit is indicated by a lower AIC. The best-fitting model, as indicated by the AIC, was the power model with non-homo-

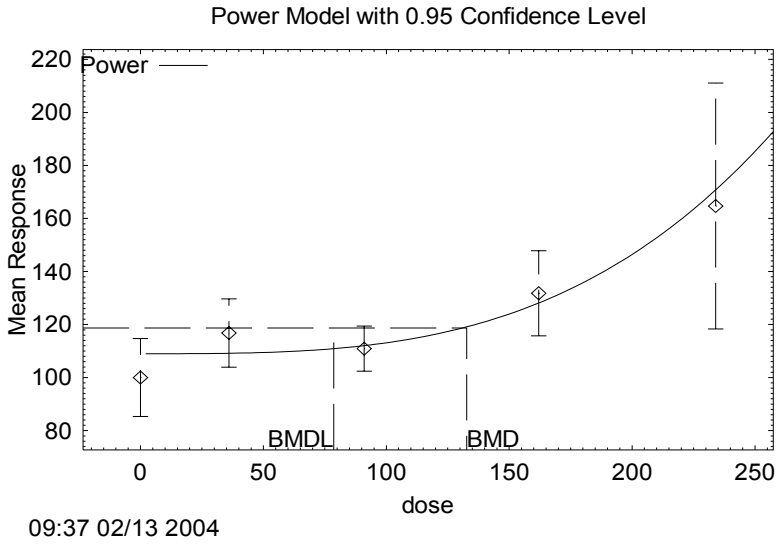
geneous variance, which predicted a rat BMC and BMCL of 133 and 79 total fibers/cc, respectively (Figure A-1).

Table A-4. BMC Modeling Results for Lung Weights in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b)

Model	BMC (total fibers/cc)	BMCL (total fibers/cc)	AIC-fitted
Linear	40	30	220.12
Linear-nonhomogeneous	.9	32	213.51
Polynomial	95	34	220.08
Polynomial-nonhomogeneous	94	43	211.52
Power	110	35	222.00
Power-nonhomogeneous*	133*	79*	209.30*
Hill	10	35	224.00
Hill-nonhomogeneous	60	6	228.90

*Best Fitting Model

Figure A-1. Predicted (Power Model with Nonhomogeneous Variance) and Observed Lung Weights in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers To Rat Exposure Concentrations, Total Fibers/cc)



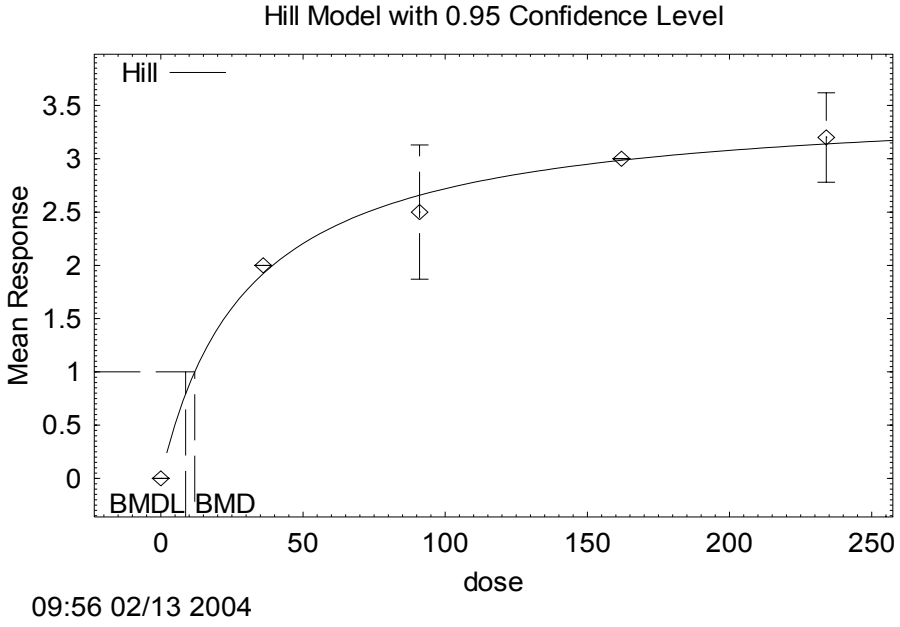
Macrophage Aggregation Scores. Adequate fits to the data (as assessed by chi-square residuals and log-likelihood fit tests in the BMDS) were obtained with the polynomial, power, and Hill models with constant variance assumed. Models with variance as a power function of dose did not improve the fits to the data. As assessed by AIC (Table A-5), the Hill model provided the best fit to the data, yielding a rat BMC and BMCL of 12 and 9 total fibers/cc, respectively (Figure A-2).

Table A-5. BMC Modeling Results for Scores for Pulmonary Macrophage Aggregation in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b)

Model	BMC (total fibers/cc)	BMCL (total fibers/cc)	AIC-fitted
Hill*	12*	9*	-33.05*
Polynomial	21	13	-12.08
Polynomial-nonhomogeneous	13	0	-8.44
Power	6	0	13.67
Power-nonhomogeneous	51	0	15.02

*Best Fitting Model

Figure A-2. Predicted (Polynomial Model with Constant Variance) and Observed Scores for Pulmonary Macrophage Aggregation in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers to Rat Exposure Concentrations, Total Fibers/cc)



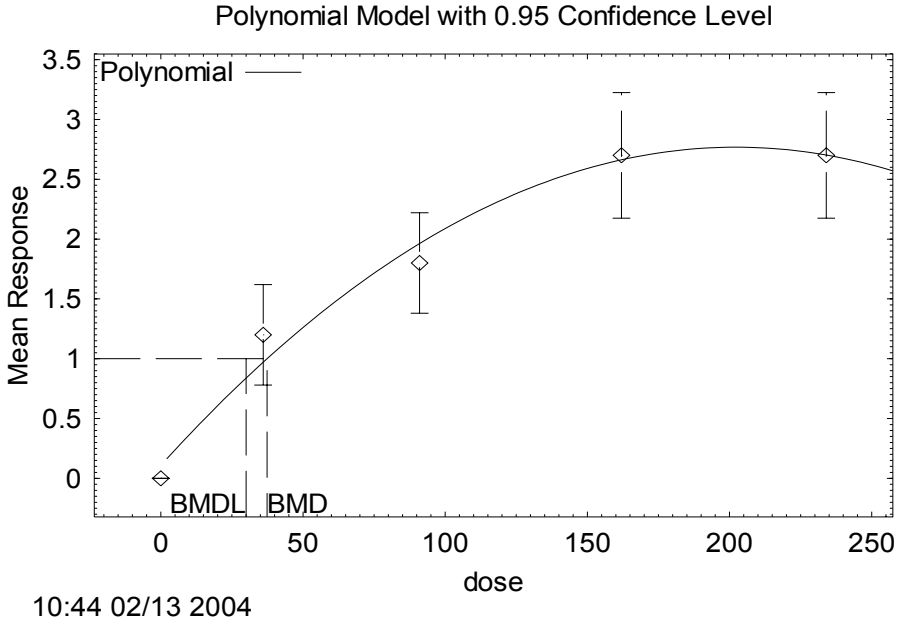
Bronchiolization Scores. Adequate fits to the data (as assessed by chi-square residuals and log-likelihood fit tests in the BMDS) were obtained with the polynomial and Hill models with constant variance assumed. Benchmark concentration calculations failed when models with variance as a power function of dose were fit to the data. The best-fitting model, as assessed by AIC, was the polynomial (2-degree) model (Table A-6), which yielded a rat BMC and BMCL of 37 and 30 total fibers/cc, respectively (Figure A-3).

Table A-6. BMC Modeling Results for Scores for Bronchiolization in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a 1995b)

Model	BMC (total fibers/cc)	BMCL (total fibers/cc)	AIC-fitted
Polynomial*	37*	30*	-19.91*
Hill	30	22	-18.28

*Best Fitting Model

Figure A-3. Predicted (Polynomial Model with Constant Variance) and Observed Scores for Bronchiolization in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers to Rat Exposure Concentrations, Total Fibers/cc)



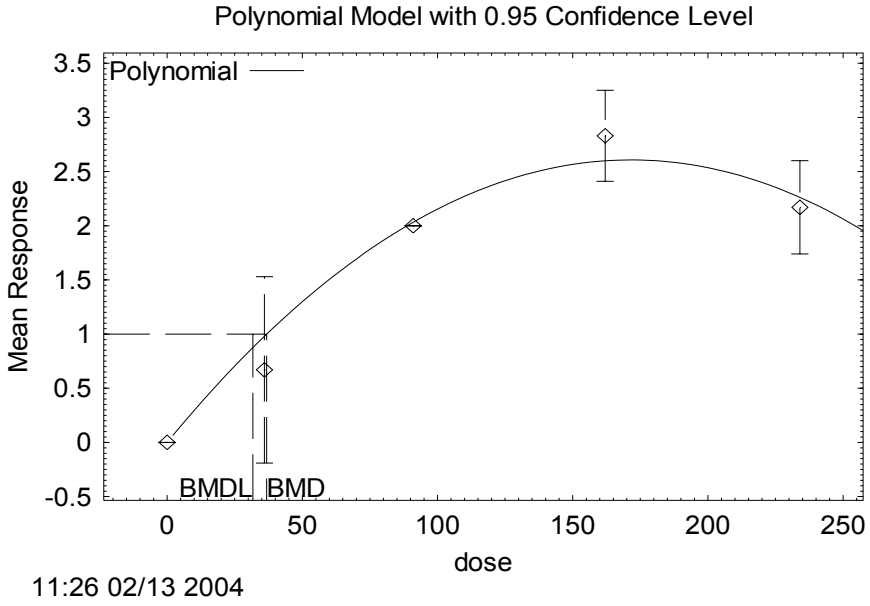
Collagen Deposition Scores. Adequate fits to the data (as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS) were obtained with the polynomial and Hill models with constant variance assumed. Benchmark concentration calculations failed when models with variance as a power function of dose were fit to the data. The best-fitting model, as assessed by AIC, was the polynomial (2-degree) model (Table A-7), which yielded a rat BMC and BMCL of 37 and 32 total fibers/cc, respectively (Figure A-4).

Table A-7. BMC Modeling Results for Scores for Collagen Deposition at the Bronchoalveolar Junction in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b)

Model	BMC (total fibers/cc)	BMCL (total fibers/cc)	AIC-fitted
Polynomial*	37*	32*	-12.52*
Hill	45	37	-5.25

*Best Fitting Model

Figure A-4. Predicted (Polynomial Model with Constant Variance) and Observed Scores for Collagen Deposition at the Bronchoalveolar Junction in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b) (Dose Refers to Rat Exposure Concentrations, Total Fibers/cc)



Selection of Point of Departure for the MRL. BMCs and BMCLs for the four modeled end points are shown in Table A-8. The BMCL for lung weight represents the 95% lower confidence limit on the concentration estimated to increase lung weight by a mean of 10% over control values. The BMCLs for the pulmonary lesion scores represent the 95% lower confidence limits on the concentration estimated to produce a mean score of 1 (minimal severity) for each lesion.

Table A-8. BMCs and BMCLs for Lung Weight and Pulmonary Lesion Scores in Rats Exposed to RCF1 for 24 Months (Mast et al. 1995a, 1995b).

End point	BMC (total fiber/cc)	BMCL (total fiber/cc)
Lung weight	133	79
Pulmonary macrophage aggregation	12	9
Bronchiolization	37	30
Collagen deposition at the bronchoalveolar junction	37	32

The rat BMCL of 9 total fiber/cc for pulmonary macrophage aggregation was selected as the point of departure for the MRL, because this lesion is the most sensitive among those measured in the bioassay (as indicated by having the lowest BMCL in Table A-8). ATSDR considers minimal pulmonary inflammation a reversible response to fibers and nonfibrous particles that, although near the boundary between adverse and nonadverse, is an appropriate critical effect on which to base the MRL. As shown in the data in Table A-3, the severity of pulmonary macrophage aggregation in rats in the principal study showed a clear increase in severity with increasing exposure levels of RCF1, as well as with increasing concentrations of fibers in the lungs of the rats sacrificed after 24 months of exposure.

Dosimetric Adjustment of Rat Benchmark Concentrations to Human Equivalent Concentrations (HECs)
The BMC and BMCL for pulmonary aggregation in rats were converted to human equivalent exposure levels using an average scaling factor derived from rat and human lung deposition and clearance models for RCF1 developed by Dr. C.P. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b). Equations for deposition in the models are functions of fiber length, fiber diameter, and time. The equations for mechanical macrophage-mediated clearance rate are functions of fiber length, alveolar macrophage volume, and lung burden (total accumulated volume of fibers and particles). The clearance models include dissolution-rate and transverse breakage-rate equations.

Values for key parameters in the dosimetric models included the following (Maxim et al. 2003b;Yu and Oberdörster 2000):

Rat lung weight: 1.48 g; Human lung weight: 1,000 g
Rat lung surface area: 4.3×10^3 cm^2; Human lung surface area: 6.5×10^5 cm^2
Rat macrophage volume per lung: 26 mm^3; Human macrophage volume per lung: 1.75×10^4 mm^3
Rat macrophage diameter: 10.68 μm; Human macrophage diameter: 16.82 μm
Dissolution rate (same in rats and humans): 6.46×10^{-5} (μm/day) or 0.73 ng/cm^2/hour
Breakage rate and scheme: same in rats and humans
Size distribution of refractory ceramic fibers in the human model:
Bivariate lognormal distribution (geometric mean±standard deviation) similar to workplace RCF size data: fiber diameter: 0.84 μm (±2.05); fiber length: 14.1 μm (±2.48)
Rat model: retained volume of nonfibrous plus fibrous particles (lung burden) impacts clearance rate
Human model: only retained fibrous particle volume impacts clearance rate.

Initially, Yu and Oberdörster (2000) calculated HECs from the rat exposure levels, using number of WHO fibers per cm^2 of lung surface area as the cross species lung burden normalization unit. The rat models were set to the exposure scenarios experienced by rats in the Mast et al. (1995a, 1995b) bioassays (6 hours/day, 5 days/week for 2 years), and two human exposure scenarios were examined, one involving continuous, lifetime (70-year) exposure assuming a tidal volume of 750 cc and nasal breathing with a respiratory frequency of 14.5 per minute, and a second involving occupational exposure (8 hours/day,

5 days/week, 50 weeks/year for 40 years) assuming a tidal volume of 1290 cc and nasal breathing with a respiratory frequency of 15.5 per minute. Calculated HECs for the two human exposure scenarios from the rat exposure levels are shown in Table A-9. The mean ratios of the rat:human equivalent exposure concentrations were 14.7 for the continuous exposure scenario and 7.3 for the occupational exposure scenario. From these ratios, mean rat-to-human dosimetric scaling factors are 0.07 (1/14.7) for the continuous exposure scenario and 0.13 (1/7.3) for the occupational exposure scenario.

Table A-9. HECs Calculated for Two Human Exposure Scenarios from Rat Exposure Levels Using WHO Fibers per cm^2 of Lung Surface area for Cross-Species Normalization. (Source: Tables 7.1 and 7.2; Yu and Oberdörster, 2000)

Human exposure scenario	Rat exposure levels (total fibers/cc)					Mean ratio rat:human (±SD)
	0	36	91	162	234	
	HECs (WHO fibers/cc)					
Continuous	0	2.4	8.1	11.0	13.2	14.7 ±2.7
Occupational	0	4.7	16.2	22.3	27.1	7.3 ±1.3

More recently, Maxim et al. (2003) showed that selection of the cross species lung burden normalization unit (i.e., number of fibers per cm2 of lung surface area versus number of fibers per mg dry weight of lung) is a key determinant in species conversion of exposure levels when using the lung and deposition models developed by Yu and colleagues. Using a human occupational exposure scenario assuming a tidal volume of 1,060 cc and nasal breathing with a respiratory frequency of 12.74 per minute and a minute ventilation of 13.5 L per minute, human equivalent concentrations corresponding to a rat exposure level of 36 total fiber/cc were calculated to be 5.7 total fiber/cc, based on a WHO fibers per cm^2 of lung surface area normalization, compared with 33.8 total fibers/cc, based on a WHO fibers per lung mg dry weight normalization. The ratios of rat:human equivalent exposure concentrations for these occupational exposure scenarios were 6.3 on a lung surface area basis (similar to the mean of 7.3 shown in Table A-9) and 1.1 on a lung dry weight basis. For this occupational exposure scenario, rat-to-human dosimetric scaling factors based on lung surface area normalization or lung dry weight normalization are 0.16 (i.e., 1/6.3) and 0.9 (1/1.1), respectively, indicating an approximate 6-fold difference between lung surface area and lung dry weight normalizations.

A rat-to-human scaling factor of 0.07, based on a human continuous exposure scenario and lung surface area cross-species normalization, was used to convert the rat BMC and BMCL of 12 and 9 total fibers/cc to human equivalent concentrations of 0.8 and 0.6 WHO fibers/cc, respectively. This scaling factor was used, because data are not available to confirm which cross-species lung burden normalization method is more accurate, and calculations of mean rat-to-human dosimetric scaling factors, based on lung dry weight normalization with continuous exposure scenarios, are not available. It is recognized that the analysis by Maxim et al. (2003) indicates that an alternative scaling factor, based on lung dry weight cross species normalization, could be about 6-fold higher. The point of departure for the MRL is the BMCLHEC of 0.6 WHO fibers/cc, rounded to 1 WHO fibers/cc.

Uncertainty Factors used in MRL derivation:

[X] 3 for interspecies extrapolation with dosimetric adjustment. The dosimetric adjustment takes into account physiological differences between rats and humans expected to influence deposition and clearance of refractory ceramic fibers from the lung. It is recognized that the cross species dosimetric scaling factor used (based on fiber per lung surface area normalization) may underestimate the human equivalent concentration associated with the development of pulmonary lesions, compared with a scaling factor based on a fiber per lung dry weight basis. As such, the scaling factor based on lung surface area

normalization is likely to be protective of the public health, and an additional factor to account for this dosimetric uncertainty is unnecessary. The derivation assumes that rats and humans are equally responsive to retained fibers in the lung, in the absence of conclusive evidence to indicate otherwise. The uncertainty factor of 3 accounts for the uncertainty associated with this assumption of interspecies pharmacodynamic equivalence.

[ ] 10 for use of a LOAEL: No uncertainty factor was necessary for the use of a BMCLHEC for minimal pulmonary macrophage aggregation, an effect just above the boundary between nonadverse and adverse.

[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

Was a conversion used from intermittent to continuous exposure? Yes. The human lung and deposition model used a continuous, 70-year, exposure scenario, whereas the rat lung and deposition model used the experimental exposure conditions, 6 hours/day, 5 days/week for 2 years.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: See previous discussion of the derivation of the rat-to-human dosimetric scaling factor of 0.07.

Other additional studies or pertinent information which lend support to this MRL: The Mast et al. (1995a, 1995b) study provides the best available data describing exposure-response relationships for nonneoplastic lesions in the lung and pleura from chronic inhalation exposure to refractory ceramic fibers. The study identifies pulmonary inflammation as the critical nonneoplastic end point of concern and identifies other more serious effects at higher exposure levels (pulmonary and pleural fibrosis and cancer of the lung and pleura). Other studies of rats exposed to RCF1 by inhalation provide strong support for pulmonary inflammation as the critical end point (Bellman et al. 2001; Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995), as well as other animal inhalation studies of other refractory ceramic fibers (Mast et al. 1995a) and other synthetic vitreous fibers such as insulation glass wools, MMVF10 and MMVF11 (Hesterberg et al.1993c; McConnell et al. 1999), slag wool MMVF22 (McConnell et al. 1994), and rock wool MMVF21 (McConnell et al. 1994).

There are distinct differences between laboratory animal species and humans in respiratory tract size and geometry, ventilation rate and pattern, and macrophage sizes that influence the retention (the net result of deposition and clearance) of fibers in the lung. Yu and colleagues (Yu et al. 1995a, 1995b, 1996, 1997, 1998a, 1998b) have developed lung retention models for RCF1 in rats and humans that incorporate many of these interspecies differences. Although these models significantly decrease uncertainty in extrapolating doses from rats to humans, in vivo human data on internal doses of inhaled synthetic vitreous fibers are limited, and validation exercises with the human model are correspondingly limited.

Several reviewers of draft versions of this Toxicological Profile disagreed with ATSDR's selection of macrophage aggregation as the critical effect for the MRL. Reasons for not selecting macrophage aggregation included: (1) this end point is not a response that is specific to fibers (nonfibrous particles can also cause this effect), and (2) it is a reversible and adaptive effect and therefore nonadverse. The ATSDR MRL Workgroup acknowledged that although there were confounding effects from nonfibrous particles in the principal study, the data in Table 2 show that there was a clear relationship between concentrations of fibers in the lung and increasing severity of macrophage aggregation. The MRL Workgroup acknowledged the reversibility of macrophage aggregation, but does not consider reversibility as a criterion for not selecting a critical effect for MRL derivation.

The ATSDR MRL Workgroup discussed an alternative MRL derivation with collagen deposition as the critical effect, but preferred selection of macrophage aggregation as the critical effect. If collagen deposition was selected as the critical effect for the MRL, an alternative MRL of 0.02 WHO fibers/cc was derived as follows (using a benchmark response=a concentration that would produce an average score of 1 for bronchoalveolar collagen deposition in a population and a total uncertainty factor of 90: 3 for cross-species extrapolation, 10 for human variability, and 3 for the selection of a potentially serious adverse effect as the critical effect):

1. [Rat $BMCL_{collagen\ deposition}$] x [cross-species scaling factor] = $BMCL_{collagen\ depositionHEC}$

   32 total fiber/cc x 0.07 = 2.24 WHO fibers/cc = 2 WHO fibers/cc (rounded)

2. MRL = $BMCL_{collagen\ depositionHEC}$ ÷ 90 = 2 ÷ 90 = 0.02 WHO fibers/cc.

The Workgroup noted the similarity of the values of the MRLs based on macrophage aggregation (0.03 WHO fibers/cc) or collagen deposition (0.02 WHO fibers/cc). The approximate 3-fold difference in the benchmark concentrations (9 total fibers/cc for macrophage aggregation and 32 total fibers/cc for collagen deposition) was offset by the 3-fold difference in the total uncertainty factors (30 for macrophage aggregation and 90 for collagen deposition).

The MRL derivation assumes that rats and humans are equally sensitive to the inflammatory effects of refractory ceramic fibers. Understanding of the relative pharmacodynamic sensitivity of rodents and humans to synthetic vitreous fibers, asbestos fibers, or nonfibrous particulate matter is poor. Varying opinions on the relative sensitivity of rodents and humans to deposited fibers have been expressed by Rodelsperger and Woitowitz (1995), Rowe and Springer (1986), Yu and Oberdörster (2000), Maxim and McConnell (2001), and Maxim et al. (2003). The uncertainty factor of 3 is used in the MRL derivation to account for the uncertainty of the assumption of pharmacodynamic equivalence between rats and humans.

Available comparative data with other refractory ceramic fibers (e.g., data for RCF2, RCF3, and RCF4 reported by Mast et al. 1995a) suggest that RCF1 is as potent or more potent in inducing various pulmonary effects than other refractory ceramic fibers. Thus, the chronic MRL based on RCF1 data is expected to be protective of the public health for exposure to other refractory ceramic fibers.

A significant contributing factor to the high potency of RCF1 relative to other refractory ceramic fibers is the high content of nonfibrous particles in RCF1. Bellmann et al. (2001) have reported that the mass concentration of total fibers (particles with aspect ratio >3:1) and nonfibrous particles (with aspect ratios <3:1) in RCF1 are 0.76 and 0.26 ng/ng RCF1, respectively. Evidence that the presence of the nonfibrous particles can enhance the effects on the lung was provided by comparing responses in rats exposed by inhalation for 3 weeks to concentrations of about 125 fibers (with lengths >20 μm)/cc of either RCF1 or a sample of refractory ceramic fibers, called RCF1a, in which only 2% of the mass was accounted for by nonfibrous particles (Bellmann et al. 2001). Expressed as WHO fibers/cc, the respective mean concentrations were 481 fibers/cc for RCF1a and 679 fibers/cc for RCF1. Pulmonary clearance ability was markedly depressed by RCF1, but not by RCF1a, and indices of pulmonary inflammation were more persistently increased by RCF1 than by RCF1a (Bellmann et al. 2001).

The ratio of nonfibrous particles:fibers for the RCF1 material used in the 2-year rat bioassay (Mast et al., 1995a, 1995b) has been reported to be about 3:1 by Bellmann et al. (2001), about 1-2:1 from data reported by Mast et al. (1995a, 1995b), and 9:1 by Maxim et al. (1997) and Mast et al. (2000). In contrast, workplace air samples (n=10) showed a ratio of about 0.5:1 (Mast et al. 2000; Maxim et al. 1997). Thus, a key uncertainty associated with the MRL is that the nonfibrous particles likely contributed

to the observed lung responses to some undetermined degree. As such, the MRL may underestimate the daily human exposure that is likely to be without appreciable risk of adverse noncancer health effects, and is expected to be protective of public health.

Bernstein et al. (2001b) conducted an analysis to determine if there was a statistically significant relationship between scores for collagen deposition at the bronchoalveolar junction and lung fiber concentrations (of various size classes) in the data collected in chronic rat bioassays with five types of synthetic vitreous fibers (RCF1, MMVF21—a stone wool, MMVF 11—an insulation glass wool, MMVF10—an insulation glass wool, and MMVF22—a slag wool). In the analysis, logistic and proportional odds regression models were fit to data for scores for collagen deposition at the broncho-alveolar junction and associated lung fiber concentrations in the rats sacrificed after 24 months of exposure. In these analyses, lesion score was the dependent variable and lung fiber concentration (of various size classes) was the explanatory variable. Bernstein et al. (2001b; Figure 2) noted that the score for collagen deposition showed a statistically significant relationship with increasing lung concentrations of the five types of fibers with lengths >20 μm (and not with lung concentrations of fibers in smaller length categories).

In comments provided to ATSDR (ATSDR Docket No. ATSDR-187; January 23, 2003), Dr. Bernstein noted that his analysis extended to 10 other pulmonary end points evaluated in these bioassays (including scores for macrophage aggregation and bronchiolization), and that he did not find statistically significant relationships for these scores with the concentrations of the various types of fibers in the lungs of the rats. Dr. Bernstein's analysis indicates that only the scores for collagen deposition (and not the other pulmonary end points) showed a statistically significant relationship with lung burden across the five types of synthetic vitreous fibers included in the analysis. Dr. Bernstein interpreted this to mean that, among the 11 pulmonary end points evaluated in these bioassays and this analysis, only collagen deposition had a statistically significant relationship with fiber lung burden at 24 months. Dr. Bernstein proposed that one reason for selecting bronchoalveolar collagen deposition as the critical end point for MRL derivation is that there was a lack of association for the other end points with lung fiber concentration at 24 months. An alternative interpretation of Dr. Bernstein's analysis is that it shows that only the most biopersistent of the fibers evaluated (i.e., those, such as RCF1, that accumulated to a sufficiently high level in the lung after 2 years) produced moderate collagen deposition and that all of the fiber types included in the analysis induced the other less adverse responses (such as macrophage aggregation and bronchiolization) to degrees that were indistinguishable between fiber types. The data from the principal RCF1 study shown in Table A-3 clearly show that the severity of all of the pulmonary end points (including scores for macrophage aggregation and bronchiolization) increased with increasing exposure level and with increasing lung fiber concentration at 24 months. Thus, even though the nonfibrous particles in the RCF1 atmospheres may have contributed to the pulmonary responses in the rats, the data show a clear relationship between the severity of macrophage aggregation (and other more severe end points) and the internal dose of fibers deposited in the lung. As such, it appears reasonable to select macrophage aggregation as the critical effect for MRL derivation.

The chronic MRL is expected to be appropriately applied to intermediate-duration exposure scenarios, based on evidence from interim sacrifice data from the Mast et al. (1995b) bioassay that exposure-response relationships for pulmonary inflammation and chronic exposure are similar to those for intermediate-duration exposure. Scores for pulmonary inflammation progressed to only a limited degree with progression from intermediate to chronic duration. For example, mean scores for macrophage aggregation in rats exposed to 3, 9, 16, and 30 mg/m^3 at 3 months were 1.7, 2, 2, and 2, respectively. The respective scores were 2, 2.3, 3, and 3 at 12 months and 2, 2.5, 3, and 3.2 at 24 months.

Exposure-response relationships for pulmonary inflammation from acute inhalation exposure to synthetic vitreous fibers are inadequately characterized for deriving an acute inhalation MRL for any type of synthetic vitreous fiber.

Any use of the MRL for refractory ceramic fibers in assessing health hazards from the insulation wools should acknowledge the evidence that many of the insulation wools are markedly less durable and less potent than refractory ceramic fibers (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a). There are data from multiple-exposure-level 2-year rat inhalation bioassays on the glass wools, MMVF10 and MMVF11 (Hesterberg et al.1993c; McConnell et al. 1999), the slag wool MMVF22 (McConnell et al. 1994), and the rock wool MMVF21 (McConnell et al. 1994) that adequately describe exposure-response relationships for nonneoplastic pulmonary effects from intermediate- and chronic-duration exposure to these materials. However, lung deposition and clearance models for these synthetic vitreous fibers (such as those developed by C.P. Yu and colleagues for RCF1) are not yet fully developed to carry out physiologically based dosimetric calculations of human equivalent concentrations. When these models are available, they could be used to convert rat exposure concentrations to human equivalent concentrations, and use the data for MMVF10, MMVF11, MMVF22, and MMVF21 to derive inhalation MRLs for insulation wools.

There are no adequate data (from multiple-exposure level studies) for deriving inhalation MRLs for the other types of synthetic vitreous fibers (special applications glass fibers or continuous filament glass fibers that are woven).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38r is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the

EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

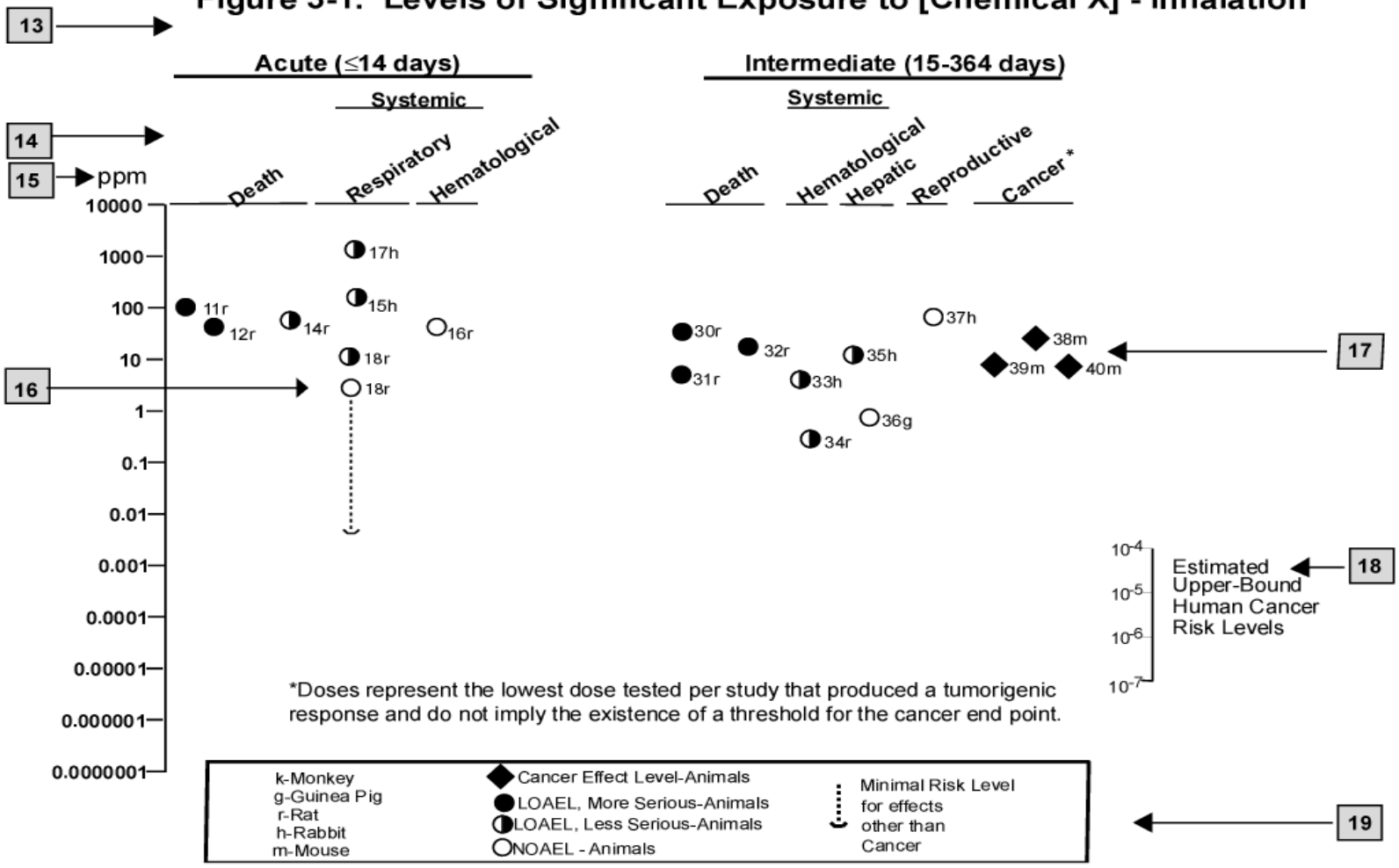
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX